

MAGNESIUM SULFATE

INJECTION, 500 MG/ML IN 2-ML
AND 10-ML AMPOULE

GENERAL PRODUCT INFORMATION

Pre-eclampsia and eclampsia is the second-leading cause of maternal death in low- and middle-income countries. It is most often detected through the elevation of blood pressure during pregnancy, which can be followed by seizures, kidney and liver damage, and maternal and fetal death, if untreated.

Magnesium sulfate is recognized by WHO as the safest, most effective, and lowest-cost medicine for treating severe pre-eclampsia and eclampsia. It is also considered an essential medicine by the UN Commission on Life-Saving Commodities for Women and Children. Other anticonvulsant medicines, such as diazepam and phenytoin, are less effective and riskier. Magnesium sulfate should be the only treatment of severe pre-eclampsia and eclampsia and should be procured over other anticonvulsants and made available in all health facilities to help lower maternal death rates and improve overall maternal health.

Additionally, WHO recommends the use of magnesium sulfate for women at risk of imminent preterm birth before 32 weeks of gestation for prevention of neurological complications (neuroprotection). Magnesium sulfate for neuroprotection should only be given if preterm birth is likely within the next 24 hours. Magnesium sulfate should be administered regardless of the cause for preterm birth and the number of babies in utero.¹

¹ WHO Recommendations on Interventions to Improve Preterm Birth Outcomes. Geneva: World Health Organization; 2015. Available from: http://apps.who.int/iris/bitstream/handle/10665/183037/9789241508988_eng.pdf?sequence=1

KEY CONSIDERATIONS IN PROCUREMENT

1. Procurement should be made from trusted sources. This includes manufacturers prequalified by WHO or approved by a SRA for magnesium sulfate injection and those with a proven record of quality products.
2. Procurers need to focus on product quality to ensure that it is sterile and safe for patient use as magnesium sulfate is an injectable medicine.

KEY QUALITY CONSIDERATIONS

Product specification

Products that are procured must comply with pharmacopeial specifications, such as those of the International Pharmacopoeia, US Pharmacopeia, and British Pharmacopoeia, as detailed in the “Supply” section 4 below.

Packaging and labeling

The container-closure system (ampoule) must be sufficient to preserve sterility during the shelf life of the product.

Procurement of 500 mg/mL (50% w/v) in 2-mL and 10-mL ampoule presentations as per the WHO EML is recommended. The WHO EML recommends magnesium sulfate 500 mg/mL (50% w/v) in 2-mL and 10-mL ampoule presentations, for convenient use in both Pritchard (IV/IM) and Zuspan (IV/IV) dosing regimens for the treatment of eclampsia and severe pre-eclampsia. Some SRA-approved products are presented in different packaging and/or concentrations, which require an adaptation of the dilution process during dosage preparation. The additional burden of recalculation is time-consuming and can introduce potential errors.

Additional information about the packaging and labeling can be found in the Annex.

Storage, transportation, and distribution

Magnesium sulfate must be stored safely to ensure that ampoules do not break or leak, which would compromise their sterility. Products do not need to be maintained in the cold chain.

Name of the Medicinal Product	Magnesium sulfate injection
Chemical Name	Magnesium sulfate (1:1) heptahydrate
Chemical Structure	MgSO ₄ , 7H ₂ O
Pharmaceutical Form	Sterile solution for injection A clear, colorless solution
Qualitative and Quantitative Composition	Magnesium sulfate injection is a sterile solution of magnesium sulfate heptahydrate in water for injection. It contains 500 mg of magnesium sulfate heptahydrate per mL (50% w/v), approximately 2 millimoles magnesium ions (Mg ²⁺) per mL 1 ampoule (2 mL) contains 1,000 mg of magnesium sulfate heptahydrate. 1 ampoule (10 mL) contains 5,000 mg of magnesium sulfate heptahydrate. List of typical excipients: – Water for injections – Sulfuric acid/Hydrochloric acid and/or sodium hydroxide, for pH adjustment
Packaging and Presentation	The WHO Essential Medicines List includes two presentations: 500 mg/mL in 2-mL ampoule (equivalent to 1 g in 2 mL; 50% w/v) and 500 mg/mL in 10-mL ampoule (equivalent to 5 g in 10 mL; 50% w/v). These ampoules would need to be mixed with IV solution to dilute to 20 percent solution for an IV loading dose.

SUPPLY



Generally, products prequalified by the WHO PQP and/or approved by an SRA are considered quality-assured and highly recommended for procurement. In the absence of WHO-prequalified, SRA-approved or ERP-recommended products, medicines from the trusted sources, such as manufacturers approved by UN agencies, can be considered for procurement. Alternatively, the procurement agency may conduct its own quality assessment as described in [Module II](#).

WHO-prequalified products

As of June 2022, there are seven magnesium sulfate injections prequalified by the WHO PQP, as shown in the table below. It is recommended to check the updated information at the time of procurement, which can be found at <https://extranet.who.int/pqweb/medicines/prequalified-lists/finished-pharmaceutical-products>.

Magnesium Sulfate

Table MS-1. List of WHO-Prequalified Magnesium Sulfate Injection

WHO REF. NUMBER	MARKETING AUTHORIZATION HOLDER	MANUFACTURING SITE	DOSAGE FORM AND STRENGTH	PACKAGING AND PRESENTATION	DATE OF PRE-QUALIFICATION	SHELF LIFE	STORAGE CONDITION
RH062(a)	Inresa Arzneimittel GmbH, Obere Hardtstraße 18, 79114, Freiburg, Germany	FPP manufacturing site: Laboratoire Renaudin, ZA Errobi, 64250, Itxassou, France API manufacturing site: – K+S KALI GmbH, Bertha-von-Suttner-Strasse 7, Kassel, Germany – Macco Organiques, S.R.O, Zahradni 1938/46c, Bruntál, 792 01, Czech Republic	Solution for injection 50%	Ampoule: type I glass 10 mL x 5's 10 mL x 10's 10 mL x 50's 10 mL x 100's	15-Aug-16	3 years	Do not store above 25°C.
RH063	AS Kalceks, Krustpils iela 71E, Rīga, LV-1057, Latvia	FPP manufacturing site: – HBM Pharma SRO, Sklabinska 30, Martin, 036 80, Slovakia – Mefar Ilac Sanayii A.S., Ramazanoglu Mah. Ensar Cad. No: 20, Kurtkoy-Pendik, Istanbul, TR-34906, Turkey API manufacturing site: – K+S KALI GmbH, Werk Werra, Hattorfer Strasse, 36269, Philippsthal (Werra), Germany – Macco Organiques, S.R.O, Zahradni 1938/46c, Bruntál, 792 01, Czech Republic	Solution for injection 500 mg/mL (2 mL)	Ampoule: type I glass 2 mL x 10's 2 mL x 100's	4-Jul-17	5 years	Do not store above 30°C.
RH064	AS Kalceks, Krustpils iela 71E, Rīga, LV-1057, Latvia	FPP manufacturing site: – HBM Pharma sro, Sklabinska 30, Martin, 036 80, Slovakia – Mefar Ilac Sanayii A.S., Ramazanoglu Mah. Ensar Cad. No: 20, Kurtkoy-Pendik, Istanbul, TR-34906, Turkey	Solution for injection 500 mg/mL (10 mL)	Ampoule: type I glass 10 mL x 5's 10 mL x 10's 10 mL x 100's	4-Jul-17	5 years	Do not store above 30°C.

Magnesium Sulfate

WHO REF. NUMBER	MARKETING AUTHORIZATION HOLDER	MANUFACTURING SITE	DOSAGE FORM AND STRENGTH	PACKAGING AND PRESENTATION	DATE OF PRE-QUALIFICATION	SHELF LIFE	STORAGE CONDITION
		<p>API manufacturing site:</p> <ul style="list-style-type: none"> – K+S KALI GmbH, Werk Werra, Hattorfer Strasse, 36269, Philippsthal (Werra), Germany – Macco Organiques, S.R.O, Zahradni 1938/46c, Bruntál, 792 01, Czech Republic 					
RH072(a)	Labesfal, Laboratorios Almiro SA, Unit 2, Zona Industrial do Lagedo, Santiago de Besteiros, 3465-157, Portugal	<p>FPP manufacturing site: Labesfal, Laboratorios Almiro SA, Unit 2, Zona Industrial do Lagedo, Santiago de Besteiros, 3465-157, Portugal</p> <p>API manufacturing site:</p> <ul style="list-style-type: none"> – K+S KALI GmbH, Werk Werra, Hattorfer Strasse, 36269, Philippsthal (Werra), Germany – Macco Organiques, S.R.O, Zahradni 1938/46c, Bruntál, 792 01, Czech Republic 	Solution for injection 500 mg/mL (10 mL)	Ampoule: type I glass, colorless 10 mL x 50's	19-Jun-18	5 years	Do not store above 30°C.
RH073(a)	Aurum Pharmaceuticals Ltd, Bampton Road, Harold Hill, Romford, Essex, RM3 8UG, United Kingdom	<p>FPP manufacturing site: Macarthys Laboratories Limited, Bampton Road, Harold Hill, Romford, Essex, RM3 8UG, United Kingdom</p> <p>API manufacturing site:</p> <ul style="list-style-type: none"> – K+S KALI GmbH, Werk Werra, Hattorfer Strasse, 36269, Philippsthal (Werra), Germany – Macco Organiques, S.R.O, Zahradni 1938/46c, Bruntál, 792 01, Czech Republic 	Solution for injection 50% w/v, 2 mL	Ampoule; neutral type I glass 2 mL x 10's	12-Dec-17	3 years	Do not store above 30°C.
RH077(a)	Aurum Pharmaceuticals Ltd, Bampton Road, Harold Hill,	FPP manufacturing site: Macarthys Laboratories Limited, Bampton Road, Harold Hill, Romford, Essex, RM3 8UG, United Kingdom	Solution for injection 50% w/v, 10 mL	Ampoule; neutral type I glass 10 mL x 10's	12-Dec-17	3 years	Do not store above 30°C.

Magnesium Sulfate

WHO REF. NUMBER	MARKETING AUTHORIZATION HOLDER	MANUFACTURING SITE	DOSAGE FORM AND STRENGTH	PACKAGING AND PRESENTATION	DATE OF PRE-QUALIFICATION	SHELF LIFE	STORAGE CONDITION
	Romford, Essex, RM3 8UG, United Kingdom	API manufacturing site: – K+S KALI GmbH, Werk Werra, Hattorfer Strasse, 36269, Philippsthal (Werra), Germany – Macco Organiques, S.R.O, Zahradni 1938/46c, Bruntál, 792 01, Czech Republic					
RH086	Joint-Stock Company Halychpharm, 6/8, Opryshkivska Str., Lviv, 79024, Ukraine	FPP manufacturing site: Joint-Stock Company Halychpharm, 6/8, Opryshkivska Str., Lviv, 79024, Ukraine API manufacturing site: Macco Organiques, S.R.O, Zahradni 1938/46c, Bruntál, 792 01, Czech Republic	Solution for injection 500 mg/mL (10 mL)	Ampoule: type I glass 10 mL x 5's x 2	16-Mar-20	4 years	Do not store above 30°C. Do not freeze.

(a) Indicates SRA-approved product that has been prequalified based on abbreviated assessment.

SRA-approved products

Table MS-2. Examples of SRA-Approved Magnesium Sulfate 500 mg/mL in 2-mL and 10-mL Ampoule

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING AND PRESENTATION	SHELF LIFE	STORAGE CONDITION
Magnesium sulfate 50% w/v solution for injection or infusion	UK MHRA	Torbay and South Devon NHS Foundation Trust, UK	PL 13079/0004	Glass ampoule: 2 mL, 10 mL	3 years	This medicinal product does not require any special storage conditions.
Magnesium Sulfate 50%w/v Solution for Injection	UK MHRA	Aurum Pharmaceuticals Ltd, UK	PL 12064/0013	Glass ampoule: 2 mL, 10 mL	3 years	Do not store above 25°C.
Magnesium Sulfate 50% w/v Solution for Injection/ Infusion	UK MHRA	AS KALCEKS, Latvia	PL 47015/0010	Glass ampoule: 2 mL, 10 mL	30 months	Do not freeze.
Magnesium sulfate 50% w/v solution for injection	Swissmedic	Grosse Apotheke Dr. G. Bichsel AG, Switzerland	56394	Glass ampoule: 2 mL, 10 mL	Not specified	Store at room temperature (15–25°C).

Note: Magnesium sulfate injection 50% products that are approved by the US FDA (e.g. those supplied by Fresenius Kabi, Hospira Inc, Exela Pharma) are not included in the list above, as they are available in glass vials of 10 mL, 20 mL, and 50 mL different from the presentations as per the WHO recommendation.

It should be noted that the list of SRA-approved products provided above is not exhaustive. The list may be changed over time. When a manufacturer claims that its product is approved by an SRA, it should provide the following information/documents to prove the SRA approval:

- A copy of the marketing authorization issued by the reference SRA
- The approved product information (e.g., Summary of Product Characteristics, product information leaflet, and the labeling by the reference SRA).
- A statement confirming the FPP—including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, and product information—will in all respects be the same as the product approved by the reference SRA
- Product sample

The procurer may cross check the submitted information with the corresponding NMRA websites:

- US FDA: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>
- UK MHRA: <https://products.mhra.gov.uk/>
- EU regulatory authorities: https://ec.europa.eu/health/documents/community-register/regca_en
- Swissmedic: <https://www.swissmedicinfo.ch/>
- Health Canada: <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>
- TGA Australia: <https://www.tga.gov.au/australian-register-therapeutic-goods>.

Related products

Other formulations of magnesium sulfate injection on the market include the following products:

Magnesium sulfate 10% w/v

Indicated in adults, adolescents, and children for: i) treatment of magnesium deficiency in proven hypomagnesemia; and ii) prevention and treatment of hypomagnesemia in patients receiving total parenteral nutrition

Indicated in parturients for: i) control and prevention of seizures in severe pre-eclampsia; and ii) control and prevention of recurrent seizures in eclampsia.

Magnesium sulfate 20% w/v

Indicated for prevention of further seizures associated with eclampsia, and for treatment of magnesium deficiency in hypomagnesemia where the oral route of administration may be inappropriate.

STORAGE, STABILITY, AND DEGRADATION



Magnesium sulfate is very stable at ambient temperatures and is unlikely to undergo any significant degradation as a result of heat if it is properly manufactured, packaged, sterilized, and sealed.

Shelf life: 3–5 years, depending on the manufacturer. It is recommended to check the product label before use.

Storage condition: Do not store above 30°C. Do not freeze.

The shelf life and storage condition of each WHO-prequalified and SRA-approved product can be found in Table MS-1 and Table MS-2 above respectively.

PRODUCT SPECIFICATIONS



The product must meet pharmacopeial specifications, such as those of the International Pharmacopeia, US Pharmacopeia, and British Pharmacopeia, depending on the quality assurance policy of the procurement agency, or the equivalent thereof. The testing parameters and acceptance criteria of the three pharmacopeias are the same, except for the assay and bacterial endotoxin limits.

Table MS-3. International Pharmacopeia Specifications for Magnesium Sulfate Injection

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Appearance	Clear, colorless solution, free from visible particulate matter	Visual inspection
Identification	Yield the reactions characteristic of magnesium salts	As per IP monograph of magnesium sulfate injection
a) Magnesium		
b) Sulfate	Yields the reactions characteristic of sulfates	2.1 General identification tests
pH	pH of the injection, diluted to contain 50 mg of magnesium sulfate heptahydrate per mL: 5.5–7.0	1.13 pH value
Assay	90.0–110.0%	2.5 Complexometric titrations
Bacterial endotoxins	Less than 0.18 IU of endotoxin per mg magnesium sulfate heptahydrate	3.4 Test for bacterial endotoxins
Sterility	Sterile	3.2 Test for sterility
Extractable volume	Comply	5.6 Extractable volume for parenteral preparations
Particulate matter	Comply	5.7 Tests for particulate contamination: subvisible particles

Table MS-4. US Pharmacopeia Specifications for Magnesium Sulfate Injection

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Appearance	Clear, colorless solution, free from visible particulate matter	Visual inspection
Identification	Yield the reactions characteristic of magnesium salts	USP<191>
a) Magnesium		
b) Sulfate	Yields the reactions characteristic of sulfates	USP<191>
pH	pH of the injection, diluted to contain 50 mg of magnesium sulfate heptahydrate per mL: 5.5–7.0	USP<791>
Assay	93.0–107.0%	Titration, USP monograph
Bacterial endotoxins	Not more than 0.09 USP endotoxin unit/mg of magnesium sulfate	USP<85>
Sterility	Sterile	USP<71>
Extractable volume	Comply	USP<1>

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Particulate matter	Meet the requirements for small-volume injections	USP<788>

Table MS-5. British Pharmacopeia Specifications for Magnesium Sulfate Injection

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Appearance	Clear, colorless solution, free from visible particulate matter	Visual inspection
Identification	Yield the reactions characteristic of magnesium salts	Appendix VI
a) Magnesium		
b) Sulfate	Yields the reactions characteristic of sulfates	Appendix VI
pH	pH of the injection, diluted to contain 5% w/v of magnesium sulfate heptahydrate per mL: 5.5–7.0	Appendix V L
Assay	95.0–105.0%	Titration, BP monograph
Bacterial endotoxins	Comply	Appendix XIV C
Sterility	Sterile	Appendix XVI A
Extractable volume	Comply	Appendix XII C5
Particulate matter	Comply	Appendix XIII A

PART I: CLINICAL PARTICULARS

Therapeutic indications

- 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)

Posology, method, and duration of administration

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 regarding dilution for IV use

*Magnesium sulfate injection **must** be diluted to a $\leq 20\%$ 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 injection with 15 mL of diluent.*

Intravenous dosing should be done using an infusion pump if available.

From a microbiological point of view, the reconstituted/diluted 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 2–8°C, unless reconstitution/dilution (etc.) has taken place in controlled and validated aseptic conditions.

Pritchard regimen (IV/IM)

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.

If convulsions recur after 15 minutes, give 2 g (10 mL of the diluted 20% magnesium sulfate solution intravenously over 5 minutes.

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.

Zuspan regimen (IV/IV)

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 5 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 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.

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:

- 4 g (20 mL of the diluted 20% magnesium sulfate solution) infused intravenously over 20 minutes, then 1 g (5 mL of the diluted 20% magnesium sulfate solution) per hour until delivery or for 24 hours, whichever comes first.
- 4 g (20 mL of the diluted 20% magnesium sulfate solution) infused intravenously over 30 minutes, or as a single intravenous bolus.
- 6 g (30 mL of the diluted 20% magnesium sulfate solution) infused intravenously over 20–30 minutes, followed by maintenance infusion of 2 g (10 mL of the diluted 20% magnesium sulfate solution) per hour.

When Magnesium sulfate is administered, women should be monitored for clinical signs of magnesium toxicity at least every 4 hours by recording pulse, blood pressure, respiratory rate, and deep tendon (for example, patellar) reflexes.

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.

Contraindications

- Hypersensitivity to the active substance, its salts or to any of the excipients
- Heart block
- Severe renal impairment

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 is used in pregnant women, fetal heart rate should be monitored (see also “Fertility, pregnancy and lactation” section below).

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 also “Interaction with other medicinal products and other forms of interaction” section below).

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

Parenteral magnesium sulfate administration is contraindicated in patients with severe renal impairment (see also “[Contraindications](#)” section above). It should be used with caution in less severe degrees of renal impairment.

Interaction with other medicinal products and other forms of interaction

Extreme caution must be used when β -adrenergic agonists and calcium-channel blocking agents (e.g. nifedipine) 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).

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

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

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.

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).

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 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 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

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.

Effects on ability to drive and use machines

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

Undesirable effects

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

Table MS-6. Adverse Events Related to Treatment with Magnesium Sulfate Injection

SYSTEM ORGAN CLASS	ADVERSE DRUG REACTION
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
Gastrointestinal disorders	Nausea, vomiting
Respiratory, thoracic, and mediastinal disorders	Respiratory depression*
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 also "Interaction with other medicinal products and other forms of interaction" section above).

Overdose

Symptoms of intoxication

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 of intoxication

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 hypermagnesemia.

PART 2: SPECIAL CONSIDERATIONS IN QUALITY ASSESSMENT

Information contained in this annex is intended to assist procurement agencies that plan to perform a full prequalification of magnesium sulfate injection products. When assessing the complete quality/CMC documentation, assessors should consider the following information on magnesium sulfate injection.

API

As of June 2022, no magnesium sulfate API is prequalified by the WHO PQP.

There are two manufacturers of magnesium sulfate API that have obtained the certificate of suitability to monographs of the European Pharmacopoeia (CEP), confirming its suitable quality for use in medicinal products.

Table MS-7. Manufacturers of Magnesium Sulfate API with CEP Certificate

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE	TYPE
Magnesium sulfate heptahydrate (monograph number 44)	Macco Organiques, SRO CZ 792 01 Bruntál, Czech Republic	R0-CEP 2016-148-Rev 00	10/20/2017	Chemistry
Magnesium sulfate heptahydrate (monograph number 44)	PQ CORPORATION, Malvern, USA	R0-CEP 2018-109-Rev 00	6/17/2020	Chemistry

Other manufacturers of magnesium sulfate API should provide evidence for GMP compliance. However, magnesium sulfate is an atypical API; the manufacturing process and controls are not typically designed to meet API GMP. As an alternative, there should be a clear specification, the site should have been audited, changes should be controlled, and appropriate checks should be made on incoming goods.

The specifications of magnesium sulfate API should be in line with a pharmacopeial monograph (Ph.Int., Ph.Eur./BP, or USP) with additional tests/limits for arsenic if not included in that monograph, as well as tests/limits for bacterial endotoxins. Such additional tests may be based on another pharmacopeial monograph (Ph.Int., Ph.Eur./BP, or USP).

Excipients

The excipients of magnesium sulfate injection include water for injection and sulfuric acid/hydrochloric acid and/or sodium hydroxide for pH adjustment. There are no special concerns on the excipients. No excipient with the risk of transmitting TSE/BSE is used.

Manufacturing process

Magnesium sulfate injection is a straightforward product to manufacture, but the main quality concern is the sterilization process and sterility of the facility where it is made.

The manufacturing process of magnesium sulfate injection is a standard process—conducted under appropriate aseptic conditions, including the steps of preparation of the solution with adjustment of pH, pre- and sterile filtration, and filling and sealing of the ampoules. Finally, steam sterilization by autoclaving of the filled ampoules is performed. The headspace of the ampoules should be replaced with nitrogen during the filling process to prevent oxidation of the API. Satisfactory operating parameters and in-process controls should be defined at each stage of manufacture.

For the sterilization process using an autoclave, details such as F0 range, temperature range and peak dwell time for the FPP and the container-closure system should be provided. Although standard autoclaving cycles of 121°C for 15 minutes or more would not need a detailed rationale, such justifications should be provided for reduced temperature cycles or elevated temperature cycles with shortened exposure times.

A manufacturing process validation protocol for the validation of the first three production-scale batches should be submitted. In addition, completed process validation reports for the sterile processes for three cycles/runs should be submitted. If the manufacturer is already manufacturing production-scale batches, the full validation data for the production of at least three (3) consecutive production scale batches should be submitted.

Note: The risk for potential presence of elemental impurities in the finished drug product needs to be assessed according to the ICH Q3D “Guideline for Elemental Impurities”. Elemental impurity sources include the API, excipients, utilities in direct contact with the product or manufacturing equipment (compressed air, water, etc.), the manufacturing equipment and the container closure system. Depending on the risk assessment and results from batches tested for the relevant elemental impurities, routine testing of the final product may not be necessary.

Packaging

Neutral type I glass ampoule should be used.

Suitability of the container should be demonstrated, including the following properties.

Safety

- The material must meet compendial requirements such as USP<660> and USP<I660>. Washing and sterilization/depyrogenation, if applicable, should be supported by process validation data.

Protection

- Container integrity regarding microbial contamination should be demonstrated by microbial or dye ingress or other methods:
 - One-time test reported as part of product development
 - Routine leak testing performed as part of the product manufacture

Compatibility

- Compatibility of the FPP with diluents (such as 5% dextrose injection or 0.9% sodium chloride as per the label instruction), if relevant, over the proposed dilution range (label) in specified containers such as PVC may also need to be demonstrated.

Bioequivalence requirements

A biowaiver can be requested as per WHO Technical Report Series, No. 992, which indicates that no bioequivalence study is necessary when the pharmaceutical product is to be administered parenterally (e.g., intravenously, subcutaneously or intramuscularly) as an aqueous solution containing the same API in the same molar concentration as the comparator product and the same or similar excipients in comparable concentrations as in the comparator product.

The appropriate comparator product is magnesium sulfate 500 mg/mL (solution for injection, Fresenius Kabi, USA). The composition of the proposed product should be the same as the comparator product.