SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Magnesium sulfate-Kalceks 500 mg/ml solution for injection, BP *

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 500 mg of magnesium sulfate heptahydrate
1 ampoule (2 ml) contains 1000 mg of magnesium sulfate heptahydrate.

Excipient (s) with known effect: sodium hydroxide
This medicine contains less than 1 mmol sodium (23 mg) per ampoule, i.e. essentially "sodium free"

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

A clear colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Magnesium sulfate-Kalceks is indicated for:

- treatment of women with eclampsia
- prevention of eclampsia in women with severe pre-eclampsia
- prevention of cerebral palsy in the infant in women at risk of imminent preterm birth before 32 weeks of gestation

The most recent published guidelines should be consulted, including those of WHO (see References).

4.2 Posology and method of administration

Posology

Magnesium sulfate regimens for severe pre-eclampsia and eclampsia
The full intravenous or intramuscular magnesium sulfate regimens are recommended for the prevention and treatment of eclampsia. For settings where it is not possible to administer the full magnesium sulfate regimen, the use of a magnesium sulfate loading dose followed by immediate transfer to a higher level health-care facility is recommended.

Note re dilution for IV use:
Magnesium sulfate-Kalceks MUST be diluted to a ≤20% solution for intravenous use. Diluents commonly used are 5 % glucose solution and 0.9 % sodium chloride solution. For a 20% solution, dilute 10 ml of Magnesium sulfate-Kalceks with 15 ml of diluent.
Intravenous dosing should be done using an infusion pump if available.

* Trade names are not prequalified by WHO. This is national medicines regulatory authority's (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

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 to 8 C, unless reconstitution / dilution (etc) has taken place in controlled and validated aseptic conditions.

Intramuscular Regimen

Loading dose (IV and IM):
• Give 4 g IV over five minutes (20 ml of the diluted 20% magnesium sulfate solution).
• Follow promptly with 10 g of 50% magnesium sulfate solution: Give 5 g (10 ml of the undiluted 50% solution) in each buttock as a deep IM injection with 1 ml of 2% lidocaine in the same syringe. Ensure aseptic technique when giving magnesium sulfate deep IM injection. Warn the woman that she will have a feeling of warmth when the magnesium sulfate is given.

Maintenance dose (intramuscular):
• Give 5 g (10 ml of the undiluted 50% magnesium sulfate solution) with 1 ml of 2% lidocaine in the same syringe by deep IM injection into alternate buttocks every four hours.
Continue treatment for 24 hours after birth or the last convulsion, whichever occurs last.

Intravenous Regimen

See note above on how to dilute the product to a 20% solution.

Intravenous administration, using an infusion pump if available:
Loading dose:
• Give 4 g IV over five minutes (20 ml of the diluted 20% magnesium sulfate solution).
• If convulsions recur after 15 minutes, give 2 g (10 ml of the diluted 20% magnesium sulfate solution) IV over five minutes.

Maintenance dose (intravenous):
• Give intravenous infusion 1 g (5 ml of the diluted 20% magnesium sulfate solution) per hour.
Continue treatment for 24 hours after childbirth or the last convulsion, whichever occurs last.

Although magnesium toxicity is rare, a key component of monitoring women with severe pre-eclampsia and eclampsia is assessing for signs of magnesium toxicity. Before repeat administration, ensure that:
- respiratory rate is at least 16 per minute;
- patellar reflexes are present;
- urinary output is at least 30 ml per hour over four hours.

• If there are signs of toxicity, delay the next IM dose or withhold the IV infusion of magnesium sulfate.

Signs indicating the need to withhold or delay maintenance dose of magnesium sulfate

Closely monitor the woman for signs of magnesium toxicity.
To prevent magnesium intoxication, it is important to evaluate respiratory rate, deep tendon reflexes and urinary output before administering an additional dose.

Withhold or delay drug if:
• respiratory rate falls below 16 breaths per minute;
• patellar reflexes are absent;
• urinary output falls below 30 ml per hour over preceding four hours.

Keep antidote ready. In case of respiratory arrest:
• assist ventilation (mask and bag, anaesthesia apparatus, intubation);
• give calcium gluconate 1 g (10 ml of 10% solution) IV slowly over three minutes,
until respiration begins to counteract the effect of magnesium sulfate.

Magnesium sulfate regimens for prevention of cerebral palsy in the infant in women at risk of imminent preterm birth before 32 weeks of gestation

Note re dilution for IV use:
This product MUST be diluted to a ≤20% solution for intravenous use. Diluents commonly used are 5 % glucose solution and 0.9 % sodium chloride solution. For a 20% solution, dilute 10 ml of magnesium sulfate-Kalceks with 15 ml of diluent.
Intravenous dosing should be done using an infusion pump if available.

Magnesium sulfate for neuroprotection should only be given if preterm birth is likely within the next 24 hours.

Three dosing regimens have been used for this indication for prevention of cerebral palsy. There is insufficient evidence at present to recommend one over the others.
Intravenous dosing should be done using an infusion pump if available.

• IV 4 g (20 ml of the diluted 20% magnesium sulfate solution) over 20 minutes, then 1g/hr (5 ml of the diluted 20% magnesium sulfate solution) until delivery or for 24 hrs, whichever comes first.
• IV 4 g (20 ml of the diluted 20% magnesium sulfate solution) over 30 minutes, or IV bolus of 4 g (20 ml of the diluted 20% magnesium sulfate solution) given as a single dose.
• IV 6 g (30 ml of the diluted 20% magnesium sulfate solution) over 20-30 minutes, followed by IV maintenance of 2 g (10 ml of the diluted 20% magnesium sulfate solution) per hour.

Use in patients with renal impairment
In patients with mild to moderate renal impairment dosage should be reduced. For safe use, vigilance is advised for clinical signs of magnesium toxicity (i.e. respiratory rate falling below 16/min., absent patellar reflexes, urine output below 30 ml per hour in preceding 4 hours). Monitoring of blood magnesium levels may also be helpful.

In patients with severe renal impairment magnesium sulfate is contraindicated (see section 4.3).

4.3 Contraindications

- Hypersensitivity to the active substance, it salts or to any of the excipients listed in section 6.1.
- Heart block.
- Severe renal impairment.

4.4 Special warnings and precautions for use

Clinical indicators of a safe regimen include:
- respiratory rate is above 16 breaths per minute;
- patellar reflexes are present;
- urinary output is above 30 ml per hour over preceding four hours.

When magnesium sulfate used in pregnant women, fetal heart rate should be monitored. (See section 4.6).

Parenteral magnesium sulfate should be used with caution in patients with *myasthenia gravis*.

Magnesium sulfate should be administered with extreme caution in patients receiving β-adrenergic agonists, calcium antagonists, CNS depressants, cardiac glycosides and neuromuscular blocking agents (see section 4.5).

Alcohol abuse increases the excretion of magnesium resulting in decreased magnesium levels.

Renal impairment
Parenteral magnesium sulfate administration is contraindicated in patients with severe renal impairment (see section 4.3).
It should be used with caution in less severe degrees of renal impairment (see section 4.2 regarding dose reduction, and clinical and laboratory monitoring).

4.5 Interactions with other medicinal products and other forms of interaction

β-adrenergic agonists and calcium-channel blocking agents (e.g. nifedipine)
β-adrenergic agonists and calcium-channel blocking agents concomitantly with magnesium sulfate must be used with extreme caution due to risk of serious adverse maternal effects (reduced heart rate, contractility, and left ventricular systolic pressure, neuromuscular blockade).

CNS depressants (e.g. barbiturates, opiates, general anaesthetics)
When CNS depressants administered concomitantly with magnesium sulfate, dosage of these medicines must be carefully adjusted because of the additive central depressant effect.

Cardiac glycosides (e.g. digoxin)
Magnesium sulfate should be used with extreme caution in patients taking digoxin, as it may cause serious changes in cardiac conduction, including heart block.

Neuromuscular blocking agents
Concomitant use of neuromuscular blocking agents with magnesium sulfate leads to excessive neuromuscular blockade; these medicines should be administered concomitantly only with caution. Patients should be monitored for respiratory depression.

Other
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. It should not be used in conjunction with benzylpenicillin, nafcillin, polymyxin, dobutamine, procaine (novocaine), tetracyclines.

Diuretics, aminoglycoside antibiotics (such as gentamycin, tobramycin, amphotericin B), immunosuppressants (such as ciclosporin A) and cytostatics (such as cisplatin) cause increased excretion of magnesium via the kidneys.

4.6 Pregnancy and lactation

Pregnancy
Magnesium crosses the placenta. When used in pregnant women, fetal heart rate should be monitored.
Continuous administration of magnesium sulfate injection beyond 5-7 days to pregnant women can cause low calcium and bone abnormalities in the baby. Fetal magnesium toxicity impairs bone mineralization and can lead to serious bone demineralization that may cause fractures in the newborn period that complicate recovery from respiratory disease.

Breast-feeding
Magnesium sulfate in negligible amounts excreted into breast milk, therefore the use of magnesium sulfate is compatible with breast-feeding.

4.7 Effects on ability to drive and use machines

No studies have been done on the ability to drive and use machines.

4.8 Undesirable effects

- Hypersensitivity reactions.
- Hypocalcemia.
- Pain with intramuscular injection.
- Hypermagnesemia characterised by flushing, thirst, hypotension, drowsiness, nausea, vomiting, confusion, slurred speech, double vision, loss of tendon reflexes due to neuromuscular blockade, muscle weakness, respiratory depression, electrolyte/fluid abnormalities (hypophosphatemia, hyperosmolar dehydration), ECG changes (prolonged PR, QRS and QT intervals), bradycardia, cardiac arrhythmias, coma and cardiac arrest.

There is a risk of respiratory depression if magnesium sulfate is administered concomitantly with high doses of barbiturates, opioids or hypnotics (see 'Interactions').

4.9 Overdose

Symptoms
Magnesium intoxication is manifested by a sharp drop in blood pressure and respiratory paralysis. Excessive parenteral doses of magnesium salts lead to the development of hypermagnesemia, important signs of which are respiratory depression and loss of deep tendon reflexes, both due to neuromuscular blockade.
Other symptoms and signs of hypermagnesemia may include nausea, vomiting, flushing, thirst, hypotension due to peripheral vasodilatation, drowsiness, confusion, slurred speech, double vision,

muscle weakness, low heart rate, cardiac arrhythmias, electrolyte/fluid abnormalities. In severe cases coma and cardiac arrest occurs.

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

Treatment
Assisted ventilation.
Calcium gluconate 1 g (10 ml of 10% solution) IV slowly over three minutes, until respiration begins to counteract the effect of magnesium sulfate.
Dialysis may be necessary in patients with renal impairment or severe hypermagnesemia.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: electrolyte solutions, ATC code: B05XA05

Magnesium is a significant cation in intracellular fluid and an essential electrolyte involved in maintaining ionic cellular balance and membrane stabilization. It is involved in functioning of the Na^+/K^+-ATPase pump, and acts as a cofactor in numerous enzyme systems. These include those of glucose metabolism, fatty acid synthesis and breakdown, DNA and protein synthesis. It is involved in neurochemical transmission and muscular excitability. Parenterally administered magnesium sulfate has a depressant effect on the CNS, and anti-seizure, tocolytic, vasodilator, antiarrhythmic, bronchodilator, and neuroprotective effects. It acts as a weak calcium channel blocker, an NMDA receptor blocker in the CNS, and an inhibitor of parasympathetic effects.

5.2 Pharmacokinetic properties

Absorption
Following intravenous administration, the onset of action is immediate and the duration of action is about 30 minutes. Following intramuscular administration, the onset of action occurs in about 1 hour and the duration of action is 3-4 hours.
About 40% of plasma magnesium is protein bound.

Distribution
Magnesium sulfate administered parenterally is initially distributed into the intravascular compartment. The intravascular unbound magnesium ion diffuses into the extra-vascular extra-cellular space, into bone, crosses the placenta and fetal membranes, and diffuses into the fetus and amniotic fluid. The apparent volume of distribution increases rapidly and becomes constant within 2 hours in healthy nonpregnant individuals, but in pregnant women, volume of distribution does not approach a constant value until between the 3^{th} and 4^{th} hour.

Biotransformation
Magnesium sulfate is not metabolized in the body.

Elimination
Magnesium sulfate is eliminated by renal excretion. Urinary excretion is very rapid and increases 20-fold during magnesium sulfate infusion. By 24 hours after the infusion more than 90 % has been eliminated. The half-life of magnesium sulfate in patients with normal renal function is 4 hours. Therefore, patients with impaired renal function can develop hypermagnesemia.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, or toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

0.1 M solution of sulfuric acid and/or 0.1 M solution of sodium hydroxide (for adjustment of pH)
Water for injections

6.2 Incompatibilities

Magnesium sulfate is incompatible with alkali hydroxides (forming insoluble magnesium hydroxide), alkali carbonates (forming insoluble magnesium carbonate) and salicylates. See also section 4.5.

6.3 Shelf life

60 months

Chemical and physical in use stability has been demonstrated for 24 hours at 2 to 8°C.

6.4 Special precautions for storage

Do not store above 30 °C. Do not freeze.
Single use ampoules. Discard unused portion.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

2 ml of solution is filled in type I hydrolytic class colourless borosilicate glass ampoules with break line or open point cut. Ampoules could be marked with coloured rings.
5 ampoules are packed in a polyvinylchloride film liner and then two or twenty liners together with leaflet are placed in a cardboard box.
Pack sizes: 2x5x2 ml (10 ampoules)
: 20x5x2ml (100 ampoules)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORIZATION HOLDER

AS KALCEKS
Krustpils iela 71E, Rīga, LV-1057, Latvia

8. WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)

RH063

9. DATE OF FIRST PREQUALIFICATION

04 July 2017

10. DATE OF REVISION OF THE TEXT

October 2017
Section 6 updated in February 2018
Section 6 updated in March 2019
Section 6 updated in March 2021
Section 7 updated in July 2022

Detailed information on this medicine is available on the World Health Organization (WHO) web site: https://extranet.who.int/prequal/

References:

General
WHO recommendations for Prevention and treatment of pre-eclampsia and eclampsia
http://apps.who.int/iris/bitstream/10665/44703/1/9789241548335_eng.pdf

WHO, Managing complications in pregnancy and childbirth: a guide for midwives and doctors, 2nd ed., 2017
http://www.who.int/maternal_child_adolescent/documents/managing-complications-pregnancy-childbirth/en/

WHO recommendations on interventions to improve preterm birth outcomes
http://apps.who.int/iris/bitstream/10665/183037/1/9789241508988_eng.pdf