Magnesium Sulfate 50% w/v Solution for Injection

By Intramuscular/Intravenous

1. Qualitative and quantitative composition:

Each ml Contains:

Magnesium Sulfate USP.

Eq. to 4m Eq. of Mg and S04/ml ……. 500mg

Water for Injection USP …… q.s.

2. Pharmaceutical form:

Solution for Injection

3. Clinical Particulars

3.1 Therapeutic indications

1. Treatment of Magnesium deficiency in hypomagnesaemia where the oral route of administration may be inappropriate.
2. To prevent further seizures associated with eclampsia.

3.2 **Posology and method of administration:**

Dosage should be individualized according to patient's needs and responses. Plasma levels should also be monitored throughout therapy.

a) Treatment of magnesium deficiency in hypomagnesaemia:

For intravenous administration, a concentration of 20% or less should be used; the rate of injection not exceeding 1.5ml/minute of a 10% solution or its equivalent.

Up to 40g $MgSO_4$ (equivalent to 160mmol Mg^{2+}) by slow intravenous infusion (in glucose 5%) over up to 5 days, may be required to replace the deficit (allowing for urinary losses).

Mild magnesium deficiency

1g intramuscularly every 6 hours for 4 doses.

Severe magnesium deficiency

Up to 250mg/kg intramuscularly given within a period of 4 hours or 5g/litre of infusion solution intravenously over 3 hours

Paediatric population

It is recommended that the solution be diluted to 20% w/v prior to intramuscular injection

Elderly

No special recommendation except in renal impairment, see below

Renal impairment:

Dosage should be reduced in renal impairment. Plasma magnesium concentrations should be monitored throughout therapy

b) To prevent further seizures associated with eclampsia:

An initial intravenous (IV) loading dose is followed for 24h by either an IV infusion, or regular intramuscular (IM) injections.

Intramuscular Maintenance Regimen

A loading dose of 4g $MgSO_4$ (approx. 16mmol Mg^{2+}) IV (usually in 20% solution) over 5min (minimum, preferably 10-15 min) is followed immediately by 5g $MgSO_4$ (approx. 20mmol Mg^{2+}) (usually in 50% solution) as a deep IM injection into the upper outer quadrant of each buttock.

Maintenance therapy is a further 5g $MgSO_4$ (approx. 20mmol Mg^{2+}) IM every 4h, continued for 24h after the last fit (provided the respiratory rate is >16/min, urine output >25ml/h, and knee jerks are present).

Intravenous Maintenance Regimen

A loading dose of 4g $MgSO_4$ (approx. 16mmol Mg^{2+}) IV (or in some cases 5g $MgSO_4$ (approx. 20mmol Mg^{2+}) IV), as described above, is followed by an infusion of 1g/h continued for 24h after the last fit.

Recurrent Convulsions: In both the IM and IV regimens, if convulsions recur, a further 2-4g $MgSO_4$ (approx. 8 - 16mmol Mg^{2+}) (depending on the woman's weight, 2g $MgSO_4$ (approx. 8mmol Mg^{2+}) if less than 70Kg) is given IV over 5 min.

Appropriate reductions in dosage should be made for patients with renal impairment; a suggested dose reduction in severe renal impairment is a maximum of 20g $MgSO_4$ (approx. 80mmol Mg^{2+}) over 48 hours.

Method of administration

Magnesium sulfate injection may be administered by intramuscular or intravenous routes.

Intramuscular therapy should be used only when peripheral venous access is impossible.

3.3 Contraindications

Hypersensitivity to magnesium and its salts or to any of the excipients.

Magnesium sulfate is contraindicated in patients with severely impaired renal function

3.4 Special Warnings and Special Precautions for Use

Magnesium sulfate must be used with caution in patients suspected of or known to have renal impairment.

Magnesium sulfate should not be used in hepatic coma if there is a risk of renal failure.

Parenteral magnesium salts should be used with caution in patients with myasthenia gravis.

Serum calcium levels should be routinely monitored in patients receiving magnesium sulfate.

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3.5 Interaction with other medicinal products and other forms of interaction

Administer with caution to patients receiving digitalis glycosides. Magnesium sulfate should not be administered concomitantly with high doses of barbiturates, opiods or hypnotics due to the risk of respiratory depression

The action of non-depolarising muscle relaxants such as tubocurarine is potentiated and prolonged by parenteral magnesium salts.

Concomitant use of calcium channel blockers such as nifedipine or nimodipine may rarely lead to a calcium ion imbalance and could result in abnormal muscle function.

The neuromuscular blocking effects of parenteral magnesium and aminoglycoside antibacterials may be additive.

3.6 Fertility, Pregnancy and Lactation

Pregnancy

Safety in human pregnancy has not been established, however, in the medical emergency of a patient having Eclampsia, Magnesium Sulfate can be administered to relieve this condition, which may be life threatening to both mother and baby.

Magnesium crosses the placenta. When used in pregnant women, foetal heart rate should be monitored and use within 2 hours of delivery should be avoided.

Magnesium sulfate can cause skeletal adverse effects when administered continuously for more than 5 to 7 days to pregnant women. There are retrospective epidemiological studies and case reports documenting fetal adverse effects including hypocalcaemia, skeletal demineralization, osteopenia and other skeletal adverse effects with maternal administration of magnesium sulfate for more than 5 to 7 days. The clinical significance of the observed effects is unknown.

If prolonged or repeated exposure to magnesium sulfate occurs during pregnancy monitoring of neonates for abnormal calcium or magnesium levels and skeletal adverse effects should be considered.

Breast-feeding

As with all drugs it is not advisable to administer magnesium sulfate during pregnancy or breastfeeding unless considered essential, and it must be administered under medical supervision.

Fertility

No studies and/or data are available on the effects on fertility.

3.7 Effects on ability To Drive and use Machines

No studies on the effects on the ability to drive and use machines have been performed.

3.8 Undesirable Effects

Metabolism and nutrition disorders

Electrolyte/fluid abnormalities (hypophosphataemia, hypertonic dehydration)

Hypersensitivity reactions.

Hypocalcaemia.

Pain or burning at the injection site following IV/IM administration.

Hypermagnesaemia characterised by flushing, sweating, thirst, hypotension, drowsiness, dizziness, headache, risk of itching and tingling, nausea, vomiting, confusion, slurred speech, double vision, loss of tendon reflexes due to neuromuscular blockade, muscle

weakness, respiratory depression, electrolyte/fluid abnormalities (hypophosphataemia, hyperosmolar dehydration), ECG changes (prolonged PR, QRS and QT intervals), bradycardia, tachycardia cardiac arrhythmias, coma and cardiac arrest.

There have been isolated reports of maternal and fetal hypocalcaemia with high doses of magnesium sulfate

3.9 Overdose

Appropriate action should be taken to reduce the blood level of magnesium to avoid hypermagnesaemia. Neuromuscular blockade associated with hypermagnesaemia may be reversed with calcium salts, such as Calcium Gluconate, which should be administered intravenously in a dose equivalent to 2.5 to 5mmol of calcium.

4. Pharmacological Properties

4.1 Pharmacodynamics :

Pharmacotherapeutic group: Mineral Supplements,

ATC code: A12CC02.

Magnesium is the second most abundant cation in intracellular fluid and is an essential body electrolyte. Magnesium is a factor in a number of enzyme systems, and is involved in neurochemical transmission and muscular excitability.

Parenterally administered magnesium sulfate exerts a depressant effect on the central nervous system and acts peripherally to produce vasodilation.

4.2 Pharmacokinetic:

Absorption

When magnesium is administered intravenously, the onset of action is immediate and last for approximately 30 minutes. Following intramuscular administration, the onset of action occurs within 1 hour and the duration of action is 3 to 4 hours.

Upon intramuscular administration, the plasma concentration of magnesium sulfate shows a slow increase that reaches a plateau within 1 to 2 hours and is followed by a slow decline back to baseline within the next 6 to 8 hours. At the end of 4 hours, after another intramuscular injection of magnesium sulfate, the plasma concentration remains constant.

Distribution

Plasma protein binding of injected magnesium is comparable to endogenous magnesium. About 40% to 50% of plasma magnesium is protein bound and not ultrafiltrable.

The amount of ionised magnesium (the active form of magnesium according to both in vivo and in vitro studies) rose proportionately to the total serum magnesium concentration. In a pharmacokinetic study in women with preeclampsia, demonstrated lack of correlation between total magnesium and ionised magnesium levels in both physiologic and hypermagnesmic (pharmacologic) ranges.

Several attempts have been made to estimate the apparent volume of distribution (Vd) of magnesium. Unlike non-pregnant healthy volunteers, where Vd reaches constant values within 2 hours after administration, the apparent Vd in pregnant women becomes constant within 3 to 4 hours and ranges from 0.250 to 0.442 L/kg. Another study estimated the Vd in the range of 0.370 to 0.430 L/kg 24 hours after administration. The pharmacokinetic profile of magnesium sulfate after intravenous administration can be described by a 2-compartment model with a rapid distribution (a) phase, followed by a relative slow beta phase of elimination, where central compartment (Vc) and terminal phase (Vβ) volumes were 0.250±0.010 L/kg and 0.570±0.022 L/kg, respectively.

The unbound magnesium ions diffuse into the extravascular-extracellular space, bones, cross the placenta and are rapidly taken up by foetal tissues and thus magnesium in amniotic fluid, the foetus and in neonates of mothers treated with magnesium sulfate show increased concentrations as compared to untreated mothers.

When the mother receives 1 to 2 g/h magnesium infusions, foetal serum magnesium concentrations are twice as high as control concentrations, the highest concentrations observed in umbilical and venous and arterial blood. Foetal magnesium plasma concentrations equalise with the maternal within 2 hours, while the increase in amniotic fluid occurs more slowly. The mean baseline cerebrospinal fluid (CSF) magnesium level in preeclamptic women was 1.1 ±0.05 mmol/L.

Intrapartum magnesium sulfate treatment increased breast milk/colostrum magnesium levels significantly only for 24 hours. After 24 hours magnesium levels in breast milk

comes back to normal. Breast milk/colostrum calcium levels were not affected by magnesium sulfate therapy.

Biotransformation and Elimination

Magnesium sulfate is not metabolised and is excreted solely by the kidney.

Urinary excretion is very rapid with a 20-fold increase during magnesium sulfate infusion. About 38 to 53% of the total injected magnesium is excreted 4 hours after the end of the infusion and >90% are eliminated within 24 hours after the infusion.

In patients with normal renal function, the increase in magnesium clearance is linear to the serum magnesium concentrations and the half-life of magnesium is 4 hours. Half-life increases with decrease in glomerular filtration rate.

Urinary calcium concentration increases 4.5-fold during infusion of magnesium sulfate and there is a 3-fold increase in urinary calcium excretion rate which is likely due to competition for common reabsorption sites.

4.3 Preclinical Safety Data

Not Applicable

5. Pharmaceutical Particulars

5.1 List of Excipients

Water For Injection USP

5.2 Incompatibilities

Streptomycin sulfate and tetramycin sulfate activity is inhibited by magnesium ions

5.3 Shelf Life

36 Months

5.4 Special Precautions for Storage

Do not store above 25°C.

5.5 Nature and Contents of Container

10 ml clear glass ampoule and 5 ampoules are tray packed in packed in carton with pack insert.

6. Registrant (Marketing Authorization Holder And Manufacturing Site Addresses)

6.1 Name and Address of Marketing Authorization Holder

6.2 **Name and Address of manufacturing site(s)**

Divine Laboratories Pvt. Ltd.

Block No.:471, Dabhasa, Tal.; Padra, Dist. Vadodara, India.

6.3 **Marketing Authorization Number**

To be included after obtaining first registration.

6.4 **Date of First <Registration> / Renewal of The <Registration>**

It will be applicable after registration of this product.

6.5 **Date of Revision of the Text**

6.6 **Dosimetry (If Applicable)**

Not Applicable

6.7 **Instructions for preparation of radiopharmaceuticals (if Applicable)**

Not Applicable