PRESCRIBING INFORMATION

MAGNESIUM SULFATE INJECTION USP

Anticonvulsant

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Date of revision: February 13, 2026

Submission Control No: 277135

Magnesium Sulfate Injection USP

THERAPEUTIC CLASSIFICATION

Anticonvulsant

ACTION AND CLINICAL PHARMACOLOGY

When administered parentally in doses sufficient to produce hypermagnesemia (serum magnesium concentrations greater than 2.5 mEq/L), the drug may depress the CNS and block peripheral neuromuscular transmission, producing anticonvulsant effects. The exact mechanism of this depressant activity is not fully known; however, excess magnesium appears to decrease the amount of acetylcholine liberated by the motor nerve impulse.

When serum concentration of magnesium exceed 4 mEq/L, deep-tendon reflexes may be depressed. At serum concentration of 10 mEq/L, deep-tendon reflexes may disappear and respiratory paralysis may occur. Serum magnesium concentration in excess of 12 mEq/L may be fatal. Complete heart block can also occur at high serum concentrations of magnesium (approximately 10 mEq/L). Animal studies suggest that the effect of magnesium ions on cardiac muscle is to slow the rate of the sinoatrial node impulse formation and prolong conduction time. Limited data in patients with no evidence of heart disease indicate that IV infusion of magnesium prolongs PR interval, H (atria-His bundle) interval, antegrade AV nodal effective refractory period, and sinoatrial conduction time. Magnesium also acts peripherally, producing vasodilatation. Moderate doses produce flushing and sweating, and higher doses lower blood pressure. Both the CNS depression and the peripheral neuromuscular transmission blockade produced by hypermagnesemia can be antagonized by administration of excess calcium.

Pharmacokinetics

When magnesium sulfate is administered IV, the onset of action is immediate and the duration of action is about 30 minutes. Following IM administration of the drug, the onset of action occurs in about 1 hour and the duration of action is 3-4 hours. As an anticonvulsant, effective serum concentrations of magnesium have been reported to range from 2.5 - 7.5 mEq/L.

Magnesium readily crosses the placenta and is distributed into milk following parenteral administration of magnesium sulfate.

Magnesium sulfate is excreted by the kidneys at a rate proportional to the serum concentration and glomerular filtration.

INDICATIONS AND CLINICAL USE

Magnesium Sulfate Injection USP is mainly used as an anticonvulsant for the prevention and control of seizures in severe preeclampsia or in eclampsia. Parentally administrated magnesium sulfate is an important drug in the empirical management of convulsive toxemia of pregnancy.

- Magnesium Sulfate Injection USP is used to treat acute magnesium deficiency which may be associated with a variety of clinical conditions including malabsorption syndromes, alcoholism, cirrhosis of the liver, acute pancreatitis, or prolonged IV therapy with magnesium-free fluids.

- Magnesium Sulfate Injection USP is also used to prevent magnesium deficiency in patients receiving total parenteral nutrition.

- To control hypertension or encephalopathy associated with acute nephritis in children.

- For paroxysmal atrial tachycardia.

- Magnesium sulfate is administered IV to counteract the intense muscle stimulating effects of barium poisoning.

WARNINGS AND PRECAUTIONS

Patients receiving parenteral magnesium sulfate should be observed carefully, and serum magnesium concentrations should be monitored to avoid overdosage. **Intoxication may appear with serum concentration of 4 mEq/L.** Disappearance of the patellar reflex is a useful clinical sign to detect the onset of magnesium intoxication. When repeated doses of the drug are given parenterally, knee jerk reflexes should be tested before each dose and if they are absent, no additional magnesium should be given until they return.

In addition, the respiration rate should be at least 16 per minute prior to parenteral administration of magnesium sulfate, and therapy should not be continued unless urine output is 100 mL or more during the 4 hours preceding each dose.

Magnesium sulfate should be administered with caution to patients with impaired renal function because of the danger of magnesium intoxication. Parenteral administration of the drug is contraindicated in patients with heart block or myocardial damage.

Pregnancy: The neonate is usually not compromised when IM magnesium sulfate is administered to the toxemic mother. However, when magnesium sulfate therapy is administered by continuous IV infusion (especially if for more than 24 hours preceding delivery), the possibility of the neonate showing signs of magnesium toxicity, including neuromuscular or respiratory depression, is increased.

IV magnesium should not be given during the 2 hours preceding delivery.

Lactation: Since magnesium is distributed into milk during parenteral magnesium sulfate administration, the drug should be used with caution in nursing women. Milk concentrations of magnesium are increased for only about 24 hours after discontinuance of parenteral magnesium

sulfate therapy; the amount of magnesium ingested by a nursing infant during this period is probably too small to be of clinical importance.

DRUG INTERACTIONS

When barbiturates, opiates, general anesthetics, or other CNS depressants, are administered concomitantly with magnesium sulfate, dosage of these agents must be carefully adjusted because of the additive central depressant effects.

Magnesium salts should be administered with extreme caution in digitalized patients, because serious changes in cardiac conduction which can result in heart block may occur if administration of calcium is required to treat magnesium toxicity.

Excessive neuromuscular blockade has occurred in patients receiving parenteral magnesium sulfate and a neuromuscular blocking agent; these drugs should be administered concomitantly only with caution.

ADVERSE REACTIONS

Adverse effects associated with parenteral magnesium sulfate therapy are caused by magnesium intoxication. Signs of hypermagnesemia, which may begin at serum magnesium concentrations of 4 mEq/L, include flushing, sweating, hypotension, depression of reflexes, flaccid paralysis, hypothermia, circulatory collapse, depression of cardiac function, and CNS depression. These symptoms can proceed to fatal respiratory paralysis. Hypocalcemia with signs of tetany secondary to magnesium sulfate therapy for eclampsia has been reported.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Treatment: In the case of an overdosage, patient should be artificially ventilated until IV calcium salt is administered.

In adults, IV administration of 5-10 mEq of calcium (e.g. 10-20 mL of 10% calcium gluconate) will usually reverse respiratory depression or heart block caused by magnesium intoxication. An IV preparation of calcium salt (e.g. calcium gluconate) should be readily available for use when magnesium sulfate is given IV. In extreme cases of hypermagnesemia, peritoneal dialysis or hemodialysis may be required.

Overdosage: Management of the neonate with hypermagnesemia may require resuscitation and assisted ventilation via endotracheal intubation and/or intermittent positive-pressure ventilation, as well as IV calcium.

DOSAGE AND ADMINISTRATION

Administration

For IV administration, magnesium sulfate concentration should generally not be greater than 200 mg/mL (20%), and the rate of injection usually should not exceed 150 mg/minutes (e.g. 1.5 mL of a 10% concentration or equivalent).

For IM administration in adults, magnesium sulfate solution in concentrations of 250 mg/mL (25%) or 500 mg/mL (50%) is generally used.

For IM use in infants and children, the drug concentration usually should not exceed 200 mg/mL (20%).

Dosage
Dosage of magnesium sulfate must be carefully adjusted according to individual requirements and response; and administration of the drug should be discontinued as soon as the desired effect is obtained.

For the management of severe preeclampsia or eclampsia: An initial dose of 4 g of magnesium sulfate in 250 mL 5% dextrose injection may be administered by IV infusion. In addition to the initial IV dose, 4-5 g is given IM into each buttock, followed by IM doses of 4-5 g into alternate buttocks at 4-hour intervals as needed, depending on the patient's response and the absence of signs of magnesium toxicity.

After the initial IV dose, some clinicians administer 1-2 g/hour by constant IV infusion.

Alternatively, an initial dosage of 8-15 g, depending on the weight of the patient (0.170 g/kg); 4 g in 250 mL 5% Dextrose injection is given IV and the remainder of the initial dose is given IM. Dosage for the next 24 hours should be based on the serum concentration and urinary excretion of magnesium following the initial dose.

Subsequent doses should be sufficient to replace the magnesium excreted in the urine and will be approximately 65% of the initial dose administered IM at 6-hour intervals.

For the treatment of mild magnesium deficiency: The usual adult dosage of magnesium sulfate is 1 g administered IM or 3 g orally every 6 hours for 24 hours.

Patients with severe magnesium deficiency: As much as 250 mg/kg may be administered IM over a 4-hour period. Alternatively, 5 g of magnesium sulfate in 5% dextrose or in 0.9% sodium chloride may be administered by IV infusion over a 3-hour period.

Total parenteral nutrition: Adults are usually given 0.5-3 g of magnesium sulfate (4-24 mEq of magnesium) daily.

In barium poisoning: The usual dose of magnesium sulfate is 1-2 g given IV.

For controlling seizures associated with epilepsy: The usual adult dose is 1 g administered IV or IM.

For the management of hypertension, encephalopathy, and seizure associated with acute nephritis in children: 100 mg/kg (0.2 mL/kg of a 50% solution) has been administered IM at 4 to 6 hour intervals as needed.

Children have also received magnesium sulfate IM in a dosage of 20-40 mg/kg to control seizures. If symptoms are severe, the drug may be administered IV as a 1-3% solution in a dosage of 100-200 mg/kg. The total IV dose should be administered within 1 hour, with one-half the dose administered in the first 15-20 minutes.

Paroxysmal atrial tachycardia: The usual dose is 3-4 g administered IV over 30 seconds with extreme caution.

STORAGE AND STABILITY

Store between 15 and 30˚C. Protect from light. Protect from freezing. Discard unused portion.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Magnesium Sulfate Injection USP 20% is available in 10 mL vials, boxes of 10.

The chlorobutyl rubber stopper is not made with natural rubber latex.

PHARMACEUTICAL INFORMATION

Drug Substance

Chemical Name:	Magnesium sulfate heptahydrate
Molecular formula :	$MgSO_4 \cdot 7H_2O$
Molecular mass:	246.38
Physicochemical properties:	Magnesium sulfate heptahydrate is a bitter crystalline salt, soluble in water (1 g in 100 mL at 20°C) and slightly soluble in ethanol. The pH of an aqueous solution is 6-7.

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