PRODUCT MONOGRAPH

OMNISCAN™

(Gadodiamide injection USP)

287 mg/mL (0.5 mmol/mL)
For intravenous Injection Only

Contrast Enhancement Agent for Magnetic Resonance Imaging (MRI)

GE Healthcare Canada Inc.
1919 Minnesota Court,
Mississauga, Ontario,
L5N 0C9

Date of Revision:
May 22, 2019

Control No.: 225072

PRODUCT MONOGRAPH

OMNISCAN™
(Gadodiamide injection USP)

287 mg/mL (0.5 mmol/mL)
For intravenous injection only

THERAPEUTIC CLASSIFICATION

Contrast Enhancement Agent for Magnetic Resonance Imaging (MRI)

ACTIONS AND CLINICAL PHARMACOLOGY

OMNISCAN (gadodiamide) injection was developed as a contrast agent for diagnostic use in magnetic resonance imaging (MRI). Gadodiamide is a paramagnetic agent with unpaired electron spins which generate a local magnetic field. As water protons move through this local magnetic field, the changes in magnetic field experienced by the protons reorient them with the main magnetic field more quickly than in the absence of a paramagnetic agent.

In magnetic resonance imaging, visualization of normal and pathological brain and spinal tissue depends in part on variations in the radiofrequency signal intensity. These variations occur due to: changes in proton density; alteration of the spin-lattice or longitudinal relaxation time (T_1); and variation of the spin-spin or transverse relaxation time (T_2).

By increasing the relaxation rate, OMNISCAN decreases both the T_1 and T_2 relaxation times in tissues where it is distributed. At clinical doses, the effect is primarily on the T_1 relaxation time, and produces an increase in signal intensity.

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. [Lack of enhancement need not indicate absence of pathology since some types of low grade malignancies or inactive MS-plaques fail to enhance; it can be used for differential diagnosis between different pathologies.] Disruption of the blood-brain barrier or abnormal vascularity allows accumulation of OMNISCAN in lesions such as neoplasms, abscesses and subacute infarcts. The extended time for OMNISCAN to be accumulated in the lesions is unknown.

Pharmacokinetics:

The pharmacokinetics of intravenously administered OMNISCAN in normal subjects conforms to an open, two-compartment model with mean distribution and elimination half-lives (reported as mean ± SD) of 3.7 ± 2.7 minutes and 77.8 ± 16 minutes, respectively.

Gadodiamide is eliminated primarily in the urine with 95.4 ± 5.5% (mean ± SD) of the administered dose eliminated by 24 hours. There is no detectable biotransformation or decomposition of gadodiamide. The renal and plasma clearance rates of gadodiamide are nearly identical (1.7 and 1.8 mL/min/kg, respectively), and are similar to that of substances excreted primarily by glomerular filtration. The volume of distribution of gadodiamide (200 ± 61 mL/kg) is equivalent to that of extracellular water. No protein binding has been observed.

Plasma clearance and elimination half-life were independent of dose after injection of 0.1 and 0.3 mmol/kg. No metabolites have been detected.

Following GBCA administration, trace amounts of gadolinium is present for months or years in brain, bone, skin, and other organs

Secondary Pharmacodynamics:

There were no clinically significant deviations from preinjection values in hemodynamic, blood and urine laboratory parameters following intravenous injection of gadodiamide in healthy volunteers. However, a minimal transient increase in serum iron levels 8 to 48 hours after gadodiamide injection was observed.

INDICATIONS

OMNISCAN (gadodiamide) injection is indicated in adults and the pediatric population for contrast enhancement of magnetic resonance imaging (MRI) of lesions of the central nervous

system with expected abnormal vascularity or those thought to cause abnormalities in the blood-brain barrier. OMNISCAN has been shown to facilitate visualization of central nervous system lesions including but not limited to tumors.

OMNISCAN is also indicated for intravenous administration for use in MRI in adults to facilitate the visualization of lesions with abnormal vascularity within the thoracic, abdominal, pelvic cavities, breast, retroperitoneal space and musculoskeletal system.

OMNISCAN is indicated for intravenous administration for use in magnetic resonance angiography (MRA) for the detection and localization of stenosis in renal arteries and aorto-iliac arteries.

CONTRAINDICATIONS

OMNISCAN is contraindicated in:

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

Omniscan is contraindicated in 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 Pharmaceutical Information section of the product monograph.

WARNINGS

SERIOUS WARNINGS

NOT FOR INTRATHECAL USE

Inadvertent intrathecal use of Omniscan has caused convulsions, coma, sensory and motor neurologic deficits.

WARNINGS: NEPHROGENIC SYSTEMIC FIBROSIS

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

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

NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle, and internal organs. Before administering Omniscan, screen all 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 these patients, avoid use of GBCAs unless the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI). 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 WARNINGS - General, Skin, Renal, and ADVERSE REACTIONS sections).

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

Omniscan should be used with caution in infants less than 1 year of age.

General

Nephrogenic Systemic Fibrosis (NSF)

There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of OMNISCAN (gadodiamide) and other gadolinium containing contrast agents 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). For patients receiving hemodialysis, healthcare professionals may consider prompt hemodialysis following GBCA administration in order to enhance the contrast agent's elimination. However, it is unknown if hemodialysis prevents NSF.

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 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 renal dysfunction. 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. 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 Warnings and Precautions).

A skin biopsy is necessary in order to exclude the diagnosis of similarly presenting skin disorders (e.g. scleromyxedema). (See WARNINGS - Serious Warnings, Renal, Skin, and ADVERSE REACTIONS sections).

When administering a GBCA, do not exceed the recommended dose.

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 clearance of the drug from the body. A period of at least 7 days should elapse if a repeat scan is considered.

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.

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 - Serious Warnings, General, Renal, and ADVERSE REACTIONS sections).

Renal

- Exposure to GBCAs increases the risk for NSF in patients with:
  - acute or chronic severe renal insufficiency (glomerular filtration rate <30 mL/min/1.73m^2),

- Screen patients for acute kidney injury 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.

- 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. Omniscan 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) (*see* *WARNINGS*).
- In patients with renal insufficiency, acute renal failure requiring dialysis or worsening renal function have occurred, mostly within 48 hours of OMNISCAN Injection. The risk of renal failure may increase with increasing dose of gadolinium contrast. Use the lowest necessary dose of contrast and evaluate renal function in patients with renal insufficiency. Acute renal failure was observed in < 1% of patients in OMNISCAN clinical studies (see Adverse Reactions).

As with other contrast media, OMNISCAN can be associated with anaphylactoid/hypersensitivity or other idiosyncratic reactions, characterized by cardiovascular, respiratory or cutaneous manifestations, which can be life threatening or even fatal. Most of these reactions occur within 30 minutes of administration.

Therefore, post procedure observation of the patient is recommended for at least 30 minutes after the administration of OMNISCAN.

As with other contrast media, delayed reactions occurring hours or days after administration have been observed, though rarely.

The decision to use OMNISCAN should be made after careful evaluation of the risk-benefit ratio in patients with a history of previous reaction to other contrast media (OMNISCAN is contraindicated in patients who are hypersensitive to this drug (see Contraindication)), allergic disposition, bronchial asthma or female patients.

Patients with history of allergy, drug reactions or other hypersensitivity-like disorders should be closely observed for several hours after drug administration.

OMNISCAN injection in patients with sickle cell anemia and other hemoglobinopathies has not been studied.

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

Accumulation of Gadolinium in 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.

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.

USE IN PREGNANCY

There are no adequate and well-controlled studies in pregnant women. GBCAs cross the placenta and result in foetal exposure and gadolinium retention. Human data on the association between GBCA and adverse foetal outcomes are limited and inconclusive. OMNISCAN should therefore be used during pregnancy only if the potential benefit justifies the potential risk to the fetus and the pregnant woman.

There are no clinical data available with regard to effects on fertility. OMNISCAN had no effects on fertility or reproductive performance in rats or in teratology studies in rats and rabbits at doses that did not cause maternal toxicity (1.0 mmol/kg).

GBCAs administered to pregnant mice (2 mmol/kg daily on gestational days 16 through 19) result in measurable gadolinium concentrations in the pups in bone, brain, kidney, liver, blood, muscle, and spleen at one month postnatal age.

Use of macrocyclic agents may be preferable in certain patients such as those for whom repeated

GBCA doses may need to be considered due to individual clinical circumstances and in other potentially vulnerable patients such as pregnant women.

USE DURING LACTATION

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 OMNISCAN is administered to a nursing woman. If lactating patients receive OMNISCAN, they should stop breast feeding for 24 hours and discard the milk.

PEDIATRICS

Due to immature renal function, Omniscan should be used with caution in infants less than 1 year of age. (see WARNINGS box).

Omniscan is contraindicated in neonates up to 4 weeks of age.

The cautious utilization of the lowest possible dose of Omniscan for children is recommended, (see WARNINGS – General).

No studies have been conducted in pediatric patients with severe renal or hepatic dysfunction; clinically unstable hypertension or uncontrolled hypertension; and in premature infants (see **ADVERSE REACTIONS**).

A period of at least 7 days should elapse if a repeat scan is considered. (See Warnings and Precautions). See **ACTIONS AND CLINICAL PHARMACOLOGY** section for information on the Pharmacokinetics in adults. Gadolinium is retained in paediatric brains similar in amount and

distribution to adults. Developing paediatric brains may be more susceptible to the potential effects of gadolinium exposure.

Use of macrocyclic agents may be preferable in potentially vulnerable patients such as children.

PRECAUTIONS

GENERAL

Diagnostic procedures involving the use of contrast agents should be conducted under supervision of a physician with the prerequisite training and a thorough knowledge of the procedure to be performed. OMNISCAN (gadodiamide) injection should be drawn into the syringe and used immediately. If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Since OMNISCAN is cleared from the body by glomerular filtration, caution should be exercised in patients with impaired renal function. OMNISCAN can be removed from circulation by hemodialysis.

Adequate time should elapse between administration of iodine containing contrast media and enhanced MRI examination, due to the possibility of inducing reversible renal failure. A single case of reversible renal failure occurred in a clinical study when a patient with previously reported normal kidney function, was administered a high dose of OMNISCAN within 24 hours of prior examination with an iodine containing contrast agent.

If, in the clinical judgment of the physician, sequential or 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.

The effect of OMNISCAN on QT prolongation has not been studied in a dedicated QT prolongation clinical study.

CONVULSIVE STATES

While there is no evidence suggesting that OMNISCAN directly precipitates convulsions, the possibility that it may decrease the convulsive threshold in susceptible patients cannot be ruled out. Appropriate precautionary measures should be taken with patients predisposed to seizure.

LABORATORY TEST FINDINGS

OMNISCAN interferes with serum calcium measurements with some colorimetric (complexometric) methods commonly used in hospitals. There is also the potential for OMNISCAN to interfere with serum iron, magnesium and zinc measurements resulting in asymptomatic transitory changes. The clinical significance is unknown. In patients with normal renal function, this effect lasts for 12-24 hours. In patients with decreased renal function this effect can last longer.

After patients receive OMNISCAN, careful attention should be used in selecting the type of method used for these measurements.

Elevation of creatine kinase has been observed in clinical trials. The source and clinical significance of this is unknown.

DRUG-DRUG INTERACTION

Administration of iodine-containing contrast agents was restricted to 24 hours pre-injection and 24 hours post OMNISCAN injection. Similarly, administration of other gadolinium-based contrast agents was restricted to 24 hours pre-injection and 24 hours post OMNISCAN injection.

Therefore, safety data of administration of OMNISCAN in conjunction with iodine-containing contrast agents or other gadolinium-based contrast agents are not available.

GERIATRIC PATIENTS

No specific precautions other than those pertinent to MRI and OMNISCAN in general are applicable for elderly patients.

ADVERSE REACTIONS

Adults

The most frequent adverse reactions observed in adult patients during OMNISCAN (gadodiamide) clinical trials were nausea, headache and dizziness with an incidence of 3% or less. This includes all reported adverse events regardless of attribution. The majority of these adverse reactions were of mild to moderate intensity.

The following adverse reactions occurred in less than 1% of the adult patients:

Application Site Disorders: Injection site reaction.
Autonomic Nervous System Disorders: Vasodilation.
Body as a Whole-General Disorders: Anaphylactoid reactions (characterized by cardiovascular, respiratory, and cutaneous symptoms), asthenia, chest pain, fatigue, fever, hot flushes, malaise, pain, rigors, syncope, feeling hot.
Cardiovascular Disorders: Cardiac failure, rare arrhythmia and myocardial infarction resulting in death in patients with ischemic heart disease, flushing, deep thrombophlebitis.
Central and Peripheral Nervous System Disorders: Aggravated migraine, ataxia, convulsions (including grand mal), abnormal coordination, aggravated multiple sclerosis (characterized by sensory and motor disturbances), paresthesia, tremor.
Gastro-Intestinal System Disorders: Abdominal pain, diarrhea, eructation, melena, dry mouth, vomiting.
Hearing and Vestibular Disorders: Tinnitus.
Musculoskeletal System Disorders: Arthralgia, myalgia.
Psychiatric Disorders: Anorexia, anxiety, personality disorder, somnolence.
Respiratory System Disorders: Rhinitis, dyspnea.
Skin and Appendage Disorders: Pruritus, rash, erythematous rash, skin discoloration, sweating

increased, urticaria.
Special Senses Other, Disorders: Taste loss, taste perversion.
Urinary System Disorders: Acute reversible renal failure. In patients with renal insufficiency: acute (nonreversible) renal failure, increase in blood creatinine.
Vision Disorders: Abnormal vision.

Pediatrics

Three adverse events occurred in 3 of 91 (3%) patients during OMNISCAN clinical trials in pediatric patients. This includes all adverse events regardless of attribution.

Body as a Whole-General Disorders: Fever.
Liver and Biliary System Disorders: Abnormal hepatic function.
Skin and Appendage Disorders: Rash.

The fever and rash were of mild intensity and the abnormal hepatic function was of severe intensity (although of uncertain relationship to administration of OMNISCAN).

Post-Marketing

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 severe renal insufficiency who received gaoddiamide, 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.

There are rare reports of pathologic skin changes including gadolinium associated plaques in patients with normal renal function.

Postmarketing reports of adverse events involving multiple organ systems in patients with normal renal function have been received. A causal link to gadolinium retention has not been established. These events include fatigue, asthenia, pain syndromes, and heterogeneous clusters of symptoms in the neurological, cutaneous, and musculoskeletal systems. While clinical consequences of gadolinium retention have not been established in patients with normal renal function, certain patients might be at higher risk. These include patients requiring multiple lifetime doses, pregnant and paediatric patients.

(See WARNINGS - Serious Warnings, General, Skin and Renal sections).

Body as a Whole-General Disorders: Hypersensitivity, injection site pain, shivering, anaphylactic / anaphylactoid shock.
Cardiovascular Disorders: tachycardia.
Central and Peripheral Nervous System Disorders: transient parosmia.
Respiratory System Disorders: coughing, bronchospasm, respiratory distress, throat irritation, sneezing.
Skin and Appendage Disorders: Nephrogenic systemic fibrosis (NSF), face oedema, angioedema, skin plaque*

* Cases of gadolinium associated skin plaques with demonstrated sclerotic bodies on histology have been reported with gadodiamide in patients who do not otherwise have symptoms or signs of nephrogenic systemic fibrosis

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Clinical consequences of overdosage have not been reported and acute symptoms of toxicity are unlikely in patients with normal renal function. Treatment is symptomatic. There is no antidote for this contrast medium. In patients with delayed elimination due to renal insufficiency and in patients who have received excessive doses, the contrast medium may theoretically be eliminated by hemodialysis. It is unknown if hemodialysis reduces the risk of NSF.

DOSAGE AND ADMINISTRATION

OMNISCAN (gadodiamide) injection should be drawn into the syringe and used immediately. If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Contrast-enhanced MRI should start shortly after administration of the contrast medium. Optimal enhancement is generally observed within 45 minutes after injection of OMNISCAN. T_1-weighted scanning sequences are particularly suitable for contrast-enhanced examinations with OMNISCAN. In the investigated range of field strengths, from 0.15 Tesla up to 1.5 Tesla, the relative image contrast was found to be independent of the applied field strength.

The recommended dose of OMNISCAN for imaging of the central nervous system is 0.2 mL/kg (0.1 mmol/kg) administered as a bolus intravenous injection. (See the Dosage Chart). If medically indicated, preprocedural medication (e.g., sedatives) may be administered according to the normal routine for MR examinations.

The recommended dose of OMNISCAN for imaging of the body is 0.6 mL/kg (0.3 mmol/kg), administered as a bolus intravenous injection (See the Dosage Chart).

The recommended dose of OMNISCAN for MRA is 0.2 mL/kg (0.1 mmol/kg) administered as a bolus intravenous injection at an injection rate of 1–4 mL/sec.

The lowest effective dose should be used. Calculate the dose based on the patient's body weight, and do not exceed the recommended dose per kilogram of body weight.

Use of macrocyclic agents may be preferable in certain patients such as those for whom repeated GBCA doses may need to be considered due to individual clinical circumstances and in other potentially vulnerable patients such as children and pregnant women (See Warnings and Precautions).

DOSAGE CHART

BODY WEIGHT		PEDIATRIC 0.1 mmol/kg	ADULT 0.1 mmol/kg	ADULT 0.3 mmol/kg
kg	lb	VOLUME (mL)	VOLUME (mL)	
5	11	1.0		
10	22	2.0		
12	26	2.4		
14	31	2.8		
16	35	3.2		
18	40	3.6		
20	44	4.0		
22	48	4.4		
24	53	4.8		
26	57	5.2		
28	62	5.6		
30	66	6.0		
40	88	8.0	8.0	24.0
50	110	10.0	10.0	30.0
60	132	12.0	12.0	36.0
70	154	14.0	14.0	42.0
80	176	16.0	16.0	48.0
90	198	-	18.0	54.0
100	220	-	20.0	60.0
110	242	-	22.0	66.0
120	264	-	24.0	72.0
130*	286	-	26.0	78.0

* The heaviest patient in clinical studies weighed 136 kg.

To ensure complete injection of the contrast medium, the injection should be followed by a 5 mL flush of 0.9% sodium chloride. The imaging procedure should be completed within 1 hour of administration of OMNISCAN.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use the solution if it is discolored or particulate matter is present. Any unused portion must be discarded.

PHARMACEUTICAL INFORMATION

Drug Substance

Common Name: (USAN) - gadodiamide

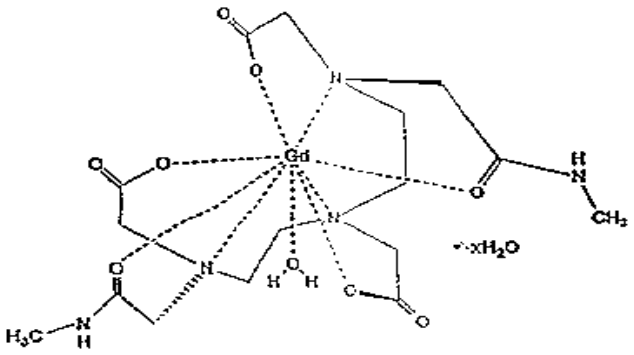
Synonyms: GdDTPA-BMA; gadolinium diethylenetriaminepentaacetic acid bis(methylamide); gadolinium diethylenetriaminepentaacetate bis (methylamide); GdDTPA bis(methylamide)

Chemical Name:

Aqua[5,8-bis(carboxymethyl)-11-[2-(methylamino)-2-oxoethyl]

-3-oxo-2,5,8,11-tetraazatridecan-13-oato(3-)- N^5,N^8,N^{11},O^3,O^5,O^8,O^{11},O^{13}]gadolinium hydrate

Structural Formula:



Molecular Formula: $C_{16}H_{28}GdN_5O_9 \cdot xH_2O$, where x is the number of adsorbed water molecules (the molecular formula includes one water molecule coordinated to gadolinium), or $C_{16}H_{26}GdN_5O_8$ (anhydrous, no adsorbed or coordinated water).

Molecular Weight: 573.66 (anhydrous, no adsorbed or coordinated water)

Physical Form: Gadodiamide is a crystalline solid, appearing as a fine white powder.

Solubility: Gadodiamide is freely soluble in water and methanol, soluble in ethanol and slightly soluble in acetone and chloroform.

pKa: The two most basic groups of the DPTA-BMA ligand have pK_a values of 9.37 and 4.38. The third amine of the ligand has a pK_a of 3.31 and the carboxylates all have pK_a values below 2. The gadolinium ion interferes with the measurement of pK_a values in gadodiamide.

Partition co-efficient: The log of P, the partition co-efficient, between butanol and water is -2.13

Melting Point: Gadodiamide has no discrete melting point. It loses water of hydration below 200 degrees C and shows decomposition at 300 degrees C and above. Melting point behaviour, thermogravimetric analysis and differential scanning calorimetry failed to disclose the presence of polymorphic forms.

Dissociation Constant: The metal-ligand thermodynamic stability constant was determined by competitive titration procedures, with log K equal to 16.85.

Composition

OMNISCAN (gadodiamide) injection is a 0.5 mol/L solution of the gadolinium complex of diethylenetriaminepentaacetic acid bismethylamide. It is a nonionic extracellular enhancing agent for magnetic resonance imaging and is provided as a sterile, clear, colorless to slightly yellow, aqueous solution. Each mL contains 287 mg gadodiamide, 12 mg caldiamide sodium and water for injection. The pH is adjusted between 5.5 and 7.0 with hydrochloric acid and/or sodium hydroxide.

Pertinent physicochemical data for OMNISCAN are noted below:

PARAMETER		
Osmolality (mOsm/kg water)	@ 37ºC	789
Viscosity (cp)	@ 20ºC @ 37ºC	2.0 1.4
Density (g/cm^3)	@ 20ºC	1.15

OMNISCAN has an osmolality 2.8 times that of plasma (285 mOsm/kg water) at 37ºC and is hypertonic under conditions of use.

Stability and Storage Recommendations

All solutions are sterilized by autoclaving and contain no preservatives. Unused portions must be discarded. Protect from light. Do not freeze. If inadvertently frozen, do not use OMNISCAN solutions, as freezing could cause small cracks in the vials which would compromise the sterility of the product.

OMNISCAN should be stored at controlled room temperature 15°C - 30°C.

AVAILABLE DOSAGE FORMS

OMNISCAN (gadodiamide) injection is supplied in the following sizes:

5 mL fill in 10 mL vial, box of 10

10 mL vial, box of 10

15 mL fill in 20 mL vial, box of 10

20 mL vial, box of 10

PRECLINICAL PHARMACOLOGY

PHARMACODYNAMICS:

Study type	Animal species (strain; age)	Total no. of animals M	F	Number of dosings (control)	Route	Dose mg/kg	Dose mmol/kg	Results
Brain tumor imaging	Rat (Fischer 344)	1	0	1	IV inj.	57.4	0.1	Enhancement of tumor in 9L glioma model.
Imaging normal genitourinary system	Rabbit (2-8 months)	1	0	1	IV inj.	57.4	0.1	Enhancement of renal parenchyma.
Genitourinary system imaging: hydronephrosis model	Rabbit (2-8 months)	1	0	1	IV inj.	57.4	0.1	Demonstrated differentiation of the outer and inner medulla, and demonstrated increased water content in the kidney.
Brain tumor imaging	Dog	1 gender unknown		1	IV inj.	57.4	0.1	Enhancement of brain tumor in veterinary referral case.
Brain abscess imaging	Cat (1-3 years)	0	1	1 (on Day 2)	IV inj.	57.4	0.1	Cerebritis detected early; capsular phase detected late.
Brain trauma imaging	Cat (1-3 years)	0	1	2 (on Day 2 and at Week 2 post-trauma)	IV inj.	114.8	0.2	Enhancement consistent with trauma at 2 days; enhancement of areas secondary to trauma.
Imaging normal brain	Cat (1-3 years)	0	1	1	IV inj.	189.42	0.33	Enhancement of intracranial structures lacking a blood-brain barrier.

PRECLINICAL PHARMACOLOGY

BIOCHEMICAL PHARMACOLOGY:

Study type	Animal species (strain; age)	Total no. of animals M F	Number of dosings (control)	Route	Dose		Results
					mg/kg	mmol/kg	
*Lysozyme activity	In vitro (Micrococcus lysodeikticus)	5**	1 [buffer]	N/A	0.1, 0.25, 0.50, 1.00, 2.50 and 5.00 mM		Gadodiamide injection and Magnevist[R] caused no change (<5%) in lysozyme activity.
*Cholinesterase activity	In vitro	5**	1 [buffer]	N/A	0.1, 0.25, 0.50, 1.00, 2.50 and 5.00 mM		Gadodiamide injection and Magnevist[R] produced no change in cholinesterase activity.
*Erythrocyte fragility	In vitro	3**	1 [saline]	N/A	50, 100, 150 and 250 mM		Only Magnevist[R] at 250 mM caused significant effects.
*Erythrocyte morphology	In vitro	3**	1 [saline]	N/A	50, 100, 150 and 250 mM		Gadodiamide injection produced macrocytosis (a minor effect) at all concentrations and poikilocytosis at 250 mM. Magnevist[R] caused poikilocytosis at 100, 150 and 250 mM.

* Study in which effects of gadodiamide injection and Magnevist[R] (gadopentetate dimeglumine) were compared at equivalent doses.
** Number represents sample size per dose level.
N/A Not applicable (in vitro study).

PRECLINICAL PHARMACOLOGY

CENTRAL NERVOUS SYSTEM:

Study type	Animal species (strain; age)	Total no. of animals M F	Number of dosings (control)	Route	Dose		Results
					mg/kg	mmol/kg	
*Intracisternal tolerance	Mouse (NMRI; 4-5 weeks)	5**	1 (Ringer acetate)	Intracis-ternal inj.		0.001 0.003 0.01 0.03 0.1 0.3	Two high dose (gadodiamide 0.3 mmol/kg) animals died under anaesthesia; otherwise, both gadodiamide and Magnevist^{R} were well tolerated in doses up to 0.3 mmol/kg.
Neurotoxic potential following blood-brain barrier disruption	Dogs (Labrador or labrador cross-bred; adult)	7	1	IV inj.		0.2	Two dogs did not survive surgical procedure. Three were sacrificed on Days 39, 40 and 43 and showed no clinical evidence of neurotoxicity. One animal was sacrificed 3 days post-BBBD^{+} due to development of an extensive hematoma and bleeding from the neck wound. One dog developed status epilepticus (plus extensive hematoma) 7 days post-BBBD. Thrombocytopenia (platelet counts <100 x $10^3/mm^3$) was observed in all 5 dogs with a nadir 3-5 days post-BBBD, and showing evidence of reversibility over 1-6 days.
MRI enhancement following blood-brain barrier disruption		3					Excellent imaging of BBBD, 15 min.-3 hrs. post-surgical procedure. Image enhancement corresponded to Evans blue staining.
*Thrombocytopenia induction potential (Follow-up to above-noted study)	Dogs (Beagle; 10-18 months)	4**	1 (saline)	IV inj.		0.2 2.0	In all dogs, platelet counts were normal (>200,000 per µl) at all time points. No treatment-related effects were observed.

* Study in which effects of gadodiamide injection and Magnevist^{R} (gadopentetate dimeglumine) were compared at equivalent doses.
** Number represents sample size per dose level.
\+ Blood Brain Barrier Disruption

PRECLINICAL PHARMACOLOGY

CARDIOVASCULAR EFFECTS:

Study type	Animal species (strain; age)	Total no. of animals M	F	Number of dosings (control)	Route	Dose mg/kg	Dose mmol/kg	Results
Cardiovascular	Dog (mongrel; young adult)	11	1	4 (two sequences) [saline]	IV inj.	57.4 172.2 401.8 574.0	0.1 0.3 0.7 1.0	No physiologically significant hemodynamic findings.
*Cardiovascular	Dog (mongrel; young adult)	11	1	4 (six sequences with two doses each of gadodiamide injection and Magnevist[R]) [saline]	IV inj.	574.0 861.0	1.0 1.5	Gadodiamide injection produced 22% and 26% drecreases in systemic vascular resistance at 1.0 and 1.5 mmol/kg, respectively. Magnevist[R] produced marked hemodynamic changes in several parameters; including >50% decrease in systemic vascular resistance at both doses.
*Blood pressure	Rat (Wistar)	34	0	1 [saline]	IV inj.	287.0 574.0	0.5 1.0	Neither gadodiamide injection nor Magnevist[R] produced any hemodynamic effects.
*Bovine mesenteric arteries	In vitro	6**		1 (sucrose)	N/A	50mM		Gadodiamide injection produced one-sixth the tension produced by Magnevist[R].

* Study in which effects of gadodiamide injection and Magnevist[R] (gadopentetate dimeglumine) were compared at equivalent doses.
** Number represents sample size per dose level.
N/A Not applicable (in vitro study).

PRECLINICAL PHARMACOLOGY

ABSORPTION, DISTRIBUTION, METABOLISM & EXCRETION:

Study type	Animal species (strain; age)	Total no. of animals M	F	Number of dosings (control)	Route	Dose mg/kg	Dose mmol/kg	Results
Pharmacokinetics with ^{153}Gd	Rat (Sprague-Dawley; 8 weeks)	30	30	1	IV inj.	57.4	0.1	Data fit two-compartment model with bolus input, first-order output. Distribution half-life . 4.6 min, elimination half-life . 18 min.
Pharmacokinetics	Monkey (Cynomolgus; 2.5-5 years)	3	3	1	IV inj.	57.4	0.1	Data fit two-compartment model with bolus input, first-order output. Distribution half-life . 7 min, elimination half-life . 75 min.
Gadolinium retention 7 and 21 days post-dose	Mouse (NMRI; 4-5 weeks)	21	0	1 (one group killed Day 7 the others on Day 21) [saline]	IV inj.	287	0.5	There was a significant reduction in gadolinium retention in the liver from 7 days post-dosing (0.04% retained) to 21 days post-dosing (0.007% still present).
*Gadolinium retention 7 days post-dose	Rat (Sprague-Dawley; males: 7 weeks and females: 11 weeks)	24	24	1 [saline]	IV inj.	57.4 574	0.1 1.0	In all cases, retained gadolinium was less than 0.14% of the administered gadolinium. Gadolinium from gadodiamide injection was retained at higher levels in the liver and kidneys than was gadolinium from Magnevist^{R}.
Distribution and excretion 24 hours post-dose with ^{153}Gd	Rat (Sprague-Dawley; 81-101 days)	3	3	1	IV inj.	57.4	0.1	94.4% of radioactivity excreted in urine. 99.8% mean total recovery. Residual radioactivity accounted for 3.65% of the administered dose, with 0.78% in the solid organs (liver and kidneys) and 2.87% in the GI tract.
Distribution and excretion 6 days post-dose with ^{153}Gd	Rat (Sprague-Dawley; 83-87 days)	3	3	1	IV inj.	57.4	0.1	89.7% of radioactivity excreted in urine. 95.4% mean total recovery. Residual radioactivity was 0.47%; almost all of which was in the liver (0.22%), kidneys (0.14%) or GI tract (0.07%).
Biotransformation	Rat (Wistar)	6 (serum) 6 (urine)		1	IV inj.		0.3	Within 1 hr. after injection, the amount of radiolabelled unknown compound in serum was <1% of the injected dose. Urine samples up to 6 hrs. revealed no higher than 1.3% of total radioactivity in each sample. Biotransformation of gadodiamide injection at a dose of 0.3 mmol/kg is negligible and is excreted unchanged in the urine of rats.

* Study in which effects of gadodiamide injection and Magnevist^{R} (gadopentetate dimeglumine) were compared at equivalent doses.

CLINICAL STUDIES

OMNISCAN was evaluated in two controlled clinical trials enrolling a total of 794 patients who were referred for diagnosis of suspected stenosis of the renal or aorto-iliac arteries. These patients (496 men and 298 women) had a mean age of 64 years (range 17 to 94 years). Patients received one dose of OMNISCAN (0.1 mmol/kg, administered as a single bolus at an injection rate of 1–4 mL/sec via power injector) for the detection of stenoses in the renal arteries or aorto-iliac arteries.

The MRA images were evaluated blindly (3 readers) and the results compared to intra arterial digital subtraction angiography (IA DSA), which served as standard of truth, and unenhanced (time-of-flight, TOF) MRA. OMNISCAN-enhanced MRA was shown to be superior to unenhanced MRA and showed comparable results to the standard of truth with sensitivity and specificity values of 86–90% and 85–90%, respectively, for the renal arteries and of 82–90% and 89–96%, respectively, for the aorto-iliac arteries.

However, no conclusions were reached for three of the seven segments (infra-renal aorta; right and left common iliac arteries; right and left external iliac arteries; and right and left common femoral arteries) of the aorto-iliac arteries as the number of subjects with a stenosis in these segments was too small; these were the infra-renal aorta and the left and right common femoral arteries.

In the detection of stenoses in the renal arteries and the aorto-iliac arteries, sensitivity, specificity and accuracy values for OMNISCAN-enhanced (3D CE) MRA and unenhanced (2D TOF) MRA relative to IA DSA are presented below. The respective differences between OMNISCAN-enhanced MRA and unenhanced MRA will also be presented. It should be noted that 3D CE MRA can lead to overestimation of stenosis.

Renal Arteries

		3D CE MRA		2D TOF MRA		Difference CE – TOF	
	Reader	**%**	**95% CI***	**%**	**95% CI***	**%**	**95% CI§**
Sensitivity	Reader A	87.4	80.3	83.9	66.3	-6.9	-25.8
	Reader B	90.3	83.7	79.8	69.6	12.0	2.2
	Reader C	85.7	78.8	70.6	60.7	16.3	5.9
	Majority Decision	89.1	82.3	78.3	66.7	9.8	-1.9
Specificity	Reader A	87.0	80.8	56.9	44.0	34.5	22.0
	Reader B	89.5	83.9	79.7	72.0	9.0	2.6
	Reader C	85.1	79.3	74.3	66.9	8.4	1.7
	Majority Decision	88.9	83.2	78.6	70.6	8.5	3.0
Accuracy	Reader A	87.2	82.7	65.6	55.2	20.2	8.9
	Reader B	89.8	85.8	79.7	73.8	10.2	4.7
	Reader C	85.4	81.1	72.9	67.1	11.3	5.6
	Majority Decision	89.0	84.9	78.5	72.2	9.0	3.5

NOTE: Sensitivity, specificity and accuracy were calculated for all subjects with evaluable images for a specific modality, following the judgement of the respective reader. Calculation of sensitivity, specificity and accuracy was based on subject level. All efficacy values were calculated based on the standard of truth (IA DSA). Differences between 3D CE MRA and 2D TOF MRA were calculated for those patients who had both 3D CE MRA and 2D TOF MRA results available. The efficacy results in the table are for the main haemodynamically relevant stenosis.

%=degree of sensitivity, specificity or accuracy; 95% CI*=lower limit of the two-sided exact 95% confidence interval; 95% CI§=asymptotic lower confidence limit.

Aorto-iliac Arteries:

		3D CE MRA		2D TOF MRA		Difference CE – TOF	
	Reader	**%**	**95% CI***	**%**	**95% CI***	**%**	**95% CI§**
Sensitivity	Reader A	83.4	78.1	77.9	71.6	6.8	1.0
	Reader B	81.3	75.9	76.3	70.5	4.9	-1.1
	Reader C	89.8	85.2	81.3	75.9	8.7	3.5
	Majority Decision	86.4	81.5	80.3	74.6	6.5	1.0
Specificity	Reader A	94.9	93.7	95.8	94.6	-1.1	-2.4
	Reader B	96.3	95.3	89.9	88.4	6.1	4.6
	Reader C	89.3	87.7	84.0	82.2	4.7	2.7
	Majority Decision	95.2	94.1	92.5	91.1	2.1	0.7
Accuracy	Reader A	84.8	80.4	82.1	77.1	4.0	-1.0
	Reader B	83.5	79.1	78.1	73.1	5.4	0.3
	Reader C	86.1	81.9	79.8	75.0	6.3	1.6
	Majority Decision	86.8	82.6	81.1	76.3	6.3	1.6

NOTE: Sensitivity, specificity and accuracy were calculated for all subjects with evaluable images (sensitivity and accuracy) or segments (specificity) for a specific modality, following the judgement of the respective reader. All efficacy values were calculated based on the standard of truth (IA DSA). Calculation of sensitivity and accuracy was based on a subject level, whereas calculation of specificity was based on all segments combined. Differences between 3D CE MRA and 2D TOF MRA were calculated for those patients who had both 3D CE MRA and 2D TOF MRA results available. The efficacy results in the table are for the main haemodynamically relevant stenosis.

%=degree of sensitivity, specificity or accuracy; 95% CI*=lower limit of the two-sided exact 95% confidence interval; 95% CI§= lower limit of the asymptotic 95% confidence interval.

No conclusions were reached for three of the seven segments of the aorto-iliac arteries as the number of subjects with a stenosis in these segments was too small; these were the infra-renal aorta and the left and right common femoral arteries.

TOXICOLOGY

- Acute Toxicity -

Species (sex, number of animals per group)	Route	Dose		Results
		mg/kg	mmol/kg	
Mouse M 5 F 5	IV infusion	2870	5.0	No deaths or signs of toxicity. Minimum lethal dose > 2870 mg/kg (5 mmol/kg)
Mouse M 4 F 4	IV inj.	5740 11480 17220 22960 28700	10 20 30 40 50	LD_{50} = 19746 mg/kg (34.4 mmol/kg) Male LD_{50} = 38.1 mmol/kg Female LD_{50} = 28.0 mmol/kg
Rat M 5 F 5	IV infusion	2870	5.0	No deaths or signs of toxicity. Minimum lethal dose > 2870 mg/kg (5 mmol/kg)
Rat M 10 F 0	IV inj.	229.6 5740 11480	0.4 10 20	One animal died during dosing. The cause of death is not known. The animal was replaced and there were no deaths or signs of morbidity other than a slight decrease in activity in the ten animals dosed at 20 mmol/kg. Dose-related, partially reversible cortical tubule cell vacuolation was observed.

TOXICOLOGY
- Subacute Toxicity -

Species (sex, number of animals per group)	Number of dosings (control)	Route	Dose		Results
			mg/kg	mmol/kg	
Rat M 3 F 3	3 per week for 3 weeks (saline) ****	IV inj.	57.4 574 1722 2870 4305	0.1 1.0 3.0 5.0 7.5	Renal tubular epithelial vacuolation; dose-related in incidence and severity.
Monkey M 3 F 3 *****	10 doses over 22 days (saline)	IV inj.	57.4 2870	0.1 5.0	Moderate vacuolation in proximal tubular cell cytoplasm and increased absolute and relative kidney weights at 5.0 mmol/kg.
Rat M 5	Daily dosing for 14 days (saline)	IV inj.		0.1 0.125 0.25 0.5 1.0 Magnevist 1.0	Following 14 consecutive injections, blood appeared in urinary sediments microscopically with positive urinary occult blood for 0.1-1.0 mmol/kg dosing. Histopathologically, cystitis was observed at > 0.1 mmol/kg, and dose related cytoplasmic vacuolation of renal tubular epithelium was seen. These changes were not seen for Magnevist.
Rabbit M 3	Daily dosing for 14 days (saline)	IV inj.		0.05 0.1 0.5	Unlike the rat, no occult blood was observed. No clinico-pathological evidence to suggest cystitis was seen. Histopathological findings were stomach edema, testicular tubular degeneration and skin calcinosis all considered to be due to zinc deficiency. No kidney cytoplasmic vacuolation was observed. These results suggest a species-difference between rats and rabbits with regard to cystitis induction.
Monkey M 3 F 3	Daily dosing for 28-30 days (saline)	IV		0.05 0.25 1.25	Renal tubular epithelial changes were noted at the 1.25 mmol/kg/day dose. Serum chemistry revealed a dose related reduction in zinc and phosphate levels. Bone marrow myelograms showed a myeloid left shift in the 1.25 mmol group, corresponding to decreases in group mean myeloblast, neutrophilic myelocyte and neutrophilic polymorph values and an increase in group mean intermediate normoblast values. 0.05 and 0.25 mmol/kg groups also showed reduced mean myeloblast and neutrophilic myelocyte values. Most animal values, however, were within the control ranges. The toxicological significance of these changes is uncertain.

**** **Two/sex/group killed on Day 22; one/sex/group killed on Day 29 after 7-day recovery period.**

***** **One female less than 2.5 years of age.**

Carcinogenesis, mutagenesis, teratology, impairment of fertility

No long-term animal studies have been performed to evaluate the carcinogenic potential of gadodiamide.

Gadodiamide did not demonstrate mutagenic potential in three in vitro tests (the Ames test, the CHO/HGPRT forward mutation assay and the Chromosomal Aberration Frequency assay in CHO cells) or in an in vivo mouse micronucleus test.

Teratology studies showed no effects on the fetuses of rats given doses of up to 1.0 mmol/kg/day. In rabbits intravenous administration of 1.0 mmol/kg of gadodiamide injection during the period of major organogenesis (Days 6 through 18 of pregnancy), demonstrated a no-effect level in terms of embryo/fetal toxicity and teratogenicity.

Gadodiamide injection had no effects on fertility and reproductive performance in rats.

Irritancy Studies

Gadodiamide injection was found to be non-irritating following intravenous, and intraarterial administration in rabbits, and paravenous, intramuscular and subcutaneous administration in dogs. Dermal and eye application in rabbits also resulted in a non-irritating effect.

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 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.

BIBLIOGRAPHY

1. Cacheris, W.P., Quay, S.C., Rocklage, S.M.: The Relationship Between Thermodynamics and the Toxicity of Gadolinium Complexes. Mag. Res. Imaging, 1990; 8: 467-81.

2. Chang, C. Allen, Sieving, Paul F., Watson, Alan D. et al: Ionic versus Nonionic MR Imaging Contrast Media: Operational Definitions. Radiology -JMRI, 1992; 2(1): 95-8.

3. Chang, C. Allen: Magnetic Resonance Imaging Contrast Agents: Design and Physicochemical Properties of Gadodiamide. Inv. Radiology, 1993; 28 (Suppl. 1): S21-S27.

4. Greco, A., McNamara, M., Lanthiez, P. et al: Gadodiamide Injection: Nonionic Gadolinium Chelate for MR Imaging of the Brain and Spine - Phase II-III Clinical Trial. Radiology, 1990; 176(2): 451-6.

5. Harpur, Ernest, S., Worah, Dilip, Hals, Peter-Arnt et al: Preclinical Safety Assessment and Pharmacokinetics of Gadodiamide Injection, a New Magnetic Resonance Imaging Contrast Agent. Inv. Radiology, 1993; 28 (Supp. 1): S28-S43.

6. Kaplan, G.D., Aisen, A.M. and Aravapalli, S.R.:Preliminary Clinical Trial of Gadodiamide Injection: A New Nonionic Gadolinium Contrast Agent for MR Imaging. J. Magn. Reson. Imaging, 1991; 1: 57-62.

7. Muhler, Andreas, Saeed, Maythem, Brasch, Robert C. and Higgins, Charles B.: Hemodynamic Effects of Bolus Injection of Gadodiamide Injection and Gadopentetate Dimeglumine as Contrast Media at MR Imaging in Rats. Radiology, 1992; 183: 523-28.

8. Sze, G., Brant-Zawadzki, M., Haughton, V.M. et al: Multicenter Study of Gadodiamide Injection as a Contrast Agent in MR Imaging of the Brain and Spine. Neuroradiology, 1991; 181(3): 693-99.

9. Van Wagoner, M., O'Toole, M., Quay, S.: Nonionic Magnetic Resonance Imaging Contrast Agents - Clinical Trial Experience of Safety, Tolerance, and Efficacy of Gadodiamide Injection. Inv. Radiology, 1990; 25 (Supp. 1): S39-S41.

10. Dillman et al. Frequency and severity of acute allergic-like reactions to gadolinium-containing i.v. contrast media in children and adults. AJR Am J Roentgenol 2007;189(6):1533–1538.

11. Prince et al. Incidence of immediate gadolinium contrast media reactions. AJR Am J Roentgenol 2011; 196(2): W138–W143.

12. Jung et al. Immediate hypersensitivity reaction to Gadolinium-based MR Contrast Media. Radiology 2012; 64:414–422.

CONSUMER INFORMATION

OMNISCAN™
Gadodiamide Injection USP

This leaflet is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about OMNISCAN™. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Omniscan is a contrast agent for use in magnetic resonance imaging (MRI) of the central nervous system and other body parts.

Omniscan can also be used in magnetic resonance angiography (MRA) to view abnormal blood vessels.

What it does:
Omniscan helps tissues appear brighter in MRI and MRA so the doctor can better visualize the tissues and any abnormalities.

When it should not be used:
Do not use Omniscan if you are allergic to gadodiamide or any other ingredients in the formulation (see below for list of nonmedicinal ingredients).

What the medicinal ingredient is:
Gadodiamide

What the important nonmedicinal ingredients are:
Caldiamide sodium, hydrochloric acid, sodium hydroxide, water for injection

What dosage forms it comes in:
Omniscan is available in a solution for intravenous injection containing 287 mg/mL of gadodiamide (0.5 mmol./mL).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Gadolinium-based contrast agents (such as Omniscan) increase the risk of a rare disease called Nephrogenic Systemic Fibrosis (NSF) in patients with:

- **severe kidney disease or acute kidney injury**
- **immature renal function, such as newborns and infants**

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

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

BEFORE you are given Omniscan talk to your doctor if any of the following situations apply to you. The doctor will decide whether the intended examination is possible or not:

- You are pregnant or could be pregnant
- You are breastfeeding or intend to breastfeed
- You have sickle cell disease
- You have poor kidney function or kidney problems
- You have diabetes
- You have high blood pressure
- You have seizures
- You are allergic or have had a hypersensitivity (allergic) reaction to contrast media products similar to Omniscan

Nephrogenic Systemic Fibrosis
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 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.

Patients with severe kidney disease should avoid the use of Omniscan unless the health care professional believes the possible benefits outweigh the potential risks. 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 Omniscan, if you are considered to be at risk for developing NSF.

Accumulation of gadolinium in the brain
Recent information shows that gadolinium (as in Omniscan) 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

INTERACTIONS WITH THIS MEDICATION

Drug interaction studies have not been done with Omniscan.

PROPER USE OF THIS MEDICATION

Usual dose:

Omniscan should be administered by a healthcare professional as a bolus (all at once) intravenous injection at a dose of 0.2 mL/kg for MRI of the central nervous system or for MRA. A dose of 0.6 mL/kg is to be administered as a bolus injection for MRI of the body.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Common side effects reported with Omniscan include nausea, headache and dizziness.

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

Symptom / effect		Talk with your doctor or pharmacist	
		Only if severe	In all cases
Anaphylactoid reactions, sometimes fatal	**Symptoms include rash, heart problems, swelling of the mouth and throat, difficulty breathing**		**X**

This is not a complete list of side effects. For any unexpected effects while taking Omniscan contact your doctor or pharmacist.

HOW TO STORE IT

Omniscan will be stored by your healthcare professional at controlled room temperature between 15-30°C.

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 0701D
Ottawa, Ontario
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 can be obtained by contacting the sponsor, GE Healthcare Canada Inc. at: 1-800-387-7146
This leaflet was prepared by GE Healthcare

Last revised: May 22, 2019