FRESENIUS KABI

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Gadoterate Meglumine Injection, USP

Macrocyclic & Ionic Gadolinium-Based Contrast Agent

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.

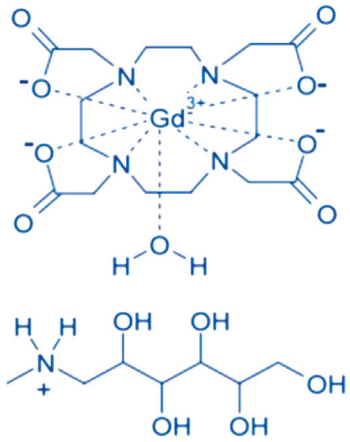
- **The risk for NSF appears highest among patients with:**
  - **Chronic, severe kidney disease (GFR less than 30 mL/min/1.73 m^2), or**
  - **Acute kidney injury.**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (for example, age more than 60 years, hypertension, or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.**

Please see Important Safety Information on the following pages.

Gadoterate Meglumine Injection, USP

Macrocyclic & Ionic Gadolinium-Based Contrast Agent (GBCA)

Gadoterate meglumine has a cage-like structure that encases the Gd^{3+}ion. As suggested by *in vitro* data, combining a macrocyclic structure for high kinetic stability, with ionicity for the thermodynamic stability, may help reduce the potential risk of gadolinium dissociation.[1,2]



Macrocyclic ionic GBCAs offer the strongest bond between the gadolinium atom and the chelate in comparison to other GBCAs. This greater stability means that the gadolinium has a higher likelihood to be excreted from the body as opposed to separating from the chelate and being retained in the body.[3,4]

Ionic vs. Non-Ionic[3,4]

- GBCAs are also described as ionic or non-ionic based on their net charge in solution.
- Ionic GBCAs offer a stronger binding between the gadolinium atom and the chelate in comparison to the non-ionic preparations.

Stability Properties[5]

Thermodynamic stability is the proportion of GBCA that remains intact (chelated) versus dissociated in equilibrium. It represents the final equilibrium state between chelated and unchelated gadolinium. When thermodynamic stability is high, the chelate less readily releases the gadolinium.

Kinetic stability is the speed at which the gadolinium ion is released from the gadolinium complex. When kinetic stability is high, the dissociation rate is considerably slower than the elimination rate from the body.

Sources:

1. Port M, Idée JM, Medina C, Robic C, Sabatou M, Corot C. Efficiency, thermodynamic and kinetic stability of marketed gadolinium chelates and their possible clinical consequences: a critical review. Biometals. 2008;21(4):469-490.
2. Frenzel T, Lengsfeld P, Schirmer H, Hütter J, Weinmann HJ. Stability of gadolinium-based magnetic resonance imaging contrast agents in human serum at 37 degrees C. Invest Radiol. 2008;43(12):817-828.
3. Fox-Rawlings S, Zuckerman D. National Center for Health Research. NCHR Report: The health risks of MRIs with gadolinium-based contrast agents; 2019.
4. Morcos SK. Extracellular gadolinium contrast agents: differences in stability. Eur J Radiol. 2008;66(2):175-179.
5. Ramalho J, Semelka RC, Ramalho M, Nunes RH, AlObaidy M, Castillo M. Gadolinium-based contrast agent accumulation and toxicity: An update. AJNR Am J Neuroradiol. 2016;37(7):1192-1198.

INDICATIONS AND USAGE

Gadoterate Meglumine Injection 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

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Gadoterate Meglumine has the highest thermodynamic and kinetic stability among all GBCAs currently in the market.*

Thermodynamic & Kinetic Stability of Gadolinium-Based Contrast Agents Currently Available in the United States**[6,7]

GBCA		Structure	Ionicity	Thermodynamic Stability		Kinetic Stability
				log K_{therm}	Log K_{cond} (at pH 7.4)	$T_{1/2}$ at pH 1.0 at 25ºC
Gadoterate Meglumine						
Gadoterate Meglumine Injection, USP	Fresenius Kabi	**Macrocyclic**	**Ionic**	**25.6**	**19.3**	†
Dotarem®	Guerbet					**338 hours*** **
Clariscan™	GE Healthcare					†
Gadobutrol		Macrocyclic	Non-ionic	21.8	15.3	43 hours
Gadavist®	Bayer					
Gadoteridol		Macrocyclic	Non-ionic	23.8	17.1	3.9 hours
ProHance®	Bracco					
Gadobenate Dimeglumine		Linear	Ionic	22.6	18.4	< 5 seconds
MultiHance®	Bracco					
Gadodiamide		Linear	Non-ionic	16.9	14.9	< 5 seconds
Omniscan™	GE Healthcare					

*Based on in vitro studies, the clinical significance of these data is unknown.
**List of non-specific extracellular fluid agents only.
***Study was halted at 338 hours.
†Data shown related to gadoterate meglumine were not derived from a study using GE Healthcare's Clariscan or Fresenius Kabi's Gadoterate Meglumine Injection, USP, however Clariscan and Gadoterate Meglumine Injection, USP have an active pharmaceutical ingredient equivalent to the study drug.

Sources Continued:
6. Contrast-Enhanced Neuroimaging with Dotarem (Gadoterate Meglumine): The Benefits of a Macrocyclic, Ionic Contrast Agent – An Expert Forum Summary. Supplement to Applied Radiology. November-December 2020.
7. Gadavist Package Insert, August 2021

Gadoterate Meglumine Injection, USP

- **FDA-approved, AP Rated**
- **Macrocyclic**
- **Ionic**
- **Preservative Free**
- **The container closure is not made with natural rubber latex**
- **Bioequivalent and fully substitutable to Dotarem®‡**

‡Dotarem® is a registered trademark of Guerbet.

Gadoterate Meglumine Injection is contraindicated in clinically important hypersensitivity reactions to Gadoterate Meglumine Injection.

Nephrogenic Systemic Fibrosis has occurred in patients with impaired elimination of GBCAs. Higher than recommended dosing or repeat dosing appear to increase the risk.

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.

Gadolinium is retained for months or years in brain, bone, and other organs.

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

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

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176, option 5, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

This Important Safety Information does not include all the information needed to use Gadoterate Meglumine Injection, USP safely and effectively. Please see full prescribing information, including BOXED WARNING, for Gadoterate Meglumine Injection, USP at www.fresenius-kabi.com/us.

For more information on FDA-approved, cost-effective generic Gadoterate Meglumine Injection, USP, that is fully substitutable to Dotarem®,‡ visit: **GenericContrastAgents.com.**

Unit of Sale NDC	Description	Concentration	Fill Volume (mL)	Unit of Sale
65219-080-05	Single Dose Vial	0.5 mmol per mL	5 mL	10
65219-082-10	Single Dose Vial	0.5 mmol per mL	10 mL	10
65219-084-15	Single Dose Vial	0.5 mmol per mL	15 mL	10
65219-086-20	Single Dose Vial	0.5 mmol per mL	20 mL	10
65219-088-50	Pharmacy Bulk Package	0.5 mmol per mL	100 mL	6

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Ordering Information

Please contact your account representative or our Customer Service Department Monday through Friday, 7:00AM – 6:00PM (CST) at:

Toll-Free: (888) 386-1300
Fax: (800) 743-7082
E-mail: customerservice.usa@fresenius-kabi.com
For more information visit: GenericContrastAgents.com

If you are interested in establishing a new account with Fresenius Kabi USA, contact us for additional information and necessary forms.

Please see single dose vial package insert and pharmacy bulk package vial package insert for full prescribing information, including BOXED WARNING, for Gadoterate Meglumine Injection. Full prescribing information is also available at www.fresenius-kabi.com/us.

Fresenius Kabi an Experienced, Reliable Supplier

Committed to Helping You

Fresenius Kabi is a global healthcare company that specializes in lifesaving medicines and technologies for infusion, transfusion and clinical nutrition – with a comprehensive portfolio of injectable drugs and delivery systems used to treat a broad spectrum of patients. As a leading provider of generic medications, we leverage our 100-year history to deliver innovative therapies that are safe, effective and affordable. **That's how Fresenius Kabi brings confidence within reach.**

‡Dotarem® is a registered trademark of Guerbet.

FRESENIUS KABI
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