



OMNISCANTM (gadodiamide) Injection

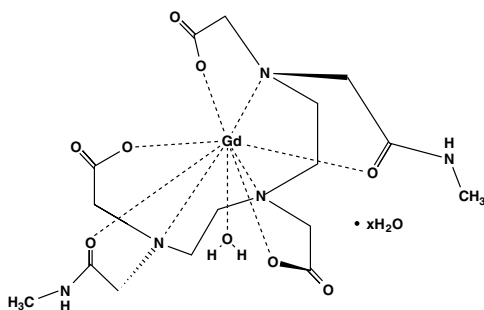
STERILE AQUEOUS INJECTION 287 mg/mL

R_x ONLY

DESCRIPTION

OMNISCAN (gadodiamide) Injection is the formulation of the gadolinium complex of diethylenetriamine pentaacetic acid bismethylamide, and is an injectable, nonionic extracellular enhancing agent for magnetic resonance imaging. OMNISCAN is to be administered by intravenous injection.

OMNISCAN is provided as a sterile, clear, colorless to slightly yellow, aqueous solution. Each mL contains 287 mg gadodiamide, 12 mg calcium chloride sodium and water for injection. The pH is adjusted between 5.5 and 7.0 with hydrochloric acid and/or sodium hydroxide. OMNISCAN contains no antimicrobial preservative. OMNISCAN is a 0.5 mol/L solution of aqua[5,8-bis(carboxymethyl)-11-¹²⁵-(methylamino)-2-oxoethyl]-3-oxo-2,5,8,11-tetraazatridecan-13-oato (3-)-N⁸, N⁹, N¹¹, O⁵, O⁶, O⁸, O¹¹, O¹³] gadolinium hydrate, with a molecular weight of 573.66 (anhydrous), an empirical formula of C₁₆H₂₈GdN₅O₉•xH₂O, and the following structural formula:



Pertinent physicochemical data for OMNISCAN are noted below:

| PARAMETER | | |
|------------------------------|--------|------|
| Osmolality (mOsmol/kg water) | @ 37°C | 789 |
| Viscosity (cP) | @ 20°C | 2.0 |
| | @ 37°C | 1.4 |
| Density (g/mL) | @ 25°C | 1.14 |
| Specific gravity | @ 25°C | 1.15 |

OMNISCAN has an osmolality approximately 2.8 times that of plasma at 37°C and is hypertonic under conditions of use.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetics of intravenously administered gadodiamide 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. 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. Gadodiamide does not bind to human serum proteins *in vitro*.

Pharmacodynamics

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 (T₁); and variation of the spin-spin or transverse relaxation time (T₂). OMNISCAN 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.

By increasing the relaxation rate, OMNISCAN decreases both the T₁ and T₂ relaxation times in tissues where it is distributed. At clinical doses, the effect is primarily on the T₁ relaxation time, and produces an increase in signal intensity. OMNISCAN does not cross the intact blood-brain barrier and, therefore, does not accumulate in normal brain or in lesions that do not have an abnormal blood-brain barrier (e.g., cysts, mature postoperative scars, etc). However, disruption of the blood-brain barrier or abnormal vascularity allows accumulation of OMNISCAN in lesions such as neoplasms, abscesses, and subacute infarcts. The pharmacokinetic parameters of OMNISCAN in various lesions are not known.

Metabolism

There is no detectable biotransformation or decomposition of gadodiamide.

Special Populations:

Pharmacokinetic and pharmacodynamic studies have not been systematically conducted to determine the optimal dose and optimal imaging time in patients with abnormal renal function or renal failure, in the elderly, or in pediatric patients with immature renal function.

CLINICAL TRIALS

CNS (Central Nervous System)

In early clinical trials of 439 adults, OMNISCAN 0.1 mmol/kg was evaluated and found to be useful in providing contrast enhancement in CNS MRI in adults. OMNISCAN was also evaluated in a trial in 57 adults (34 men, 23 women) who had an indication for CNS MRI. These patients had a mean age of 47 years (range 21 to 82 years). Of these, 93% were Caucasian, 2% Black, and 5% other races. All patients were studied with sequential dosing of OMNISCAN 0.1 mmol/kg followed by 0.2 mmol/kg within 20 minutes (for cumulative dose of 0.3 mmol/kg). The results of the noncontrast enhanced MRI, the OMNISCAN 0.1 mmol/kg enhanced, and the cumulative OMNISCAN 0.3 mmol/kg (0.1 followed by 0.2 mmol/kg) enhanced MRIs were compared blindly. In 54/56 (96%) of all patients, contrast enhancement was evident with both the 0.1 mmol/kg and cumulative 0.3 mmol/kg (0.1 mmol/kg followed by 0.2 mmol/kg) doses.

In comparison to the noncontrast MRI, increased numbers of brain and spine lesions were noted in approximately 42% of patients who received OMNISCAN at any dose. In comparisons of 0.1 mmol/kg versus 0.3 mmol/kg, the results were comparable in 25/56 (45%); in 1/56 (2%) OMNISCAN 0.1 mmol/kg dose provided more diagnostic value and in 30/56 (54%) the cumulative OMNISCAN 0.3 mmol/kg dose provided more diagnostic value.

The relative usefulness of a single 0.3 mmol/kg bolus in comparison to the cumulative 0.3 mmol/kg (0.1 mmol/kg followed by 0.2 mmol/kg) has not been established.

OMNISCAN was evaluated in two double-blind, parallel studies with MAGNEVIST[®] (gadopentetate dimeglumine) in a total of 173 children who were referred for CNS MRI. The children received either OMNISCAN or MAGNEVIST in a single 0.1 mmol/kg dose. OMNISCAN was administered to 84 children (45 boys and 39 girls) with a mean age of 8.9 (2-18) years; of these patients, 92% were Caucasian, 7% Black, and 1% other races. The demographics were similar for the 89 children who received MAGNEVIST. Postcontrast MRI results showed that added diagnostic information, diagnostic confidence, and new patient management information were provided in approximately 76%, 67% and 52%, respectively, of children who received OMNISCAN. These findings were similar to those of MAGNEVIST. CT or histopathology was performed in 70/173 (42%) children who received OMNISCAN and MAGNEVIST. Of these, 69/70 (98.6%) were confirmed.

Body (Intrathoracic [noncardiac], Intra-abdominal, Pelvic and Retroperitoneal)

OMNISCAN was evaluated in a controlled trial of 276 patients who were referred for MRI of the internal thoracic, abdominal, pelvic or retroperitoneal organs. These patients (170 men and 106 women) had a mean age of 57 (9-88) years. Patients received 0.1 mmol/kg OMNISCAN for imaging body areas that included the internal thorax (noncardiac), abdomen, and pelvis, or a dose of 0.05 mmol/kg for imaging the kidney. Pre- and post-OMNISCAN images were evaluated

blindly for the degree of contrast, diagnostic value, and lesion detection. These were rated on a scale of remarkably improved, improved, no change, worse, and cannot be determined. The postcontrast results showed remarkably improved or improved diagnostic value in 90% of the thorax, liver, and pelvis patients, and in 95% of the kidney patients. These findings were similar to those of MAGNEVIST 0.1 mmol/kg.

In a dose ranging study of 258 patients who were referred for MRI of the internal thoracic, abdominal, pelvic, or retroperitoneal organs, the evaluated doses included OMNISCAN 0.025, 0.05, 0.1 mmol/kg. The lowest effective dose of OMNISCAN for the kidney was 0.05 mmol/kg.

INDICATIONS AND USAGE

CNS (Central Nervous System)

OMNISCAN is indicated for intravenous use in MRI to visualize lesions with abnormal vascularity (or those thought to cause abnormalities in the blood-brain barrier) in the brain (intracranial lesions), spine, and associated tissues.

Body (Intrathoracic [noncardiac], Intra-abdominal, Pelvic and Retroperitoneal Regions)

OMNISCAN is indicated for intravenous administration to facilitate the visualization of lesions with abnormal vascularity within the thoracic (noncardiac), abdominal, pelvic cavities, and the retroperitoneal space.

CONTRAINDICATIONS

None known.

WARNINGS

Deoxygenated sickle erythrocytes have been shown in *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 paramagnetic contrast agents may possibly potentiate sickle erythrocyte alignment. OMNISCAN has not been studied in patients with sickle cell anemia and other hemoglobinopathies.

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

Patients with history of allergy or drug reaction should be observed for several hours after drug administration.

PRECAUTIONS

General

Some paramagnetic contrast agents may impair the visualization of existing lesions which are seen on the unenhanced, noncontrast MRI. This may be due to effects of the paramagnetic contrast agent, imaging parameters, misregistration, etc. CAUTION SHOULD BE EXERCISED WHEN A CONTRAST ENHANCED INTERPRETATION IS MADE IN THE ABSENCE OF A COMPANION UNENHANCED MRI.

OMNISCAN is cleared from the body by glomerular filtration. Significant hepatobiliary enteric pathway excretion has not been demonstrated. Dose adjustments in renal or hepatic impairment have not been studied. Caution should be exercised in patients with impaired renal insufficiency with or without hepatic impairment. For elimination of OMNISCAN in pediatric patients, see the Pediatric Use section.

The possibility of a reaction, including serious, life threatening, fatal, anaphylactoid or cardiovascular reactions or other idiosyncratic reactions should always be considered especially in those patients with a known clinical hypersensitivity, a history of asthma, or other allergic respiratory disorders (see ADVERSE REACTIONS).

Repeat procedures: Sequential use during the same diagnostic session has been studied in adult central nervous system use only. Data for sequential injections during the same session or repeated injections for monitoring in other indications are not available. If the physician determines repeat dosing is required in non-CNS use in adults or in CNS pediatric administration, in patients with normal renal function the time interval between repeat doses should be at least 7 hours to allow for normal clearance of the drug from the body (see Pharmacokinetics section).

OMNISCAN 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.

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.

INFORMATION FOR PATIENTS

Patients receiving OMNISCAN should be instructed to:

1. Inform their physician if they are pregnant or breast feeding.
2. Inform their physician if they have anemia or diseases that affect red blood cells.
3. Inform their physician if they have a history of renal or hepatic disease, seizure, asthma or allergic respiratory disorders, or hemoglobinopathies.

LABORATORY TEST FINDINGS

Asymptomatic, transitory changes in serum iron have been observed. The clinical significance is unknown.

Omniscan interferes with serum calcium measurements with some colorimetric (complexometric) methods commonly used in hospitals, resulting in serum calcium concentrations lower than the true values. Thus, it is recommended not to use such methods for 12-24 hours after administration of Omniscan. If such measurements are necessary, the use of other methods is recommended. All patients in whom this effect was observed remained asymptomatic.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Long-term animal studies have not been performed to evaluate the carcinogenic potential of gadodiamide. The results of the following genotoxicity assays were negative: bacterial reverse mutation assay, CHO/HGPRT forward mutation assay, CHO chromosome aberration assay, and the *in vivo* mouse micronucleus assay at intravenous doses up to 27 mmol/kg. Impairment of male or female fertility was not observed in rats after intravenous administration three times per week at 1.0 mmol/kg, the maximum dose tested.

PREGNANCY CATEGORY C

OMNISCAN has been shown to have an adverse effect on embryo-fetal development in rabbits that is observed as an increased incidence of flexed appendages and skeletal malformations at dosages as low as 0.5 mmol/kg/day for 13 days during gestation (approximately 2 times the maximum human cumulative dose of 0.3 mmol/kg based on a mmol/kg comparison or 0.6 times the human dose based on a mmol/m² comparison). Skeletal malformations may be due to maternal toxicity since the body weight of the dams was significantly reduced in response to OMNISCAN administration during pregnancy. In rat studies, fetal abnormalities were not observed at doses up to 2.5 mmol/kg/day for 10 days during gestation (8 times the maximum human cumulative dose, or 1.3 times the human dose on a mg/m² comparison); however, maternal toxicity was not achieved in these studies and a definitive conclusion about teratogenicity in rats at doses above 2.5 mmol/kg/day cannot be made at this time. Adequate and well controlled studies in pregnant women have not been conducted. OMNISCAN should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

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.

PEDIATRIC USE

The safety and efficacy of OMNISCAN at a single dose of 0.05 to 0.1 mmol/kg have been established in the pediatric population over 2 years of age. The safety and efficacy for doses greater than 0.1 mmol/kg and the clinical benefit of repeated procedures have not been studied in pediatric patients. The use of OMNISCAN in these age groups is supported by evidence from adequate and well controlled studies of OMNISCAN in adults, a pediatric study of the MR imaging of the central nervous system and additional safety data obtained in the literature.

Pharmacokinetics of OMNISCAN have not been studied in the pediatric population. Literature reports that the glomerular filtration rate of neonates and infants is much less than that of adults. The pharmacokinetics volume of distribution is different as well. The effect of these differences on the elimination and dosing regimen in pediatric patients under 2 years of age has not been studied. Whether the dose administered or optimal imaging times should be adjusted has not been studied.

However, in the 173 pediatric patients in the central nervous system study with OMNISCAN (see the CLINICAL TRIALS section) and the 144 pediatric patients in the literature, the adverse events were similar to those reported in adults.

GERIATRIC USE

Of the total number of patients in clinical studies of OMNISCAN, 19.3 percent were 65 to 80, while 1.2 percent were over 80. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In general, dose selection for an elderly patient should be cautious usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

The most frequent adverse events observed during OMNISCAN clinical trials were nausea, headache, and dizziness that occurred in 3% or less of the patients; other adverse events that occurred in 1% or less of the patients are listed below. This includes all reported adverse events regardless of attribution. The majority of these adverse events were of mild to moderate intensity. Dose and adverse event relationships are not fully clarified.

The following adverse events occurred in 1% or less of the 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.

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.

Gastrointestinal System Disorders: Abdominal pain, diarrhea, eructation, melena, dry mouth, vomiting.

Hearing and Vestibular Disorders: Tinnitus.

Liver and Biliary System Disorders: Abnormal hepatic function.

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.

Vision Disorders: Abnormal vision.

OVERDOSAGE

Clinical consequences of overdose with OMNISCAN have not been reported. The minimum lethal dose of intravenously administered OMNISCAN in rats and mice is greater than 20 mmol/kg (200 times the recommended human dose of 0.1 mmol/kg; 67 times the cumulative 0.3 mmol/kg dose). Gadodiamide has been shown to be dialyzable in an *in vitro* study. Clinical data are not currently available.

DOSAGE AND ADMINISTRATION**CNS (Central Nervous System)**

Adults: The recommended dose of OMNISCAN is 0.2 mL/kg (0.1 mmol/kg) administered as a bolus intravenous injection. An additional 0.4 mL/kg (0.2 mmol/kg) can be given within 20 minutes of the first dose. (See the Dosage Chart.)

Pediatric Patients (2-16 years): The recommended dose of OMNISCAN is 0.2 mL/kg (0.1 mmol/kg) administered as a bolus intravenous injection. (See the Dosage Chart.)

Body (Intrathoracic [noncardiac], Intra-abdominal, Pelvic and Retroperitoneal Regions)

Adult and Pediatric Patients (2-16 years of age): For the kidney, the recommended dose of OMNISCAN is 0.1 mL/kg (0.05 mmol/kg). For the intrathoracic (noncardiac), intra-abdominal, and pelvic cavities, the recommended dose of OMNISCAN is 0.2 mL/kg (0.1 mmol/kg). (See the Dosage Chart.)

DOSAGE CHART

| BODY WEIGHT kg lb | | PEDIATRIC 0.05 0.1 (mmol/kg) | | ADULTS 0.05 0.1 0.2 (mmol/kg) | | |
|---------------------------|-----|---------------------------------------|------|---|------|------|
| | | VOLUME (mL) | | VOLUME (mL) | | |
| 12 | 26 | 1.2 | 2.4 | - | - | - |
| 14 | 31 | 1.4 | 2.8 | - | - | - |
| 16 | 35 | 1.6 | 3.2 | - | - | - |
| 18 | 40 | 1.8 | 3.6 | - | - | - |
| 20 | 44 | 2.0 | 4.0 | - | - | - |
| 22 | 48 | 2.2 | 4.4 | - | - | - |
| 24 | 53 | 2.4 | 4.8 | - | - | - |
| 26 | 57 | 2.6 | 5.2 | - | - | - |
| 28 | 62 | 2.8 | 5.6 | - | - | - |
| 30 | 66 | 3.0 | 6.0 | - | - | - |
| 40 | 88 | 4.0 | 8.0 | 4.0 | 8.0 | 16.0 |
| 50 | 110 | 5.0 | 10.0 | 5.0 | 10.0 | 20.0 |
| 60 | 132 | 6.0 | 12.0 | 6.0 | 12.0 | 24.0 |
| 70 | 154 | 7.0 | 14.0 | 7.0 | 14.0 | 28.0 |
| 80 | 176 | 8.0 | 16.0 | 8.0 | 16.0 | 32.0 |
| 90 | 198 | - | - | 9.0 | 18.0 | 36.0 |
| 100 | 220 | - | - | 10.0 | 20.0 | 40.0 |
| 110 | 242 | - | - | 11.0 | 22.0 | 44.0 |
| 120 | 264 | - | - | 12.0 | 24.0 | 48.0 |
| 130* | 286 | - | - | 13.0 | 26.0 | 52.0 |

*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, as provided in the Prefill Plus needle-free system. 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.

HOW SUPPLIED

OMNISCAN (gadodiamide) Injection is a sterile, clear, colorless to slightly yellow, aqueous solution containing 287 mg/mL of gadodiamide in rubber stoppered vials and polypropylene syringes. OMNISCAN is supplied in the following sizes:

5 mL fill in 10 mL vial, box of 10, (NDC 0407-0690-05)
10 mL vial, box of 10, (NDC 0407-0690-10)
15 mL fill in 20 mL vial, box of 10, (NDC 0407-0690-15)
20 mL vial, box of 10, (NDC 0407-0690-20)
50 mL vial, box of 10, (NDC 0407-0690-55)
10 mL fill in 20 mL prefilled syringe, box of 10, (NDC 0407-0690-12)
15 mL fill in 20 mL prefilled syringe, box of 10, (NDC 0407-0690-17)
20 mL prefilled syringe, box of 10, (NDC 0407-0690-22)

Prefill Plus™ needle-free system

Omniscan 15 mL, box of 10, (NDC 0407-0690-62)

Contains: Omniscan 15 mL fill in 20 mL Single Dose Prefilled Syringe and 5 mL 0.9% Sodium Chloride Injection, USP I.V. Flush Syringe

Prefill Plus™ needle-free system

Omniscan 20 mL, box of 10, (NDC 0407-0690-63)

Contains: Omniscan 20 mL fill in 20 mL Single Dose Prefilled Syringe and 5 mL 0.9% Sodium Chloride Injection, USP I.V. Flush Syringe

Storage: OMNISCAN should be stored at controlled room temperature 15°C - 30°C (59°F - 86°F).

Protect from light.

Do not freeze. Freezing could cause small cracks in the vials which would compromise the sterility of the product. Do not use if the product is inadvertently frozen.

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