SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Magnesium Sulfate 20% w/v Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Magnesium sulfate heptahydrate 20% w/v (approximately 0.8 mmol Mg^{2+}/mL).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion.

Clear and colourless solution, pH 5.5 -7.0 and osmolarity of approximately 964 mOsmol/L.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of magnesium deficiency in hypomagnesaemia.

Prevention and control of seizures in severe pre-eclampsia.

Prevention and control of recurrent seizures in eclampsia.

4.2 Posology and method of administration

Posology

Dosages should be adjusted according to the patient's needs, responses and weight. Plasma magnesium levels should also be monitored during treatment to determine the rate and duration of infusion.

Close monitoring for ECG changes is required (see section 4.8). The infusion rate should be reduced or stopped if the patient develops signs of changes to cardiac condition (ECG changes).

Treatment of magnesium deficiency in hypomagnesaemia:

Treatment should be given via an infusion pump and an infusion rate of 1 g magnesium sulfate (5 mL of a 20% w/v solution equivalent to 4 mmol of magnesium ions) per hour is recommended, with a maximum rate of 2 g magnesium sulfate (10 mL of a 20% w/v solution approximately 8 mmol magnesium ions) per hour (not exceeding 28 g in 24 hours).

Higher infusion rates may be given in the management of emergencies. Up to 40 g (200 mL of a 20% w/v solution equivalent to 160 mmol of magnesium ions) by slow intravenous infusion (in glucose 5% w/v) given over a period of up to 5 days, may be required to replace the deficit (allowing for urinary losses).

In exceptional circumstances and under close supervision a higher dose within the range of 2 g to 5 g of magnesium sulfate (10 mL to 25 mL of a 20% w/v solution equivalent to 8 to 20 mmol of magnesium ions) in at least 100 mL of Glucose 5% w/v or Sodium Chloride 0.9% w/v over 6 hours may be considered.

Prevention and control of seizures in severe pre-eclampsia:

An intravenous loading dose of typically 4 g (20 mL of a 20% w/v solution equivalent to 16 mmol of magnesium ions) given slowly over a period of 5-15 minutes is followed by an infusion of 1 g (5 mL of a 20% w/v solution equivalent to 4 mmol of magnesium ions) per hour for 24 hours after the last seizure.

Prevention and control of recurrent seizures in eclampsia:

An intravenous loading dose of typically 4 g (20 mL of a 20% w/v solution equivalent to 16 mmol of magnesium ions) given slowly over a period of 5-15 minutes is followed by an infusion of 1 g (5 mL of a 20% w/v solution equivalent to 4

mmol of magnesium ions) per hour continued for 24 hours after the last seizure or delivery postpartum (whichever is later).

If seizures recur, a further 2-4 g (10-20 mL of a 20% w/v solution equivalent to 8-16 mmol of magnesium ions), depending on the woman's weight, 2 g (8 mmol) if less than 70 kg, is given intravenously over 5 minutes.

Renal impairment

Appropriate reductions in dosage should be made for patients with renal impairment due to increased risk of toxicity (see section 4.4). Caution must be observed to prevent exceeding the renal capacity. The dosage should not exceed 20 g in 48 hours (100 mL of a 20% w/v Solution equivalent to 80 mmol of magnesium ions).

Elderly

There are no special recommendations for use in the elderly but caution needs to be exercised in this population due to the risk of renal impairment (see section 4.4).

Paediatric Population

There is no relevant use of Magnesium Sulfate 20% w/v Solution for Injection or Infusion in the paediatric population for the indication of hypomagnesaemia.

Limited studies of the use of the magnesium sulfate in adolescent females with pre-eclampsia and eclampsia show there are no contraindications, however it should be used with caution.

Method of administration

For intravenous administration.

For peripheral administration a concentration of magnesium sulfate 5% w/v (diluted with Glucose 5% w/v or Sodium Chloride 0.9% w/v) is recommended. For example, dilute 25 mL of Magnesium Sulfate 20% w/v to 100 mL using Glucose 5% w/v or Sodium Chloride 0.9% w/v. The resultant admixture contains 20 mmol (5 g) of magnesium ions per 100 mL.

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

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6.1.

Severe renal failure.

Hepatic encephalopathy, hepatic failure.

Parenteral magnesium salts should generally be avoided in patients with a heart block.

4.4 Special warnings and precautions for use

Concentrations of more than 5% w/v magnesium sulfate have a high osmolarity and may cause venous irritation and tissue damage in cases of extravasation, monitor the insertion site closely.

Magnesium salts are excreted mainly by the kidney and should be administered with caution to patients with impaired renal function and appropriate dosage reduction should be made due to the risk of hypermagnesaemia (See section 4.2).

Due to the risk of respiratory depression as a result of hypermagnesaemia, patients should be closely monitored for signs and symptoms of magnesium toxicity. In particular, caution is required in patients with respiratory disease.

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. A risk-benefit assessment should be performed in the individual cases prior to initiation of treatment.

Serum calcium levels should be routinely monitored in patients receiving magnesium sulfate. Maternal administration of magnesium sulfate for longer than 5–7 days in pregnancy has been associated with skeletal adverse effects and hypocalcaemia and hypermagnesaemia in neonates. If use of magnesium sulfate in pregnancy is prolonged or repeated, consider monitoring of neonates for abnormal calcium and magnesium levels and skeletal adverse effects.

4.5 Interaction with other medicinal products and other forms of interaction

Muscle relaxants

Non-depolarising neuromuscular blocking drugs, such as rocuronium or vecuronium muscle relaxants are enhanced by parenteral magnesium salts.

Cardiac glycosides

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

Electrolyte imbalance

Diuretic agents (e.g. furosemide), antacids and laxatives may lead to an electrolyte imbalance and has been associated with an increase in cardiopulmonary events.

Vasodilators

Magnesium causes vasodilation and therefore vasodilator agents such as non-selective alpha-adrenergic blockers (e.g. phentolamine) may be enhanced.

Calcium channel blockers

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

Magnesium sulfate potentially increases the risk of hypotension when given concomitantly with oral calcium ion channel blockers such as nifedipine, lercanidipine and amlodipine. Profound hypotension was produced in two women who were given oral nifedipine.

CNS depressants

Parenteral administration of magnesium sulfate may enhance the effects of central nervous system depressants. The neuromuscular blocking effects of parenteral magnesium and aminoglycoside antibacterials may be additive. When general anaesthetics, or other CNS depressants are administered concomitantly with magnesium sulfate, dosage of these agents must be carefully adjusted because of the additive central depressant effects.

Other drugs

Certain drugs, such as Cisplatin, amphotericin B and ciclosporin, have been associated with magnesium wasting, increasing the risk of acute hypomagnesaemia due to inadequate absorption.

Intravenous calcium will antagonise the effects of magnesium.

4.6 Fertility, Pregnancy and lactation

Pregnancy

As eclampsia may be life threatening to mother and baby, magnesium sulfate may be administered for this condition.

Magnesium crosses the placenta and may produce hypotonia, hypoflexia and hypotension. If administered during labour it may cause respiratory depression of the newborn infant.

Magnesium sulfate can cause skeletal adverse effects when administered continuously for more than 5-7 days in pregnant women. There are retrospective epidemiological studies and case reports documenting foetal adverse effects including hypocalcaemia, skeletal demineralisation, osteopenia and other skeletal adverse effects with maternal administration of magnesium sulfate for more than 5 -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

There is evidence that an increased level of magnesium is present in breast milk following treatment with magnesium sulfate. Safety during breast feeding has not been established. Therefore, as with all drugs, it is not advisable to administer magnesium sulfate during breast feeding unless considered essential.

Fertility

The long-term experience reports no effects of magnesium sulfate on fertility. However, there are no controlled studies on the effects of magnesium sulfate on fertility.

4.7 Effects on ability to drive and use machines

Not relevant

4.8 Undesirable effects

Summary of Safety Profile

Commonly reported adverse reactions include flushing, nausea and vomiting, thirst, muscle weakness. The most important serious adverse reactions associated with magnesium sulfate relate to hypermagnesaemia. These include respiratory depression leading to cardiac arrest.

Tabulated Summary of Adverse Reactions

Adverse reactions associated with intravenous magnesium sulfate from clinical studies and case reports are tabulated below. The table is presented in order of system organ class.

System Organ Class	Adverse reaction
Immune system disorders	Hypersensitivity reactions

Metabolic and nutritional disorders	Hypophosphataemia, hyperosmolar dehydration, hypocalcaemia, hypermagnesaemia, hypoglycaemia
Nervous system disorders	Headache, dizziness, slurred speech, drowsiness and confusion, coma
Eye disorders	Visual disturbances including diplopia ptosis or abnormal vision
Cardiac disorders	ECG changes (prolonged PR, QRS and QT intervals), bradycardia, tachycardia, cardiac arrythmias, cardiac arrest
Vascular disorders	Flushing, peripheral vasodilation leading to hypotension
Respiratory, thoracic and mediastinal disorders	Dyspnoea, pulmonary oedema, respiratory depression, respiratory arrest
Gastrointestinal disorders	Nausea, vomiting, thirst
Skin and subcutaneous tissue disorders	Urticaria
Musculoskeletal and connective tissue disorders	Loss of tendon reflexes due to neuromuscular blockade, muscle weakness
General disorders and administration site conditions	Pain, burning, inflammation and bruising at injection site

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

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.

4.9 Overdose

Signs

Clinical signs of overdose will be those of hypermagnesaemia, including nausea, vomiting, flushing, thirst, hypotension, drowsiness, confusion, absence of reflexes,

respiratory depression, slurred speech, diplopia, muscle weakness, arrythmias, coma and cardiac arrest.

Treatment

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 5 mmol of calcium.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: IV additives- electrolyte solution

ATC Code: B05XA05

Mechanism of action

Magnesium is the second most abundant cation in intracellular fluid and is an essential body electrolyte. It is a cofactor in numerous enzyme systems and is involved in phosphate transfer, muscle contractility and neuronal transmission.

The precise site of action of magnesium sulfate in eclampsia is not known. Experimentally, magnesium has been shown to block the NMDA subtype of glutamate channel through which calcium enters the cell and cause neuronal damage during cerebral ischaemia. Ischaemia leads to lowering of the transmembrane potential allowing calcium ion influx across the membrane and from the endoplasmic reticulum and mitochondria. This leads to further calcium influx as membrane phospholipids are hydrolysed by activated enzymes. Magnesium blocks calcium at intracellular sites in addition to the outer lipid membrane.

Pharmacodynamic effects

Serum magnesium levels in the range of 1.5 - 2.5 mmol/L cause vasodilation in the peripheral and coronary circulation. Within this concentration range there are no detectable effects on CNS function or neuromuscular transmission.

There is evidence that with serum magnesium levels above 12 mg/dL, there is abnormal cardiac conduction. Studies suggest that the effect of magnesium ions on cardiac muscle is to slow the rate of the AV node impulse formation and prolong conduction time. With increased magnesium levels there is a decrease in calcium, with lower levels of calcium leading to prolonged QT interval.

Clinical efficacy and safety

At a serum magnesium level of 2-3 mmol/L platelet disaggregation has been reported, possibly mediated by stimulation of prostacyclin release from the vascular endothelium.

5.2 Pharmacokinetic properties

Absorption

Following a single intravenous loading dose of 4 g to 6 g there is an immediate but transient increase in plasma levels to 2.1-3.8 mmol/L which will fall to 1.3-1.7 mmol/L within 60 minutes.

Distribution

The concentration of magnesium in plasma is normally tightly regulated in the range of 0.75- 0.95 mmol/L.

When given intravenously magnesium sulfate has an immediate onset of action; its duration of activity is about 30 minutes.

Biotransformation

IV preparations of Magnesium Sulfate are 100% bioavailable.

Elimination

Small and clinically irrelevant amounts of magnesium are excreted in breast milk. The major excretory pathway is renal and intravenous loads are rapidly eliminated in this way. In renal impairment there may be accumulation of magnesium. Magnesium crosses the placenta.

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, toxicity to reproduction and development.

No carcinogenicity studies in animals have been conducted, the risk of tumorigenicity in humans is unlikely but otherwise unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sulfuric Acid (for pH-adjustment)

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

36 months

Chemical and physical in-use stability has been demonstrated for 24 hours at a maximum of 25ºC. 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 responsibility of the user and would normally not be longer than 24 hours at 2-8ºC, unless dilution 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.

The product must be used immediately after the opening of the container and the storage of opened vials should be avoided.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Magnesium Sulfate 20% w/v Solution for Injection or Infusion is presented in 20 mL and 50 mL type 1 glass vials closed with a bromobutyl rubber stopper with an aluminium tamper-proof flip-top cap.

The product is packed into cartons containing 1 vial or 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

For single use only.

Magnesium Sulfate 20% w/v Solution for Injection or Infusion can be diluted with Glucose 5% w/v and Sodium Chloride 0.9% w/v solutions. To obtain an admixture containing 20 mmol (5 g) of magnesium ions per 100 mL, dilute 25 mL of Magnesium Sulfate 20% w/v to 100 mL using Glucose 5% w/v or Sodium Chloride 0.9% w/v.

Disposal

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 56021/0015

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