MAGNESIUM SULFATE
IN WATER FOR INJECTION

Flexible Plastic Container

Rx only

For Intravenous Use Only

DESCRIPTION

Magnesium Sulfate in Water for Injection is a sterile, nonpyrogenic solution of magnesium sulfate heptahydrate in water for injection. May contain sulfuric acid and/or sodium hydroxide for pH adjustment. The pH is 4.5 (3.5 to 6.5). It is available in 4% concentration. See ***HOW SUPPLIED*** section for the content and characteristics of available dosage forms and sizes.

Magnesium Sulfate, USP heptahydrate is chemically designated $MgSO_4 \cdot 7H_2O$, colorless crystals or white powder freely soluble in water.

Water for Injection, USP is chemically designated H_2O.

Water can permeate from inside the flexible plastic container into the overwrap but not in amounts sufficient to affect the solution significantly. Solutions in contact with the plastic container may leach out certain chemical components from the plastic in very small amounts; however, biological testing was supportive of the safety of the plastic container materials. Exposure to temperatures above 25°C/77°F during transport and storage will lead to minor losses in moisture content. Higher temperatures lead to greater losses. It is unlikely that these minor losses will lead to clinically significant changes within the expiration period.

CLINICAL PHARMACOLOGY

Magnesium (Mg^{++}) is an important cofactor for enzymatic reactions and plays an important role in neurochemical transmission and muscular excitability.

Magnesium prevents or controls convulsions by blocking neuromuscular transmission and decreasing the amount of acetylcholine liberated at the end plate by the motor nerve impulse. Magnesium is said to have a depressant effect on the central nervous system, but it does not adversely affect the mother, fetus or neonate when used as directed in eclampsia or pre-eclampsia. Normal serum magnesium levels range from 1.3 to 2.1 mEq/liter.

As serum magnesium rises above 4 mEq/liter, the deep tendon reflexes are first decreased and then disappear as the serum level approaches 10 mEq/liter. At this level respiratory paralysis may occur. Heart block also may occur at this or lower serum levels of magnesium.

Magnesium acts peripherally to produce vasodilation. With low doses only flushing and sweating occur, but larger doses cause lowering of blood pressure. The central and peripheral effects of magnesium poisoning are antagonized to some extent by intravenous administration of calcium.

With intravenous administration the onset of anticonvulsant action is immediate and lasts about 30 minutes. Following intramuscular administration the onset of action occurs in about 1 hour and persists for 3 to 4 hours. Effective anticonvulsant serum levels range from 2.5 to 7.5 mEq/liter.

Pharmacokinetics:

Absorption: Intravenously administered magnesium is immediately absorbed.

Distribution: Approximately 1-2% of total body magnesium is located in the extracellular fluid space. Magnesium is 30% bound to albumin.

Metabolism: Magnesium is not metabolized.

Excretion: Magnesium is excreted solely by the kidney at a rate proportional to the serum concentration and glomerular filtration.

Special Populations:
Renal Insufficiency: Magnesium is excreted solely by the kidney. In patients with severe renal insufficiency, the dose should be lower and frequent serum magnesium levels must be obtained (see ***DOSAGE AND ADMINISTRATION***).
Hepatic Insufficiency: Magnesium is excreted solely by the kidney. No dosing adjustments are necessary in hepatic insufficiency.
Drug-Drug Interactions: Drug induced renal losses of magnesium occur with the following drugs or drug classes:

Aminoglycosides	Amphotericin B
Cyclosporine	Diuretics
Digitalis	Cisplatin
Alcohol	

INDICATIONS AND USAGE
Magnesium Sulfate in Water for Injection is indicated for the prevention and control of seizures in pre-eclampsia and eclampsia, respectively. When used judiciously it effectively prevents and controls the convulsions of eclampsia without producing deleterious depression of the central nervous system of the mother or infant. However, other effective drugs are available for this purpose.

CONTRAINDICATIONS
Intravenous magnesium should not be given to mothers with toxemia of pregnancy during the 2 hours preceding delivery.

WARNINGS
FETAL HARM: Continuous administration of magnesium sulfate beyond 5-7 days to pregnant women can lead to hypocalcemia and bone abnormalities in the developing fetus. These bone abnormalities include skeletal demineralization and osteopenia. In addition, cases of neonatal fracture have been reported. The shortest duration of treatment that can lead to fetal harm is not known. Magnesium sulfate should be used during pregnancy only if clearly needed. If magnesium sulfate is given for treatment of preterm labor, the woman should be informed that the efficacy and safety of such use have not been established and that use of magnesium sulfate beyond 5-7 days may cause fetal abnormalities.

Parenteral use in the presence of renal insufficiency may lead to magnesium intoxication.

PRECAUTIONS
Because magnesium is removed from the body solely by the kidneys, the drug should be used with caution in patients with renal impairment. Urine output should be maintained at a level of 100 mL every 4 hours. Monitoring serum magnesium levels and the patient's clinical status is essential to avoid the consequences of overdosage in toxemia. Clinical indications of a safe dosage regimen include the presence of the patellar reflex (knee jerk) and absence of respiratory depression (approximately 16 breaths or more/minute). Serum magnesium levels usually sufficient to control convulsions range from 3 to 6 mg/100 mL (2.5 to 5 mEq/liter). The strength of the deep tendon reflexes begins to diminish when serum magnesium levels exceed 4 mEq/liter. Reflexes may be absent at 10 mEq magnesium/liter, where respiratory paralysis is a potential hazard. An injectable calcium salt should be immediately available to counteract the potential hazards of magnesium intoxication in eclampsia.

Magnesium Sulfate in Water for Injection should be administered slowly to avoid producing hypermagnesemia.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies with Magnesium Sulfate in Water for Injection have not been performed to evaluate carcinogenic potential, mutagenic potential or effects on fertility.

Pregnancy (See ***WARNINGS*** and ***PRECAUTIONS*****)**

Teratogenic Effects:

Magnesium Sulfate in Water for Injection, can cause fetal abnormalities when administered beyond 5-7 days to pregnant women. There are retrospective epidemiological studies and case reports documenting fetal abnormalities such as hypocalcemia, skeletal demineralization's, osteopenia and other l skeletal abnormalities with continuous maternal administration of magnesium sulfate for more than 5-7 days.[1-12] Magnesium Sulfate in Water for Injection should be used during pregnancy only if clearly needed. If this drug is used during pregnancy the woman should be apprised of the potential harm to the fetus.

Nonteratogenic Effects:

When administered by continuous IV infusion (especially for more than 24 hours preceding delivery) to control convulsions in a toxemic woman, the newborn may show signs of magnesium toxicity, including neuromuscular or respiratory depression. (See ***OVERDOSAGE.***)

Labor and Delivery:

Continuous administration of magnesium sulfate is an unapproved treatment for preterm labor. The safety and efficacy of such use have not been established. The administration of Magnesium Sulfate in Water for Injection outside of its approved indication in pregnant women should be by trained obstetrical personnel in a hospital setting with appropriate obstetrical care facilities.

Nursing Mothers:

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Magnesium Sulfate in Water for Injection is administered to a nursing mother.

ADVERSE REACTIONS

The adverse effects of parenterally administered magnesium usually are the result of magnesium intoxication. These include flushing, sweating, hypotension, depressed reflexes, flaccid paralysis, hypothermia, circulatory collapse, cardiac and central nervous system depression proceeding to respiratory paralysis.

Hypocalcemia with signs of tetany secondary to magnesium sulfate therapy for eclampsia has been reported.

OVERDOSAGE

Magnesium intoxication is manifested by a sharp drop in blood pressure and respiratory paralysis. Disappearance of the patellar reflex is a useful clinical sign to detect the onset of magnesium intoxication. In the event of overdosage, artificial ventilation must be provided until a calcium salt can be injected IV to antagonize the effects of magnesium.

For Treatment of Overdose

Artificial respiration is often required. Intravenous calcium, 10 to 20 mL of a 5% solution (diluted if desirable) with isotonic sodium chloride for injection) is used to counteract effects of hypermagnesemia. Subcutaneous physostigmine, 0.5 to 1 mg may be helpful.

Hypermagnesemia in the newborn may require resuscitation and assisted ventilation via endotracheal intubation or intermittent positive pressure ventilation as well as IV calcium.

DOSAGE AND ADMINISTRATION

Magnesium Sulfate in Water for Injection is intended for intravenous use only. For the management of pre-eclampsia or eclampsia, intravenous infusions of dilute solutions of magnesium (1% to 8%) are often given in combination with intramuscular injections of 50% Magnesium Sulfate Injection, USP. Therefore, in the clinical conditions cited below, both forms of therapy are noted, as appropriate.

<u>Continuous maternal administration of magnesium sulfate in pregnancy beyond 5-7 days can cause fetal abnormalities.</u>

In Eclampsia

In severe pre-eclampsia or eclampsia, the total initial dose is 10 to 14 g of magnesium sulfate. To initiate therapy, 4 g of Magnesium Sulfate in Water for Injection may be administered intravenously. The rate of I.V. infusion should generally not exceed 150 mg/minute, or 3.75 mL of a 4% concentration (or its equivalent) per minute, except in severe eclampsia with seizures. Simultaneously, 4 to 5 g (32.5 to 40.6 mEq) of magnesium sulfate may be administered intramuscularly into each buttock using undiluted 50% Magnesium Sulfate Injection, USP. After the initial I.V. dose, some clinicians administer 1 to 2 g/hour by constant I.V. infusion.

Subsequent intramuscular doses of 4 to 5 g of magnesium sulfate may be injected into alternate buttocks every 4 hours, depending on the continuing presence of the patellar reflex, adequate respiratory function, and absence of signs of magnesium toxicity. Therapy should continue until paroxysms cease.

A serum magnesium level of 6 mg/100 mL is considered optimal for control of seizures. A total daily (24 hr) dose of 30 to 40 g magnesium sulfate should not be exceeded. In the presence of severe renal insufficiency, frequent serum magnesium concentrations must be obtained and the maximum dosage of magnesium sulfate is 20 g per 48 hours.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Do not administer unless solution is clear. Discard unused portion.

HOW SUPPLIED

Magnesium Sulfate in Water for Injection is supplied in single-dose flexible plastic containers as follows:

NDC Number (Unit of Sale)	Concentration	Total Magnesium Sulfate**	Total Magnesium Ion	Magnesium Sulfate** Concentration	Magnesium Ion Concentration	Osmolarity (calc.)
NDC 0409-6729-23 Case of 24 single-dose flexible plastic containers	4 g/100 mL (40 mg/mL)	4 g	32.5 mEq	4% (40 mg/mL)	32.5 mEq/100 mL	325 mOsmol/liter
NDC 0409-4121-24 Case of 24 single-dose flexible plastic containers	4 g/100 mL (40 mg/mL)	4 g	32.5 mEq	4% (40 mg/mL)	32.5 mEq/100 mL	325 mOsmol/liter
NDC 0409-2050-20 Case of 20 single-dose flexible plastic containers	20 g/500 mL (40 mg/mL)	20 g	162.3 mEq	4% (40 mg/mL)	32.5 mEq/100 mL	325 mOsmol/liter
NDC 0409-3164-12 Case of 12 single-dose flexible plastic containers	40 g/1000 mL (40 mg/mL)	40 g	325 mEq	4% (40 mg/mL)	32.5 mEq/100 mL	325 mOsmol/liter
NDC 0409-6729-24 Case of 24 single-dose flexible plastic containers	2 g/50 mL* (40 mg/mL)	2 g	16.25 mEq	4% (40 mg/mL)	16.25 mEq/50 mL	325 mOsmol/liter
NDC 0409-5239-24 Case of 24 single-dose flexible plastic containers	2 g/50 mL* (40 mg/mL)	2 g	16.25 mEq	4% (40 mg/mL)	16.25 mEq/50 mL	325 mOsmol/liter

* Partial fill container 50 mL volume in 100 mL container.

** As the heptahydrate.

WARNING: DO NOT USE FLEXIBLE CONTAINER IN SERIES CONNECTIONS.

Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.] Protect from freezing.

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This product's labeling may have been updated. For the most recent prescribing information, please visit www.pfizer.com.

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