SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Magnesium sulfate / DEMO 10% w/v solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 mL ampoule contains 1 g magnesium sulfate heptahydrate (100 mg/mL).

1 mL contains 0.406 mmol (9.86 mg = 0.811 mEq) magnesium anions.

Each ampoule contains 1 g of magnesium sulfate heptahydrate, 98.6 mg or 4.06 mmol (8.11 mEq) of elemental magnesium.

Clear, colourless solution, free from visible particles.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection or infusion, with a pH of between 5.5 and 7 and osmolality of 400 mOsm/kg approximately.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Parenteral administration of magnesium is indicated in:
- treatment and prophylaxis of acute hypomagnesemia.
- prevent hypomagnesemia in patients receiving total parenteral nutrition.
- prevention and treatment of life-threatening seizures in the treatment of toxemias of pregnancy (pre-eclampsia and eclampsia).

4.2 Posology and method of administration

Magnesium sulfate 10% w/v solution is to be administered by the intravenous route (see below for method of administration and section 4.4).

Posology

Dosage should be tailored according to the individual's needs and responses and should be reduced in renal impairment. Plasma magnesium concentrations should be measured to determine the rate and duration of infusion and should be monitored throughout therapy.

1 g Magnesium sulfate heptahydrate = 98.6 mg or 8.2 mEq or 4.1 mmol Mg^{2+}.

Treatment of magnesium deficiency in proven hypomagnesaemia

Adults:
Up to 400 mL Magnesium sulfate 10% w/v solution (corresponding to 160 mmol ≈ 4 g Mg^{2+}) should be administered by slow intravenous infusion over a period of up to five days and titrated to clinical need. The usual regimen is 80 – 120 mL Magnesium sulfate 10% w/v solution (corresponding to 32 – 48 mmol ≈ 0.8 – 1.2 g Mg^{2+}) in the first 24 hours followed by 40 – 60 mL Magnesium sulfate 10% w/v solution (corresponding to 16 – 24 mmol ≈ 0.4 – 0.6 g Mg^{2+}) per day for 3 or 4 days.

Children and adolescents:

Neonate
1 mL/kg Magnesium sulfate 10% w/v solution (corresponding to 0.4 mmol/kg ≈ 0.01 g/kg Mg^{2+}) every 6 – 12 hours as required, to be given by intravenous injection over at least 10 minutes.
Child 1 month – 11 years
0.5 mL/kg Magnesium sulfate 10% w/v solution (corresponding to 0.2 mmol/kg ≈ 0.005 g/kg Mg^{2+}) every 12 hours as required, to be given by intravenous injection over at least 10 minutes.
Adolescent 12-17 years
10 mL Magnesium sulfate 10% w/v solution (corresponding to 4 mmol ≈ 0.1 g Mg^{2+}) every 12 hours as required, to be given by intravenous injection over at least 10 minutes.

Elderly:
There are no specific recommendations for dosage in elderly adults. Magnesium sulfate 10% w/v solution should be used with caution in elderly because of often renal impairment in this age group.

Prevention of hypomagnesaemia in patients receiving total parenteral nutrition

Adults:
25 – 50 mL Magnesium sulfate 10% w/v solution (corresponding to 10 – 20 mmol ≈ 0.25 – 0.5 g Mg^{2+}) daily, usual dose 30 mL Magnesium sulfate 10% w/v solution (corresponding to 12 mmol ≈ 0.3 g Mg^{2+}) daily, by intravenous infusion.

Neonates and infants (up to 12 months):
0.5 mL/kg Magnesium sulfate 10% w/v solution (corresponding to 0.2 mmol/kg = 0.005 g/kg Mg^{2+}) daily by intravenous infusion.

Children (1 – 13 years) and adolescents (14 – 18 years):
0.25 mL/kg Magnesium sulfate 10% w/v solution (corresponding to 0.1 mmol/kg ≈ 0.0025 g/kg Mg^{2+}) daily by intravenous infusion.

Control and prevention of recurrent seizures in severe pre-eclampsia and eclampsia

Adult women:
Loading dose: An initial IV loading dose of approximately 40 – 50 mL Magnesium sulfate 10% w/v solution (corresponding to 16 – 20 mmol ≈ 0.4 – 0.5 g Mg^{2+}) diluted to an appropriate volume over 5 – 15 minutes is followed by a maintenance regimen of either an intravenous infusion of Magnesium sulfate 10% w/v solution, or regular IM injections using Magnesium sulfate 50% w/v solution for 24 hours after the last fit, provided respiratory rate is > 16/min, urine output > 25 mL/min and knee jerks are present, as follows:

IV Maintenance Regimen
The IV loading dose (above) is followed by an infusion of approximately 10 mL Magnesium sulfate 10% w/v solution (corresponding to 4 mmol ≈ 0.1 g Mg^{2+}) per hour for at least 24 hours after the last fit.

IM Maintenance Regimen
This concentration is not suitable for intramuscular use.
The IM injections are possible only using another, higher concentrated preparation (e.g. Magnesium sulfate 50% w/v solution).

The IV loading dose (above) is immediately followed by deep IM injection of 10 mL Magnesium sulfate 50% w/v solution (corresponding to 20 mmol ≈ 0.5 g Mg^{2+}).
Thereafter, 10 mL Magnesium sulfate 50% w/v solution (corresponding to 20 mmol ≈ 0.5 g Mg^{2+}) is administered every four hours IM, and continued for 24 hours after the last fit.

Recurrent convulsions: In both IV and IM regimens, a further 20 – 40 mL Magnesium sulfate 10% w/v solution (corresponding to 8 – 16 mmol ≈ 0.2-0.4 g Mg^{2+}) depending on body weight [if less than 70 kg 20 mL Magnesium sulfate 10% w/v solution (corresponding to 8 mmol ≈ 0.2 g Mg^{2+})] are given IV over a period of 5 minutes.

Renal impairment
Magnesium sulfate 10% w/v solution is contraindicated in patients with severe renal impairment (see section 4.3)
Magnesium sulfate 10% w/v solution should be used with caution in mild to moderate renal impairment. A reduction in dosage to 200 mL Magnesium sulfate 10% w/v solution (corresponding to 80 mmol ≈ 2 g Mg^{2+}) over 48 hours may be given.

Patients with impaired liver function
There are no recommended special dosage instructions for patients with impaired liver function because of insufficient data.

Method of administration

For the intravenous route the 10% solution does not require dilution. Magnesium sulfate 10% w/v solution is not appropriate for intramuscular administration. Only the 50% w/v solution available may be used intramuscularly.

Intravenous use in children:
Rate of administration should not exceed 0.1 mL/kg/min Magnesium sulfate 10% w/v solution (corresponding to 0.04 mmol/kg/min ≈ 0.001 g/kg/min Mg^{2+}).

Use in adults and adolescents

Intravenous infusion: Infuse via a volumetric infusion device at a rate appropriate to the indication (see posology above).

Intravenous injection: Give by slow IV injection at a rate appropriate to the indication (see posology above).

Deep intramuscular injection: Magnesium sulfate 10% w/v solution is not recommended for intramuscular injection. However, when using the IV loading/IM maintenance regimen above, ensure that the 50% w/v solution is used undiluted or diluted to 25% w/v solution. If the total dose to be administered exceeds 5 mL, the injection volume should be divided between more than one deep muscular injection site.

Compatibilities: Magnesium sulfate 50% w/v admixtures with Sodium chloride 9 mg/mL solution for injection and Dextrose 50 mg/mL solution for injection, is stable for 48 hours at 25 ± 2°C and at 5 ± 3°C at a concentration of 20% (equal to 200 mg/mL).

4.3 Contraindications

Hypersensitivity to magnesium and its salts or to any of the excipients listed in section 6.1.
Hepatic encephalopathy, hepatic failure, renal failure.
Severe renal impairment (glomerular filtration rate under 25 mL/h), anuria.
Parenteral administration of the medicinal product is contraindicated in patients with heart block (class I-III) or myocardial damage and myasthenia gravis.

Magnesium sulfate 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 hypermagnesemia 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 (eg 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 Interaction with other medicinal products and other forms of interaction

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 magnesium sulfate heptahydrate 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).

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 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the National Pharmaceutical Regulatory Agency (NPRA) Adverse Drug Reaction Centre by visiting the website www.npra.gov.my.

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

Pharmacotherapeutic group: Other mineral supplements, magnesium sulfate
ATC code: A12CC02

Magnesium is the second most abundant cation in intracellular fluid and is an essential body electrolyte.
The body contains about 25 g of magnesium (about 14 mmol per kg body weight), approximately 60% of which is found in the skeleton. The daily amount of magnesium required by an adult is of the order of 270 to 350 mg (about 11 to 14 mmol). Symptomatic hypomagnesaemia is associated with a deficit of 0.5 – 1.0 mmol/kg.

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 efficacy and safety
The normal concentration of magnesium in plasma is around 0.65 to 1.0 mmol/L. Serum magnesium levels in the range 1.5 – 2.5 mmol/L cause vasodilatation in the peripheral and coronary circulation and corresponding increases of 20 – 25% in cardiac output and coronary blood flow. There is little change in heart rate or blood pressure. Animal studies suggest that the effect of magnesium ions on cardiac muscle is to slow the rate of the sinoatrial node impulse formation and prolong conduction time. Limited data on patients with no evidence of heart disease indicate that intravenous magnesium prolongs PR interval, H (atria-His bundle) interval, antegrade AV nodal effective refractory period and sinoatrial conduction time. Within this concentration range there are no detectable effects on CNS function or neuromuscular transmission.
When given intravenously, magnesium sulfate has an immediate onset of action and its duration of activity is about 30 minutes. The onset of action of intramuscular magnesium sulfate is about one hour and its duration of action 3 – 4 hours.

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 intravenous injection is nearly immediate. The duration of action after intravenous injection is about 30 minutes.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber additional to those already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections
Sulfuric acid (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products/diluents except Glucose 5% or sodium chloride 0.9%.

Magnesium sulfate is incompatible with alkali hydroxides (forming insoluble magnesium hydroxide), alkali carbonates (forming insoluble magnesium carbonate) and salicylates. The activities of streptomycin sulfate and tetramycin sulfate are inhibited by magnesium ions.

6.3 Shelf life

36 months

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibilities of the user.

6.4 Special precautions for storage

Store below 30˚C.
After opening, the product should be used immediately.

6.5 Nature and contents of container

Polypropylene ampoules of 10 mL containing a 10% w/v solution of magnesium sulfate as heptahydrate for injection/infusion. Packed in cartons to contain 10, 20 or 50 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For intramuscular use, a 50% w/v solution should be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT REGISTRATION HOLDER

Pahang Pharmacy Sdn. Bhd., Lot 5979, Jalan Teratai, 5 ½ Mile Off Jalan Meru, 41050 Klang, Selangor, Malaysia

8. PRODUCT REGISTRATION NUMBER(S)

<[To be completed nationally]>

9. MANUFACTURER

DEMO S.A., Pharmaceutical Industry, 21st km National Road Athens-Lamia, 14568 Krioneri, Attiki, Greece, T: +30 210 8161802, F: +30 210 8161587.

10. DATE OF REVISION OF THE TEXT

11/10/2022

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