1. NAME OF THE MEDICINAL PRODUCT

Magnesium Sulfate Kalceks 50%

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1mL contains 500 mg magnesium sulfate heptahydrate (2 mmol =49 mg or 4 mEq) magnesium (Mg^{2+}).
Each 2 ml ampoule contains 1 g magnesium sulfate heptahydrate.
Each 10 ml ampoule contains 5 g magnesium sulfate heptahydrtae.
1g of magnesium sulfate heptahydrate provides 4 mmol (8.1 mEq) of elemental magnesium (Mg^{2+}).

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 or infusion, with a pH of between 5.5 and 7.
Clear colourless solution, free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Magnesium Sulfate Kalceks 50% is indicated for:
1) the treatment of magnesium deficiency in hypomagnesaemia.
2) the prevention and treatment of hypomagnesaemia in patients receiving total parenteral nutrition.
3) the control and prevention of seizures in severe pre-eclampsia.
4) the control and prevention of recurrent seizures in eclampsia.

4.2 Posology and method of administration

Magnesium Sulfate Kalceks 50% 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 8.1 mEq or 4 mmol Mg^{2+}.

Treatment of magnesium deficiency in hypomagnesaemia
Adults:
Intravenous Route: Up to 80 mL Magnesium sulfate Kalceks 50% (corresponding to 160 mmol ≈ 4 g Mg^{2+}) diluted should be administered by slow intravenous infusion over a period of up to five days and titrated to clinical need. The usual regimen is 16 – 24 mL Magnesium Sulfate Kalceks 50% (corresponding to 32-48 mmol ≈0.8 – 1.2 g Mg^{2+}) diluted in the first 24 hours followed by 8 – 12 mL Magnesium Sulfate Kalceks 50% (corresponding to 16 – 24 mmol ≈ 0.4 – 0.6 g Mg^{2+}) diluted per day for 3 or 4 days.

Intramuscular Route:
2 – 4 mL Magnesium Sulfate Kalceks 50% (corresponding to 4 – 8 mmol ≈ 0.1 – 0.2 g Mg^{2+}) undiluted or 4 – 8 mL of Magnesium sulfate Kalceks 50% diluted to 25% solution can be given intramuscularly every 6 hours for 24 hours (a total of 4 doses).

Children and adolescents:
Neonate
0.2 mL/kg Magnesium Sulfate Kalceks 50% (corresponding to 0.4 mmol/kg ≈ 0.01 g/kg Mg^{2+}) diluted to 20% solution (i.e. 0.5 mL/kg of a 20% solution) every 6 – 12 hours as required, to be given by intravenous injection over at least 10 minutes.
Child 1 month – 11 years

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

Adolescent 12 – 17 years

2mL Magnesium Sulfate Kalceks 50% (corresponding to 4 mmol ≈ 0.1 g Mg^{2+}) diluted to 20% solution (i.e. 5 mL of a 20% 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 Kalceks 50% 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:

5 – 10 mL Magnesium Sulfate Kalceks 50% (corresponding to 10 – 20 mmol ≈ 0.25 – 0.5 g Mg^{2+}) diluted daily, usual dose 6 mL Magnesium sulfate Kalceks 50% (corresponding to 12 mmol ≈ 0.3 g Mg^{2+}) diluted daily, by intravenous infusion or intramuscular injection.

Neonates and infants (up to 12 months):

0.1 mL/kg Magnesium Sulfate Kalceks 50% (corresponding to 0.2 mmol/kg ≈ 0.005 g/kg Mg^{2+}) diluted daily by intravenous infusion.

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

0.05 mL/kg Magnesium Sulfate Kalceks 50% (corresponding to 0.1 mmol/kg ≈ 0.0025 g/kg Mg^{2+}) diluted 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 8 – 10 mL Magnesium Sulfate Kalceks 50% (corresponding to 16 – 20 mmol ≈ 0.4 – 0.5 g Mg^{2+}) diluted to an appropriate volume is administered over 5 – 15 minutes, followed either by maintenance intravenous infusion or regular IM injections for 24 hours, as follows:

IV Maintenance Regimen The IV loading dose (above) is followed by an infusion of approximately 2 mL Magnesium Sulfate Kalceks 50% (corresponding to 4 mmol ≈ 0.1 g Mg^{2+}) diluted per hour for at least 24 hours after the last fit.

IM Maintenance Regimen

The IV loading dose (above) is immediately followed by deep IM injection of 10 mL Magnesium sulfate Kalceks 50% (corresponding to 20 mmol ≈ 0.5 g Mg^{2+}) undiluted.

Maintenance therapy is a further 10 mL Magnesium Sulfate Kalceks 50% (corresponding to 20 mmol ≈ 0.5 g Mg^{2+}) undiluted IM every four hours, continued for 24 hours after the last fit (provided respiratory rate is > 16/min, urine output > 25mL/min and knee jerks are present).

Recurrent convulsions: In both IV and IM regimens, a further 4 – 8 mL Magnesium Sulfate Kalceks 50% (corresponding to 8 – 16 mmol ≈ 0.2 – 0.4 g Mg^{2+}) diluted depending on body weight [if less than 70 kg 4 mL Magnesium sulfate Kalceks 50% (corresponding to 8 mmol ≈0.2 g Mg^{2+}) diluted] are given IV over a period of 5 minutes.

Renal impairment

Magnesium Sulfate Kalceks 50% is contraindicated in patients with severe renal impairment (see section 4.3). Magnesium Sulfate Kalceks 50% should be used with caution in mild to moderate renal impairment. A reduction in dosage to 40 mL Magnesium Sulfate Kalceks 50% (corresponding to 80 mmol ≈ 2 g Mg^{2+}) diluted 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

Intravenous use in adults and adolescents

Intravenous infusion: For the intravenous route, the 50% solution requires dilution to a concentration of not more than 20% (≤ 200 mg/mL magnesium sulfate heptahydrate) – with a suitable diluent, such as 5%Glucose or

0.9%sodium chloride solution. 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).

Intravenous use in children:

Rate of administration should not exceed 0.02 mL/kg/min of appropriately diluted Magnesium sulfate Kalceks 50% (corresponding to 0.04 mmol/kg/min ≈ 0.001 g/kg/min Mg^{2+}).

Deep Intramuscular injection (adults only)
For the intramuscular route, the 50% solution should be used undiluted or diluted to 25%. If the total dose to be administered exceeds 5 mL, the injection volume should be divided between more than one deep muscular injection site.

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.

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.
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 (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 0.02 mL/kg/min of appropriately diluted Magnesium sulfate Kalceks 50% (corresponding to 0.04 mmol/kg/min = 0.001 g/kg/min Mg^{2+}) (see section 4.2).

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

For the intramuscular route, use good clinical practice for intramuscular injections. The 50% solution should be used undiluted or diluted to 25%. 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. 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 or diuretics (such as thiazides, nifedipine, 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
Safety in human pregnancy has not been established, however, in the medical emergency of a patient having Eclampsia, Magnesium Sulfate can be administered to relieve this condition, which may be life threatening to both mother and baby.
Magnesium crosses the placenta. 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 hypocalcemia, 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.

Breastfeeding
Safety during breast feeding has not been established. Therefore, as with all medicinal products, it is not advisable to administer magnesium sulfate during lactation 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
Magnesium Sulfate Kalceks 50% is unlikely to affect the ability to drive or to operate machinery. However, some people may feel dizzy or drowsy when given Magnesium Sulfate Kalceks 50%. 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 injection 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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

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 (mmol/L)	Symptoms and undesirable effects
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). 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.

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 amount of elemental magnesium provided by each 1 g of magnesium sulfate heptahydrate is 4.1 mmol; therefore 2 mL of a 50% solution will provide approximately 4 mmol of magnesium ions.

Distribution

Infused magnesium is distributed rapidly throughout the entire extracellular fluid space and some is taken up by bone but none by red blood cells.

About 40% of plasma magnesium is protein bound and is not ultrafiltrable. Most of the plasma Mg is bound with albumin, globulin and proteins and therefore not filterable at the glomerulus. The injected magnesium sulfate is promptly bound to plasma proteins to the same degree as that of endogenous magnesium.

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 above.

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.

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

The expiry date of the product is indicated on the packaging materials.

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 30°C and 2 – 8°C when diluted to a concentration of not more than 200 mg/mL magnesium sulfate heptahydrate in 0.9% Sodium chloride or 5%

Glucose solution.

Solutions diluted to 25% should be used immediately.

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 – 8°C unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 30ºC , 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

2 ml or 10 ml of solution in type I hydrolytic class colourless borosilicate glass ampoules with one point cut. Ampoules are packed in liner. Liners are packed into outer carton.

Pack size:

10 ampoules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For intramuscular use, a 50% solution is used undiluted or diluted to 25%. For intravenous use, the 50% solution must be diluted before use., with a suitable diluent, such as 5% Glucose or 0.9%sodium chloride solution.

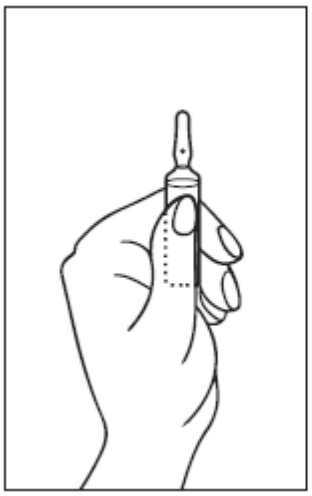
For single use only. Discard any unused contents.

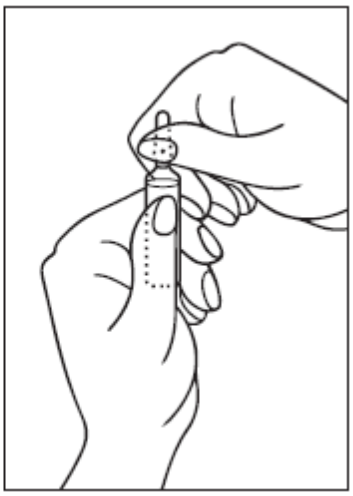
This medicinal product should be used immediately after opening the ampoule (section 6.3).

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

Instruction of ampoule opening:

1) Turn the ampoule with coloured point up. 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 Authorization Holder and Importer:

A.L.Medi-Market Ltd., 3 Hakatif street, Emek Hefer Industrial Park, 3877701

8.MANUFACTURER

HBM Pharma s.r.o.,

Sklabinska 30, 036 80 Martin, Slovakia

9.MARKETING AUTHORISATION NUMBER(S)

165-51-35894-00

10. DATE OF REVISION OF THE TEXT

Revised in May 2021