SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Magnesium Sulfate 10% w/v Solution for Injection/Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Magnesium sulfate heptahydrate 10% w/v (0.4 mmol Mg^{2+} in 1 ml).

Each 1 ml of solution contains 0.4 mmol Mg^{2+} (equivalent to 100 mg magnesium sulfate heptahydrate).

Each 10 ml ampoule contains 4 mmol Mg^{2+} (equivalent to 1 g magnesium sulfate heptahydrate).

The concentrations of magnesium ions (Mg^{2+}) in millimoles are given as approximate values.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection/Infusion

Clear colourless solution, free from visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Magnesium Sulfate 10% w/v Solution for Injection/Infusion is indicated in adults, adolescents and children for

i) 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);

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

Magnesium Sulfate 10% w/v Solution for Injection/Infusion 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 10% w/v solution may be administered by intravenous or subcutaneous routes (see Method of administration below).

Posology

Magnesium sulfate heptahydrate 1 g = 98.6 mg or 8.1 mEq or approximately 4 mmol magnesium (Mg^{2+}).

Therapeutic levels are reached almost immediately with appropriate intravenous doses.

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 (16-24 mmol Mg^{2+}) per 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.

Usually, 10-20 ml Magnesium Sulfate 10% w/v solution (4-8 mmol Mg^{2+}) is administered slowly intravenously (at a rate of 1.5 ml/minute) or, exceptionally, subcutaneously (painful), repeatedly if necessary.

Severe pre-eclampsia or eclampsia

Intravenously an initial loading dose of 4-5 g of magnesium sulfate (16-20 mmol Mg^{2+}) diluted to an appropriate volume may be infused. This is followed by a maintenance regimen of either an intravenous (IV) infusion or regular intramuscular (IM) injections using Magnesium Sulfate 50% w/v solution as follows (see also Method of administration below):

- IV maintenance regimen: the loading dose is followed by an IV infusion of 1-2 g/hour (4-8 mmol Mg^{2+}/hour);

- IM maintenance regimen: the loading dose is followed by regular IM injections of 4-5 g of magnesium sulfate (8-10 ml of undiluted Magnesium Sulfate 50% w/v solution corresponding to 16-20 mmol Mg^{2+}) into alternate buttocks every 4 hours, depending on the continuing presence of the patellar reflex and adequate respiratory function (see section 4.4).

Therapy should continue until paroxysms cease.

Paediatric population

Hypomagnesaemia

Magnesium Sulfate 10% w/v solution may be administered intravenously to children. For the intravenous use in children the rate of administration should not exceed 0.1 ml/kg/minute (10 mg/kg/minute) Magnesium Sulfate 10% w/v solution (corresponding to 0.04 mmol/kg/minute = 0.001 g/kg/minute magnesium).

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

No special dosage instructions are available.

Elderly

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

Method of administration

For intravenous or subcutaneous injection or infusion.

Intravenous (IV):

For intravenous injection, the 10% w/v solution does not require dilution.

For intravenous infusion, the medicinal product should be diluted.

Subcutaneous (SC):

For subcutaneous administration, the medicinal product should be diluted.

Magnesium Sulfate 10% w/v solution is not appropriate for intramuscular administration. For intramuscular injection and in case the IV loading/IM maintenance regimen above is applied, Magnesium Sulfate 50% w/v solution should be used.

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.

- Hepatic encephalopathy, hepatic failure.
- Severe renal impairment (glomerular filtration rate <25 ml/h), renal failure, 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 (see section 4.2).

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

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

The serum magnesium level 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 hypermagnesaemia.

The presence of the patellar reflex should be checked.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Muscle relaxants

The action of non-depolarizing muscle relaxants is potentiated and prolonged by parenteral magnesium salts and 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. However, magnesium sulfate given intravenously in adequate quantities (2 to 3 g in one minute followed by 2 g/h for 4 to 5 hours) is effective in controlling ventricular irritability caused by toxic levels of digitalis preparations.

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 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.

Drug transporters

Pretreatment with magnesium has been reported in the rat to attenuate cisplatin (CDDP)-induced nephrotoxicity (CIN). Magnesium co-administration reduced platina accumulation by regulating the expression of the renal transporters, rOct2 and rMate1 and, thereby, attenuated CIN.

4.6 Fertility, pregnancy and lactation

Pregnancy

Magnesium sulfate easily crosses the placenta, and fetal serum levels will closely mirror maternal estimations.

As eclampsia may be life-threatening to mother and baby, magnesium sulfate may be administered in this condition. Sufficient amount of magnesium may cross the placenta in mothers treated with high doses e.g. in pre-eclampsia, causing hypotonia and respiratory depression in newborns. When used in pregnant women, fetal 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. Serum magnesium levels in preterm infants are higher than adult levels.

Breast-feeding

Magnesium concentration of mature human milk is 31 mg/l. Based on a mean milk transfer of 0.8 l/day and a concentration of magnesium in mature breast milk of 31 mg/l, a secretion of 25 mg/day of magnesium in breast milk is estimated during the first six months of lactation.

Safety during breast-feeding has not been established. Therefore, it is not advisable to administer magnesium sulfate during breast-feeding unless considered essential.

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

As with all medicines, hypersensitivity reactions cannot be ruled out.

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

Metabolism and nutrition disorders

Electrolyte/fluid abnormalities (hypophosphatemia, hypertonic dehydration).

There have been isolated reports of maternal and fetal hypocalcaemia with high doses of magnesium sulfate (see section 4.6).

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 effects

Too rapid administration: quickly developing vasodilatation, reduced blood pressure.

Local: as all parenteral medicines, magnesium sulfate injections 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 injection volume have been described for other magnesium sulfate solutions for injection.

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

4.9 Overdose

Symptoms

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

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 hypermagnesaemia are as follows:

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
7.0-12	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 symptomatic hypermagnesaemia, administration of calcium, usually at a dose of 100 to 200 mg intravenously over 5 to 10 min, antagonizes the toxic effects of magnesium.

In patients with severe renal dysfunction, peritoneal dialysis or haemodialysis will rapidly and effectively lower serum magnesium levels.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other mineral supplements, magnesium sulfate,

ATC code: A12CC02

Magnesium is a cofactor of more than 300 enzymatic reactions, 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.

Absorption and 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 20-33% 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.

The most important transport system 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.

No intramuscular or subcutaneous pharmacokinetic data are available 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

Sulfuric acid (for pH adjustment)

Sodium hydroxide (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

Unopened ampoule: 4 years

Shelf life after first opening

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

Shelf life after dilution

Chemical and physical in-use stability has been demonstrated for 72 hours at 25°C and 2 to 8°C after dilution with 0.9% sodium chloride or 5% glucose solution.

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 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not freeze.

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 hydrolytic class colourless borosilicate glass ampoules with red one point cut. Ampoules are packed in polyvinylchloride film liner. Liners are packed into a cardboard box.

Pack size:

5 ampoules

10 ampoules

100 ampoules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

For single use only. Discard any unused contents.

Can be diluted with 0.9% sodium chloride or 5% glucose solutions.

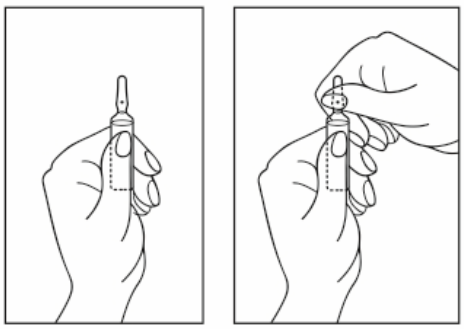
The medicinal product should be used immediately after opening the ampoule (see section 6.3).

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

Instruction of ampoule opening

1) Hold the ampoule upright. If there is any solution in the upper part of the ampoule, gently tap with your finger to get all the solution to the lower part of the ampoule.

2) Use both hands to open; while holding the lower part of the ampoule in one hand, use the other hand to break off the upper part of the ampoule in the direction away from the coloured point (see the pictures below).



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

7 MARKETING AUTHORISATION HOLDER

AS KALCEKS
Krustpils iela 71E,

Rīga, LV-1057,
Latvia

8 MARKETING AUTHORISATION NUMBER(S)

PL 47015/0009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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