GADOTRAST* Injection
Gadoteric Acid

COMPOSITION
Each ml contains:
Gadoteric Acid 279.32mg
Meglumine .....97.80 mg
Water for Injection IP .....q.s.

INDICATIONS
GADOTRAST is a gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissue in adult and pediatric patients (2 years of age and older) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.

DOSE AND METHOD OF ADMINISTRATION
Dosing Guidelines
For adult and pediatric patients (2 years and older), the recommended dose of GADOTRAST is 0.2mL/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 GADOTRAST Injection by Body Weight

Body Weight	Volume
Kilograms (kg)	Milliliters (mL)
10	2
20	4
30	6
40	8
50	10
60	12
70	14
80	16
90	18
100	20
110	22
120	24
130	26
140	28
150	30

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

Drug Handling
Visually inspect GADOTRAST for particulate matter prior to administration. Do not use the solution if particulate matter is present or if the container appears damaged. GADOTRAST should be a clear, colorless to yellow solution. Do not mix with other drugs or parenteral nutrition. Discard any unused portions of the drug.
When GADOTRAST is to be injected using plastic disposable syringes, the contrast medium should be drawn into the syringe and used immediately.

USE IN SPECIAL POPULATIONS
Pregnancy & Lactation:
- Risk summary: - There are no adequate and well-controlled studies with Gadoterate meglumine conducted in pregnant women.Limited published human data on exposure to other GBCAs during pregnancy did not show adverse effects in exposed neonates. No effects on embryo fetal development were observed in rats or rabbits at doses up to 10 mmol/kg/day in rats or 3 mmol/kg/day in rabbits. The doses in rats and rabbits were respectively 16 and 10 times the recommended human dose based on body surface area. GADOTRAST should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- Human Data:- While it is unknown if Gadoterate meglumine crosses the human placenta, other GBCAs do cross the placenta in humans and result in fetal exposure.
- Animal Data:- Reproductive and developmental toxicity studies were conducted with gadoterate meglumine in rats and rabbits. Gadoterate meglumine was administered intravenously in doses of 0, 2, 4 and 10 mmol/kg/day (or 3.2, 6.5 and 16.2 times the recommended human dose based on body surface area) to female rats for 14 days before mating throughout the mating period and until gestation day (GD) 17. Pregnant rabbits were intravenously administered gadoterate meglumine at the dose levels of 0, 1, 3 and 7 mmol/kg/day (or 3.3, 10 and 23 times the human doses based on body surface area) from GD6 to GD10. No effects on embryo fetal development were observed in rats or rabbits at doses up to 10 mmol/kg/day in rats or 3 mmol/kg/ day in rabbits. Maternal toxicity was observed in rats at 10 mmol/kg/day (or 16 times the human dose based on body surface area) and in rabbits at 7 mmol/kg/day (23 times the human dose based on body surface area).

Nursing Mothers:
It is not known whether Gadoterate meglumine is excreted in human milk. Limited case reports on use of GBCAs in nursing mothers indicate that 0.01 to 0.04% of the maternal gadolinium dose is excreted in human breast milk. Because many drugs are excreted in human milk, exercise caution when Gadoterate meglumine is administered to a nursing woman. Nonclinical data show the gadoterate meglumine is excreted into breast milk in very small amounts (<0.1% of the dose intravenously administered) and absorption via the gastrointestinal tract is poor.

Paediatrics:
The safety and efficacy of Gadoterate meglumine at a single dose of 0.1 mmol/kg have been established in pediatric patients from 2 to 17 years of age. No dosage adjustment according to age is necessary in this population. The safety and efficacy of Gadoterate meglumine have not been established in pediatric patients below 2 years of age. GFR does not reach adult levels until 1 year of age.

Geriatric:
In clinical studies of Gadoterate meglumine, 900 patients were 65 years of age and over, and 312 patients were 75 years of age and over. No overall difference in safety or efficacy were observed between these subjects and younger subjects. In general, use of Gadoterate meglumine 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 Gadoterate meglumine dosage adjustment is recommended for patients with renal impairment. Gadoterate meglumine can be removed from the body by hemodialysis.

Contra-Indications:
History of clinically important hypersensitivity reactions to Gadoterate meglumine

Warnings & Precautions:
A. 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.
Screen patients for acute kidney injury and other conditions that may reduce renal function. Features of acute kidney injury consist of rapid (over hours to days) and usually reversible decrease in kidney function, commonly in the setting of surgery, severe infection, injury or drug-induced kidney toxicity. Serum creatinine levels and estimated GFR may not reliably assess renal function in the setting of acute kidney injury. For patients at risk for chronically reduced renal function (e.g., age > 60 years, diabetes mellitus or chronic hypertension), estimate the GFR through laboratory testing. Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA and the degree of renal impairment at the time of exposure. Record the specific GBCA and the dose administered to a patient. For patients at highest risk for NSF, do not exceed the recommended Gadoterate meglumine dose and allow a sufficient period of time for elimination of the drug prior to re-administratio. 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.

B. Hypersensitivity Reactions
Anaphylactic and anaphylactoid reaction 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 administered and resolved with prompt emergency treatment
- Before Gadoterate meglumine 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 Gadoterate meglumine.
- Administer Gadoterate meglumine 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 Gadoterate meglumine administration, observe patients for signs and symptoms of hypersensitivity reactions.

C. 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 followup renal function assessments for patients with a history of renal dysfunction.

D. Extravasation and Injection Site Reactions
Ensure catheter and venous patency before the injection of Gadoterate meglumine Extravasation into tissues during Gadoterate meglumine administration may result in tissue irritation

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

PACKAGING INFORMATION
Available in 10ml and 20ml vials

STORAGE AND HANDLING INSTRUCTIONS
Store at a temperature below 25°C. Protect from light. Do not freeze.

Further information available on request from:
Diagnostic Division
J. B. CHEMICALS & PHARMACEUTICALS LIMITED
Cnergy IT Park, Unit A2, 3rd Floor, Unit A, 8th Floor, Appa Saheb Marathe Marg, Prabhadevi, Mumbai - 400 025. Phone: +91 22 2439 5200 / 2439 5500. Website: www.jbcpl.com

Unique's

GADOTRAST* Injection
Gadoteric Acid

- Macrocyclic Agent
- Highly stable compound
- Excellent safety profile
- Optimal Performance
- Ionic contrast

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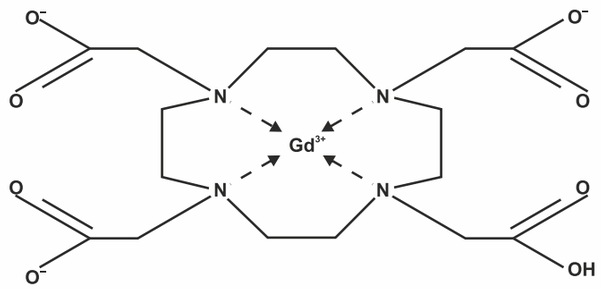
Macrocyclic vs Linear Gadolinium-based Contrast Agents

There are 2 structurally distinct categories of commercially available GBCAs: linear ("open chain") or macrocyclic. In the macrocyclic structure, the gadolinium ion is "caged" in the preganized cavity of the ligand. The rates of dissociation of gadolinium from macrocyclic ligands are slower than dissociation from linear ligands and are thus considered to be the most "stable." Stability refers to how tightly bound the gadolinium ion is attached to the chelating molecule and how likely it is to dissociate. When this happens, the released gadolinium ion is picked up by a variety of competing anions and cation-binding proteins in the circulating blood. The higher the dissociation constant, the more likely is the possibility of dechelation and release of free gadolinium into the body. The rate of dissociation of the complex in vivo is thought to be an important factor that determines, at least in part, the likelihood of a specific GBCA being associated with NSF, a serious adverse event (AE).



Macrocyclic agent form a cage-like ligand structure with the ion trapped in a preformed central cavity

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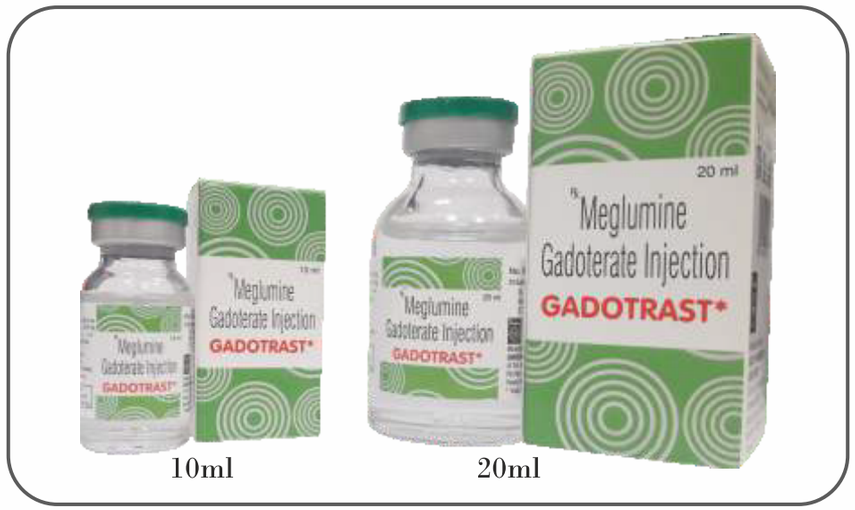
Indication:

- **MRI of brain, spine and associated tissue**
- **To detect and visualize areas with disruption of the blood brain barrier (BBB)**
- **Abnormal vascularity**

Various types of patients:

- **Elderly**
- **Pediatric**
- **Impaired hepatic function**
- **Impaired renal function** including severe impairment (GFR <30ml/min/1.73m^2) considering risk/benefit assessment



10ml 20ml