SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Magnesium sulfate 20% w/v solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains 200 mg of magnesium sulfate heptahydrate (approximately 0.8 mmol Mg^{2+}).
Each 10 ml ampoule contains 2000 mg of magnesium sulfate heptahydrate (approximately 8 mmol Mg^{2+}).

Magnesium sulfate heptahydrate 1 g (5 ml of solution) = 98.6 mg or 8.1 mEq or 4.1 mmol magnesium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion
Clear, colourless to almost colourless solution, free of visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Magnesium sulfate is indicated in:

- the treatment of magnesium deficiency in proven hypomagnesaemia (e.g., children with primary congenital hypomagnesaemia, adults with malabsorption syndrome after persistent diarrhoea, chronic alcoholism or long-term parenteral nutrition);
- the prevention and treatment of hypomagnesaemia in patients receiving total parenteral nutrition;
- the control and prevention of seizures in severe pre-eclampsia;
- the control and prevention of recurrent seizures in eclampsia.

The product is intended for use in adults, adolescents and children.

4.2 Posology and method of administration

Posology

Therapeutic levels are reached almost immediately with appropriate intravenous doses and within 60 minutes following intramuscular injection.

Adults

Hypomagnesaemia

The dose is strictly individual. As a general guideline, 8-12 g of magnesium sulfate (32-48 mmol Mg^{2+}) can be administered in the first 24 hours followed by 4-6 g/day (16-24 mmol Mg^{2+}/day) for 3 or 4 days, to replete body stores. Maximum infusion rates should not exceed 2 g/hour (8 mmol Mg^{2+}/hour). The aim should be to maintain serum magnesium concentrations above 0.4 mmol/l.

Prevention and treatment of hypomagnesemia in total parenteral nutrition

The dose is strictly individual. As a general recommendation, 1-3 g/day (4-12 mmol Mg^{2+}/day) intravenous magnesium sulfate can be administered.

Severe pre-eclampsia or eclampsia

Intravenously an initial loading dose of 4 g (16 mmol Mg^{2+}) diluted to an appropriate volume, e.g., 4 g of magnesium sulfate (16 mmol Mg^{2+}) in 250 ml 5% glucose or 0.9% sodium chloride solution at maximum 4 ml/min (= 64 mg/min), may be infused. This is followed by a maintenance regimen of either an intravenous infusion of 1-2 g/hour (4-8 mmol Mg^{2+}/hour), or regular intramuscular injections (refer to section 4.4), depending on the continuing presence of the patellar reflex and adequate respiratory function and urine output. Therapy should continue until paroxysms cease.

It is important that in the administration of magnesium sulfate by any of these schedules, certain clinical observations should be made before each injection:

- deep tendon reflexes must be present;
- respiration must be at least 16 breaths/minute;
- 100 ml of urine must have been excreted since the preceding injection.

In addition, 1 g of calcium gluconate should be available as an antidote for hypermagnesemia.

Paediatric population

Hypomagnesaemia

Magnesium sulfate may be administered intravenously to children. For the intravenous use in children the rate of administration should not exceed 10 mg/kg/minute magnesium sulfate (corresponding to 0.04 mmol Mg^{2+}/kg/minute = 0.001 g/kg/minute magnesium).

Prevention and treatment of hypomagnesemia in total parenteral nutrition

The dose strictly is individual. As a general recommendation, the following intravenous magnesium sulfate doses can be administered:

Table 1. Dosage in total parenteral nutrition in children

Age	Magnesium (mg/kg/day)
Preterm infants during the first days of life	2.5 – 5 (0.01 – 0.02 mmol Mg^{2+})
Growing premature infants	5 – 7.5 (0.02 – 0.03 mmol Mg^{2+})
0-6 months	2.4 – 5 (0.0096 – 0.02 mmol Mg^{2+})
7-12 months	4 (0.016 mmol Mg^{2+})
1-18 years	2.4 (0.0096 mmol Mg^{2+})

Renal insufficiency
Patients with renal insufficiency should receive 25-50% of the initial dose recommended for patients with normal kidney function. ECG monitoring is recommended with high doses and in the elderly.

Hepatic impairment
Because of insufficient data there are no recommended special dosage instructions for patients with impaired liver function.

Elderly
Parenteral magnesium sulfate should be used with caution in the elderly, because renal disorders are more frequent in this age group and the tolerance to adverse effects may be lower.

Method of administration
For intravenous (injection or infusion) or intramuscular use, in line with the information provided for each indication.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to magnesium and its salts or to any of the excipients listed in section 6.1
- Hypermagnesemia.
- Severe renal impairment or renal failure if the dialysis or other blood purification methods are unachievable.

4.4 Special warnings and precautions for use

Increased risk of hypotension and bradycardia
During administration of magnesium sulfate, vital function monitoring is needed as the risk of profound hypotension and bradycardia is increased.
An antidote of injectable 1 g calcium gluconate solution should be immediately available.

Renal impairment

Magnesium salts should be administered with caution to patients with impaired renal function and appropriate dosage reduction should be made (see section 4.2).

Calcium-magnesium-ammonium-phosphate stone diathesis
In such cases, the product should be avoided, mainly in patients with renal impairment.

Myasthenia gravis
Parenteral magnesium should be used with caution in individuals with myasthenia gravis, to prevent an exacerbation of the condition or the precipitation of a myasthenic crisis and a benefit-risk assessment should be performed in individual cases prior to initiation of treatment.

Hepatic impairment
Liver diseases are often accompanied by hypoalbuminemia, which per se may have an effect on the level of total serum magnesium.

Known increased risk of heart block/heart block
Magnesium can cause heart block, the risk being higher in patients who are already on calcium or beta receptor antagonists.

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

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 hypermagnesemia.

The presence of the patellar reflex should be checked.

CNS depressants
When barbiturates, narcotics or other hypnotics (or systemic anaesthetics) 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 (see section 4.5).

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

Method of administration
The medicine should be administered with caution if flushing and sweating occurs.

Too rapid administration can lead to quickly developing vasodilatation, reduced blood pressure.

As all parenteral medicines, magnesium sulfate injections may be irritant to veins; extravasation may cause tissue damage.

Intramuscular injections

The medicine should not be administered into muscles which are emaciated or atrophied. For intramuscular administration, dorsogluteal muscle and sciatic nerve should be avoided.

If the total dose to be administered exceeds 5 ml, the injection volume should be divided between more than one deep muscular injection site.

Intramuscular injections are painful and are complicated by local abscess formation in 0.5% of cases. The intravenous route is therefore preferred. However, the intramuscular regimen becomes the better option when intravenous infusion pumps are not available or continuous monitoring is not feasible.

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
Magnesium sulfate enhances non-depolarizing muscle relaxant vecuronium action at adult muscle type nicotinic acetylcholine receptor *in vitro*.

Nifedipine
Profound hypotension has been reported.

Calcium channel blockers or diuretics
There is a risk of cardiopulmonary events when intravenous magnesium sulfate is used concomitantly with calcium channel blockers or diuretics (such as thiazides and furosemide).

Calcium salts
Calcium salts may reduce the efficacy of magnesium. Several magnesium activated enzymes are inhibited by calcium.

Digitalis glycosides
Magnesium salts should also be administered with caution to those patients receiving digitalis glycosides. Magnesium has been shown to block the transient inward current carried by calcium, which digitalis glucosides generate.

Neuromuscular blocking agents
Parenteral administration of magnesium salts may enhance the effects of neuromuscular blocking agents.

Antibacterials
The neuromuscular blocking effects of parenteral magnesium and aminoglycoside antibacterial agents may be additive.

CNS depressants
When barbiturates, narcotics or other hypnotics (or systemic anaesthetics) 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
Studies on pregnant women indicate no malformative nor foeto/neonatal toxicity (see section 5.3).

The use of Magnesium sulfate may be considered during pregnancy, if necessary. Magnesium crosses the placenta in mothers treated with high doses e.g., in pre-eclampsia, causing hypotonia and respiratory depression in new-borns. 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 foetal 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.

Serum magnesium levels in preterm infants are higher than adult levels.

Breastfeeding
Magnesium sulfate is excreted in human milk, but at therapeutic doses of Magnesium sulfate no effects on the breastfed new-borns/infants are anticipated. Magnesium sulfate can be used during breast-feeding.

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

Parenteral magnesium sulfate is unlikely to affect the ability to drive or to operate machinery.

However, on the basis of the potential adverse effects, some people may feel dizzy or drowsy after receiving parenteral magnesium sulfate. Patients should be advised not to drive or operate machinery.

4.8 Undesirable effects

The frequency of undesirable effects is not known (cannot be estimated from the available data).

Immune system disorders
Hypersensitivity reactions.

Metabolism and nutrition disorders
Hypermagnesemia (see section 4.9).
Electrolyte/fluid abnormalities (hypophosphatemia, hypertonic dehydration). There have been isolated reports of maternal and foetal 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.

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. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

Symptoms
Intravenous magnesium infusions can result in hypermagnesemia even in the presence of normal kidney function. Clinical signs of overdose will be those of hypermagnesemia.

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

Disappearance of the deep tendon reflex is a useful clinical sign to detect the onset of magnesium intoxication. Magnesium intoxication is manifested by a sharp drop in blood pressure and respiratory paralysis. The potential symptoms of hypermagnesemia are presented in Table 2.

Table 2. The potential symptoms of hypermagnesemia

Magnesium levels			**Manifestation of overdose symptoms**
mg/dl	**mEq/l**	**mmol/l**	
< 1.2	< 1	< 0.5	Tetany Seizures Arrhythmias
1.2 – 1.8	1.0 – 1.5	0.5 – 0.75	Neuromuscular irritability Hypocalcaemia Hypokalaemia
1.8 – 2.5	1.5 – 2.1	0.75 – 1.05	Normal magnesium level
2.5 – 5.0	2.1 – 4.2	1.05 – 2.1	Typically asymptomatic
5.0 – 7.0	4.2 – 5.8	2.1 – 2.9	Lethargy Drowsiness Flushing Nausea and vomiting Diminished deep tendon reflex
7.0 – 1.2	5.8 - 10	2.9 - 5	Somnolence Loss of deep tendon reflexes Hypotension ECG changes
> 12	> 10	> 5	Complete heart arrest Apnoea Paralysis Coma

Treatment

In patients with mild hypermagnesemia, simply withdrawing magnesium therapy is often sufficient to restore normal magnesium concentrations.

In severe hypermagnesemia, calcium salts can reverse hypotension and respiratory depression.

Patients are typically given 100-200 mg of elemental calcium (10 to 20 ml of 10% calcium gluconate) intravenously over 5 to 10 minutes.

Alternatively, patients with severe magnesium intoxication can be given 1 g of intravenous calcium gluconate. This should be followed by the infusion of 150-100 mg of calcium over 5 to 10 minutes. If renal function is adequate fluids should be given to promote renal magnesium clearance. This may be increased by the use of furosemide.

In patients with severe renal dysfunction, or for whom other methods prove ineffective, a magnesium-free dialysis offers a way to rapidly clear magnesium. Both peritoneal and haemodialysis are effective at lowering magnesium levels.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Magnesium is a cofactor for over 600 enzymes and an activator for additional 200 enzymes, acting either on the substrate (especially for reactions involving ATP, where its binding to the nucleotide induces an adequate conformation and helps to weaken the terminal O–P bond of ATP, thereby facilitating the transfer of phosphate) or on the enzyme itself as a structural or catalytic component. As ATP utilisation is involved in many metabolic pathways, magnesium is essential in the intermediary metabolism for the synthesis of carbohydrates, lipids, nucleic acids and proteins, as well as for specific actions in various organs such as the neuromuscular or cardiovascular system.

Magnesium can interfere with calcium at the membrane level or bind to membrane phospholipids, thus modulating membrane permeability and electrical characteristics. Magnesium has an impact on bone health through its role in the structure of hydroxyapatite crystals in bone.

5.2 Pharmacokinetic properties

The approximate amount of magnesium: each 1 g of magnesium sulfate heptahydrate will provide 4.1 mmol magnesium.

<u>Absorption</u>
Intramuscular administration
4 g i.v. and 10 g i.m. loading dose, and 5 g i.m. maintenance dose every 4 hours (Pritchard regimen):
In a study, following the loading dose, serum magnesium levels rose sharply from the baseline to at least two-fold by ½ hour. After the initial rise, a slight decline was reported in serum magnesium at 1 hour but relatively steady levels between until 12 hours of the maintenance injection. Serum level peaked at 1½ hours following the initiation of treatment. Overall, the serum-concentration data fluctuated much more with this regimen than with continuous intravenous regimens.

10 g i.m. loading dose and 5 g i.m. maintenance dose every 4 hours: In a study, the mean levels of serum magnesium at 1, 2, and 4 hours were observed to be 1.36, 1.56 and 1.48 mmol/l, respectively.

Another study only reported a steady state level of 1.83 mmol/l.

3 g i.v. and 10 g i.m. (13 g) loading dose only: With this regimen, one study reported a baseline serum magnesium of 2.10 mmol/l. The mean magnesium levels rose to 2.25 and 2.30 mmol/l at 1 and 2 hours following treatment, respectively. Another study only reported a steady state level of 1.83 mmol/l.

Distribution

Magnesium is approximately equally distributed in bone and soft tissues, less than 1% being present in blood compartments. Cellular magnesium concentrations are constantly in the range of 17-20 mmol/l, despite rapid movements across cell membranes through multiple carriers and channels. Intracellular concentrations have been observed to decrease linearly with increasing age, without parallel changes in plasma magnesium concentration.

Total body magnesium content in a healthy adult is around 20-28 g. Approximately 99% of total body magnesium is intracellular. Of this, about 60% is in bone, either strongly bound to apatite, where it is difficult to mobilise, or loosely adsorbed at the surface of mineral crystals, where it can be easily mobilised in response to variation in dietary supply. About 25% of body magnesium is in muscle, where mitochondria are considered to be the intracellular storage site.

About 25-30% is bound to proteins, the remaining about 80% is unbound. Only the ionized magnesium is physiologically active.

In the whole body, compartmental analysis using stable isotopes showed the existence of at least two major extraplasma compartments: the first compartment represents 80% of the rapidly exchangeable pool with an exchange rate of 48 mg/h; the second pool has a faster exchange rate of 179 mg/h. The sum of these rapidly exchangeable compartments amounts to around 25% of the magnesium body pool.

One of the most important transport systems to tissues appears to be the transient receptor potential melastatin 7 (TRPM7).

Biotransformation

Magnesium sulfate is not metabolized.

Elimination

The kidney plays a major role in magnesium homeostasis and maintenance of serum concentrations.

Around 80% of serum magnesium is ultrafiltrable through the glomerulus, but only around 3% of the filtered fraction appears in the urine, owing to an efficient reabsorption taking place mainly (60-70%) in the thick ascending loop of Henle.

The main stimuli that increase urinary magnesium excretion are high natriuresis, osmotic load and metabolic acidosis; those that reduce it are metabolic alkalosis, parathyroid hormone and, possibly, calcitonin. The

remaining part of the reabsorption takes place in the distal convoluted tubule via an active transcellular mechanism that finally controls the amount excreted in the urine.

Faecal loss is very limited. The endogenous routes of elimination of absorbed magnesium through the digestive tract are bile, pancreatic and intestinal juices, and intestinal cells; part of these endogenous losses can be reabsorbed. Using stable isotopes, endogenous faecal excretion has been determined to be 49 ± 11 mg/day in six healthy men aged 26-41 years, around 15 mg/day (0.1-0.9 mg/kg body weight/day) in 9- to 14-year-old boys and girls and from 4.7 to 21.7 mg/day in five girls aged 12-14 years, without influence of calcium intake.

Magnesium losses through sweat are likely to be modest, in the range of 1-5 mg/day, on the basis of a daily sweat volume of around 0.5 l/day.

Magnesium losses through menstruation in women are negligible.

Special populations

Paediatric population

The pharmacokinetics of intravenous magnesium sulfate have been studied in 2-14 years old children.

The covariate analysis found that only weight was a significant predictor of magnesium concentrations in children. Estimated model parameters suggested that magnesium exhibits a short serum half-life (2.7 h) in children.

Elderly

No specific pharmacokinetic studies have been performed with parenteral (i.v., i.m. or s.c.) magnesium sulfate in the elderly.

Hepatic impairment

Liver diseases are often accompanied by hypoalbuminemia, which per se may have an effect on the level of total serum magnesium. The serum ionized/total magnesium ratio is inversely related to serum albumin. According to a study, patients with the lowest levels of serum albumin have a greater part of their serum magnesium in free biologically active form, as ionized magnesium. In patients with alcoholic hepatopathy the mean concentrations of both serum total and ionized magnesium were lower than normal.

Renal impairment

In renal impairment, there may be accumulation of magnesium.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened ampoule: 3 years
The medicinal product should be used immediately after opening the ampoule (see section 6.6).

After dilution:
The product should be used immediately after dilution.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
For storage conditions after dilution or first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 ml of solution in type I clear glass ampoules with one point cut.

Pack size:
10 ampoules

6.6 Special precautions for disposal

For single use only.
Can be diluted with 0.9% sodium chloride or 5% glucose solutions (see section 4.2).

The medicinal product should be used immediately after opening the ampoule. Any unused portion should be discarded.

This medicine should not be used if there are any visible signs of deterioration (e.g., particles).

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

7 MARKETING AUTHORISATION HOLDER

SVP Pharma Ltd.
Unit 1, 39 Mahoney Green
Rackheath, Norwich, NR13 6JY
United Kingdom

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