

DBL™ Magnesium Sulfate Concentrated Injection (Magnesium Sulfate Heptahydrate)

1. NAME OF THE MEDICINE

Magnesium sulfate heptahydrate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains 2.465 g magnesium sulfate heptahydrate (493 mg/mL). Each mL of injection contains 2 mmol (4 mEq) of magnesium ions and 2 mmol (4 mEq) of sulfate ions.

For the full list of excipients, see Section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

DBL™ Magnesium Sulfate Concentrated Injection is a clear, colourless, sterile solution. The pH of the solution ranges between 5.5 and 7.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Parenteral administration of magnesium is indicated in the treatment of acute hypomagnesaemia.

Magnesium salts are also indicated to prevent hypomagnesaemia in patients receiving total parenteral nutrition.

Magnesium sulfate heptahydrate is also indicated in the prevention and treatment of life threatening seizures in the treatment of toxemias of pregnancy (pre-eclampsia and eclampsia).

4.2 Dose and Method of Administration

Magnesium sulfate heptahydrate is administered intravenously or intramuscularly.

Intravenous doses should be diluted to a concentration of 20% magnesium or less. For intravenous dosing, each 5 mL ampoule of DBL™ Magnesium Sulfate Concentrated Injection should be diluted by adding at least 7.5 mL of a compatible solution (see section 4.2 **Dose and Method of Administration - Compatibilities**).

For intramuscular dosing, a concentration of 25 to 50% is satisfactory for adults, while a concentration of 20% should be used for infants or children. For adult intramuscular

administration dilution of DBL™ Magnesium Sulfate Concentrated Injection is not required, but each 5 mL ampoule could be diluted by adding up to 5 mL of a compatible solution.

The dose of magnesium should be adjusted according to the patients individual requirements and response.

The total adult daily dose should not exceed 30 to 40 g of magnesium sulfate heptahydrate per day.

Mild hypomagnesaemia: *Adults:* A dose of 1 g magnesium sulfate heptahydrate (8 mEq) intramuscularly every 6 hours for 4 doses is recommended.

Severe hypomagnesaemia: *Adults:* A dose of 0.25 g/kg magnesium sulfate heptahydrate intramuscularly over 4 hours is recommended. Alternatively a dose of 5 g may be given by slow intravenous infusion over 3 hours.

Total parenteral nutrition: *Adults:* A dose of 0.5 to 3.0 g magnesium sulfate heptahydrate (4 to 24 mEq) daily may be administered.

Infants: A dose of 0.25 to 1.25 g magnesium sulfate heptahydrate (2 to 10 mEq) daily may be administered.

Toxemia of pregnancy: An initial intravenous dose of 4 g magnesium sulfate heptahydrate is recommended. This is followed by an intramuscular dose of 4 to 5 g into each buttock. This may be followed by a dose of 4 to 5 g into alternate buttocks every four hours as needed.

Alternatively, the initial IV dose may be followed by an infusion of 1 to 2 g/hr.

Compatibilities

Magnesium sulfate heptahydrate is reported to be chemically stable and compatible with either sodium chloride 0.9%, lactated Ringer's injection, glucose 5% in water, or glucose 5% in sodium chloride 0.9%. It has been reported that at a concentration of 15 g/L, magnesium sulfate heptahydrate is chemically stable and compatible in all the infusion fluids listed above for 24 hours and stored below 25°C. However, in order to reduce microbial contamination, the further diluted solutions should be prepared, stored and used within 24 hours.

4.3 Contraindications

Magnesium is contraindicated in patients with heart block, since magnesium may exacerbate this condition.

Magnesium is also contraindicated in patients with renal failure (creatinine clearance <20 mL/min), since there is an increased risk of hypermagnesaemia in these patients.

Magnesium sulfate heptahydrate should not be administered to pregnant women in the two hours prior to delivery, unless it is the only therapy available to prevent eclamptic seizures. There is a risk that the neonate will be born with hypermagnesaemia and

depressed breathing.

4.4 Special Warnings and Precautions for Use

Magnesium sulfate heptahydrate may precipitate an acute myasthenic crisis. Sensitivity to parenteral magnesium has been reported.

An intravenous preparation of a calcium salt (e.g., calcium gluconate) should be readily available for use when magnesium sulfate heptahydrate is given intravenously.

Use in renal impairment

Magnesium should be administered with caution in patients with impaired renal function, since the risk of hypermagnesaemia is increased in these patients.

Use in the elderly

No data available.

Paediatric use

No data available.

Effects on laboratory tests

Monitoring of serum magnesium levels is advised at periodic intervals during therapy to ensure that normal serum magnesium levels are not exceeded.

The patellar reflex should be tested prior to administering repeat doses of magnesium sulfate heptahydrate. Suppression of the reflex is an indication of magnesium intoxication.

Respiration rate should be determined and should be at least 16 per minute prior to each dose of magnesium sulfate heptahydrate, as respiratory depression is the most critical side effect of the medication.

Urine output should be monitored and should be at least 100 mL during the four hours preceding dosing, to ensure adequate excretion of magnesium.

4.5 Interactions with Other Medicines and Other Forms of Interactions

Cardiac glycosides/digitalis: Magnesium salts should be administered with caution in patients treated with cardiac glycosides, since heart block may occur if calcium salts are required to treat magnesium toxicity (see section 4.9 **Overdose**).

CNS depressants: Concurrent use of magnesium salts and CNS depressant drugs may result in an enhanced CNS depressant effect.

Neuromuscular blocking agents: Concurrent use of magnesium salts with neuromuscular blocking agents may result in an excessive neuromuscular blockade.

Nifedipine: Concurrent use of magnesium sulfate heptahydrate and nifedipine may result in an exaggerated hypotensive response.

Also refer to section 6.2 **Incompatibilities**.

4.6 Fertility, Pregnancy and Lactation

Effects on fertility

No data available.

Use in pregnancy

Magnesium sulfate heptahydrate is administered to pregnant women to treat seizures associated with severe pre-eclampsia and eclampsia. Magnesium sulfate heptahydrate readily crosses the placenta. Foetal serum concentrations approximate those of the mother. If magnesium sulfate heptahydrate is administered in the two hours preceding delivery, the neonate may be born with signs of hypermagnesaemia, including respiratory depression, and therefore DBL™ Magnesium Sulfate Concentrated Injection should not be given in the two hours preceding delivery unless it is the only therapy available to prevent or treat eclamptic seizures.

Bony abnormalities and congenital rickets have been reported in neonates born to mothers treated with parenteral magnesium sulfate heptahydrate for prolonged periods of time (5-7 days duration).

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.

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.

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.

Use in lactation

After intravenous administration, magnesium is distributed into breast milk, and the concentration of magnesium in the breast milk is approximately twice that in the maternal serum. Magnesium salts should therefore be used with caution in lactating patients. However, magnesium is cleared from the breast milk within 24 hours of the cessation of the infusion.

4.7 Effects on Ability to Drive and Use Machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse Effects (Undesirable Effects)

Excessive administration of magnesium sulfate heptahydrate may result in hypermagnesaemia. The signs of hypermagnesaemia may include: nausea, vomiting, flushing, hypotension, muscle weakness, muscle paralysis, blurred or double vision, CNS depression and loss of reflexes. More severe hypermagnesaemia may result in

respiratory depression, respiratory paralysis, renal failure, coma, cardiac arrhythmias and cardiac arrest. Hypocalcaemia with tetany, secondary to hypermagnesaemia, has been reported.

After intramuscular injection, irritation and pain at the injection site may result.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

Clinical features

Hypermagnesaemia may occur when large doses of magnesium are given, especially in patients with renal failure. Signs of hypermagnesaemia include: nausea, vomiting, flushing, hypotension, muscle weakness, muscle paralysis, blurred or double vision, CNS depression and loss of reflexes. More severe hypermagnesaemia may result in respiratory depression, respiratory paralysis, renal failure, coma, cardiac arrhythmias and cardiac arrest.

Treatment

In the treatment of hypermagnesaemia, the following measures may be required:

- blood pressure and respiratory support
- intravenous administration of 2.5 to 10 mmol calcium salts (such as calcium gluconate) reverses the effects of magnesium toxicity
- dialysis may be required, particularly if renal function is impaired
- if renal function is normal, adequate fluids should be given so that urine output is at least 60 mL/hr to assist removal of magnesium from the body.
- physostigmine (0.5 to 1.0 mg subcutaneously) may be helpful, but routine use is not recommended due to the potential toxicity.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Magnesium is the second most abundant cation of intracellular fluid. It is an essential cation in over 300 enzymatic processes, and is necessary for several steps in glycolysis, the Krebs cycle and in protein and nucleic acid synthesis. It is thus vital for normal energy storage and transfer. Magnesium plays an important role in neurochemical transmission, and is essential for proper neurochemical functioning.

Magnesium has an anticonvulsant effect. It possibly has antiarrhythmic effects and a role in calcium homeostasis and bone mineralisation. There is conflicting evidence that the routine use of intravenous magnesium sulfate heptahydrate in the setting of acute myocardial infarction is beneficial.

Deficiency of magnesium is closely associated with other electrolyte disturbances,

particularly hypocalcaemia and hypokalaemia. The specific symptoms of hypomagnesaemia are therefore difficult to determine, but may include nausea, vomiting, muscle weakness, neuromuscular dysfunction such as paraesthesia, tremor and cramp, tachycardia and cardiac arrhythmias.

Clinical trials

No data available.

5.2 Pharmacokinetic Properties

The 95% confidence intervals for magnesium levels in healthy Australian subjects are: neonate 0.6 to 0.9 mmol/L and adult 0.8 to 1.0 mmol/L.

Approximately 50% of magnesium in the body is found in bone, with the majority of the remainder stored in muscle and soft tissue. 1% or less is contained in the extracellular compartment, of which approximately 33% is protein-bound, with a further 12% bound to anions.

Magnesium is primarily excreted in the urine, with small amounts excreted in faeces, saliva and breast milk. Over 90% of magnesium filtered by the kidneys is reabsorbed, mainly in the ascending limb of the Loop of Henle, with significant amounts also absorbed in the proximal and distal tubules. The clearance is proportional to the plasma magnesium concentration and the glomerular filtration rate. The onset of action after intramuscular injection is about 1 hour and after intravenous injection is nearly immediate. The duration of action after intramuscular injection is 3 to 4 hours, and after intravenous injection is about 30 minutes.

5.3 Preclinical Safety Data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Water for injections

6.2 Incompatibilities

Magnesium sulfate is incompatible with calcium salts. Calcium sulfate may precipitate when calcium salts are mixed with magnesium sulfate in the same intravenous solution.

Magnesium salts have also been reported to be incompatible with alkali carbonates and bicarbonates and soluble phosphates.

Also refer to section 4.5 **Interactions with Other Medicines and Other Forms of Interactions.**

6.3 Shelf Life

Please refer to the outer carton for the expiry date.

6.4 Special Precautions for Storage

Please refer to the outer carton for recommended storage condition.

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