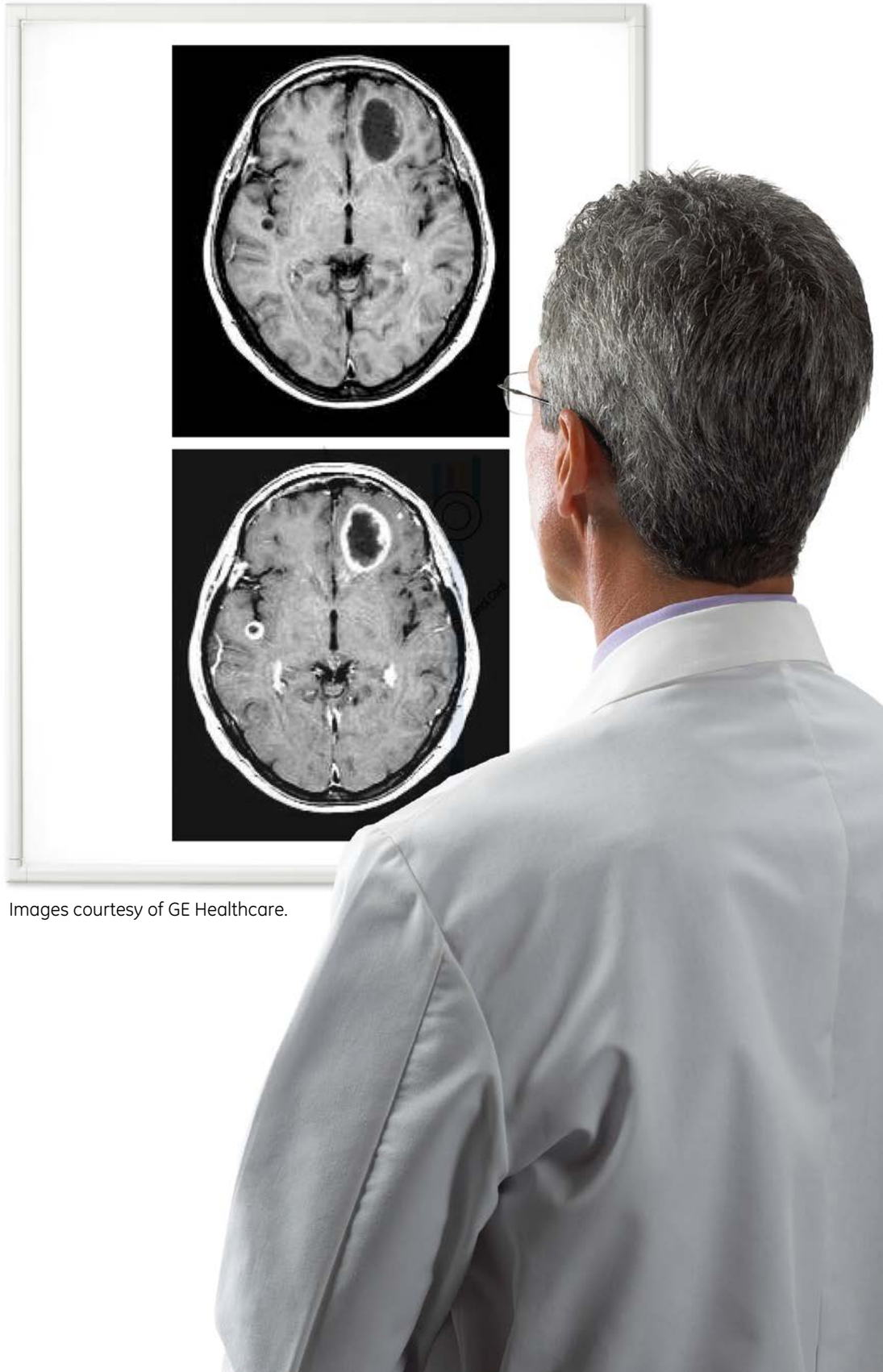
GE Healthcare

OMNISCAN™
(GADODIAMIDE) INJECTION

For contrast-enhanced MRI images across multiple CNS and body indications



Images courtesy of GE Healthcare.

Important Risk and Safety Information About Omniscan™ (gadodiamide) Injection

WARNING — NOT FOR INTRATHECAL USE: Inadvertent intrathecal use of Omniscan has caused convulsions, coma, sensory, and motor neurologic deficits.
WARNING — NEPHROGENIC SYSTEMIC FIBROSIS (NSF):

- **Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with noncontrast magnetic resonance imaging (MRI) or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle, and internal organs.**
- **Do not administer Omniscan to patients with**
  - **Chronic, severe kidney disease (glomerular filtration rate [GFR] <30 mL/min/1.73m^2) or acute kidney injury (AKI)**
- **Screen patients for AKI and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (eg, age >60 years, hypertension, or diabetes), estimate GFR via laboratory testing.**
- **Do not exceed the recommended dose and allow a sufficient period of time for elimination of the drug from the body prior to any readministration.**

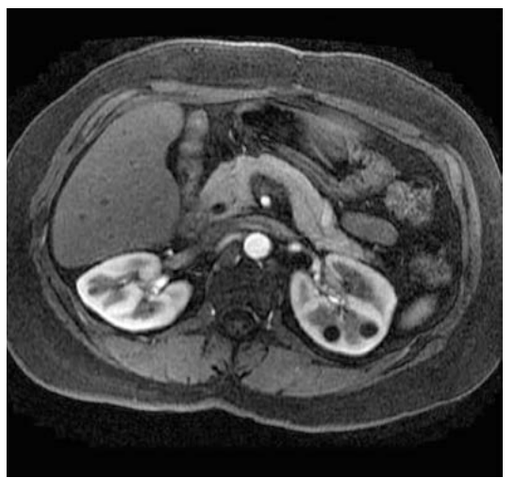
INDICATIONS: Omniscan is indicated for intravenous use in MRI to visualize lesions with abnormal vascularity in the brain, spine, and associated tissues; and within the thoracic (noncardiac), abdominal, pelvic cavities, and the retroperitoneal space. **CONTRAINDICATIONS:** Omniscan is contraindicated in patients with chronic, severe kidney disease (GFR <30 mL/min/1.73m^2), AKI, or prior hypersensitivity reaction to Omniscan. **WARNINGS AND PRECAUTIONS — Hypersensitivity:** Anaphylactoid and anaphylactic reactions, with cardiovascular, respiratory, and/or cutaneous manifestations, resulting in death have occurred. **Acute Renal Failure:** In patients with renal insufficiency, acute renal failure requiring dialysis or worsening renal function have occurred, mostly within 48 hours of dosing. The risk of renal failure may increase with increasing dose. **Impaired Visualization:** GBCAs such as Omniscan might impair the visualization of lesions that are seen on the noncontrast MRI. **ADVERSE REACTIONS:** In adult clinical trials, the most frequent adverse reactions were nausea, headache, and dizziness. In pediatric clinical trials, the adverse reactions were similar to those reported in adults. **Postmarketing Experience — Nervous System:** Inadvertent intrathecal use causes seizures, coma, paresthesia, and paresis. **General:** Nephrogenic systemic fibrosis. **Renal and Urinary System Disorders:** In patients with preexisting renal insufficiency: Acute renal failure, renal impairment, and increased blood creatinine. **SPECIFIC POPULATIONS — Pregnancy:** Adequate and well-controlled studies in pregnant women have not been conducted. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when administering Omniscan to a nursing woman. **Pediatric Use:** The safety and efficacy of a single dose of 0.05 to 0.1 mmol/kg have been established in pediatric patients 2 years of age and older, based on adequate and well-controlled studies of Omniscan in adults, a pediatric CNS imaging study, and safety data in the scientific literature. The optimal dosing regimen and imaging times in patients younger than 2 years of age have not been established. **Geriatric Use:** Clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity in the elderly cannot be ruled out. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. The risk of toxic reactions to Omniscan is greater in patients with impaired renal function. **Renal/Hepatic Impairment:** Dose adjustments in renal or hepatic impairment have not been studied. Caution should be exercised in patients with impaired renal insufficiency

Prior to Omniscan administration, please read the Full Prescribing Information at the end of this document.

Approved for multiple indications*[1]

indication			dose
CNS (central nervous system)	adult	pediatric (2-16 years)	
brain	✓	✓	0.1 mmol/kg IV bolus
spine	✓	✓	0.1 mmol/kg IV bolus
head and neck	none	none	
Body	adult	pediatric (2-16 years)	
kidney	✓	✓	0.05 mmol/kg IV bolus
intrathoracic	✓	✓	0.1 mmol/kg IV bolus
intra-abdominal	✓	✓	0.1 mmol/kg IV bolus
pelvic	✓	✓	0.1 mmol/kg IV bolus

*Please refer to the Dosage and Administration section of the Omniscan Prescribing Information for recommended dosing details.



Images courtesy of GE Healthcare.

Physical and chemical properties of MR contrast agents
(agents indicated for brain and spine)

	Dotarem® (gadoterate meglumine)	**Magnevist®** (gadopentetate dimeglumine)	**MultiHance®** (gadobenate dimeglumine)	**Gadavist®** (gadobutrol)	**Omniscan™** (gadodiamide)	**Optimark®** (gadoversetamide)	**ProHance®** (gadoteridol)
Ionicity	Ionic	Ionic	Ionic	Nonionic	Nonionic	Nonionic	Nonionic
Osmolality (mOsm/kg H_2O)	1,350	1,960	1,970	1,603	789	1,110	630
Viscosity							
cP @ 20°C	3.4	4.9	9.2	NA	2.0	3.1	2.0
cP @ 37°C	2.4	2.9	5.3	4.9	1.4	2.0	1.3

Nephrogenic systemic fibrosis (NSF) adverse event reporting

It is challenging to draw conclusions about adverse events related to drug exposure using data collected through a voluntary spontaneous reporting system. Cases of NSF related to Omniscan exposure have been reported to GE Healthcare or identified by the Company through literature, legal filings, reports to health authorities (eg, FDA MedWatch), reports directly to GE Healthcare, and other sources.

Reports of NSF are often received with significant delay after onset of NSF, which itself may occur with variable delay after exposure to a GBCA. In many reports received by GE Healthcare, the date of onset of NSF and/or GBCA exposure is not available. There are no confirmed reports of NSF associated with a post-November 2007 administration of Omniscan.

Please refer to the Important Risk and Safety Information on the second screen and read the Full Prescribing Information at the end of this document before using Omniscan.

Available in a variety of packaging options

- Glass vials
- Prefill Plus™ prefilled syringes
- *+PLUS*PAK™ (polymer bottle)
  - 100 mL *+PLUS*PAK (polymer bottle) Pharmacy Bulk Packaging provides convenience when drawing multiple single doses
  - *+PLUS*PAK (polymer bottle) packaging has been approved as an ecomagination[SM] product within GE
  - *+PLUS*PAK container meets both OSHA and The Joint Commission safety standards for packaging
  - *+PLUS*PAK container label provides peel-off tracking labels

Please see Important Risk and Safety Information About Omniscan™ (gadodiamide) Injection Pharmacy Bulk Packaging on the second screen and below.

Important Information About Omniscan Pharmacy Bulk Packaging[1]

Omniscan (gadodiamide) Injection is a sterile, clear, colorless to slightly yellow, aqueous solution containing 287 mg/mL of gadodiamide in rubber-stoppered vials and prefilled syringes.

Protect Omniscan from strong daylight and direct exposure to sunlight. Do not freeze. Freezing can cause small cracks in the vials, which would compromise the sterility of the product. Do not use if the product is inadvertently frozen. Store Omniscan at controlled room temperature 20°- 25°C (68°- 77°F); excursions permitted to 15°- 30°C (59° -86°F) [see USP].

A. Use only a suitable work area, such as a laminar flow hood, to transfer Omniscan Injection from the Pharmacy Bulk Package.

B. Penetrate the container closure only once using a suitable transfer device and aseptic technique.

C. Once the closure is penetrated, withdraw the container contents without delay. If delay is unavoidable, complete the fluid transfer as soon as possible within a maximum time of eight hours.

D. Once the closure is penetrated, keep the container in the aseptic area and at room temperature (do not exceed 30°C).

E. Use each individual dose of Omniscan Injection immediately following withdrawal from the Pharmacy Bulk Package; discard any unused portion of the Omniscan Injection not used immediately.

F. Discard any unused Omniscan doses remaining in the Pharmacy Bulk Package eight hours after the penetration of the container closure.

imagination at work

Reference: 1. Omniscan Injection [prescribing information]. Princeton, NJ: GE Healthcare; 2013.

Customer Service: 800 292 8514 (option 4)
Reimbursement Hotline: 800 767 6664
www.gehealthcare.com

February 2014 63-JB13965USf

GE Healthcare

ONC-2U-OSLO

OMNISCAN™ (gadodiamide) Injection

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OMNISCAN safely and effectively. See full prescribing information for OMNISCAN.

OMNISCAN™ (gadodiamide) Injection for Intravenous Use

Initial U.S. Approval: 1993

WARNING: NOT FOR INTRATHECAL USE and NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

See full prescribing information for complete boxed warning.

NOT FOR INTRATHECAL USE:

- **Inadvertent intrathecal use of OMNISCAN has caused convulsions, coma, sensory and motor neurologic deficits (5.1).**

NSF:

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities.

- **Do not administer OMNISCAN to patients with:**
  - **chronic, severe kidney disease (GFR < 30 mL/min/1.73m^2), or**
  - **acute kidney injury (4).**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g., age > 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing (5.2).**

RECENT MAJOR CHANGES

Contraindications (4)	08/2013
Warnings and Precautions, Hypersensitivity Reactions (5.3)	08/2013

INDICATIONS AND USAGE

OMNISCAN is a gadolinium-based contrast agent for diagnostic magnetic resonance imaging (MRI) indicated for intravenous use to:

- Visualize lesions with abnormal vascularity in the brain, spine, and associated tissues (1.1)
- Facilitate the visualization of lesions with abnormal vascularity within the thoracic, abdominal, pelvic cavities, and the retroperitoneal space (1.2)

DOSAGE AND ADMINISTRATION

- CNS – Adults and Pediatrics; 2-16 years of age: 0.2 mL/kg (0.1 mmol/kg) (2.1, 2.4)
- Body – Adults and Pediatrics; 2-16 years of age:
  Kidney: 0.1 mL/kg (0.05 mmol/kg)
  Intrathoracic, intra-abdominal, and pelvic cavities: 0.2 mL/kg (0.1 mmol/kg) (2.2, 2.4)

DOSAGE FORMS AND STRENGTHS

Sterile aqueous solution for intravenous injection; 287 mg/mL (3)

CONTRAINDICATIONS

Patients with chronic, severe kidney disease (GFR < 30 mL/min/1.73m^2), acute kidney injury, or prior hypersensitivity reaction to OMNISCAN (4)

WARNINGS AND PRECAUTIONS

- *Nephrogenic Systemic Fibrosis (NSF)* has occurred in patients with impaired elimination of GBCAs. Higher than recommended dosing or repeat dosing appears to increase the risk (5.2).
- *Anaphylactoid and other serious hypersensitivity reactions* including fatal reactions have occurred particularly in patients with history of allergy or drug reactions. Monitor patients closely for need of emergency cardiorespiratory support (5.3).
- *Acute renal failure* has occurred in patients with preexisting renal insufficiency. Use the lowest necessary dose of OMNISCAN and evaluate renal function in these patients (5.4).

ADVERSE REACTIONS

- The most frequent adverse reactions (≤ 3%) observed during OMNISCAN adult clinical studies were nausea, headache, and dizziness (6.1)
- Serious or life-threatening reactions include: cardiac failure, arrhythmia and myocardial infarction (6.1, 6.3)

To report SUSPECTED ADVERSE REACTIONS, contact GE Healthcare at 1-800-654-0118 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 08/2013

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FULL PRESCRIBING INFORMATION

WARNING: NOT FOR INTRATHECAL USE and NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

NOT FOR INTRATHECAL USE:

Inadvertent intrathecal use of OMNISCAN has caused convulsions, coma, sensory and motor neurologic deficits [*see Warnings and Precautions (5.1)*].

NSF:

- **Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.**
- **Do not administer OMNISCAN to patients with:**
  - **chronic, severe kidney disease (GFR < 30 mL/min/1.73m^2), or**
  - **acute kidney injury [*see Contraindications (4)*].**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g., age > 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.**
- **Do not exceed the recommended OMNISCAN dose and allow a sufficient period of time for elimination of the drug from the body prior to any readministration [*see Warnings and Precautions (5.2)*].**

1 INDICATIONS AND USAGE

1.1 CNS (Central Nervous System)

OMNISCAN is a gadolinium-based contrast agent 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 [*see Clinical Studies (14.1)*].

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

OMNISCAN is a gadolinium-based contrast agent indicated for intravenous use in MRI to facilitate the visualization of lesions with abnormal vascularity within the thoracic (noncardiac), abdominal, pelvic cavities, and the retroperitoneal space [*see Clinical Studies (14.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 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.

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 Dosage and Administration (2.3)*].

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

Adult and Pediatric Patients (2-16 years of age): For imaging the kidney, the recommended dose of OMNISCAN is 0.1 mL/kg (0.05 mmol/kg). For imaging the intrathoracic (noncardiac), intra-abdominal, and pelvic cavities, the recommended dose of OMNISCAN is 0.2 mL/kg (0.1 mmol/kg) [*see Dosage and Administration (2.3)*].

2.3 Dosage Chart

BODY WEIGHT		PEDIATRIC 0.05 (mmol/kg)	PEDIATRIC 0.1 (mmol/kg)	ADULTS 0.05 (mmol/kg)	ADULTS 0.1 (mmol/kg)
kg	lb	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	4	-	-
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	6	-	-
40	88	4	8	4	8
50	110	5	10	5	10
60	132	6	12	6	12
70	154	7	14	7	14
80	176	8	16	8	16
90	198	-	-	9	18
100	220	-	-	10	20
110	242	-	-	11	22
120	264	-	-	12	24
130*	286	-	-	13	26

*The heaviest patient in clinical studies weighed 136 kg.

2.4 Dosing Guidelines

Inspect OMNISCAN visually for particulate matter and discoloration before administration, whenever solution and container permit.

Do not use the solution if it is discolored or particulate matter is present.

Draw OMNISCAN into the syringe and use immediately. Discard any unused portion of OMNISCAN Injection.

To ensure complete delivery of the desired volume of contrast medium, follow the injection of OMNISCAN with a 5 mL flush of 0.9% sodium chloride, as provided in the Prefill Plus needle-free system. Complete the imaging procedure within 1 hour of administration of OMNISCAN.

3 DOSAGE FORMS AND STRENGTHS

Sterile aqueous solution for intravenous injection; 287 mg/mL.

4 CONTRAINDICATIONS

OMNISCAN is contraindicated in patients with:

- chronic, severe kidney disease (glomerular filtration rate, GFR < 30 mL/min/1.73m^2), or
- acute kidney injury
- prior hypersensitivity to OMNISCAN

5 WARNINGS AND PRECAUTIONS

5.1 Not for Intrathecal Use

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

5.2 Nephrogenic Systemic Fibrosis

Gadolinium-based contrast agents (GBCAs) increase the risk for nephrogenic systemic fibrosis (NSF) among patients with impaired elimination of the drugs. Avoid use of GBCAs among these patients unless the diagnostic information is essential and not available with non-contrast enhanced MRI or other modalities. The GBCA-associated NSF risk appears highest for patients with chronic, severe kidney disease (GFR < 30 mL/min/1.73m^2) as well as patients with acute kidney injury. Do not administer OMNISCAN to these patients. The risk appears lower for patients with chronic, moderate kidney disease (GFR 30-59 mL/min/1.73m^2) and little, if any, for patients with chronic, mild kidney disease (GFR 60-89 mL/min/1.73m^2). NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs. Report any diagnosis of NSF following OMNISCAN administration to GE Healthcare (1-800-654-0118) or FDA (1-800-FDA-1088 or www.fda.gov/medwatch).

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.

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 impairment at the time of exposure. Record the specific GBCA and the dose administered to a patient. When administering OMNISCAN, do not exceed the recommended dose and allow a sufficient period of time for elimination of the drug prior to any readministration [*see Boxed Warning, Contraindications (4), Clinical Pharmacology (12.2) and Dosage and Administration (2)*].

5.3 Hypersensitivity Reactions

Anaphylactoid and anaphylactic reactions, with cardiovascular, respiratory and/or cutaneous manifestations, resulting in death have occurred. Personnel trained in resuscitation techniques and resuscitation equipment should be present prior to OMNISCAN administration. If a hypersensitivity reaction occurs, stop OMNISCAN Injection and immediately begin appropriate therapy. Observe patients closely, particularly those with a history of drug reactions, asthma, allergy or other hypersensitivity disorders, during and up to several hours after OMNISCAN Injection.

5.4 Acute Renal Failure

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 (6)*].

OMNISCAN is cleared by glomerular filtration. Hemodialysis also enhances OMNISCAN clearance [*see Use in Specific Populations (8.5, 8.6)*].

5.5 Impaired Visualization of Lesions Detectable with Non-contrast MRI

Paramagnetic contrast agents such as OMNISCAN might impair the visualization of lesions which are seen on the non-contrast MRI. This may be due to effects of the paramagnetic contrast agent, or imaging parameters. Exercise caution when OMNISCAN MRI scans are interpreted in the absence of a companion non-contrast MRI.

5.6 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. In patients with normal renal function, this effect lasts for 12-24 hours. In patients with decreased renal function, the interference with calcium measurements is expected to last during the prolonged elimination of OMNISCAN. After patients receive OMNISCAN, careful attention should be used in selecting the type of method used to measure calcium.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Nephrogenic systemic fibrosis [*see Warnings and Precautions (5.2)*]
- Hypersensitivity reactions [*see Warnings and Precautions (5.3)*]

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be

directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

6.1 Clinical Studies Experience (Adults)

In clinical studies 1160 patients were exposed to OMNISCAN. The most frequent adverse reactions were nausea, headache, and dizziness that occurred in 3% or less of the patients. The majority of these reactions were of mild to moderate intensity.

The following adverse reactions occurred in 1% or less of 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), fever, hot flushes, rigors, fatigue, malaise, pain, syncope.

Cardiovascular Disorders: Cardiac failure, rare arrhythmia and myocardial infarction resulting in death in patients with ischemic heart disease, flushing, chest pain, deep thrombophlebitis.

Central and Peripheral Nervous System Disorders: Convulsions including grand mal, ataxia, abnormal coordination, paresthesia, tremor, aggravated multiple sclerosis (characterized by sensory and motor disturbances), aggravated migraine.

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

Hearing and Vestibular Disorders: Tinnitus.

Liver and Biliary System Disorders: Abnormal hepatic function.

Musculoskeletal System Disorders: Arthralgia, myalgia.

Respiratory System Disorders: Rhinitis, dyspnea.

Skin and Appendage Disorders: Pruritus, rash, erythematous rash, sweating increased, urticaria.

Special Senses, Other Disorders: Taste loss, taste perversion.

Urinary System Disorders: Acute reversible renal failure.

Vision Disorders: Abnormal vision.

6.2 Clinical Studies Experience (Pediatrics)

In the 97 pediatric patients in CNS studies with OMNISCAN [*see Clinical Studies (14.1)*] and the 144 pediatric patients in published literature, the adverse reactions were similar to those reported in adults.

6.3 Postmarketing Experience

Because postmarketing 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 drug exposure.

The following adverse reactions have been identified during the postmarketing use of OMNISCAN:

Nervous System Disorders: Inadvertent intrathecal use causes seizures, coma, paresthesia, paresis.

General Disorders: Nephrogenic Systemic Fibrosis (NSF) [*see Warnings and Precautions (5.2)*].

Renal and Urinary System Disorders: In patients with pre-existing renal insufficiency: acute renal failure, renal impairment, blood creatinine increased [*see Warnings and Precautions (5.4)*].

7 DRUG INTERACTIONS

Specific drug interaction studies have not been conducted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: OMNISCAN has been shown to have an adverse effect on embryo-fetal development in rabbits at dosages as low as 0.5 mmol/kg/day for 13 days during gestation (approximately 0.6 times the human dose based on a body surface area comparison). These adverse effects are observed as an increased incidence of flexed appendages and skeletal malformations which may be due to maternal toxicity since the body weight of the dams was 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 (1.3 times the maximum human dose based on a body surface area 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. 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.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when administering OMNISCAN to a nursing woman.

8.4 Pediatric Use

The safety and efficacy of OMNISCAN at a single dose of 0.05 to 0.1 mmol/kg have been established in pediatric patients over 2 years of age based on adequate and well controlled studies of OMNISCAN in adults, a pediatric CNS imaging study, and safety data in the scientific literature. However, the safety and efficacy of doses greater than 0.1 mmol/kg and of repeated doses have not been studied in pediatric patients.

Pharmacokinetics of OMNISCAN have not been studied in pediatrics. The glomerular filtration rate of neonates and infants is much lower than that of adults. The pharmacokinetics volume of distribution is also different. Therefore, the optimal dosing regimen and imaging times in patients under 2 years of age have not been established.

8.5 Geriatric Use

In clinical studies of OMNISCAN, 243 patients were between 65 and 80 years of age while 15 were over 80. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity in the elderly cannot be ruled out. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

OMNISCAN is excreted by the kidney, and the risk of toxic reactions to OMNISCAN is greater in patients with impaired renal function [*see Warnings and Precautions (5.2, 5.4)*]. Because elderly patients are more likely to have decreased renal function, select dose carefully and assess eGFR by laboratory testing before OMNISCAN use.

8.6 Renal/Hepatic Impairment

Dose adjustments in renal or hepatic impairment have not been studied. Caution should be exercised in patients with impaired renal insufficiency [*see Warnings and Precautions (5.2, 5.4)*].

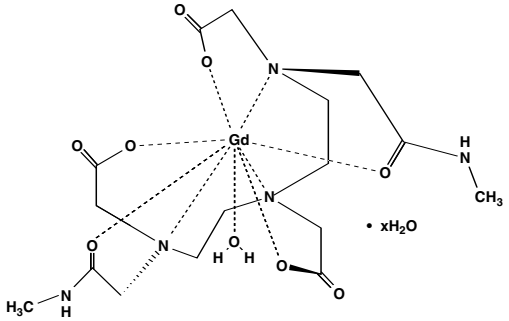
10 OVERDOSAGE

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). OMNISCAN is dialyzable.

11 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 administered by intravenous injection.

OMNISCAN is provided as a sterile, clear, colorless to slightly yellow, aqueous solution. Each 1 mL contains 287 mg gadodiamide and 12 mg caldiamide sodium in 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-[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, with a molecular weight of 573.66 (anhydrous), an empirical formula of $C_{16}H_{28}GdN_5O_9 \bullet xH_2O$, 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
	@ 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.

12 CLINICAL PHARMACOLOGY

12.1 Pharmacodynamics

In magnetic resonance imaging, visualization of normal and pathologic 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). 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 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. 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). 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. There is no detectable biotransformation or decomposition of gadodiamide.

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

13 NONCLINICAL TOXICOLOGY

13.1 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: *in vitro* bacterial reverse mutation assay, *in vitro* Chinese Hamster Ovary (CHO)/Hypoxanthine Guanine Phosphoribosyl Transferase (HGPT) forward mutation assay, *in vitro* CHO chromosome aberration assay, and the *in vivo* mouse micronucleus assay at intravenous doses of 27 mmol/kg (approximately 7 times the maximum human dose based on a body surface area comparison). Impairment of male or female fertility was not observed in rats after intravenous administration three times per week at the maximum dose tested of 1.0 mmol/kg (approximately 0.5 times the maximum human dose based on a body surface area comparison).

14 CLINICAL STUDIES

14.1 CNS (Central Nervous System)

OMNISCAN (0.1 mmol/kg) contrast enhancement in CNS MRI was evident in a study of 439 adults. In a study of sequential dosing, 57 adults received OMNISCAN 0.1 mmol/kg followed by 0.2 mmol/kg within 20 minutes (for cumulative dose of 0.3 mmol/kg). The MRIs were compared blindly. In 54/56 (96%) patients, OMNISCAN contrast enhancement was evident with both the 0.1 mmol/kg and cumulative 0.3 mmol/kg OMNISCAN doses relative to non-contrast MRI.

In comparison to the non-contrast MRI, increased numbers of brain and spine lesions were noted in 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 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 as a single 0.1 mmol/kg dose was evaluated in 97 pediatric patients with a mean age of 8.9 (2-18) years referred for CNS MRI. Postcontrast MRI provided added diagnostic information, diagnostic confidence, and new patient management information in 76%, 67%, and 52%, respectively, of pediatrics.

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

OMNISCAN was evaluated in a controlled trial of 276 patients referred for body MRI. These patients had a mean age of 57 (9-88) years. Patients received 0.1 mmol/kg OMNISCAN for imaging the thorax (noncardiac), abdomen, and pelvic organs, or a dose of 0.05 mmol/kg for imaging the kidney. Pre- and post-OMNISCAN images were evaluated blindly for the degree of diagnostic value 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.

In a dose ranging study 258 patients referred for body MRI received OMNISCAN 0.025, 0.05, 0.1 mmol/kg. The lowest effective dose of OMNISCAN for the kidney was 0.05 mmol/kg.

16 HOW SUPPLIED/STORAGE AND HANDLING

OMNISCAN (gadodiamide) Injection is a sterile, clear, colorless to slightly yellow, aqueous solution containing 287 mg/mL of gadodiamide in rubber stoppered vials and prefilled 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)

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 0407-0691-62)

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 0407-0691-63)

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

Protect OMNISCAN from strong daylight and direct exposure to sunlight. **Do not freeze.** Freezing can cause small cracks in the vials, which would compromise the sterility of the product. Do not use if the product is inadvertently frozen.

Store OMNISCAN at controlled room temperature 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP].

17 PATIENT COUNSELING INFORMATION

Patients receiving OMNISCAN should be instructed to inform their physician if they:

- are pregnant or breast feeding, or
- have a history of renal and/or liver disease, convulsions, asthma or allergic respiratory disorders, or recent administration of gadolinium-based contrast.

GBCAs increase the risk for NSF among patients with impaired elimination of the drugs. To counsel patients at risk for NSF:

- Describe the clinical manifestations of NSF
- Describe procedures to screen for the detection of renal impairment

Instruct the patients to contact their physician if they develop signs or symptoms of NSF following OMNISCAN administration such as burning, itching, swelling, scaling, hardening and tightening of the skin; red or dark patches on the skin; stiffness in joints with trouble moving, bending or straightening the arms, hands, legs or feet; pain deep in the hip bones or ribs; or muscle weakness.

GE Healthcare

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Manufactured by GE Healthcare AS, Oslo, Norway

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OMNISCAN™ (gadodiamide) Injection

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OMNISCAN safely and effectively. See full prescribing information for OMNISCAN.

OMNISCAN™ (gadodiamide) Injection for Intravenous Use

Pharmacy Bulk Package

Initial U.S. Approval: 1993

WARNING: NOT FOR INTRATHECAL USE and NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

See full prescribing information for complete boxed warning.

NOT FOR INTRATHECAL USE:

- **Inadvertent intrathecal use of OMNISCAN has caused convulsions, coma, sensory and motor neurologic deficits (5.1).**

NSF:

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities.

- **Do not administer OMNISCAN to patients with:**
  - **chronic, severe kidney disease (GFR < 30 mL/min/1.73m^2), or**
  - **acute kidney injury (4).**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g., age > 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing (5.2).**

RECENT MAJOR CHANGES

Contraindications (4)	08/2013
Warnings and Precautions, Hypersensitivity Reactions (5.3)	08/2013

INDICATIONS AND USAGE

OMNISCAN is a gadolinium-based contrast agent for diagnostic magnetic resonance imaging (MRI) indicated for intravenous use to:

- Visualize lesions with abnormal vascularity in the brain, spine, and associated tissues (1.1)
- Facilitate the visualization of lesions with abnormal vascularity within the thoracic, abdominal, pelvic cavities, and the retroperitoneal space (1.2)

DOSAGE AND ADMINISTRATION

- Pharmacy Bulk Package – Not for Direct Infusion (11)
- CNS – Adults and Pediatrics; 2-16 years of age: 0.2 mL/kg (0.1 mmol/kg) (2.1, 2.4)
- Body – Adults and Pediatrics; 2-16 years of age:
  Kidney: 0.1 mL/kg (0.05 mmol/kg)
  Intrathoracic, intra-abdominal, and pelvic cavities: 0.2 mL/kg (0.1 mmol/kg) (2.2, 2.4)

DOSAGE FORMS AND STRENGTHS

Sterile aqueous solution for intravenous injection; 287 mg/mL (3)

CONTRAINDICATIONS

Patients with chronic, severe kidney disease (GFR < 30 mL/min/1.73m^2), acute kidney injury, or prior hypersensitivity reaction to OMNISCAN (4)

WARNINGS AND PRECAUTIONS

- *Nephrogenic Systemic Fibrosis (NSF)* has occurred in patients with impaired elimination of GBCAs. Higher than recommended dosing or repeat dosing appears to increase the risk (5.2).
- *Anaphylactoid and other serious hypersensitivity reactions* including fatal reactions have occurred particularly in patients with history of allergy or drug reactions. Monitor patients closely for need of emergency cardiorespiratory support (5.3).
- *Acute renal failure* has occurred in patients with preexisting renal insufficiency. Use the lowest necessary dose of OMNISCAN and evaluate renal function in these patients (5.4).

ADVERSE REACTIONS

- The most frequent adverse reactions (≤ 3%) observed during OMNISCAN adult clinical studies were nausea, headache, and dizziness (6.1)
- Serious or life-threatening reactions include: cardiac failure, arrhythmia and myocardial infarction (6.1, 6.3)

To report SUSPECTED ADVERSE REACTIONS, contact GE Healthcare at 1-800-654-0118 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised 08/2013

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***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

WARNING: NOT FOR INTRATHECAL USE and NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

NOT FOR INTRATHECAL USE:

Inadvertent intrathecal use of OMNISCAN has caused convulsions, coma, sensory and motor neurologic deficits [*see Warnings and Precautions (5.1)*].

NSF:

- **Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.**
- **Do not administer OMNISCAN to patients with:**
  - **chronic, severe kidney disease (GFR < 30 mL/min/1.73m^2), or**
  - **acute kidney injury [*see Contraindications (4)*].**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g., age > 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.**
- **Do not exceed the recommended OMNISCAN dose and allow a sufficient period of time for elimination of the drug from the body prior to any readministration [*see Warnings and Precautions (5.2)*].**

1 INDICATIONS AND USAGE

1.1 CNS (Central Nervous System)

OMNISCAN is a gadolinium-based contrast agent 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 [*see Clinical Studies (14.1)*].

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

OMNISCAN is a gadolinium-based contrast agent indicated for intravenous use to facilitate the visualization of lesions with abnormal vascularity within the thoracic (noncardiac), abdominal, pelvic cavities, and the retroperitoneal space [*see Clinical Studies (14.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 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.

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 Dosage and Administration (2.3)*].

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

Adult and Pediatric Patients (2-16 years of age): For imaging the kidney, the recommended dose of OMNISCAN is 0.1 mL/kg (0.05 mmol/kg). For imaging the intrathoracic (noncardiac), intra-abdominal, and pelvic cavities, the recommended dose of OMNISCAN is 0.2 mL/kg (0.1 mmol/kg) [*see Dosage and Administration (2.3)*].

2.3 Dosage Chart

BODY WEIGHT		PEDIATRIC 0.05 (mmol/kg) VOLUME (mL)	PEDIATRIC 0.1 (mmol/kg) VOLUME (mL)	ADULTS 0.05 (mmol/kg) VOLUME (mL)	ADULTS 0.1 (mmol/kg) VOLUME (mL)
kg	lb				
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	4	-	-
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	6	-	-
40	88	4	8	4	8
50	110	5	10	5	10
60	132	6	12	6	12
70	154	7	14	7	14
80	176	8	16	8	16
90	198	-	-	9	18
100	220	-	-	10	20
110	242	-	-	11	22
120	264	-	-	12	24
130*	286	-	-	13	26

*The heaviest patient in clinical studies weighed 136 kg.

2.4 Dosing Guidelines

Inspect OMNISCAN visually for particulate matter and discoloration before administration, whenever solution and container permit.

Do not use the solution if it is discolored or particulate matter is present.

Draw OMNISCAN into the syringe and use immediately. Discard any unused portion of OMNISCAN Injection.

To ensure complete delivery of the desired volume of contrast medium, follow the injection of OMNISCAN with a 5 mL flush of 0.9% sodium chloride. Complete the imaging procedure within 1 hour of administration of OMNISCAN.

2.5 Directions for Proper Use of OMNISCAN Pharmacy Bulk Package

a. Use only a suitable work area, such as a laminar flow hood, to withdraw OMNISCAN Injection doses from the Pharmacy Bulk Package.

b. Penetrate the Pharmacy Bulk Package container closure only once using a suitable transfer device and aseptic technique.

c. Once the closure is penetrated, withdraw the container contents without delay. If delay is unavoidable, complete the fluid transfer as soon as possible within a maximum time of 8 hours.

d. Once the closure is penetrated, keep the Pharmacy Bulk Package container in the aseptic area and at room temperature (do not exceed 30°C).

e. Following withdrawal of any dose from the Pharmacy Bulk Package, immediately label the dose with the supplied peel-off label that identifies the dose contents as OMNISCAN and that OMNISCAN is not for intrathecal use.

f. Use each individual dose of OMNISCAN Injection immediately following withdrawal from the Pharmacy Bulk Package container; discard any unused portion of the OMNISCAN Injection dose not used immediately.

g. Discard any unused OMNISCAN doses remaining in the Pharmacy Bulk Package 8 hours after the penetration of the container closure.

3 DOSAGE FORMS AND STRENGTHS

Sterile aqueous solution for intravenous injection; 287 mg/mL.

4 CONTRAINDICATIONS

OMNISCAN is contraindicated in patients with:

- chronic, severe kidney disease (glomerular filtration rate, GFR < 30 mL/min/1.73m^2), or
- acute kidney injury
- prior hypersensitivity to OMNISCAN

5 WARNINGS AND PRECAUTIONS

5.1 Not for Intrathecal Use

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

5.2 Nephrogenic Systemic Fibrosis

Gadolinium-based contrast agents (GBCAs) increase the risk for nephrogenic systemic fibrosis (NSF) among patients with impaired elimination of the drugs. Avoid use of GBCAs among these patients unless the diagnostic information is essential and not available with non-contrast enhanced MRI or other modalities. The GBCA-associated NSF risk appears highest for patients with chronic, severe kidney disease (GFR < 30 mL/min/1.73m^2) as well as patients with acute kidney injury. Do not administer OMNISCAN to these patients. The risk appears lower for patients with chronic, moderate kidney disease (GFR 30-59 mL/min/1.73m^2) and little, if any, for patients with chronic, mild kidney disease (GFR 60-89 mL/min/1.73m^2). NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs. Report any diagnosis of NSF following OMNISCAN administration to GE Healthcare (1-800-654-0118) or FDA (1-800-FDA-1088 or www.fda.gov/medwatch).

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.

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 impairment at the time of exposure. Record the specific GBCA and the dose administered to a patient. When administering OMNISCAN, do not exceed the recommended dose and allow a sufficient period of time for elimination of the drug prior to any readministration [*see Boxed Warning, Contraindications (4), Clinical Pharmacology (12.2) and Dosage and Administration (2)*].

5.3 Hypersensitivity Reactions

Anaphylactoid and anaphylactic reactions, with cardiovascular, respiratory and/or cutaneous manifestations, resulting in death have occurred. Personnel trained in resuscitation techniques and resuscitation equipment should be present prior to OMNISCAN administration. If a hypersensitivity reaction occurs, stop OMNISCAN Injection and immediately begin appropriate therapy. Observe patients closely, particularly those with a history of drug reactions, asthma, allergy or other hypersensitivity disorders, during and up to several hours after OMNISCAN Injection.

5.4 Acute Renal Failure

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 (6)*].

OMNISCAN is cleared by glomerular filtration. Hemodialysis also enhances OMNISCAN clearance [*see Use in Specific Populations (8.5, 8.6)*].

5.5 Impaired Visualization of Lesions Detectable with Non-contrast MRI

Paramagnetic contrast agents such as OMNISCAN might impair the visualization of lesions which are seen on the non-contrast MRI. This may be due to effects of the paramagnetic contrast agent, or imaging parameters. Exercise caution when OMNISCAN MRI scans are interpreted in the absence of a companion non-contrast MRI.

5.6 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. In patients with normal renal function, this effect lasts for 12-24 hours. In patients with decreased renal function, the interference with calcium measurements is expected to last during the prolonged elimination of OMNISCAN. After patients receive OMNISCAN, careful attention should be used in selecting the type of method used to measure calcium.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Nephrogenic systemic fibrosis [*see Warnings and Precautions (5.2)*]
- Hypersensitivity reactions [*see Warnings and Precautions (5.3)*]

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

6.1 Clinical Studies Experience (Adults)

In clinical studies 1160 patients were exposed to OMNISCAN. The most frequent adverse reactions were nausea, headache, and dizziness that occurred in 3% or less of the patients.

The following adverse reactions occurred in 1% or less of 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), fever, hot flushes, rigors, fatigue, malaise, pain, syncope.

Cardiovascular Disorders: Cardiac failure, rare arrhythmia and myocardial infarction resulting in death in patients with ischemic heart disease, flushing, chest pain, deep thrombophlebitis.

Central and Peripheral Nervous System Disorders: Convulsions including grand mal, ataxia, abnormal coordination, paresthesia, tremor, aggravated multiple sclerosis (characterized by sensory and motor disturbances), aggravated migraine.

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

Hearing and Vestibular Disorders: Tinnitus.

Liver and Biliary System Disorders: Abnormal hepatic function.

Musculoskeletal System Disorders: Arthralgia, myalgia.

Respiratory System Disorders: Rhinitis, dyspnea.

Skin and Appendage Disorders: Pruritus, rash, erythematous rash, sweating increased, urticaria.

Special Senses, Other Disorders: Taste loss, taste perversion.

Urinary System Disorders: Acute reversible renal failure.

Vision Disorders: Abnormal vision.

6.2 Clinical Studies Experience (Pediatrics)

In the 97 pediatric patients in CNS studies with OMNISCAN [*see Clinical Studies (14.1)*] and the 144 pediatric patients in published literature, the adverse reactions were similar to those reported in adults.

6.3 Postmarketing Experience

Because postmarketing 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 drug exposure.

The following adverse reactions have been identified during the postmarketing use of OMNISCAN:

Nervous System Disorders: Inadvertent intrathecal use causes seizures, coma, paresthesia, paresis.

General Disorders: Nephrogenic Systemic Fibrosis (NSF) [*see Warnings and Precautions (5.2)*].

Renal and Urinary System Disorders: In patients with pre-existing renal insufficiency: acute renal failure, renal impairment, blood creatinine increased [*see Warnings and Precautions (5.4)*].

7 DRUG INTERACTIONS

Specific drug interaction studies have not been conducted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: OMNISCAN has been shown to have an adverse effect on embryo-fetal development in rabbits at dosages as low as 0.5 mmol/kg/day for 13 days during gestation (approximately 0.6 times the human dose based on a body surface area comparison). These adverse effects are observed as an increased incidence of flexed appendages and skeletal malformations which may be due to maternal toxicity since the body weight of the dams was 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 (1.3 times the maximum human dose based on a body surface area 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. 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.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when administering OMNISCAN to a nursing woman.

8.4 Pediatric Use

The safety and efficacy of OMNISCAN at a single dose of 0.05 to 0.1 mmol/kg have been established in pediatric patients over 2 years of age based on adequate and well controlled studies of OMNISCAN in adults, a pediatric CNS imaging study, and safety data in the scientific literature. However, the safety and efficacy of doses greater than 0.1 mmol/kg and of repeated doses have not been studied in pediatric patients.

Pharmacokinetics of OMNISCAN have not been studied in pediatrics. The glomerular filtration rate of neonates and infants is much lower than that of adults. The pharmacokinetics volume of distribution is also different. Therefore, the optimal dosing regimen and imaging times in patients under 2 years of age have not been established.

8.5 Geriatric Use

In clinical studies of OMNISCAN, 243 patients were between 65 and 80 years of age while 15 were over 80. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity in the elderly cannot be ruled out. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

OMNISCAN is excreted by the kidney, and the risk of toxic reactions to OMNISCAN is greater in patients with impaired renal function [*see Warnings and Precautions (5.2, 5.4)*]. Because elderly patients are more likely to have decreased renal function, select dose carefully and assess eGFR by laboratory testing before OMNISCAN use.

8.6 Renal/Hepatic Impairment

Dose adjustments in renal or hepatic impairment have not been studied. Caution should be exercised in patients with impaired renal insufficiency [*see Warnings and Precautions (5.2, 5.4)*].

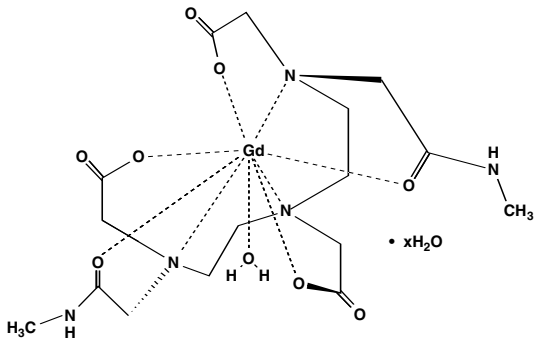
10 OVERDOSAGE

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). OMNISCAN is dialyzable.

11 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 administered by intravenous injection.

OMNISCAN is provided as a sterile, clear, colorless to slightly yellow, aqueous solution in a Pharmacy Bulk Package. A Pharmacy Bulk Package is used to dispense multiple single doses, utilizing a suitable transfer device. Each 1 mL contains 287 mg gadodiamide and 12 mg caldiamide sodium in 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-[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, with a molecular weight of 573.66 (anhydrous), an empirical formula of $C_{16}H_{28}GdN_5O_9 \bullet xH_2O$, 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
	@ 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.

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

In magnetic resonance imaging, visualization of normal and pathologic 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). 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 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. 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). 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. There is no detectable biotransformation or decomposition of gadodiamide.

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

13 NONCLINICAL TOXICOLOGY

13.1 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: *in vitro* bacterial reverse mutation assay, *in vitro* Chinese Hamster Ovary (CHO)/Hypoxanthine Guanine Phosphoribosyl Transferase (HGPT) forward mutation assay, *in vitro* CHO chromosome aberration assay, and the *in vivo* mouse micronucleus assay at intravenous doses of 27 mmol/kg (approximately 7 times the maximum human dose based on a body surface area comparison). Impairment of male or female fertility was not observed in rats after intravenous administration three times per week at the maximum dose tested of 1.0 mmol/kg (approximately 0.5 times the maximum human dose based on a body surface area comparison).

14 CLINICAL STUDIES

14.1 CNS (Central Nervous System)

OMNISCAN (0.1 mmol/kg) contrast enhancement in CNS MRI was evident in a study of 439 adults. In a study of sequential dosing, 57 adults received OMNISCAN 0.1 mmol/kg followed by 0.2 mmol/kg within 20 minutes (for cumulative dose of 0.3 mmol/kg). The MRIs were compared blindly. In 54/56 (96%) patients, OMNISCAN contrast enhancement was evident with both the 0.1 mmol/kg and cumulative 0.3 mmol/kg OMNISCAN doses relative to non-contrast MRI.

In comparison to the non-contrast MRI, increased numbers of brain and spine lesions were noted in 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 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 as a single 0.1 mmol/kg dose was evaluated in 97 pediatric patients with a mean age of 8.9 (2-18) years referred for CNS MRI. Postcontrast MRI provided added diagnostic information, diagnostic confidence, and new patient management information in 76%, 67%, and 52%, respectively, of pediatrics.

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

OMNISCAN was evaluated in a controlled trial of 276 patients referred for body MRI. These patients had a mean age of 57 (9-88) years. Patients received 0.1 mmol/kg OMNISCAN for imaging the thorax (noncardiac), abdomen, and pelvic organs, or a dose of 0.05 mmol/kg for imaging the kidney. Pre- and post-OMNISCAN images were evaluated blindly for the degree of diagnostic value 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.

In a dose ranging study 258 patients referred for body MRI received OMNISCAN 0.025, 0.05, 0.1 mmol/kg. The lowest effective dose of OMNISCAN for the kidney was 0.05 mmol/kg.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

100 mL in *+PLUS*PAK™ (polymer bottle), boxes of 10 Pharmacy Bulk Packages (NDC 0407-0690-70)

SPECIAL HANDLING AND STORAGE FOR POLYMER BOTTLES.

DO NOT USE IF TAMPER-EVIDENT RING IS BROKEN OR MISSING.

Protect polymer bottles of OMNISCAN from strong daylight and direct exposure to sunlight. **Do not freeze.** Do not use if the product is inadvertently frozen.

Store OMNISCAN at controlled room temperature 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP].

17 PATIENT COUNSELING INFORMATION

Patients receiving OMNISCAN should be instructed to inform their physician if they:

- are pregnant or breast feeding, or
- have a history of renal and/or liver disease, convulsions, asthma or allergic respiratory disorders, or recent administration of gadolinium-based contrast.

GBCAs increase the risk for NSF among patients with impaired elimination of the drugs. To counsel patients at risk for NSF:

- Describe the clinical manifestations of NSF
- Describe procedures to screen for the detection of renal impairment

Instruct the patients to contact their physician if they develop signs or symptoms of NSF following OMNISCAN administration such as burning, itching, swelling, scaling, hardening and tightening of the skin; red or dark patches on the skin; stiffness in joints with trouble moving, bending or straightening the arms, hands, legs or feet; pain deep in the hip bones or ribs; or muscle weakness.

GE Healthcare

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