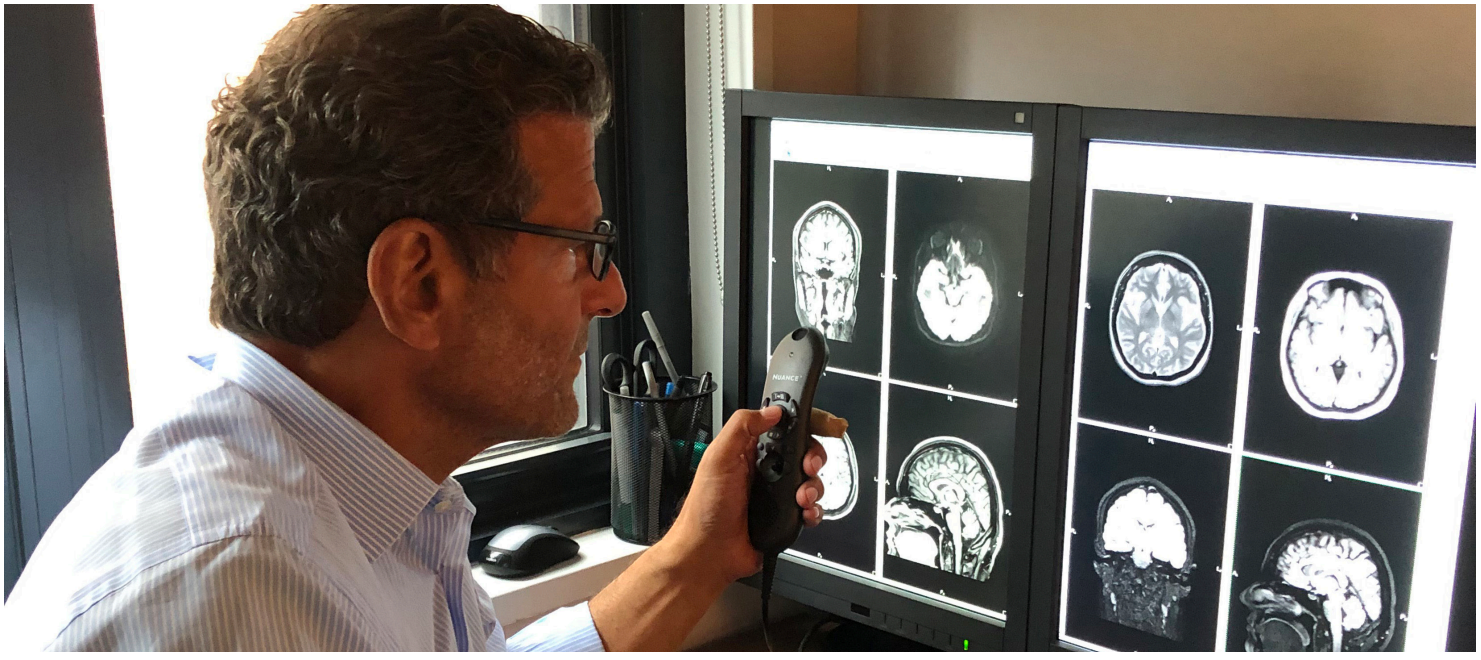
Case studies with Lawrence N. Tanenbaum, MD FACR using macrocyclic CLARISCAN (gadoterate meglumine) injection for intravenous use



Lawrence N. Tanenbaum, MD FACR is Vice President/Chief Technology Officer Director of CT, MR, and Advanced Imaging for RadNet with 37+ years experience in the medical field. He is a member of editorial boards of several journals/educational organizations and reviewer for scientific journals. He has authored 100+ scholarly and peer-reviewed articles, chairs educational/academic meetings, and has delivered 2000+ invited global lectures.*

*Dr. Tanenbaum is a consultant of GE Healthcare.

Product Indications and Use:

CLARISCAN (gadoterate meglumine) 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.

Important Safety Information About CLARISCAN:

Contraindications

History of clinically important hypersensitivity reactions to Clariscan

Please see the Brief Summary of Prescribing Information on page 14 for additional Important Safety Information About Clariscan.

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/1.73 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 (e.g. age > 60 years, hypertension, diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.
- 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.

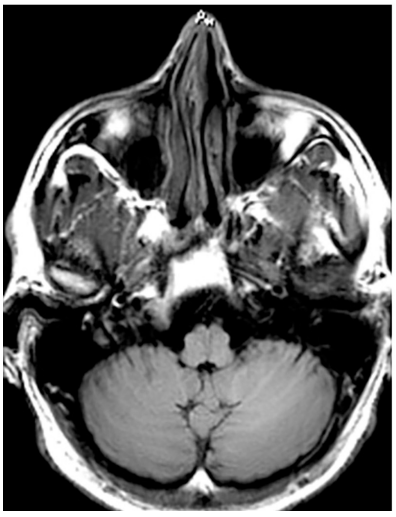
Clinical Presentation

A 32-year-old male weighing 180 lbs, presented with left facial paresthesias

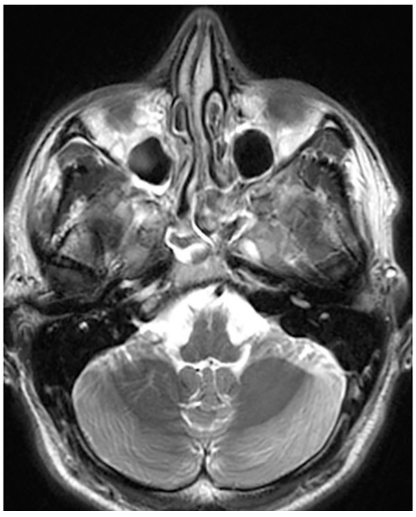
Imaging

MR of the brain with and without 18 mL of Clariscan (gadoterate meglumine)

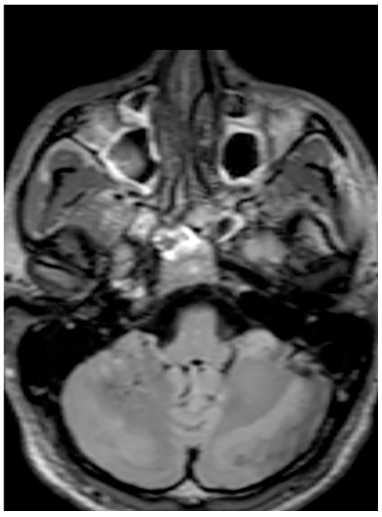
T1 axial



T2 axial

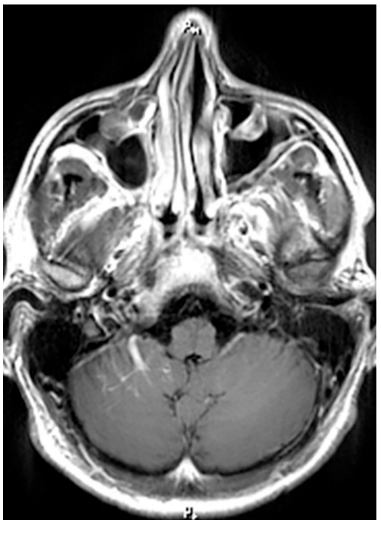


Postcontrast FLAIR axial

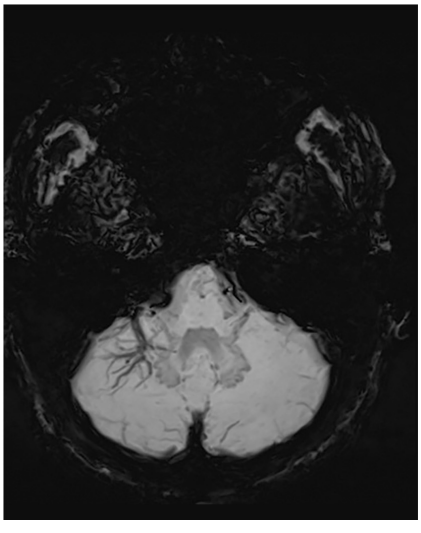


- **Precontrast images show no obvious abnormality**

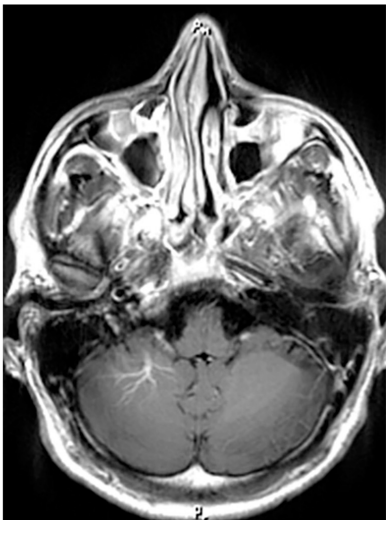
Postcontrast T1 axial



Postcontrast SWI



Postcontrast T1 axial



Imaging Findings

Multiple dendritic enhancing vascular structures coalescing on a single draining vein consistent with a developmental venous anomaly

Diagnosis

Developmental venous anomaly

TREATMENT

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION FOR CLARISCAN™ (gadoterate meglumine) Injection for Intravenous Use

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/1.73 m^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**
- **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**

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 and/or abnormal vascularity.

CONTRAINDICATIONS

History of clinically important hypersensitivity reactions to Clariscan.

WARNINGS AND PRECAUTIONS

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/1.73 m^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 /1.73 m^2) and little, if any, for patients with chronic, mild kidney disease (GFR 60 - 89 mL/ min/1.73 m^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 (1-800FDA-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.

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.

- 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 treatment of hypersensitivity reactions, including personnel trained in resuscitation.
- During and following Clariscan administration, observe patients for signs and symptoms of hypersensitivity reactions.

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. 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. 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.

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.

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.

ADVERSE REACTIONS

GBCAs have been associated with a risk for NSF. Confirmed diagnosis of NSF has not been reported in patients with a clear history of exposure to gadoterate meglumine alone. Hypersensitivity reactions and acute kidney injury are described in other sections of the labeling.

o The most common adverse reactions (≥ 0.2%) associated with gadoterate meglumine in clinical trials were nausea, headache, injection site pain, injection site coldness and rash.

o Serious adverse reactions in the postmarketing experience have been reported with gadoterate meglumine. These include but are not limited to: arrhythmia, cardiac arrest, respiratory arrest, pharyngeal edema, laryngospasm, bronchospasm, coma and convulsion.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Because of the potential risks of gadolinium to the fetus, use Clariscan only if imaging is essential during pregnancy and cannot be delayed. Advise pregnant women of the potential risk of fetal exposure to GBCAs.
- **Lactation:** While no data is available for gadoterate meglumine, published lactation data on other GBCAs indicate that 0.01 to 0.04% of the maternal gadolinium dose is present in breast milk.
- **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. Safety of gadoterate meglumine has not been established in preterm neonates.
- **Geriatric Use:** In clinical studies of gadoterate meglumine 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.
- **Renal Impairment:** No Clariscan dosage adjustment is recommended for patients with renal impairment. Gadoterate meglumine can be removed from the body by hemodialysis.

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.

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