MAGNESIUM SULFATE- magnesium sulfate heptahydrate injection, solution
Fresenius Kabi USA, LLC

Magnesium Sulfate in Water for Injection

For Intravenous Use Only

Rx 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% and 8% concentrations. 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.

The flexible container is fabricated from a specially formulated non-plasticized, film containing polypropylene and thermoplastic elastomers (**free**flex ® bag). The amount of water that can permeate from the container into the overwrap is insufficient to affect the solution significantly. Solutions in contact with the flexible container can leach out certain of the container's chemical components in very small amounts within the expiration period. The suitability of the container material has been confirmed by tests in animals according to USP biological tests for plastic containers. Exposure to temperatures above 25ºC/77ºF 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 one hour and persists for three to four 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 to 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 two hours preceding delivery.

WARNINGS:

FETAL HARM: Continuous administration of magnesium sulfate beyond 5 to 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 to 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 four 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

Teratogenic Effects

Pregnancy Category D (see WARNINGS and PRECAUTIONS) .

See **WARNINGS** and **PRECAUTIONS**.

Magnesium sulfate in water for injection, can cause fetal abnormalities when administered beyond 5 to 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 skeletal abnormalities with continuous maternal administration of magnesium sulfate for more than 5 to 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.

Continuous maternal administration of magnesium sulfate in pregnancy beyond 5 to 7 days can cause fetal abnormalities.

In Pre-eclampsia or 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 IV 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 IV dose, some clinicians administer 1 to 2 g/hour by constant IV infusion.

Subsequent intramuscular doses of 4 to 5 g of magnesium sulfate may be injected into

alternate buttocks every four 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 containers as follows:

Product Code	**Unit of Sale**	**Total Magnesium Sulfate***	**Total Magnesium Ion**	**Magnesium Sulfate* Concentration**	**Magnesium Ion Concentration**	**Osmolarity (calc.)**	**Unit of Use**
PRX610605	63323-106-26 Package of 24	2 g	16.25 mEq	4% (40 mg/mL)	16.25 mEq/50 mL	325 mOsmol/Liter	63323-106-03 50mL fill in a 100 mL **free***flex*® Bag

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

**As the heptahydrate.

WARNING: DO NOT USE FLEXIBLE CONTAINER IN SERIES CONNECTIONS.

This container is not made with natural rubber latex or polyvinyl chloride (PVC), Non-DEHP.

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

REFERENCES:

1. Yokoyama K, Takahashi N, Yada Y. Prolonged maternal magnesium administration and bone metabolism in neonates. *Early Human Dev*. 2010; 86(3):187-91. Epub 2010 Mar 12.
2. Wedig KE, Kogan J, Schorry EK et al. Skeletal demineralization and fractures caused by fetal magnesium toxicity. *J Perinatol*. 2006; 26(6):371-4.
3. Nassar AH, Sakhel K, Maarouf H, et al. Adverse maternal and neonatal outcome of prolonged course of magnesium sulfate tocolysis. *Acta Obstet Gynecol Scan*. 2006;

85(9):1099-103.
4. Malaeb SN, Rassi A, Haddad MC. Bone mineralization in newborns whose mothers received magnesium sulphate for tocolysis of premature labor. *Pediatr Radiol*. 2004; 34(5):384-6. Epub 2004 Feb 18.
5. Matsuda Y, Maeda Y, Ito M, et al. Effect of magnesium sulfate treatment on neonatal bone abnormalities. *Gynecol Obstet Invest*. 1997; 44(2):82-8.
6. Schanler RJ, Smith LG, Burns PA. Effects of long-term maternal intravenous magnesium sulfate therapy on neonatal calcium metabolism and bone mineral content. *Gynecol Obstet Invest.* 1997; 43(4):236-41.
7. Santi MD, Henry GW, Douglas GL. Magnesium sulfate treatment of preterm labor as a cause of abnormal neonatal bone mineralization. *J Pediatr Orthop*. 1994; 14(2):249-53.
8. Holocomb WL, Shackelford GD, Petrie RH. Magnesium tocolysis and neonatal bone abnormalities: a controlled study. *Obstet Gynecol*. 1991; 78(4):611-4.
9. Cumming WA, Thomas VJ. Hypermagnesemia: a cause of abnormal metaphyses in the neonate. *Am J Roentgenol*. 1989; 152(5):1071-2.
10. Lamm CL, Norton KL, Murphy RJ. Congenital rickets associated with magnesium sulfate infusion for tocolysis. *J Pediatr*. 1988; 113(6):1078-82.
11. McGuinness GA, Weinstein MM, Cruikshank DP, et al. Effects of magnesium sulfate treatment on perinatal calcium metabolism. II. Neonatal responses. *Obstet Gynecol*. 1980; 56(5):595-600.
12. Riaz M, Porat R, Brodsky NL, et al. The effect of maternal magnesium sulfate treatment on newborns: a prospective controlled study. *J Perinatol.* 1998; 18(6 pt 1):449-54.

Manufactured for:

Fresenius Kabi
Lake Zurich, IL 60047

Made in Norway

www.fresenius-kabi.com/us

451511A
Revised: April 2019

PREMIERProRx®

PACKAGE LABEL - PRINCIPAL DISPLAY - Magnesium Sulfate 50 mL Bag Label

NDC 63323-106-03
Magnesium Sulfate *in Water for Injection*

2 g total in 50 mL (0.325 mEq Mg^{++}/mL) 40 mg per mL **2 g TOTAL**

For Intravenous Infusion

Rx Only

PACKAGE LABEL - PRINCIPAL DISPLAY - Magnesium Sulfate 50 mL Foil Overwrap

To Open Overwrap - Tear at Notch

NDC 63323-106-03

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2 g total in 50 mL (0.325 mEq Mg^{++}/mL) 40 mg per mL 2 g TOTAL

For Intravenous Infusion

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MAGNESIUM SULFATE

magnesium sulfate heptahydrate injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:63323-106
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
MAGNESIUM SULFATE HEPTAHYDRATE (UNII: SK47B8698T) (MAGNESIUM CATION - UNII:T6V3LHY838)	MAGNESIUM SULFATE HEPTAHYDRATE	40 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
SULFURIC ACID (UNII: O40UQP6WCF)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
	NDC:63323-106			

1	NDC:63323-106-26	24 in 1 CASE	03/15/2016	
1	NDC:63323-106-03	50 mL in 1 BAG; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA206485	03/15/2016	

Labeler - Fresenius Kabi USA, LLC (608775388)

Establishment

Name	Address	ID/FEI	Business Operations
HP Halden Pharma AS		347747373	MANUFACTURE(63323-106) , ANALYSIS(63323-106) , PACK(63323-106)

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