GE Healthcare
Pharmaceutical
Diagnostics

Annotated Prescribing Information

Clariscan™

(gadoterate meglumine) injection for intravenous use

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Table of Contents

Learning Objectives

After completing this module, you will be able to demonstrate complete comprehension of the Prescribing Information for Clariscan by understanding:

- The indications, contraindications, and warnings and precautions associated with use of Clariscan
- The proper dosage and administration of Clariscan for intravenous use
- The structure and characteristics of Clariscan, its mechanism of action, and non-clinical toxicology data
- The safety and efficacy of Clariscan, as demonstrated in clinical trials with intravenous administration
- Key topics related to use of Clariscan, including use in specific populations and patient counseling information

Introduction

As a GE Healthcare sales professional, you must demonstrate a thorough understanding of information included in the Prescribing Information (PI) for Clariscan when discussing Clariscan with clinicians.

Therefore, this annotated PI contains important information regarding the initial U.S. Food & Drug Administration (FDA) approval of Clariscan for intravenous use. This e-zine will guide you through the specific sections of the PI for Clariscan and provide some additional context to support the information.

According to the Physician Labeling Rule (PLR), drug labels must include three components: (1) Highlights of Prescribing Information, (2) Table of Contents and (3) Full Prescribing Information. The information included in any PI is ordered in such a way as to present information deemed to be of greatest importance to a practicing clinician first. "Highlights" therefore concisely overviews information from Full Prescribing Information that physicians would most commonly reference and consider important; this section also indicates where additional details may be found on specific topics. "Contents" lists sections and subsections of the "Full Prescribing Information", which contains details needed for safe and effective use of the drug therein described.

The first half of the Full Prescribing Information contains important information about how to properly use, dose, and administer the drug, as well as warnings, precautions, and adverse effects of which the clinician and patient should be aware. The second half contains a description of the drug, including – in addition to its mechanism of action – results from non-clinical and clinical trials, and other supportive information. If information about a topic appears in more than one section of the PI, sections are cross-referenced throughout the PI.[1, 2]

This annotated PI contains important information regarding the U.S. Food & Drug Administration (FDA) approval of Clariscan for intravenous use.[3]

Highlights

In the current Physician Labeling Rule (PLR) format, every PI begins with a Highlights section, followed by a Table of Contents, and the Full Prescribing Information. The purpose of Highlights is to provide immediate access to the information to which practitioners most commonly refer and regard as important.[1, 2] *(continues on next page)*

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

CLARISCAN™ (gadoterate meglumine) injection for intravenous use

Initial U.S. Approval: 2013

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)
See full prescribing information for complete boxed warning

- **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.**
- **The risk for NSF appears highest among patients with:**
  - **Chronic, severe kidney disease (GFR < 30 mL/min/1.73 m2), or**
  - **Acute kidney injury.**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (for example, age > 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing (5.1).**

INDICATIONS AND USAGE

Clariscan is a gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adult and pediatric patients (including term neonates) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity. (1)

DOSAGE AND ADMINISTRATION

Adult and pediatric patients: The recommended dose of Clariscan is 0.2 mL/kg (0.1 mmol/kg) body weight administered as an intravenous bolus injection at a flow rate of approximately 2 mL/second for adults and 1-2 mL/second for pediatric patients

(including term neonates). The dose is delivered by manual or power injection. (2)

DOSAGE FORMS AND STRENGTHS

Clariscan Injection 0.5 mmol/mL contains 376.9 mg/mL of gadoterate meglumine and is available in vials and pre-filled syringes. (3)

CONTRAINDICATIONS

Clinically important hypersensitivity reactions to Clariscan. (4)

WARNINGS AND PRECAUTIONS

- Nephrogenic Systemic Fibrosis has occurred in patients with impaired elimination of GBCAs. Higher than recommended dosing or repeat dosing appear to increase the risk. (5.1)
- Hypersensitivity: Anaphylactoid/anaphylactic reactions with cardiovascular, respiratory or cutaneous manifestations, ranging from mild to severe, including death, have uncommonly occurred. Monitor patients closely for need of emergency cardiorespiratory support. (5.2)
- Gadolinium is retained for months or years in brain, bone, and other organs. (5.3)

ADVERSE REACTIONS

The most frequent (≥ 0.2%) adverse reactions in clinical studies were nausea, headache, injection site pain, injection site coldness, and rash. (6.1)

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.

USE IN SPECIAL POPULATIONS

Pregnancy: Use only if imaging is essential during pregnancy and cannot be delayed. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2020

Highlights (cont'd)

Note: The numbers in parentheses after text in the Highlights section are cross-references to the main sections of the PI. The content in the Highlights section is not merely a verbatim repetition of selected material from the full PI. Rather, it is intended to provide a concise, informative summary of crucial prescribing information in an easily accessible format on the front page of the PI.[1, 2]

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Revised: 11/2020

Full Prescribing Information: Contents*

*Omitted Sections

You will notice that the Clariscan PI does not contain Sections 8.3, 9, 12.4, 12.5 and 15.

According to the PI layout that has been established by the FDA, Section 8.3 is Females and Males of Reproductive Potential, which applies to drugs that impair fertility, Section 9 is Drug Abuse and Dependence, which is reserved for substances with addiction or physical dependency potential, Sections 12.4 and 12.5 are Microbiology and Pharmacogenomics, respectively (both by guidance), and 15 is References, which provides an option to include additional published information important to prescribing decisions.[1,2] The FDA did not deem these sections necessary for the Clariscan PI or find adequate data to include.

In addition, if subsequent versions of the PI for Clariscan contain substantial labeling changes, these will be listed in the PI Highlights under the heading "Recent Major Changes" for a time period of one year.

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

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

Warning: Nephrogenic Systemic Fibrosis (NSF)

Note that the Boxed Warning appears with the Contents section title, and the asterisk indicates that sections omitted from full prescribing information are not listed in the table of contents.[1, 2]

Clariscan carries a Boxed Warning on nephrogenic systemic fibrosis (NSF) that has been reported in association with gadolinium-based contrast agents (GBCAs). This Boxed Warning is a class label for all GBCAs, with slightly different language required for macrocyclic vs. linear agents (see Section 5.3 for linear and macrocyclic GBCA definitions). Linear agents (such as Omniscan) have the same class language as Clariscan (a macrocyclic agent), with an additional contraindication – namely, do not administer Omniscan to patients with (1) chronic, severe kidney disease (GFR <30 mL/min/1.73m^2) or (2) acute kidney injury. This section cross-references Warnings and Precautions (Section 5).

According to the FDA, a boxed warning is used to alert prescribers of the potential scenarios bulleted below. "Contraindications" and "Warnings and Precautions" sections are often cross-referenced within the Boxed Warning and provide additional details.4

"There is an adverse reaction so serious in proportion to the potential benefit from the drug (eg, a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug"

OR

"There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (eg, patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation)"

OR

FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted (eg, under 21 CFR 314.520 and 601.42 "Approval with restrictions to assure safe use" or under 505-1(f)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) "Risk Evaluation and Mitigation Strategies" Elements to assure safe use).

FULL PRESCRIBING INFORMATION

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (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.

- **The risk for NSF appears highest among patients with:**
  - **Chronic, severe kidney disease (GFR < 30 mL/min/1.73m^2), or**
  - **Acute kidney injury.**
- **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, diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing (5.1).**
- **For patients at highest risk for NSF, do not exceed the recommended Clariscan dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration [*see Warnings and Precautions (5.1)*].**

1 Indications and Usage

Generic Clariscan gained its US FDA approval in 2019.[3]

Magnetic resonance imaging (MRI) uses a magnet to align and radiofrequency current to stimulate protons, with sensors detecting energy release as protons realign with the magnetic field when current stops. There is no radiation exposure with this imaging technology, but MRI cannot be utilized for patients with certain metal implants.[5]

Contrast media may enhance visualization of grey and white matter in brain and spinal cord, as well as fluid (cerebrospinal fluid), air, bone and membranes. Grey matter consists of nerve cell bodies, synapses (junctions between nerve cells), and dendrites (short extensions of nerve cells that receive signals from other nerve cells) and non-myelinated axons. Axons are long extensions of nerve cells that transmit signals to other nerve cells. White matter consists of primarily myelinated axons (myelin is primarily lipid-comprised).[6, 7]

The blood-brain barrier (BBB) allows the vessels supplying the central nervous system (CNS) to regulate movement of ions, molecules and cells between neural tissue (nerve and glial cells comprising the central – brain and spinal cord - and blood. The BBB protects the brain and spinal cord from toxins and pathogens, but it may also restrict delivery of certain therapeutics. Disruptions in the BBB may reflect pathology in neurologic disease (eg, multiple sclerosis), acute injury (stroke, traumatic brain or spinal cord injury) or malignancies.[7,8]

Clariscan is a gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adult and pediatric patients (including term neonates) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.[9]

A **neonate** is a newborn from birth through 28 days after birth.[10] Full-term pregnancy is now defined as 39 weeks through 40 weeks 6 days gestation.[11]

1 INDICATIONS AND USAGE

Clariscan is a gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adult and pediatric patients (including term neonates) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.

2 Dosage and Administration

2.1 Dosing Guidelines

The Dosage and Administration section of the PI includes not only dosing information specific to patient weight (in kilograms), but also information on injection flow rates to be employed for both adult and pediatric patients (including term neonates). Table 1 provides a reference for weight-adjusted dose volumes in both pound and kilogram weight units, for easy conversion of body weight from pounds to kilograms to inform dosing.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Guidelines

For adult and pediatric patients (including term neonates), the recommended dose of Clariscan is 0.2 mL/kg (0.1 mmol/kg) body weight administered as an intravenous bolus injection, manually or by power injector, at a flow rate of approximately 2 mL/second for adults and 1-2 mL/second for pediatric patients. Table 1 provides weight-adjusted dose volumes.

Table 1: Volumes of Clariscan Injection by Body Weight

Body Weight		Volume
Pounds (lb)	Kilograms (kg)	Milliliters (mL)
5.5	2.5	0.5
2.5	5	1
0.5	10	2
11	20	4
5	30	6
1	40	8
110	50	10
132	60	12
154	70	14
176	80	16
198	90	18
220	100	20
242	110	22
264	120	24
286	130	26
308	140	28
330	150	30

To ensure complete injection of Clariscan the injection may be followed by normal saline flush. Contrast MRI can begin immediately following Clariscan injection.

Dosage and Administration (cont'd)

2.2 Drug Handling

This section details additional information on Clariscan handling and its preparation for injection.

"**Aseptic**" refers to techniques that are employed to prevent contamination with pathogens.[12]

2.2 Drug Handling

- Visually inspect Clariscan for particulate matter prior to administration. Do not use the solution if particulate matter is present or if the container appears damaged. Clariscan should be a clear, colorless to yellow solution.
- Do not mix with other drugs or parenteral nutrition.
- Discard any unused portions of the drug.

Directions for Use of the Clariscan (gadoterate meglumine) Injection:

Glass vial:
Aseptically draw up the contrast medium into a disposable syringe and use immediately.

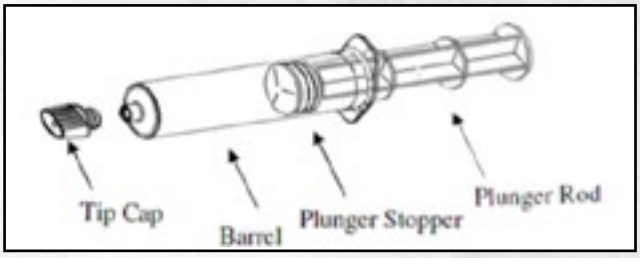
Plastic pre-filled syringe:
1) Holding the syringe vertically so the tip cap is pointed upward, aseptically remove the tip cap from the tip of the syringe and attach either a sterile, disposable needle or compatible needleless luer lock tubing set using a push- twist action. At this point, the tubing set is not attached to a patient's intravenous connection.

- If using a needleless luer lock tubing set, check the connection between the syringe and the tubing as the fluid flows. Ensure that the connection is successful before administration of Clariscan Injection.
- If using a needle, hold the syringe vertically and push plunger forward until all of the air is evacuated and fluid either appears at the tip of the needle or the tubing is filled. Following the usual venous blood aspiration procedure, complete the Clariscan injection.

2) To ensure complete delivery of the contrast medium, the injection may be followed by a normal saline flush.

3) Properly dispose of the syringe and any other materials used.

Plastic pre-filled syringe:



3 Dosage Forms and Strengths

3 DOSAGE FORMS AND STRENGTHS

Clariscan 0.5 mmol/mL is a sterile, clear, colorless to yellow, aqueous solution for intravenous injection containing 376.9 mg/mL gadoterate meglumine and is available in vials and pre-filled syringes.

4 Contraindications

According to the FDA, a drug is contraindicated only in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit.[4] This section cross-references Section 5.2 in "Warnings and Precautions".

Clinically important hypersensitivity reactions may include anaphylactic or nonimmunologic anaphylactic (ie, anaphylactoid) responses.[13] These are discussed further in Section 5.2.

4 CONTRAINDICATIONS

History of clinically important hypersensitivity reactions to Clariscan [*see Warnings and Precautions (5.2)*].

5 Warnings and Precautions

According to FDA, this section of the PI is intended to identify and describe a discrete set of adverse reactions and other potential safety hazards that are serious or otherwise clinically significant because they have implications for prescribing decisions or for patient management.[4]

As described in more detail within the PI and the following pages, there are five key warnings and precautions associated with Clariscan use. These include:

1) Nephrogenic systemic fibrosis
2) Hypersensitivity reactions
3) Gadolinium retention
4) Acute kidney injury
5) Extravasation and injection site reactions

This section cross-references "Dosage and Administration", "Adverse Reactions", "Clinical Pharmacology" and "Nonclinical Toxicology" sections.

Warnings and Precautions (cont'd)

Nephrogenic systemic fibrosis (NSF) is a rare disorder that can occur in patients with reduced kidney function after administration of gadolinium-based contrast agents (GBCA). **Fibrosis** is essentially an over-exuberant healing response to inflammation or injury that results in thickened or scarred tissue. NSF can involve skin, underlying tissues and organs, or skeletal muscle, and the disorder may develop over weeks to months post-GBCA exposure.[14]

Gadolinium is a heavy metal that, for use in contrast agents, is bound to carrier molecules to facilitate passage through the body, from which it is ultimately eliminated via renal excretion.[15]

High blood pressure is also known as **hypertension**.[16]

Serum creatinine and estimated glomerular filtration rate (eGFR) may be used to assess kidney function. **Creatinine** is a waste product of cellular metabolism that is removed by healthy kidneys. Normal adult levels range from 0.84-1.21 mg/dL and vary between men and women and with age. High creatinine levels are indicative of kidney dysfunction.[17] eGFR is derived based on the amount of blood creatine. Normal eGFR values are ≥90 mL/min/1.73 m^2; the lower the level the greater the degree of renal impairment.[18]

5 WARNINGS AND PRECAUTIONS

5.1 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 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.

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 Clariscan administration to GE Healthcare at (1-800-654-0118) or FDA at (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.

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. For patients at highest risk for NSF, do not exceed the recommended Clariscan dose and allow a sufficient period of time for elimination of the drug prior to re-administration. For patients receiving hemodialysis, physicians may consider the prompt initiation of hemodialysis following the administration of a GBCA in order to enhance the contrast agent's elimination. The usefulness of hemodialysis in the prevention of NSF is unknown [*see Dosage and Administration (2) and Clinical Pharmacology (12)*].

Warnings and Precautions (cont'd)

Anaphylactic and anaphylactoid reactions are misdirected immune responses to a substance that the body perceives as foreign.[13, 19]

The term "**cutaneous**" refers to skin.[20]

5.2 Hypersensitivity Reactions

Anaphylactic and anaphylactoid reactions have been reported with gadoterate meglumine, involving cardiovascular, respiratory, and/or cutaneous manifestations. Some patients experienced circulatory collapse and died. In most cases, initial symptoms occurred within minutes of gadoterate meglumine administration and resolved with prompt emergency treatment [*see Adverse Reactions (6)*].

- Before Clariscan administration, assess all patients for any history of a reaction to contrast media, bronchial asthma and/or allergic disorders. These patients may have an increased risk for a hypersensitivity reaction to Clariscan.
- Administer Clariscan only in situations where trained personnel and therapies are promptly available for the treatment of hypersensitivity reactions, including personnel trained in resuscitation.
- During and following Clariscan administration, observe patients for signs and symptoms of hypersensitivity reactions.

Warnings and Precautions (cont'd)

GBCAs may be classified as linear or macrocyclic in structure. Linear chelators wrap or coil around the gadolinium in an open chain structure, while macrocyclic ligands essentially "cage" the ion.[21] Linear and macrocyclic GBCAs are depicted below.

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and
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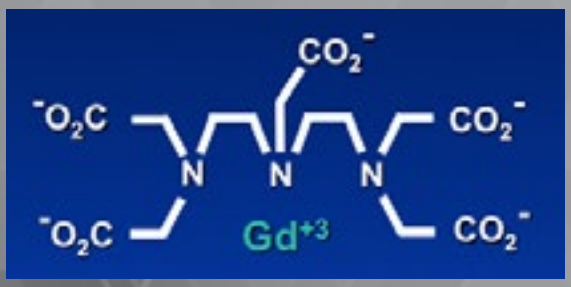
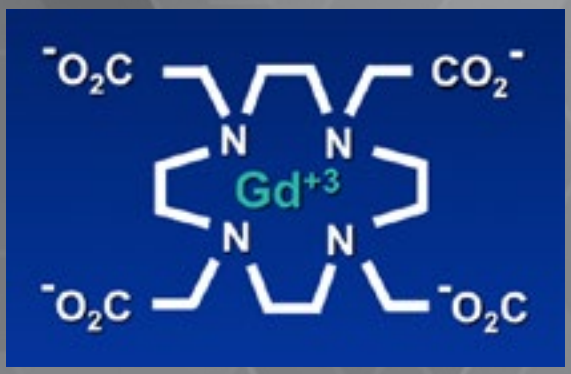




5.3 Gadolinium Retention

Gadolinium is retained for months or years in several organs. The highest concentrations (nanomoles per gram of tissue) have been identified in the bone, followed by other organs (e.g. brain, skin, kidney, liver and spleen). The duration of retention also varies by tissue and is longest in bone. Linear GBCAs cause more retention than macrocyclic GBCAs. At equivalent doses, gadolinium retention varies among the linear agents with Omniscan (gadodiamide) and Optimark (gadoversetamide) causing greater retention than other linear agents [Eovist (gadoxetate disodium), Magnevist (gadopentetate dimeglumine), MultiHance (gadobenate dimeglumine)]. Retention is lowest and similar among the macrocyclic GBCAs [Clariscan (gadoterate meglumine), Dotarem (gadoterate meglumine), Gadavist (gadobutrol), ProHance (gadoteridol)].

Consequences of gadolinium retention in the brain have not been established. Pathologic and clinical consequences of GBCA administration and retention in skin and other organs have been established in patients with impaired renal function [*see Warnings and Precautions (5.1)*]. There are rare reports of pathologic skin changes in patients with normal renal function. Adverse events involving multiple organ systems have been reported in patients with normal renal function without an established causal link to gadolinium retention [*see Adverse Reactions (6.2)*].

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 pediatric patients, and patients with inflammatory conditions. Consider the retention characteristics of the agent when choosing a GBCA for these patients. Minimize repetitive GBCA imaging studies, particularly closely spaced studies when possible.

Warnings and Precautions (cont'd)

Acute kidney injury (AKI) is sudden-onset (hours to days) organ failure or damage. AKI may be caused by many things, including decreased blood flow to the kidney, blockage of urine flow, or direct damage from disease or infection. AKI may be associated with symptoms (eg scant urine production, swelling, fatigue, shortness of breath, chest pain/pressure, confusion or even seizures or coma) or may be symptomless and only detectible through medical testing. Contrast agents may also lead to an acute (over 48-72 hours) decline in kidney function. This condition, termed **contrast induced nephropathy** or CIN, occurs rarely – although risk for CIN is higher in individuals with cardiometabolic disease and chronic kidney disease.[22, 23]

Extravasation occurs when an intravascularly-injected agent unintentionally leaks from the vessel into surrounding tissues.[24]

5.4 Acute Kidney Injury

In patients with chronically reduced renal function, acute kidney injury requiring dialysis has occurred with the use of GBCAs. The risk of acute kidney injury may increase with increasing dose of the contrast agent; administer the lowest dose necessary for adequate imaging. Screen all patients for renal impairment by obtaining a history and/or laboratory tests. Consider follow-up renal function assessments for patients with a history of renal dysfunction.

5.5 Extravasation and Injection Site Reactions

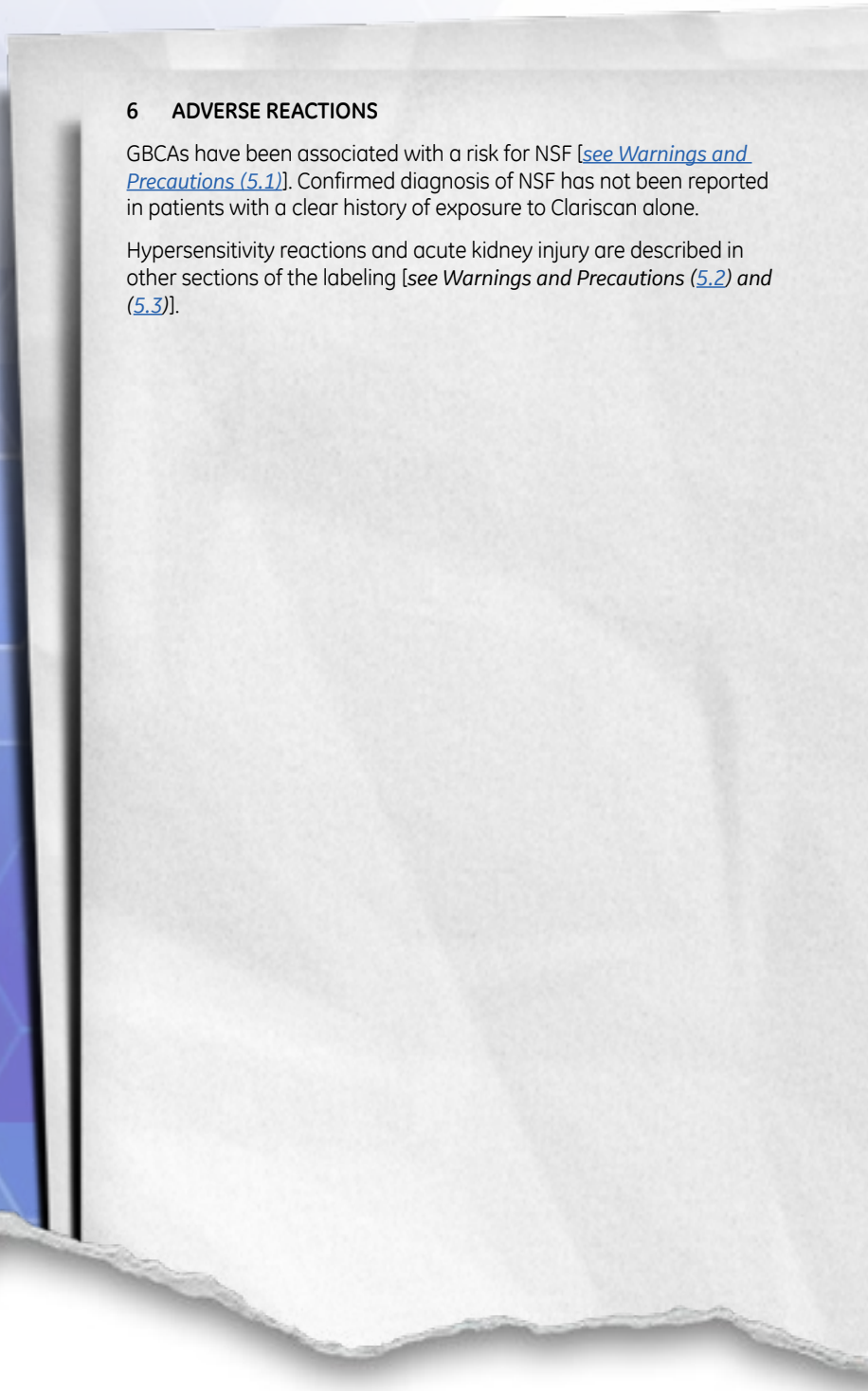
Ensure catheter and venous patency before the injection of Clariscan. Extravasation into tissues during Clariscan administration may result in tissue irritation [*see Nonclinical Toxicology (13.2)*].

6 Adverse Reactions

According to the FDA, the Adverse Reactions section should include only information that would be useful to health care practitioners making treatment decisions and monitoring and advising patients, with separate lists required for adverse reactions identified in clinical trials and for those reported in post-marketing experience.[25]

This section notes three clinically significant adverse reactions and cross-references the "Warnings and Precautions" section of the PI for additional detail:

- **NSF (5.1)**
- **Hypersensitivity Reactions (5.2)**
- **Acute Kidney Injury (5.3)**



6 ADVERSE REACTIONS

GBCAs have been associated with a risk for NSF [*see Warnings and Precautions (5.1)*]. Confirmed diagnosis of NSF has not been reported in patients with a clear history of exposure to Clariscan alone.

Hypersensitivity reactions and acute kidney injury are described in other sections of the labeling [*see Warnings and Precautions (5.2) and (5.3)*].

Adverse Reactions (cont'd)

6.1 Clinical Studies Experience

A **transient reaction** is one that is short-lived and impermanent.[26]

Somnolence is sleepiness or drowsiness.[27]

Another term for low blood pressure is **hypotension**.[28]

Asthenia is weakness or loss of energy/ strength.[29]

6.1 Clinical Studies Experience

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

The data described below reflect gadoterate meglumine exposure in 2867 patients, representing 2682 adults and 185 pediatric patients. Overall, 55% of the patients were men. In clinical trials where ethnicity was recorded, the ethnic distribution was 81% Caucasian, 11% Asian, 4% Black, and 4% others. The average age was 53 years (range from < 1 week to 97 years).

Overall, 4% of patients reported at least one adverse reaction, primarily occurring immediately or within 24 hours following gadoterate meglumine administration. Most adverse reactions were mild or moderate in severity and transient in nature.

Table 2 lists adverse reactions that occurred in ≥ 0.2% patients who received gadoterate meglumine.

Table 2: Adverse Reactions in Clinical Trials

Reaction	Rate (%) n= 2867
Nausea	0.6%
Headache	0.4%
Injection Site Pain	0.4%
Injection Site Coldness	0.2%
Rash	0.2%

Adverse reactions that occurred with a frequency < 0.2% in patients who received gadoterate meglumine include: feeling cold, feeling hot, burning sensation, somnolence, pain, dizziness, dysgeusia, blood creatinine increased, hypotension, hypertension, asthenia, fatigue, injection site reactions (inflammation, extravasation, pruritus, swelling, warmth), paraesthesia, pruritus, laryngeal discomfort, pain in extremity, vomiting, anxiety and palpitations.

Adverse Reactions in Pediatric Patients
During clinical trials, 185 pediatric patients (52 aged < 24 months, 33 aged 2 – 5 years, 57 aged 6 – 11 years and 43 aged 12 – 17 years) received gadoterate meglumine. Overall, 7 pediatric patients (3.8%) reported at least one adverse reaction following gadoterate meglumine administration. The most frequently reported adverse reaction was headache (1.1%). Most adverse events were mild in severity and transient in nature.

Adverse Reactions (cont'd)

An **arrhythmia** refers to an irregular heartbeat; bradycardia and tachycardia are abnormally slow and fast heart rates, respectively.[30]

Cardiac (heart) and respiratory (breathing) arrest are terms that describe abrupt loss of heart and lung function.[31, 32]

Cyanosis refers to bluish coloration of skin and mucosa due to insufficient blood oxygenation.[33]

Edema refers to soft tissue swelling due to excess fluid accumulation.[34] Angioedema is swelling under the skin surface.[35]

Bronchospasm is the sudden involuntary contraction of airways and laryngospasm is a sudden seize-up of vocal cords that blocks airflow into the lungs.[36, 37]

Conjunctivitis (also known as pink eye) is an inflammation or infection of the conjunctiva, the clear membrane lining eyelids and covering the white part of the eye.[38]

Ocular hyperemia describes redness of the eye.[39]

Lacrimation is the shedding of tears.[40]

Hyperhydrosis is excessive sweating.[41]

Urticaria is the medical terms for hives.[42]

Syncope (fainting) is a transient loss of consciousness that may be mediated neurally or due to insufficient blood flow to the brain.[43] Presyncope is a feeling of impending fainting without loss of consciousness.[44]

Parosmia is distorted perception of the sense of smell.[45]

A **tremor** is an abnormal repetitive shaking movement.[46]

Salivary hypersecretion, also termed **sialorrhea**, **ptyalism** or **hypersalivation**, describes a condition in which a person has excess saliva in their mouth.[47]

Phlebitis refers to vein inflammation.[48]

6.2 Postmarketing Experience

The following additional adverse reactions have been identified during postmarketing use of gadoterate meglumine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Table 3: Adverse Reactions in the Postmarketing Experience

System Organ Class	Adverse Reaction
Cardiac Disorders	bradycardia, tachycardia, arrhythmia
Immune System Disorders	hypersensitivity / anaphylactoid reactions including cardiac arrest, respiratory arrest, cyanosis, pharyngeal edema, laryngospasm, bronchospasm, angioedema, conjunctivitis, ocular hyperemia, eyelid edema, lacrimation increased, hyperhidrosis, urticaria
Nervous System Disorders	coma, convulsion, syncope, presyncope, parosmia, tremor
Musculoskeletal and Connective Tissue Disorders	muscle contracture, muscle weakness
Gastrointestinal Disorders	diarrhea, salivary hypersecretion
General Disorders and Administration Site Conditions	malaise, fever Adverse events with variable onset and duration have been reported after GBCA administration *[see Warnings and Precautions (5.3)]*. These include fatigue, asthenia, pain syndromes, and heterogeneous clusters of symptoms in the neurological, cutaneous, and musculoskeletal systems.
Skin and Subcutaneous Tissue Disorders	NSF, in patients whose reports were confounded by the receipt of other GBCAs or in situations where receipt of other GBCAs could not be ruled out. No unconfounded cases of NSF have been reported with gadoterate meglumine. Gadolinium-associated plaques.
Vascular Disorders	superficial phlebitis

7 Drug Interactions

This section of the PI describes known drug-drug interactions. While specific drug interaction studies have not been conducted, Clariscan does not interfere with plasma serum or calcium measurement.

Calcium is a mineral that is important for many body functions and is predominantly stored in bone, with only small amounts in the bloodstream. Normal blood calcium levels range between 2.2-2.7 mmol/L, with levels outside that range termed hypercalcemia (high) and hypocalcemia (low). Physicians may measure levels of calcium in blood as part of a routine health exam or when a disease that can affect calcium levels is suspected.[49, 50]

Colorimetric analysis refers to the identification or quantification of a substance based on color/ amount of light that it absorbs.[51]

7 DRUG INTERACTIONS

Gadoterate does not interfere with serum and plasma calcium measurements determined by colorimetric assays. Specific drug interaction studies with gadoterate meglumine have not been conducted.

8 Use in Specific Populations

This section of the Clariscan PI provides information on use in specific populations, including pregnant and lactating females, children and elderly patients, as well as individuals with renal impairment. "Warnings and Precautions", "Clinical Pharmacology", "Clinical Studies", "Adverse Reactions", "Dosage and Administration" and "Pharmacokinetics" sections are cross-referenced.

Organogenesis refers to the processes by which cell masses are transformed into organs. Completion of organogenesis marks the transition between embryonic and fetal development.[52]

A **retrospective cohort study** examines existing bodies of data gathered on a group of people with shared characteristic (a cohort) to try to identify risk factors associated with specific and known outcomes.[53, 54]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

GBCAs cross the human placenta and result in fetal exposure and gadolinium retention. The human data on the association between GBCAs and adverse fetal outcomes are limited and inconclusive (*see Data*). In animal reproduction studies, there were no adverse developmental effects observed in rats or rabbits with intravenous administration of gadoterate meglumine during organogenesis at doses up to 16 and 10 times, respectively, the recommended human dose (*see Data*). Because of the potential risks of gadolinium to the fetus, use Clariscan only if imaging is essential during pregnancy and cannot be delayed.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20% respectively.

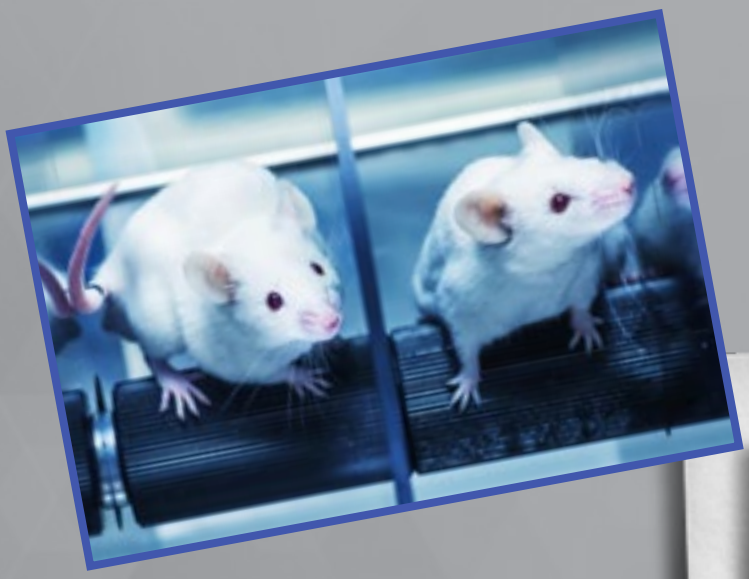
Data

Human Data

Contrast enhancement is visualized in the placenta and fetal tissues after maternal GBCA administration.

Cohort studies and case reports on exposure to GBCAs during pregnancy have not reported a clear association between GBCAs and adverse effects in the exposed neonates. However, a retrospective cohort study, comparing pregnant women who had a GBCA MRI to pregnant women who did not have an MRI, reported a higher occurrence of stillbirths and neonatal deaths in the group receiving GBCA MRI. Limitations of this study include a lack of comparison with non-contrast MRI and lack of information about the material indication for MRI. Overall, these data preclude a reliable evaluation of the potential risk of adverse fetal outcomes with the use of GBCAs in pregnancy.

Use in Specific Populations (cont'd)



Animal Data

Gadolinium Retention

GBCAs administered to pregnant non-human primates (0.1 mmol/kg on gestational days 85 and 135) result in measurable gadolinium concentration in the offspring in bone, brain, skin, liver, kidney, and spleen for at least 7 months. GBCAs administered to pregnant mice (2 m mol/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.

Reproductive Toxicology

Gadoterate meglumine was administered in intravenous doses of 0, 2, 4 and 10 mmol/kg/day [3, 7 and 16 times the recommended human dose (RHD) based on body surface area (BSA)] to female rats for 14 days before mating, throughout the mating period and until gestation day (GD) 17. Pregnant rabbits were administered gadoterate meglumine in intravenous doses of 0, 1, 3 and 7 mmol/kg/day (3, 10 and 23 times the RHD based on BSA) from GD6 to GD19. No effects on embryo-fetal development were observed at doses up to 10 mmol/kg/day in rats and 3 mmol/kg/day in rabbits. Maternal toxicity was observed in rats at 10 mmol/kg/day and in rabbits at 7 mmol/kg/day. This maternal toxicity was characterized in rats by a slightly lower litter size and gravid uterus weight compared to the control group, and in rabbits by a reduction in body weight and food consumption.

Use in Specific Populations (cont'd)

8.2 Lactation

Risk Summary

There are no data on the presence of gadoterate in human milk, the effects on the breastfed infant, or the effects on milk production. However, published lactation data on other GBCAs indicate that 0.01 to 0.04% of the maternal gadolinium dose is excreted in breast milk. Additionally, there is limited GBCA gastrointestinal absorption in the breast-fed infant. Gadoterate is present in goat milk (*see Data*). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Clariscan and any potential adverse effects on the breastfed infant from Clariscan or from the underlying maternal condition.

Data

Nonclinical data demonstrate that gadoterate is detected in goat milk in amounts < 0.1% of the dose intravenously administered. Furthermore, in rats, absorption of gadoterate via the gastrointestinal tract is poor (1.2% of the administered dose was absorbed and eliminated in urine).

8.4 Pediatric Use

The safety and efficacy of gadoterate meglumine at a single dose of 0.1 mmol/kg have been established in pediatric patients from birth (term neonates ≥ 37 weeks gestational age) to 17 years of age based on clinical data in 133 pediatric patients 2 years of age and older, and clinical data in 52 pediatric patients birth to less than 2 years of age that supported extrapolation from adult data *[see Clinical Studies (14)]*. Adverse reactions in pediatric patients were similar to those reported in adults [*see Adverse Reactions (6.1)*]. No dosage adjustment according to age is necessary in pediatric patients [*See Dosage and Administration (2.1), Pharmacokinetics (12.3)*]. The safety of gadoterate meglumine has not been established in preterm neonates.

No cases of NSF associated with gadoterate meglumine or any other GBCA have been identified in pediatric patients age 6 years and younger [*see Warnings and Precautions (5.1)*]. Normal estimated GFR (eGFR) is approximately 30 mL/minute/1.73m2 at birth and increases to adult values by 2 years of age.

Juvenile Animal Data

Single and repeat-dose toxicity studies in neonatal and juvenile rats did not reveal findings suggestive of a specific risk for use in pediatric patients including term neonates and infants.

Use in Specific Populations (cont'd)

Concomitant disease refers to a simultaneously-occurring condition.[55]

Hemodialysis removes unwanted substances from the bloodstream; the procedure involves circulation of the blood through an external filter or dialyzer; in the case of renal failure, dialysis serves the function of an external kidney.[56] Hemodialysis can also be employed to remove GBCAs.

8.5 Geriatric Use

In clinical studies of gadoterate meglumine, 900 patients were 65 years of age and over, and 304 patients were 75 years of age and over. No overall differences in safety or efficacy were observed between these subjects and younger subjects. In general, use of Clariscan in elderly patients should be cautious, reflecting the greater frequency of impaired renal function and concomitant disease or other drug therapy. No age-related dosage adjustment is necessary.

8.6 Renal Impairment

No Clariscan dosage adjustment is recommended for patients with renal impairment. Gadoterate meglumine can be removed from the body by hemodialysis [*see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)*].

10 Overdosage

This section cross-references "Clinical Pharmacology".

10 OVERDOSAGE

Clariscan administered to healthy volunteers and to adult patients at cumulative doses up to 0.3 mmol/kg was tolerated in a manner similar to lower doses. Adverse reactions to overdosage with gadoterate meglumine have not been reported. Gadoterate meglumine can be removed from the body by hemodialysis [*See Clinical Pharmacology (12.3)*].

11 Description

This section begins with a description of the contrast agent Clariscan (gadoterate meglumine) and its intended intravenous use in conjunction with magnetic resonance imaging. Chemical and structural formulas (in solution) are provided, as well as molecular weight. A physical description of the Clariscan drug formulation includes a list of all components of the aqueous solution. Physiochemical properties and thermodynamic stability constants are also provided.

As previously described (Section 5.3), Clariscan is a macrocyclic contrast agent. Macrocyclic ligands essentially "cage" the gadolinium ion.[21]

Ionic and non-ionic solutions involve compounds that do or do not dissociate into ions when dissolved in solvent, respectively. An example of an ionic solution is salt water, which is formed by dissolving the ionic compound salt (NaCl) in the solvent water; in solution, NaCl dissociates into positively-charged (cations) Na+ ions and negatively-charged (anions) Cl- ions.[57]

Paramagnetic substances, eg, ions of various metals such as gadolinium, have unpaired electrons and are attracted to magnetic fields. Because paramagnetic contrast agents generate a stronger magnetic field than water protons alone, they are utilized to enhance MRI images.[58, 59]

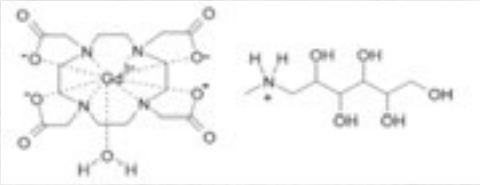
DOTA or textraxetan is a chelator that cages the Gd3+.[60, 61]

Pyrogenic is defined as something that produces or is produced by heat or fever.[62] Clariscan is non-pyrogenic, indicating that it is not associated with heat or fever.

11 DESCRIPTION

Clariscan is a paramagnetic macrocyclic ionic contrast agent administered for magnetic resonance imaging. The chemical name for gadoterate meglumine is D-glucitol, 1-deoxy-1-(methylamino)-, [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraaceto(4-)-.kappa.N1, .kappa.N4, .kappa.N7, .kappa.N10, .kappa.O1, .kappa.O4, .kappa.O7, .kappa.O10]gadolinate(1-)(1:1); it has a formula weight of 753.9 g/mol and empirical formula of $C_{23}H_{42}O_{13}N_5Gd$ (anhydrous basis).

The structural formula of gadoterate meglumine in solution is as follows:



CAS Registry No. 92943-93-6

Clariscan Injection is a sterile, nonpyrogenic, clear, colorless to yellow, aqueous solution of 0.5 mmol/mL of gadoterate meglumine. Each vial and pre-filled syringe contains 5 mmol per 10 mL, 7.5 mmol per 15 mL and 10 mmol per 20 mL. No preservative is added. Each mL of Clariscan contains 376.9 mg of gadoterate meglumine, 0.25 mg of DOTA and water for injection. Clariscan has a pH of 6.5 to 8.0.

Description (cont'd)

Contrast media may be characterized by their **osmolality,** a measure of solution concentration, expressed as number of particles per kilogram (weight measure) of solvent (units Osm/Kg).[62, 63]

Density measures the amount of mass per unit of volume, here expressed in g/cm^3.[64]

Viscosity is a measure of a fluid's resistance to flow or "thickness" that may be expressed in millipascal-second (mPa.s) units. As an example, laundry detergent is more viscous than water. Note that Clariscan viscosity decreases with increasing temperature.[65]

Solution stability of gadolinium complexes (gadolinium plus ligand) may be expressed by the **thermodynamic stability constant** (log K_{therm}) and the **conditional thermodynamic stability constant** (log K_{cond}), which describes the gadolinium-ligand equilibrium at physiologic pH (7.4).[66]

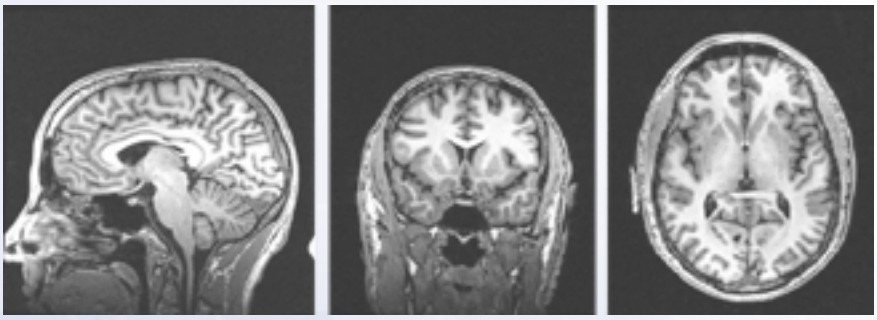
The main physiochemical properties of Clariscan are provided below:

Table 4: Physicochemical Properties

Parameter	Value
Density @ 20°C	1.1753 g/cm^3
Viscosity @ 20 °C 20°C	3.4 mPa.s
Viscosity @ 37°C	2.4 mPa.s
Osmolality	1350 mOsm/kg water

The thermodynamic stability constants for gadoterate (log K_{therm} and log K_{cond} at pH 7.4) are 25.6 and 19.3, respectively.

12 Clinical Pharmacology



http://fmri.ucsd.edu/images/T1_v3.png

12.1 Mechanism of Action

When placed in a magnetic field, paramagnetic molecules such as gadoterate develop a magnetic moment (a measure of the tendency to align with the magnetic field)[67]. This enhances relaxation rates of neighboring water protons, intensifying **tissue signal** (brightness).

MRI produces qualitative, contrast-weighted images where pixel values are relative and dependent on proton density and longitudinal (T1) and transverse (T2) relaxation times. T1 and T2 relaxation times are also termed spin-lattice and spin-spin relaxation times, respectively.[68, 69]

Note that, in T1-weighted images, cerebrospinal fluid (CSF), bone and air appear dark, while white matter (myelinated axons) looks bright.[70]

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Gadoterate is a paramagnetic molecule that develops a magnetic moment when placed in a magnetic field. The magnetic moment enhances the relaxation rates of water protons in its vicinity, leading to an increase in signal intensity (brightness) of tissues.

In magnetic resonance imaging (MRI), visualization of normal and pathological tissue depends in part on variations in the radiofrequency signal intensity that occurs with:

1) differences in proton density
2) differences of the spin-lattice or longitudinal relaxation times (T1)
3) differences in the spin-spin or transverse relaxation time (T2)

When placed in a magnetic field, gadoterate shortens the T1 and T2 relaxation times in target tissues. At recommended doses, the effect is observed with greatest sensitivity in the T1-weighted sequences.

Clinical Pharmacology (cont'd)

12.2 Pharmacodynamics and 12.3 Pharmacokinetics

According to the Merck Manual, "**pharmacodynamics** (sometimes described as what a drug does to the body) is the study of the biochemical, physiologic, and molecular effects of drugs on the body. It involves receptor binding, post-receptor effects and chemical interactions. **Pharmacokinetics** (what the body does to a drug, or the fate of a drug within the body), together with pharmacodynamics, helps to explain the relationship between dose and response – ie, the drug's effects."[71] This section cross-references "Warnings and Precautions".

Magnetic flux density is expressed in Tesla (T) units.[72]

Drug elimination half-life ($t_{1/2}$) is the time required for the amount of administered drug to decrease by half.[73]

As previously noted, disruptions in the BBB or abnormal vascularity may allow gadoterate to distribute in areas of injury or disease.[7] This facilitates detection of neoplasms (abnormal cell mass that may be malignant (cancer) or benign (not cancer)), abscess (localized collection of pus) or tissues that are infarcted (damaged or dying due to limitations in blood supply/oxygen).[74, 75, 76]

Volume of distribution (VD) describes the relationship between drug concentration and amount of drug in the body – ie, it represents the degree to which drug is distributed in body tissues vs. plasma. The higher the number, the greater the tissue distribution.[77]

Plasma protein binding refers to the degree to which drugs bind to proteins found in blood. Protein binding influences the amount of time a drug stays in the body and can affect – either enhance or decrease – drug activity.[78]

Blood cell partitioning reflects the rate and extent to which drug partitions or accumulates in red blood cells vs. plasma or serum.[79]

12.2 Pharmacodynamics

Gadoterate affects proton relaxation times and consequently the MR signal, and the contrast obtained is characterized by the relaxivity of the gadoterate molecule. The relaxivity values for gadoterate are similar across the spectrum of magnetic field strengths used in clinical MRI (0.2-1.5 T).

Disruption of the blood-brain barrier or abnormal vascularity allows distribution of gadoterate in lesions such as neoplasms, abscesses, and infarcts.

12.3 Pharmacokinetics

The pharmacokinetics of total gadolinium assessed up to 48 hours following an intravenously administered 0.1 mmol/kg dose of gadoterate meglumine in healthy adult subjects demonstrated a mean elimination half-life (reported as mean ± SD) of about 1.4 ± 0.2 hr and 2.0 ± 0.7 hr in female and male subjects, respectively. Similar pharmacokinetic profile and elimination half-life values were observed after intravenous injection of 0.1 mmol/kg of gadoterate meglumine followed 20 minutes later by a second injection of 0.2 mmol/kg (1.7 ± 0.3 hr and 1.9 ± 0.2 hr in female and male subjects, respectively).

Distribution

The volume of distribution at steady state of total gadolinium in healthy subjects is 179 ± 26 and 211 ± 35 mL/kg in female and male subjects respectively, roughly equivalent to that of extracellular water. Gadoterate does not undergo protein binding in vitro. The extent of blood cell partitioning of gadoterate is not known.

Following GBCA administration, gadolinium is present for months or years in brain, bone, skin and other organs [*see Warnings and Precautions (5.3)*].

Clinical Pharmacology (cont'd)

12.3 Pharmacokinetics (cont'd)

Elimination refers to removal of drugs from the body, either via metabolism (chemical change) or via excretion of intact or unchanged drug.[80]

Metabolism

Gadoterate is not known to be metabolized.

Elimination

Following a 0.1 mmol/kg dose of gadoterate meglumine, total gadolinium is excreted primarily in the urine with 72.9 ± 17.0% and 85.4 ± 9.7% (mean ± SD) eliminated within 48 hours, in female and male subjects, respectively. Similar values were achieved after a cumulative dose of 0.3 mmol/kg (0.1 + 0.2 mmol/kg, 20 minutes later), with 85.5 ± 13.2% and 92.0 ± 12.0% recovered in urine within 48 hrs in female and male subjects respectively.

In healthy subjects, the renal and total clearance rates of total gadolinium are comparable (1.27 ± 0.32 and 1.74 ± 0.12 mL/min/kg in females; and 1.40 ± 0.31 and 1.64 ± 0.35 mL/min/kg in males, respectively) indicating that the drug is primarily cleared through the kidneys. Within the studied dose range (0.1 to 0.3 mmol/kg), the kinetics of total gadolinium appear to be linear.

Clinical Pharmacology (cont'd)

Specific Populations

Renal Impairment

A single intravenous dose of 0.1 mmol/kg of gadoterate meglumine was administered to 8 patients (5 men and 3 women) with impaired renal function (mean serum creatinine of 498 ± 98 µmol/L in the 10-30 mL/min creatinine clearance group and 192 ± 62 µmol/L in the 30-60 mL/min creatinine clearance group). Renal impairment delayed the elimination of total gadolinium. Total clearance decreased as a function of the degree of renal impairment. The distribution volume was unaffected by the severity of renal impairment (Table 5). No changes in renal function test parameters were observed after gadoterate meglumine injection. The mean cumulative urinary excretion of total gadolinium was approximately 76.9 ± 4.5% in 48 hrs in patients with moderate renal impairment, 68.4 ± 3.5% in 72 hrs in patients with severe renal impairment and 93.3 ± 4.7% in 24 hrs for subjects with normal renal function.

Table 5: Pharmacokinetic Profile of Total Gadolinium in Normal and Renally Impaired Patients

Population	Elimination Half-life (hr)	Plasma Clearance (L/h/kg)	Distribution Volume (L/kg)
Healthy volunteers	1.6 ± 0.2	0.10 ± 0.01	0.246 ± 0.03
Patients with moderate renal impairment	5.1 ± 1.0	0.036 ± 0.007	0.236 ± 0.01
Patients with severe renal impairment	13.9 ± 1.2	0.012 ± 0.001	0.234 ± 0.01

Gadoterate was shown to be dialyzable after an IV injection of gadoterate meglumine in 10 patients with end-stage renal failure who required hemodialysis treatment. Gd serum concentration decreased over time by 88%, 93% and 97% at 0.5 hr, 1.5 hr, and 4 hrs after start of dialysis, respectively. A second and third hemodialysis session further removed Gd. After the third dialysis, Gd serum concentration decreased by 99.7%.

Clinical Pharmacology (cont'd)

Specific Populations

Pediatric Population

The pharmacokinetics of gadoterate in pediatric patients receiving gadoterate meglumine aged birth (term neonates) to 23 months, was investigated in an open label, multicenter study, using a population pharmacokinetics approach. A total of 45 subjects (22 males, 23 females) received a single intravenous dose of gadoterate meglumine 0.1 mmol/kg (0.2 mL/kg). The age ranged from less than one week to 23.8 months (mean 9.9 months) and body weight ranged from 3 to 15 kg (mean 8.1 kg). Individual level of renal maturity in the study population, as expressed by eGFR ranged between 52 and 281 mL/min/1.73 m2 and 11 patients had an eGFR below 100 mL/min/1.73 m2 (range 52 to 95 mL/min/1.73 m2).

Gadoterate concentrations obtained up to 8 hours after gadoterate meglumine administration were best fitted using a biphasic model with linear elimination from the intravascular space. The mean clearance adjusted to body weight was estimated at 0.16 ± 0.07 L/h/kg and increased with eGFR. The estimated mean elimination half-life was 1.47 ± 0.45 hr.

The body weight adjusted clearance of gadoterate after single intravenous injection of 0.1 mmol/kg of gadoterate meglumine in pediatric subjects aged less than 2 years was similar to that observed in healthy adults.

13 Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

This section cross-references "Warnings and Precautions".

A **carcinogen** is any substance known to cause cancer, while a **mutagen** promotes alteration in gene sequence (mutation).[81]

Genotoxicity refers to a drug's ability to damage genetic information, causing mutations (alterations in gene sequence), which can in turn lead to the development of cancer.[82]

There are several *in vitro* laboratory tests that are used to assess a drug's mutagenic potential. These include the Ames test, which utilizes bacteria, chromosomal aberration tests that employ mammalian Chinese hamster ovary cell lines and gene mutation assays that utilize Chinese hamster lung cells. The mouse micronucleus assay is conducted in vivo.[82, 83]

Drug intolerance refers to the reaction to a standard dosage of medication with symptoms of overdosage.[84]

Inflammation is a response to tissue injury. Damaged cells release chemicals that attract white blood cells to the site of damage where, in a process called **phagocytosis**, they engulf and destroy infectious material and dead and dying cells.[85]

A **perivenous injection** is one that occurs surrounding, rather than within, the vein.[86]

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of gadoterate meglumine.

Gadoterate meglumine did not demonstrate mutagenic potential in *in vitro* bacterial reverse mutation assays (Ames test) using Salmonella typhimurium, in an *in vitro* chromosome aberration assay in Chinese hamster ovary cells, in an *in vitro* gene mutation assay in Chinese hamster lung cells, nor in an *in vivo* mouse micronucleus assay.

No impairment of male or female fertility and reproductive performance was observed in rats after intravenous administration of gadoterate meglumine at the maximum tested dose of 10 mmol/kg/day (16 times the maximum human dose based on surface area), given during more than 9 weeks in males and more than 4 weeks in females. Sperm counts and sperm motility were not adversely affected by treatment with the drug.

13.2 Animal Toxicology and/or Pharmacology

Local intolerance reactions, including moderate irritation associated with infiltration of inflammatory cells were observed after perivenous injection in rabbits suggesting the possibility of local irritation if the contrast medium leaks around the veins in a clinical setting [*see Warnings and Precautions (5.4)*].

Toxicity of gadoterate meglumine was evaluated in neonatal and juvenile (pre- and post-weaning) rats following a single or repeated intravenous administration at doses 1, 2, and 4 times the MHD based on BSA. Gadoterate meglumine was well tolerated at all dose levels tested and had no effect on growth, pre-weaning development, behavior and sexual maturation.

14 Clinical Studies

According to the FDA, the Clinical Studies section must discuss trials that facilitate understanding safe and effective drug use by providing concise, accurate summaries of study information regarding a drug's effectiveness and safety that practitioners consider important to clinical decision-making. Generally, this includes adequate and well-controlled pivotal studies that demonstrate drug effectiveness for its approved indication, as well as those that show differences in special populations and information on dose selection or adjustment. Pivotal trial results also serve as the basis for allowed promotional claims.[87]

Efficacy describes the capacity of a drug to produce an effect in a well-monitored clinical trial setting. **Effectiveness** describes how well a drug works in a real-world setting.[88]

Gadopentetate dimeglumine is the generic name for Magnevist.[89]

Delineate means to mark, show, form or show the outline or border of a structure.[90]

Morphology describes an object's form and structure.[91]

14 CLINICAL STUDIES

CNS Imaging

Efficacy and safety of gadoterate meglumine were evaluated in a multi-center clinical trial (Study A) that enrolled 364 adult and 38 pediatric patients (aged ≥ 2 years) with known or suspected CNS lesions. Adults were randomized 2 to 1 to receive either gadoterate meglumine or gadopentetate dimeglumine, each administered at a dose of 0.1 mmol/kg. All pediatric patients received gadoterate meglumine, also at a dose of 0.1 mmol/kg. In the trial, patients first underwent a baseline (pre-contrast) MRI examination followed by the assigned GBCA administration and a post-contrast MR examination. The images (pre-contrast, post-contrast and "paired pre- and post-contrast") were interpreted by three independent off-site readers blinded to clinical information. The primary efficacy analysis compared three patient-level visualization scores (paired images) to baseline MRI (pre-contrast images) for adults who received gadoterate meglumine. The three primary visualization components were: contrast enhancement, border delineation and internal morphology. For each of these components there was a pre-defined scoring scale. Lesion counting (up to five per patient) was also reflected within each component's patient-level visualization score.

Among the adult patients, 245 received gadoterate meglumine and their data comprised the primary efficacy population. There were 114 (47%) men and 131 (53%) women with a mean age of 53 years (range 18 to 85 years), the racial and ethnic representations were 84% Caucasian, 11% Asian, 4% Black, and 1% other.

Table 6 displays a comparison of paired images (pre-and post-contrast) to pre-contrast images with respect to the proportion of patients who had paired image scores that were greater "better", or same/worse "not better" than the pre- contrast scores and with respect to the difference in the mean patient level visualization score. Across the three readers 56% to 94% of patients had improved lesion visualization for paired images compared to pre-contrast images. Gadoterate meglumine provided a statistically significant improvement for all three primary visualization components. More lesions were seen on the paired images than the pre-contrast images.

Clinical Studies (cont'd)

Table 6: Study A. Improvement in Patient-level Lesion Visualization Scores, Paired versus Pre-contrast Images[a]

Lesion Scores	Reader 1	Reader 2	Reader 3
	n = 231	n = 232	n = 237
Border Delineation			
Better	195 (84%)	215 (93%)	132 (56%)
Not Better	28 (12%)	7 (3%)	88 (37%)
Missing	8 (4%)	10 (4%)	17 (7%)
Difference in Mean Score [b]	2.26*	2.89*	1.17*
Internal Morphology			
Better	218 (94%)	214 (93%)	187 (79%)
Not Better	5 (2%)	8 (3%)	33 (14%)
Missing	8 (4%)	10 (4%)	17 (7%)
Difference in Mean Score [b]	2.74*	2.75*	1.54*
Contrast Enhancement			
Better	208 (90%)	216 (93%)	208 (88%)
Not Better	15 (6%)	6 (3%)	12 (5%)
Missing	8 (4%)	10 (4%)	17 (7%)
Difference in Mean Score [b]	3.09*	3.69*	2.92*

[a] Better: number of patients with paired (pre-and post-contrast) score greater than the pre-contrast score
Not better: number of patients with paired score same as or worse than the pre-contrast score
Missing: number of patients with missing score
[b] Difference = paired mean score minus pre-contrast mean score
*Statistically significant improvement by paired t-test

In secondary analyses, post-contrast images were improved in comparison to pre-contrast images. Gadoterate meglumine lesion visualization scores were similar to those for gadopentetate dimeglumine. Gadoterate meglumine imaging results in the pediatric patients were also similar to those seen in adults.

In a second clinical trial (Study B), MR images were reread from 150 adult patients with known CNS lesions who had participated in a previously conducted clinical trial. Gadoterate meglumine administration and image interpretation was performed in the same manner as in Study A. Similar to Study A, this trial also demonstrated improved lesion visualization with gadoterate meglumine.

Clinical Studies (cont'd)

CNS Imaging in the Sub-population of Pediatric Patients < 2 years old

A non-randomized study (Study C) with 28 pediatric patients under 2 years of age who were referred for contrast MRI of the CNS supported extrapolation of CNS efficacy findings from adults and older children. CNS lesions were identified in 16 of these 28 patients on paired pre- and post-contrast images compared to 15 patients on pre-contrast images alone. In the 16 patients who had identifiable lesions, the scores for the co-endpoints of lesion visualization were improved for at least one lesion on paired pre- and post-contrast images compared to pre-contrast images in 8 out of 16 (50%) patients for lesion border delineation, 8 out of 16 (50%) patients for lesion internal morphology, and 14 out of 16 (88%) patients for lesion contrast enhancement.

16 How Supplied Storage and Handling

Solidification refers to the process of making solid, compact or hard.[92]

16 HOW SUPPLIED/STORAGE AND HANDLING

Clariscan Injection is a clear, colorless to yellow solution containing 0.5 mmol/mL of gadoterate meglumine. It is supplied in vials and pre-filled syringes.

- Clariscan Injection is supplied in 10 mL vials containing 10 mL of solution, in 20 mL vials containing 15 mL or 20 mL of solution.

  Each single dose vial is closed with a rubber stopper and sealed with an aluminum cap and the contents are sterile. Vials are packaged in a box of 10, in the following configurations:

  5.0 mmol per 10 mL (0.5 mmol per mL) in glass vial (NDC 0407-2943-01)
  7.5 mmol per 15 mL (0.5 mmol per mL) in glass vial (NDC 0407-2943-02)
  10.0 mmol per 20 mL (0.5 mmol per mL) in glass vial (NDC 0407-2943-05)

- Clariscan Injection is supplied in 20 mL plastic pre-filled syringes containing 10 mL, 15 mL, or 20 mL of solution.

  Each syringe is sealed with rubber closures and the contents are sterile. Syringes, including plunger rod, are individually packaged in a box of 10, in the following configurations:

  5 mmol per 10 mL (0.5 mmol per mL) in plastic pre-filled syringe (NDC 0407-2943-12)
  7.5 mmol per 15 mL (0.5 mmol per mL) in plastic pre-filled syringe (NDC 0407-2943-17)
  10 mmol per 20 mL (0.5 mmol per mL) in plastic pre-filled syringe (NDC 0407-2943-22)

Storage

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP, Controlled Room Temperature].

Pre-filled syringes must not be frozen. Frozen syringes should be discarded.

Should solidification occur in the vial because of exposure to the cold, bring Clariscan to room temperature before use. If allowed to stand at room temperature for a minimum of 90 minutes, Clariscan should return to a clear, colorless to yellow solution. Before use, examine the product to assure that all solids are dissolved and that the container and closure have not been damaged. Discard the vial if solids persist.

17 Patient Counseling Information

This section of the PI cross-references "Warnings and Precautions", "Use in Special Populations" and the "Medication Guide".

17 PATIENT COUNSELING INFORMATION

- Advise the patient to read the FDA-approved patient labeling (Medication Guide)

17.1 Nephrogenic Systemic Fibrosis

Instruct patients to inform their healthcare provider if they:

1. have a history of kidney disease, or
2. have recently received a GBCA.

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 Clariscan 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 in the hip bones or ribs; or muscle weakness.

17.2 Common Adverse Reactions

Inform patients that they may experience:

- Reactions along the venous injection site, such as mild and transient burning or pain or feeling of warmth or coldness at the injection site.
- Side effects of headache, nausea, abnormal taste and feeling hot.

17.3 General Precautions

- Pregnancy: Advise pregnant women of the potential risk of fetal exposure to gadoterate [*see Use in Specific Population (8.1)*]
- Gadolinium Retention: Advise patients that gadolinium is retained for months or years in brain, bone, skin, and other organs in patients with normal renal function. The clinical consequences of retention are unknown. Retention depends on multiple factors and is greater following administration of linear GBCAs than following administration of macrocyclic GBCAs [*see Warnings and Precautions (5.3)*].

Medication Guide

Please note that - as with the Boxed Warning - all GBCA PIs contain similar, class-related information, with slight variation for linear and macrocyclic agents.

MEDICATION GUIDE
Clariscan™ (kla-ri'-skan)
(gadoterate meglumine)
injection for intravenous use

What is Clariscan?

- Clariscan is a prescription medicine called a gadolinium-based contrast agent (GBCA). Clariscan, like other GBCAs, is injected into your vein and used with a magnetic resonance imaging (MRI) scanner.
- An MRI exam with a GBCA, including Clariscan, helps your doctor to see problems better than an MRI exam without a GBCA.
- Your doctor has reviewed your medical records and has determined that you would benefit from using a GBCA with your MRI exam.

What is the most important information I should know about Clariscan?

- Clariscan contains a metal called gadolinium. Small amounts of gadolinium can stay in your body including the brain, bones, skin and other parts of your body for a long time (several months to years).
- It is not known how gadolinium may affect you, but so far, studies have not found harmful effects in patients with normal kidneys.
- Rarely patients have reported pains, tiredness, and skin, muscle or bone ailments for a long time, but these symptoms have not been directly linked to gadolinium.
- There are different GBCAs that can be used for your MRI exam. The amount of gadolinium that stays in the body is different for different gadolinium medicines. Gadolinium stays in the body more after Omniscan or Optimark than after Eovist, Magnevist or MultiHance. Gadolinium stays in the body the least after Clariscan, Dotarem, Gadavist or ProHance.
- People who get many doses of gadolinium medicines, women who are pregnant and young children may be at increased risk from gadolinium staying in the body.
- Some people with kidney problems who get gadolinium medicines can develop a condition with severe thickening of the skin, muscles and other organs in the body (nephrogenic systemic fibrosis). Your healthcare provider should screen you to see how well your kidneys are working before you receive Clariscan.

Do not receive Clariscan if you have had a severe allergic reaction to Clariscan.

Before receiving Clariscan, tell your healthcare provider about all your medical conditions, including if you:

- have had any MRI procedures in the past where you received a GBCA. Your healthcare provider may ask you for more information including the dates of these MRI procedures.
- are pregnant or plan to become pregnant. It is not known if Clariscan can harm your unborn baby. Talk to your healthcare provider about the possible risks to an unborn baby if a GBCA such as Clariscan is received during pregnancy.
- have kidney problems, diabetes, or high blood pressure.
- have had an allergic reaction to dyes (contrast agents) including GBCA.

Medication Guide (cont'd)

MEDICATION GUIDE
Clariscan™ (kla-ri'-skan)
(gadoterate meglumine)
injection for intravenous use

What are possible side effects of Clariscan?

- **See "What is the most important information I should know about Clariscan?"**
- **Allergic reactions. Clariscan can cause allergic reactions that can sometimes be serious. Your healthcare provider will monitor you closely for symptoms of an allergic reaction.**

The most common side effects of Clariscan include: nausea, headache, pain, or cold feeling at the injection site, and rash.

These are not all the possible side effects of Clariscan.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective uses of Clariscan.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your healthcare provider for information about Clariscan that is written for health professionals.

What are the ingredients in Clariscan?
Active ingredient: gadoterate meglumine
Inactive ingredients: DOTA, water for injection

Manufactured by: GE Healthcare AS Oslo, Norway
GE and the GE Monogram are trademarks of General Electric Company.
For more information, go to www.GEHealthcare.com or call 1-800-654-0118.

This Medication Guide has been approved by the U.S. Food and Drug Administration. **11/2019**

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