MODULE III

MAGNESIUM SULFATE

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Manual for Procurement & Supply of
Quality-Assured MNCH Commodities

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 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 sole first-line treatment of pre-eclampsia and eclampsia that should be procured over other anticonvulsants and made available in all health facilities to help lower maternal death rates and improve overall maternal health.

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 pharmacopoeial specifications, such as those of the International Pharmacopoeia, US Pharmacopoeia, 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 are 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 oxytocin injection packaging and labeling can be found at the

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	MgSO4, 7H2O
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 excipients: – Water for injections – Sulfuric 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 February 2018, there are five 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/prequal/content/prequalified-lists/medicines.

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	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	2 years	Do not store above 30°C.
RH063	AS Kalcecks, Krustpils iela 53, Rīga, LV-1057, Latvia	FPP manufacturing site: HBM Pharma SRO, Sklabinska 30, Martin, 036 80, Slovakia API manufacturing site: K+S KALI GmbH, Werk Werra, Standort Hattorf, Hattorfer Strasse, 36269, Philippsthal (Werra), Germany	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	3 years	Do not store above 30°C.
RH064	AS Kalckeks, Krustpils iela 53, Rīga, LV-1057, Latvia	FPP manufacturing site: HBM Pharma sro, Sklabinska 30, Martin, 036 80, Slovakia API manufacturing site: K+S KALI GmbH, Werk Werra, Standort Hattorf, Hattorfer Strasse, 36269, Philippsthal (Werra), Germany	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	3 years	Do not store above 30°C.

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

WHO REF. NUMBER	MARKETING AUTHORIZATION HOLDER	MANUFACTURING SITE	DOSAGE, FORM, AND STRENGTH	PACKAGING AND PRESENTATION	DATE OF PRE-QUALIFICATION	SHELF LIFE	STORAGE CONDITION
RH073(a)	Aurum Pharmaceuticals Ltd, Bampton Road, Harold Hill, Romford, Essex, RM3 8UG, United Kingdom	FPP manufacturing site: Macarthys Laboratories Limited, Bampton Road, Harold Hill, Romford, Essex, RM3 8UG, United Kingdom API manufacturing site: K+S KALI GmbH, Werk Werra, Hattorfer Strasse, 36269, Philippsthal (Werra), Germany	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, Romford, Essex, RM3 8UG, United Kingdom	FPP manufacturing site: Macarthys Laboratories Limited, Bampton Road, Harold Hill, Romford, Essex, RM3 8UG, United Kingdom API manufacturing site: K+S KALI GmbH, Werk Werra, Hattorfer Strasse, 36269, Philippsthal (Werra), Germany	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.

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

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	Store at 2°–25°C.
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).

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, patient 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, 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
- EU regulatory authorities: https://ec.europa.eu/health/documents/community-register/regca_en
- Swissmedic: https://www.swissmedic.ch/swissmedic/en/home/services/authorized-medicines/human-and-veterinary-medicines.html
- 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: 2–3 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 pharmacopoeial specifications, such as those of the International Pharmacopoeia, US Pharmacopoeia, and British Pharmacopoeia, depending on the quality assurance policy of the procurement agency, or the equivalent thereof. The testing parameters and acceptance criteria of the three pharmacopoeias are the same, except for the assay and bacterial endotoxin limits.

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

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Appearance	Clear, colorless solution, free from visible particulate matter	Visual inspection
Identification a) Magnesium	Yield the reactions characteristic of magnesium salts	As per IP monograph of magnesium sulfate injection
Identification 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

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
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 Pharmacopoeia Specifications for Magnesium Sulfate Injection

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Appearance	Clear, colorless solution, free from visible particulate matter	Visual inspection
Identification a) Magnesium	Yield the reactions characteristic of magnesium salts	USP<191>
Identification 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>
Particulate matter	Meet the requirements for small-volume injections	USP<788>

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

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Appearance	Clear, colorless solution, free from visible particulate matter	Visual inspection
Identification a) Magnesium	Yield the reactions characteristic of magnesium salts	Appendix VI
Identification 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: 5.5–7.0	Appendix V L
Assay	95.0–105.0%	Titration, BP monograph
Bacterial endotoxins	Comply	Ph.Eur. 2.6.14

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Sterility	Sterile	Ph.Eur. 2.6.1
Extractable volume	Comply	Ph.Eur. 2.9.17
Particulate matter	Comply	Ph.Eur. 2.9.19

MAGNESIUM SULFATE ANNEX

PART 1: CLINICAL PARTICULARS

Therapeutic indications

Pre-eclampsia, eclampsia

Posology, method, and duration of administration

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 ≤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 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.

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.

Contraindications

Marked bradycardia (slow heartbeat), myasthenia gravis (muscle weakness) and atrioventricular block (disruption of the heart's impulse conduction system) or other cardiac conduction disturbances and diathesis for infection, stones (calcium, magnesium ammonium phosphate stones), severe renal dysfunction, anuria, dehydration

Magnesium sulfate injection should not be co-administered with barbiturates, narcotics or hypnotics, due to the risk of respiratory depression.

Special warnings and precautions for use

To be used only with special caution in patients with mild to moderately pronounced renal insufficiency.

See also "Overdose" section below.

Interaction with other medicinal products and other forms of interaction

The effect of magnesium is reduced (antagonism) with concomitant IV administration of calcium salts. Muscle relaxants of the curare type potentiate the effect of magnesium on the motor end plate. Diuretics, aminoglycoside antibiotics (such as gentamicin, tobramycin, amphotericin B), immunosuppressants (such as cyclosporin A) and cytostatics (such as cisplatin), and digitalis glycosides cause increased excretion of magnesium via the kidneys. Interaction with nifedipine should also be taken into consideration, as it can lead to severe hypotension and neuromuscular blockade.

For more details, see also, "Contraindications" section above.

Pregnancy and lactation

There is no evidence of a risk of malformation. However, documented experience in humans is limited with regard to use during early pregnancy. Therefore, magnesium sulfate injection should only be used during early pregnancy after a careful benefit/risk assessment.

If magnesium is administered shortly before childbirth, the newborn infant should be monitored during the first 24–48 hours of life for signs of toxicity (neurological depression with respiratory depression, muscle weakness, loss of reflexes).

Effects on ability to drive and use machines

Magnesium sulfate injection has no influence on the ability to drive or use machines.

Undesirable effects

The following categories are used for stating the frequency of undesirable effects:

- Very common (≥ 1/10)
- Common (≥ 1/100 to < 1/10)
- Uncommon (≥ 1/1,000 to < 1/100)
- Rare (≥ 1/10,000 to < 1/1,000)
- Very rare (< 1/10,000)
- Not known (cannot be estimated from the available data)

Very common: flushing

Common: nausea or vomiting, muscle weakness, absent or reduced tendon reflexes, respiratory depression, reactions at the injection site (pain, burning, swelling, inflammation)

Uncommon: thirst, headache; hypotension, heart palpitations, tachycardia; dizziness, drowsiness or confusion, itching or tingling

In addition, the following may occur: skin rash, hyperkalemia, prolonged bleeding time as well as visual disturbances.

Overdose

Symptoms of intoxication

Magnesium intoxication is unlikely when renal function is intact and at the dosage stated. If magnesium intoxication should nevertheless occur, the following symptoms can be observed:

Symptoms of Magneisum Intoxication

MG PLASMA CONCENTRATION IN MMOL/L	POSSIBLE SYMPTOMS, POSSIBLE UNDESIRABLE EFFECTS
> 1.5	Decrease in blood pressure, retching, vomiting
> 2.5	CNS depression
> 3.5	Hyporeflexia, ECG changes
> 5.0	Incipient respiratory depression
> 5.5	Coma
> 7.0	Cardiac arrest, respiratory paralysis

Treatment of intoxication

Reduction of the dose or discontinuation of the medication leads to rapid regression of the undesirable effects.

As an immediate measure (antidote), a slow intravenous calcium injection (10–20 mL of a 10% calcium gluconate solution) can be used.

See also "Pregnancy and lactation" section above.

With high-dose magnesium sulfate therapy, the following must be checked:

- Monitoring of cardiovascular function
- Patellar tendon reflexes (knee-tendon reflexes); these must be maintained. Dose reduction if they are no longer responsive.
- Respiratory rate should be no less than 16 breaths/minute.
- Urine output should be 25 mL per hour or 100 mL per 4 hours. If it is any lower, there is a risk of hypermagnesemia (excessively high magnesium concentrations in the blood).
- As an antidote, 10% calcium gluconate ampoules must be readily available.
- If the antidote is not sufficient in life-threatening conditions, intensive care measures must be taken.

To be used only with special caution in patients with mild to moderately pronounced renal insufficiency.

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 particular information on magnesium sulfate injection.

API

As of February 2018, no magnesium sulfate API is prequalified by the WHO PQP.

Only one manufacturer of magnesium sulfate API has obtained the certificate of suitability to monographs of the European Pharmacopoeia (CEP), confirming its suitable quality for use in medicinal product.

Manufacturer 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

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 GMPs. 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 pharmacopoeial 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 pharmacopoeial monograph (Ph.Int., Ph.Eur./BP, or USP).

Excipients

The excipients of magnesium sulfate injection include water for injection and sulfuric 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 F_0 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.

Packaging

Neutral type I glass ampoule should be used.

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

Safety

- The material must meet compendial requirements such as USP<660> and USP<1660>. 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.