WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities (term to be revised).
The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

1. NAME OF THE MEDICINAL PRODUCT

[RH086 trade name]*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 500 mg of magnesium sulfate heptahydrate

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

A clear colourless solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[RH086 trade name] is indicated for:

- prevention of eclampsia in women with severe pre-eclampsia
- treatment of women with eclampsia
- prevention of cerebral palsy in the infant of 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

[RH086 trade name] MUST be diluted to a ≤20% solution for intravenous use and should be given using an infusion pump if available.

For a 20% solution, dilute as follows:

Solution	Volume of solution	Magnesium sulfate content
[RH086 trade name]	10 ml	500 mg/ml (50%)
Diluent (e.g. glucose 5%, or sodium chloride 0.9%)	15 ml	-
Final solution	25 ml	200 mg/ml (20%)

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.

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.

* Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

Intramuscular regimen

Loading dose (intravenous and intramuscular):

• Give 20 ml of the diluted 20% magnesium sulfate solution (equivalent to 4 g of magnesium sulfate) **intravenously** over 5 minutes.
• Follow promptly with 10 ml of the undiluted solution (equivalent to 5 g magnesium sulfate) in each buttock as a deep **intramuscular** injection with 1 ml of 2% lidocaine in the same syringe.
Ensure aseptic technique when giving magnesium sulfate by deep intramuscular injection. Warn the woman that she will have a feeling of warmth when the magnesium sulfate is given.
• If convulsions recur after 15 minutes, give 10 ml of the diluted 20% magnesium sulfate solution (equivalent to 2 g of magnesium sulfate) **intravenously** over 5 minutes.

Maintenance dose (intramuscular):

• Give 10 ml of the undiluted solution (equivalent to 5 g magnesium sulfate) with 1 ml of 2% lidocaine in the same syringe by deep **intramuscular** injection into alternate buttocks every 4 hours.
Continue treatment for 24 hours after birth or 24 hours after the last convulsion, whichever occurs last.

Intravenous regimen

Intravenous administration, using an infusion pump if available:

Loading dose:

• Give 20 ml of the diluted 20% magnesium sulfate solution (equivalent to 4 g of magnesium sulfate) **intravenously** over 5 minutes.
• If convulsions recur after 15 minutes, give 10 ml of the diluted 20% magnesium sulfate solution (equivalent to 2 g of magnesium sulfate) **intravenously** over 5 minutes.

Maintenance dose (intravenous):

• Give 5 ml of the diluted 20% magnesium sulfate solution (equivalent to 1 g of magnesium sulfate) per hour by **intravenous** infusion.
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 administration, it is important to ensure that:

- respiratory rate is at least 16 per minute;
- patellar reflexes are present;
- urinary output is at least 30 ml per hour over 4 hours.

If there are signs of toxicity, the next intramuscular dose should be delayed or the intravenous infusion of magnesium sulfate withheld. Signs indicating the need to withhold or delay maintenance dose of magnesium sulfate are:

- respiratory rate below 16 breaths per minute;
- patellar reflexes are absent;
- urinary output falls below 30 ml per hour over preceding 4 hours.

The antidote (calcium gluconate) should be kept ready. In case of respiratory arrest:

- assist ventilation (mask and bag, anaesthesia apparatus, intubation);
- give calcium gluconate 1 g (10 ml of 10% solution) intravenously slowly over 3 minutes, until respiration begins to counteract the effect of magnesium sulfate.

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

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

Three intravenous dosing regimens have been used for prevention of cerebral palsy. There is insufficient evidence at present to recommend one over the others:

• 20 ml of the diluted 20% magnesium sulfate solution (equivalent to 4 g of magnesium sulfate) infused intravenously over 20 minutes, then 5 ml of the diluted 20% magnesium sulfate solution (equivalent to 1 g) per hour until delivery or for 24 hours, whichever comes first.

• 20 ml of the diluted 20% magnesium sulfate solution (equivalent to 4 g of magnesium sulfate) infused intravenously over 30 minutes, or as a single intravenous bolus.

• 30 ml of the diluted 20% magnesium sulfate solution (equivalent to 6 g of magnesium sulfate) infused intravenously over 20-30 minutes, followed by maintenance infusion of 10 ml of the diluted 20% magnesium sulfate solution (equivalent to 2 g) 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).

Method of administration

[RH086 trade name] may be administered by intramuscular or intravenous routes.

Intramuscular therapy should be used only when peripheral venous access is impossible.

4.3 Contraindications

- Hypersensitivity to the active substance, its 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.

Pregnancy

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

Myasthenia gravis

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

Concomitant medication

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

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).

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per ampoule, i.e. essentially 'sodium-free'.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

β-adrenergic agonists and calcium-channel blocking agents (e.g. nifedipine)

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

CNS depressants (e.g. barbiturates, opiates, general anaesthetics)

When CNS depressants are 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 antibiotics such as streptomycin and tetracycline are inhibited by magnesium ions. Use with diuretics, aminoglycosides (such as gentamycin, tobramycin amphotericin B), and nephrotoxic immunosuppressants (such as ciclosporin) or cytotoxics (such as cisplatin) may increase the risk of adverse effects. It is also advised that magnesium sulfate not be used in conjunction with benzylpenicillin, nafcillin, polymyxin, dobutamine, or procaine (novocaine).

4.6 Fertility, pregnancy and breastfeeding

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 in the child 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 demineralisation, 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.

Breast-feeding

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

Postpartum use of intravenous magnesium sulfate for longer than 6 hours appears to delay the onset of lactation.

Fertility

No studies and/or data are available on the effects on fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adverse events related to treatment are listed below. They reflect published literature data, but reliable information on frequency is not available.

Immune system disorders

hypersensitivity reactions, flushing

Metabolism and nutrition disorders

Thirst

Nervous system disorders

double vision

Psychiatric disorders

drowsiness, confusion, slurred speech

Cardiac disorders

ECG changes (prolonged PR, QRS and QT intervals), bradycardia, cardiac arrhythmias, cardiac arrest and coma.

Vascular disorders

Hypotension

Respiratory, thoracic and mediastinal disorders

respiratory depression*

Gastrointestinal disorders

nausea, vomiting

Musculoskeletal and connective tissue disorders

loss of tendon reflexes due to neuromuscular blockade, muscle weakness

General disorders and administration site conditions

pain with intramuscular injection

Investigations

electrolyte/fluid abnormalities (hypophosphatemia, hyperosmolar dehydration), hypocalcaemia

*There is a risk of respiratory depression when magnesium sulfate is administered concomitantly with high doses of barbiturates, opioids or hypnotics (see section 4.5).

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. Health care professionals are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

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 hypermagnesaemia, important signs of which are respiratory depression and loss of deep tendon reflexes, both due to neuromuscular blockade.

Other symptoms and signs of hypermagnesaemia 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 may occur.

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

Treatment

Assisted ventilation.
Calcium gluconate 1 g (10 ml of 10% solution) given intravenously slowly over 3 minutes, until respiration begins to counteract the effect of magnesium sulfate.

Dialysis may be necessary in patients with renal impairment or severe hypermagnesaemia.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 hypermagnesaemia, important signs of which are respiratory depression and loss of deep tendon reflexes, both due to neuromuscular blockade.

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Dialysis may be necessary in patients with renal impairment or severe hypermagnesaemia.

5.2 Pharmacokinetic properties

No bioequivalence study is necessary for this product.

Pharmacokinetics of magnesium sulfate

	Magnesium sulfate
General	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.
Absorption	
Oral bioavailability	Not applicable.
Food effect	Not applicable.
Distribution	
Volume of distribution (mean)	0.250 L/kg (Vc)
Plasma protein binding *in vitro*	30-40%
Tissue distribution	After intravenous administration unbound magnesium ion diffuses from the intravascular compartment into the extra-vascular extracellular 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 for 3-4 hours.
Metabolism	
	Magnesium sulfate is not metabolised in the body.
Active metabolite(s)	None
Elimination	
	Magnesium sulfate is excreted solely by the kidneys.
Elimination half life	4 h
% of dose excreted in urine	Excreted primarily in urine
% of dose excreted in faeces	Very limited

5.3 Preclinical safety data

This product has been available for many years and its side effects and clinical profile are well understood, therefore no further data are provided.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

0.5M solution of sulfuric acid and/or 0.1M solution of sodium hydroxide (for adjustment of pH)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months

In -use

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.

6.4 Special precautions for storage

Do not store above 30 °C. Do not freeze.

6.5 Nature and contents of container

10 ml of solution is filled in type I hydrolytic, colourless borosilicate glass ampoules with an open point cut or colour breaking circle.
5 ampoules are packed in a polyvinylchloride film or polyethylene terephthalate film liner. Such 2 liners together with a leaflet are then placed in a cardboard box.

6.6 Special precautions for disposal

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

RH086

9. DATE OF PREQUALIFICATION

16 March 2020

10. DATE OF REVISION OF THE TEXT

June 2020

Section 6.3 updated in May 2021

Section 6.3 updated in March 2022

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

Section 4.6

Vigil-De Gracia P, Ramirez R, Duran Y et al. **Magnesium sulfate** for 6 vs 24 hours post delivery in patients who received **magnesium sulfate** for less than 8 hours before birth: A randomized clinical trial. BMC Pregnancy Childbirth. 2017;17:241. [PMC free article] [PubMed]

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