

## **MAGNESIUM SULFATE INJECTION, USP 50%**

**For Intravenous or Intramuscular Use Only**  
**500 mg/mL of Magnesium Sulfate heptahydrate**  
**4.06 mEq/mL of Magnesium Sulfate anhydrous**  
**2.03 mmol/mL of Magnesium Sulfate anhydrous**  
**4060 mOsmol/L**  
**pH 5.5 - 7.0 when diluted to a concentration of 5% (w/v)**

### **DESCRIPTION**

Magnesium Sulfate Injection, USP 50% is a sterile, concentrated solution of magnesium sulfate in Water for Injection.

Each mL contains 500 mg magnesium sulfate heptahydrate (49.3 mg  $\text{Mg}^{++}$  and 194.7 mg  $\text{SO}_4^{2-}$ ). pH adjusted with sulfuric acid or sodium hydroxide if necessary.

The solution contains no bacteriostatic agent or other preservatives.

Magnesium sulfate heptahydrate is chemically designated  $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$  and occurs as a white, bitter, crystalline powder which is freely soluble in water.

### **CLINICAL PHARMACOLOGY**

Magnesium is the second most plentiful cation of the intracellular fluids. It is essential for the activity of many enzyme systems and plays an important role with regard to neurochemical transmission and muscular excitability. Deficiencies are accompanied by a variety of structural and functional disturbances.

Some of the effects of magnesium on the nervous system are similar to those of calcium. An increased concentration of magnesium in the extracellular fluid causes depression of the central nervous system (CNS). Magnesium has a direct depressant effect on skeletal muscle.

Abnormally low concentrations of magnesium in the extracellular fluid result in increased acetylcholine release and increased muscle excitability that can produce tetany.

Magnesium slows the rate of SA nodal impulse formation. Higher concentrations of magnesium (greater than 15 mEq/L) produce cardiac arrest in diastole.

Excess magnesium causes vasodilation by both a direct action on blood vessels and ganglionic blockade.

Magnesium is excreted principally by the kidney by glomerular filtration.

## INDICATIONS AND USAGE

Magnesium Sulfate Injection, USP 50% may be of therapeutic value in the following conditions:

- as a CNS depressant, primarily in preeclampsia and eclampsia of pregnancy;
- as an electrolyte replenisher for hypomagnesemia and magnesium deficiency to maintain normal neuromuscular irritability.

## CONTRAINDICATIONS

Magnesium Sulfate Injection, USP 50% should not be administered parenterally in patients with heart block or myocardial damage.

## WARNINGS

The principal hazard in parenteral magnesium therapy is the production of abnormally high levels of magnesium in the plasma. The most immediate danger to life is respiratory depression. A preparation of calcium, such as the gluconate or gluceptate, should be at hand for intravenous administration as an antidote.

IV use in eclampsia should be reserved for immediate control of life-threatening convulsions.

### FETAL HARM:

Magnesium Sulfate Injection, USP 50% can cause fetal harm when administered to a pregnant woman. When Magnesium Sulfate Injection is administered to a toxic mother, the newborn is usually not compromised. When Magnesium Sulfate Injection is administered intravenously by a continuous infusion for longer than 24 hours before delivery, the possibility of the baby showing signs of neuromuscular or respiratory depression of the newborn should be considered, since fetal toxicity can occur. A baby with hypermagnesemia may require resuscitation and assisted ventilation. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Continuous administration of magnesium sulfate (intravenous or intramuscular) 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 for treatment of preeclampsia and eclampsia of pregnancy only if clearly needed and for the shortest time required.

### ALUMINIUM TOXICITY:

This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions which contain aluminum. Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 µg per kg per day accumulate aluminum at levels associated with

central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration of TPN products and of the lock-flush solutions used in their administration.

## **PRECAUTIONS**

### **General**

Administer with caution if flushing and sweating occurs. When barbiturates, narcotics or other hypnotics (or systemic anesthetics) are to be given in conjunction with magnesium, their dosage should be adjusted with caution because of additive CNS depressant effects of magnesium. A preparation of calcium salt should be readily available for intravenous injection to counteract potential serious signs of magnesium intoxication.

Since magnesium is excreted almost entirely by the kidneys, it should be given very cautiously in the presence of serious impairment of renal function.

### **Laboratory Tests**

Magnesium Sulfate Injection, USP 50% should not be given unless hypomagnesemia has been confirmed and the serum concentration of magnesium is monitored. The normal serum level is 1.5 to 2.4 mEq/L.

### **Drug Interactions**

When barbiturates, narcotics, hypnotics (or systemic anesthetics), or other central nervous system depressants are to be given in conjunction with magnesium, their dosage should be adjusted with caution because of the additive central nervous system depressant effects of magnesium.

Central nervous system depression and peripheral transmission defects produced by magnesium may be antagonized by calcium.

### **Pregnancy**

See **WARNINGS**.

Magnesium sulfate should be used for treatment of preeclampsia and eclampsia of pregnancy only if clearly needed and for the shortest time required.

Magnesium sulfate 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, osteopenia and other skeletal abnormalities with continuous maternal administration of magnesium sulfate for more than 5 to 7 days.<sup>1-10</sup>

### **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 Injection, USP 50% is administered to a nursing woman.

### **Usage in Children**

Safety and effectiveness in children have not been established.

## ADVERSE REACTIONS

Principal adverse reactions are related to the high plasma levels of magnesium and include flushing, sweating, hypotension, circulatory collapse, and cardiac and central nervous system depression. Respiratory depression is the most life-threatening effect.

### **REPORTING SUSPECTED SIDE EFFECTS**

**To monitor drug safety, Health Canada, through the Canada Vigilance Program, collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug, you may notify Canada Vigilance:**

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](http://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
  - Mail to: Canada Vigilance Program  
Health Canada  
Postal Locator 0701E  
Ottawa, ON 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](http://www.healthcanada.gc.ca/medeffect).

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

## OVERDOSAGE

Hypermagnesemia is manifested by muscle weakness, hypotension, ECG changes, sedation, and confusion. As plasma concentrations of magnesium begin to exceed 4 mEq/L, the deep-tendon reflexes are decreased and may be absent at levels approaching 10 mEq/L. At 12 to 15 mEq/L, respiratory paralysis is a potential hazard; the respiratory effects can be antagonized to some extent by the intravenous administration of calcium salts. In cases of severe renal impairment, symptomatic hypermagnesemia may be an indication for dialysis. Although man usually tolerates high concentrations of magnesium in plasma, there are occasional instances when cardiac consequences may be seen in the form of complete heart block at concentrations well below 10 mEq/L.

Before the parenteral administration of each dose, the respiratory rate should be at least 16 per minute and urinary function should be adequate. In the event of overdosage, assisted ventilation must be provided until calcium can be given intravenously. Peritoneal dialysis or hemodialysis may be required in cases of extreme hypermagnesemia.

When Magnesium Sulfate Injection, USP 50% is administered parenterally in doses that are

sufficient to induce hypermagnesemia, the drug has a depressant effect on the central nervous system and, via the peripheral neuromuscular junction, on muscle.

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

## **DOSAGE AND ADMINISTRATION**

### **Intramuscular**

Adults and older children for severe hypomagnesemia 1 to 5 g (2 to 10 mL of 50% solution) daily in divided doses; administration is repeated daily until serum levels have returned to normal. If deficiency is not severe, 1 g (2 mL of 50% solution) can be given once or twice daily. Serum magnesium levels should serve as a guide to continued dosage.

### **Intravenous**

1 to 4 g Magnesium Sulfate Injection, USP 50% may be given intravenously in 10% to 20% solution, but only with great caution; the rate should not exceed 1.5 mL of 10% solution or equivalent per minute until relaxation is obtained.

IV use in eclampsia should be reserved for immediate control of life-threatening convulsions. See **WARNINGS**.

### **Intravenous Infusion**

4 g in 250 mL of 5% Dextrose Injection, USP at a rate not exceeding 3 mL per minute.

### **Usual Dose Range**

1 to 40 g daily.

### **Electrolyte Replenisher**

Intramuscular 1 to 2 g in 50% solution four times a day until serum magnesium is within normal limits.

### **Usual Pediatric Dose**

Intramuscular 20 to 40 mg/kg of body weight in a 20% solution repeated as necessary.

### **For Pre-eclampsia or Eclampsia**

Initially 1 to 2 g in 25% or 50% solution is given intramuscularly. Subsequently, 1 g is given every 30 minutes until relief is obtained. The blood pressure should be monitored after each injection.

Magnesium sulfate should be used for treatment of preeclampsia and eclampsia of pregnancy only if clearly needed and for the shortest time required. See **WARNINGS**.

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

## AVAILABILITY OF DOSAGE FORMS

Product Number	Magnesium per mL	Sulfate per mL	Volume
C96410P*	49.3 mg	194.7 mg	10 mL in a 20 mL vial
C6450 <sup>+</sup>	49.3 mg	194.7 mg	50 mL

\*Packaged in a plastic vial.

<sup>+</sup>Pharmacy Bulk Package – Not for Direct Infusion

Store vials between 15 and 30°C.

**No preservative added.** Unused portion of container should be discarded. Use only if solution is clear, and seal intact.

## REFERENCES:

1. Yokoyama K, Takahashi N, Yada Y. Prolonged maternal magnesium administration and bone metabolism in neonates. *Early Hum 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. Holcomb 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 effects of maternal magnesium sulfate treatment on newborns: a prospective controlled study. *J Perinatol*. 1998;18(6 pt 1):449-54.

**PHARMACEUTICAL PARTNERS OF CANADA INC.**

Richmond Hill, ON L4B 3P6

☎ 1-877-821-7724

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