SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Magnesium sulfate 25% w/v Solution for injection or concentrate for solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 mL ampoule contains 2.5 g magnesium sulfate heptahydrate corresponding to approximately 10 mmol (0.245 g = 20 mEq) magnesium ions.

1 mL contains 250 mg magnesium sulfate heptahydrate corresponding to approximately 1 mmol (24.5 mg = 2 mEq) magnesium ions.

1 g of magnesium sulfate heptahydrate provides 4.1 mmol (8.2 mEq) of elemental magnesium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or concentrate for solution for injection/infusion.

Clear and colourless solution with a pH of between 5.5 and 7 and osmolality of 1050 mOsm/kg approximately.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Magnesium sulfate 25% w/v solution is indicated in adults, adolescents and children for:

i) the treatment of magnesium deficiency in proven hypomagnesaemia

ii) the prevention and treatment of hypomagnesaemia in patients receiving total parenteral nutrition

Magnesium sulfate 25% w/v solution is indicated in parturients for:

i) the control and prevention of seizures in severe pre-eclampsia

ii) the control and prevention of recurrent seizures in eclampsia

4.2 Posology and method of administration

Magnesium sulfate 25% w/v solution may be administered by the intravenous (preferred method) or intramuscular (painful, avoid if possible) routes (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+}.

For the intravenous route, the 25% w/v solution requires dilution to a concentration of not more than 20%. For instructions on dilution of Magnesium sulfate 25% w/v solution to Magnesium sulfate 20% w/v solution see section "Method of administration".

Treatment of magnesium deficiency in proven hypomagnesaemia

Adults:

Intravenous Route: intravenous infusion:

Up to 160 mL (40 g) Magnesium sulfate 25% w/v solution (corresponding to 160 mmol ≈ 4 g Mg^{2+}) diluted in an infusion solution should be administered by slow intravenous infusion over a period of up to five days and titrated to clinical need. The usual regimen is 32 – 48 mL (8-12 g) Magnesium sulfate 25% w/v solution (corresponding to 32-48 mmol ≈ 0.8 – 1.2 g Mg^{2+}) diluted in an infusion solution in the first 24 hours followed by 16 – 24 mL (4-6 g) Magnesium sulfate 25% w/v solution (corresponding to 16 – 24 mmol ≈ 0.4 – 0.6 g Mg^{2+}) diluted in an infusion solution per day for 3 or 4 days.

Intramuscular Route:

4 – 8 mL (1-2 g) Magnesium sulfate 25% w/v solution (corresponding to 4 – 8 mmol ≈ 0.1 – 0.2 g Mg^{2+}) undiluted can be given intramuscularly every 6 hours for 24 hours (a total of 4 doses).

Children and adolescents:

Intravenous Route: intravenous injection:

Neonate

0.4 mL/kg bw (100 mg/kg bw) Magnesium sulfate 25% w/v solution (corresponding to 0.4 mmol/kg bw ≈ 0.01 g/kg bw Mg^{2+}) diluted to 20% w/v solution (i.e. 0.5 mL/kg bw of a 20% w/v solution) every 6 – 12 hours as required, to be given by intravenous injection over at least 10 minutes.

Child 1 month – 11 years

0.2 mL/kg bw (50 mg/kg bw) Magnesium sulfate 25% w/v solution (corresponding to 0.2 mmol/kg bw ≈ 0.005 g/kg bw Mg^{2+}) diluted to 20% w/v solution (i.e. 0.25 mL/kg bw of a 20% w/v solution) every 12 hours as required, to be given by intravenous injection over at least 10 minutes.

Adolescent 12 – 17 years

4 mL (1 g) Magnesium sulfate 25% w/v solution (corresponding to 4 mmol ≈ 0.1 g Mg^{2+}) diluted to 20% w/v solution (i.e. 5 mL of a 20% w/v solution) 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 25% 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:

Intravenous Route: intravenous infusion:

10 – 20 mL (2.5-5 g) Magnesium sulfate 25% w/v solution (corresponding to 10 – 20 mmol ≈ 0.25 – 0.5 g Mg^{2+}) daily, diluted in an infusion solution, usual dose 12 mL (3 g) Magnesium sulfate 25% w/v solution (corresponding to 12 mmol ≈ 0.3 g Mg^{2+}) daily, diluted in an infusion solution, administered by intravenous infusion.

Neonates and infants (up to 12 months):

Intravenous Route: intravenous infusion:

0.2 mL/kg bw (50 mg/kg bw) Magnesium sulfate 25% w/v solution (corresponding to 0.2 mmol/kg bw ≈ 0.005 g/kg bw Mg^{2+}) daily, diluted in an infusion solution, administered by intravenous infusion.

Children (1 – 13 years) and adolescents (14 – 18 years):

Intravenous Route: intravenous infusion:

0.1 mL/kg bw (25 mg/kg bw) Magnesium sulfate 25% w/v solution (corresponding to 0.1 mmol/kg bw ≈ 0.0025 g/kg bw Mg^{2+}) daily, diluted in an infusion solution, administered 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 16 – 20 mL (4-5 g) Magnesium sulfate 25% w/v solution (corresponding to 16 – 20 mmol ≈ 0.4 – 0.5 g Mg^{2+}) diluted to an appropriate volume [at a final concentration of not more than 20% w/v (≤ 200 mg/mL magnesium sulfate heptahydrate), see "Method of administration"] is administered over 5 – 15 minutes, followed by maintenance therapy for 24 hours, as follows:

IV Maintenance Regimen

The IV loading dose (above) is followed by an infusion of approximately 4 mL (1 g) Magnesium sulfate 25% w/v solution (corresponding to 4 mmol ≈ 0.1 g Mg^{2+}) diluted in an infusion solution per hour for at least 24 hours after the last fit.

IM Maintenance Regimen

For the IM maintenance regimen, the Magnesium sulfate 50% w/v solution should be used.

Recurrent convulsions: In both IV and IM regimens, a further 8 – 16 mL (2-4 g) Magnesium sulfate 25% w/v solution (corresponding to 8 – 16 mmol ≈ 0.2 – 0.4 g Mg^{2+}) diluted to an appropriate volume [at a final concentration of not more than 20% w/v (≤ 200 mg/mL magnesium sulfate heptahydrate), see "Method of administration"] depending on body weight [if less than 70 kg 8 mL (2 g) Magnesium sulfate 25% w/v solution (corresponding to 8 mmol ≈ 0.2 g Mg^{2+}) diluted to an appropriate volume, as above] are given IV over a period of 5 minutes.

Renal impairment

Magnesium sulfate 25% w/v solution is contraindicated in patients with severe renal impairment (see section 4.3).

Patients with mild to moderate renal impairment should receive 50% of the dosage recommended for patients with normal kidney function.

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

Intravenous use

Concentrations of no higher than 20% w/v (≤ 200 mg/mL magnesium sulfate heptahydrate) should be given intravenously. Therefore, for the intravenous route, the 25% w/v solution requires dilution to a concentration of not more than 20% – with a suitable diluent, such as Glucose 5% or sodium chloride 0.9%.

Dilution of Magnesium sulfate 25% w/v solution to Magnesium sulfate 20% w/v solution: Dilute 1 part of Magnesium sulfate 25% w/v solution with 0.25 part of suitable diluent (i.e., dilute a 10 mL ampoule Magnesium sulfate 25% w/v with 2.5 mL diluent to get 12.5 mL of a Magnesium sulfate 20% w/v solution).

Intravenous use in adults and adolescents:

For intravenous infusion, administer via a volumetric infusion device at a rate appropriate to the indication (see posology above). For intravenous injection, give by slow IV injection at a rate appropriate to the indication (see posology above).

Intravenous use in children:

Rate of administration should not exceed 0.04 mL/kg/min (10 mg/kg/min) of Magnesium sulfate 25% w/v solution (corresponding to 0.04 mmol/kg/min ≈ 0.001 g/kg/min Mg^{2+}) diluted (either to a Magnesium sulfate 20% w/v solution or in an infusion solution).

Deep Intramuscular injection (adults only)

For the intramuscular route, the 25% w/v solution should be used undiluted. If the total dose to be administered exceeds 5 mL, the injection volume should be divided between more than one deep muscular injection site. When volumes of more than 10 mL are required, it is preferable to use the Magnesium sulfate 50% w/v solution to avoid multiple injections.

4.3 Contraindications

Hypersensitivity to magnesium and its salts or to any of the excipients listed in section 6.1.

Hepatic encephalopathy or hepatic failure.

Severe renal impairment or renal failure (glomerular filtration rate under 30 mL/min), anuria.

Parenteral administration of the medicinal product is contraindicated in patients with heart block (class I-III) or myocardial damage and myasthenia gravis.

4.4 Special warnings and precautions for use

Magnesium salts should be administered with caution to patients with impaired renal function and appropriate dosage reduction should be made.

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

The serum-magnesium-level should be monitored during the treatment (normal 0.65 – 1.0 mmol).

Monitoring of the absence of respiratory depression: the breath rate should not be under 16 breaths/min.

The excretion of urine should not be under 25 mL/h, as it could lead to hypermagnesaemia (see sections 4.2 and 4.3).

The presence of the patellar reflex should be checked.

Administer with caution if flushing and sweating occurs.

An antidote of injectable calcium gluconate solution should be immediately available.

For the intravenous use in children the rate of administration should not exceed 0.04 mL/kg/min Magnesium sulfate 25% w/v solution (corresponding to 0.04 mmol/kg/min ≈0.001 g/kg/min Mg^{2+}) diluted (see section 4.2).

The 25% w/v solution MUST be diluted before use for IV administration; concentrations up to 20% w/v are usually employed. For IM use, a 25% w/v or 50% w/v solution is acceptable.

For the intramuscular route, use good clinical practice for intramuscular injections. The 25% w/v solution should be used undiluted. Avoid muscles which are emaciated or atrophied. Avoid the dorsogluteal muscle and sciatic nerve. If the total dose to be administered exceeds 5 mL, the injection volume should be divided between more

than one deep muscular injection site. When volumes of more than 10 mL are required, it is preferable to use the Magnesium sulfate 50% w/v solution to avoid multiple injections. Use caution in older or thin patients who may only tolerate up to 2 mL in a single injection. Do not use an injection site that has evidence of infection or injury. If repeating an intramuscular dose, rotate injection sites to avoid injury or discomfort to the muscles.

4.5 Interaction with other medicinal products and other forms of interaction

Muscle relaxants

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

Calcium channel blockers or diuretics

There is a risk of cardiopulmonary events when intravenous magnesium sulfate is used concomitantly with calcium channel blockers (such as nifedipine) or diuretics (such as thiazides and furosemide). Profound hypotension has been reported with nifedipine.

Calcium salts

Calcium salts may reduce the efficacy of magnesium.

Digitalis glycosides

Magnesium salts should also be administered with caution to those patients receiving digitalis glycosides.

Neuromuscular blocking agents

Parenteral administration of magnesium salts may enhance the effects of neuromuscular blocking agents. The neuromuscular blocking effects of parenteral magnesium and aminoglycoside antibacterials may be additive.

CNS depressants

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 depressant effects of magnesium and the risk of respiratory depression.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There is no or limited experience on treatment of symptomatic magnesium deficiency with parenteral magnesium sulfate during pregnancy and safety of use during early pregnancy has not been established.

Longer term parenteral use of magnesium sulfate during pregnancy at high doses was reported to cause hypocalcemia and skeletal abnormalities in newborns and pregnant women. The clinical significance of the observed effects is unknown.

Animal studies are insufficient with respect to reproductive toxicity. Magnesium sulfate 25% w/v Solution for injection or concentrate for solution for injection/infusion should only be used during pregnancy if the clinical condition of the woman requires treatment with magnesium sulfate and must be administered under medical supervision.

If magnesium sulfate is administered shortly prior to childbirth, the newborn infant should be monitored during the first 24-48 hours of life for signs of toxicity (neurological depression with respiratory depression, muscle weakness, loss of reflexes) (see section 4.8 and 4.9).

If prolonged (≥ 24 h) or repeated exposure to magnesium sulfate occurs during pregnancy, monitoring of calcium and magnesium levels in mother's serum and postpartum in cord blood should be considered.

Breastfeeding

Magnesium sulfate is excreted in human milk but at therapeutic doses of Magnesium sulfate 25% w/v Solution for injection or concentrate for solution for injection/infusion no effects on the breastfed newborns/infants are anticipated.

Magnesium sulfate can be used during breast-feeding if necessary.

Fertility

Based on long-term experience, no effects of magnesium on male and female fertility are anticipated.

4.7 Effects on ability to drive and use machines

Magnesium sulfate 25% w/v solution is unlikely to affect the ability to drive or to operate machinery. However, some people may feel dizzy or drowsy when given Magnesium sulfate 25% w/v solution. The patient should be advised not to drive or operate machinery.

4.8 Undesirable effects

The frequency of undesirable effects is not known.

Immune system disorder:

Hypersensitivity reactions.

Excessive administration of magnesium leads to the development of symptoms of hypermagnesaemia which may include:

Metabolism and nutrition disorders

Electrolyte/fluid abnormalities (hypophosphataemia, hypertonic dehydration)

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

Nervous system disorders

Respiratory depression

Nausea, vomiting, drowsiness and confusion

Coma

Slurred speech, double vision

Loss of tendon reflexes due to neuromuscular blockade

Cardiac disorders

Cardiac arrhythmias, cardiac arrest

ECG abnormal (prolonged PR, QRS and QT intervals), bradycardia

Vascular disorders

Flushing of the skin and hypotension due to peripheral vasodilatation

Musculoskeletal and connective tissue disorders

Muscle weakness

General disorders and administration site conditions

Thirst

Especially in patients with impaired renal function, there may be sufficient accumulation of magnesium sulfate to produce toxic effects.

Injection/infusion-related

Too rapid administration: Vasodilatation, reduced blood pressure

Local: may be irritant to veins; extravasation may cause tissue damage

Intramuscular: pain, redness, swelling or warmth at the injection site, drainage at the injection site, prolonged bleeding, cellulitis, sterile abscess, signs of an allergic reaction, such as difficulty breathing or facial swelling, injury to nearby structures (blood vessels, bones, or nerves), inadvertent intravascular or intra-ostial injection, tissue necrosis, poor absorption due to high injectate volume.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard, or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Signs:

Clinical signs of overdose will be those of hypermagnesaemia - see Section 4.8.

Patients with renal failure and metabolic derangements develop toxicity at lower doses.

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.

Mg plasma concentration	Symptoms and undesirable effects

(mmol/L)	
2 to 3	nausea, flushing, headache, lethargy, drowsiness, diminished deep tendon reflexes, platelet disaggregation
3 to 5	somnolence, hypocalcemia, absent deep tendon reflexes, hypotension, bradycardia, and ECG changes
> 5	muscle paralysis, respiratory paralysis, coma. In most cases, respiratory failure precedes cardiac collapse
> 7.0	Complete heart block and cardiac arrest

Treatment:

Appropriate action should be taken to reduce the blood level of magnesium. In the event of overdosage, artificial ventilation must be provided until a calcium salt can be injected IV to antagonize the effects of magnesium.

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 5 mmol of calcium.

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).The normal concentration of magnesium in plasma is around 0.65 to 1.0 mmol/L. Symptomatic hypomagnesaemia is associated with a deficit of 0.5 – 1.0 mmol/kg.

Mechanism of action

It is a cofactor in numerous enzyme systems and is involved in phosphate transfer, muscle contractility and neuronal transmission.

5.2 Pharmacokinetic properties

The amount of elemental magnesium provided by each g of magnesium sulfate heptahydrate is 4.1 mmol; therefore 4 mL of a 25% w/v solution will provide approximately 4 mmol of magnesium ions.

Absorption

Magnesium sulfate injection is given either by the intramuscular or intravenous route.

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.

Distribution

Magnesium is approximately equally distributed in bone and the intracellular compartments of muscle and soft tissues. Less than 1% of total body magnesium is found in serum and red blood cells.

About 40% of plasma magnesium is bound to proteins, mainly to albumin, and therefore not filterable at the glomerulus.

Biotransformation

Magnesium sulfate is not metabolized.

Elimination

The major excretory pathway is renal and parenteral loads are rapidly eliminated in this way. Faecal loss is very limited.

Renal impairment

In renal impairment, there may be accumulation of magnesium.

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

After opening/dilution:

Chemical and physical in-use stability has been demonstrated for 48 hours at 23 – 27°C and 2 – 8°C when diluted to a concentration of not more than 200 mg/mL magnesium in Sodium chloride 0.9% or Glucose 5%. 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 and would normally not be longer than 48 hours at 23 – 27°C and 2 – 8°C unless reconstitution/dilution (etc.) has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polypropylene ampoules of 10 mL containing a 25% w/v solution of magnesium sulfate as heptahydrate for injection. Packed in cartons to contain 10, 20 or 50 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

For intramuscular use, the 25% w/v solution should be used undiluted. For intravenous use, the 25% w/v solution must be diluted before use, with a suitable diluent, such as Glucose 5% or sodium chloride 0.9%.

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

7 MARKETING AUTHORISATION HOLDER

DEMO S.A. PHARMACEUTICAL INDUSTRY
21st Km National Road Athens-Lamia
14568 Krioneri, Attiki, Greece,

8 MARKETING AUTHORISATION NUMBER(S)

PL 17589/0030

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/10/2023

10 DATE OF REVISION OF THE TEXT