SCIENTIFIC DISCUSSION

This part reflects the scientific knowledge and the information about this product available at the time of prequalification. Thereafter, updates may have become necessary which are included in parts 1 to 5 and, if related to pharmaceutical issues, also documented in part 8 of this WHOPAR.

Name of the Finished Pharmaceutical Product:	Magnesium sulfate-Kalceks 500 mg/ml solution for injection, BP[*]
Manufacturer of Prequalified Product:	HBM Pharma s.r.o. Sklabinska 30, 036 80 Martin, Slovakia
Active Pharmaceutical Ingredient (API):	Magnesium sulfate heptahydrate
Pharmaco-therapeutic group (ATC Code):	Electrolyte solutions (magnesium sulphate: B05XA05)
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.

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

1. Introduction

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.

Magnesium sulfate-Kalceks should be initiated by a health care provider experienced in the management of reproductive health indications in women.

2 Assessment of Quality

The assessment was done in accordance with the requirements of *WHO's Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part.*

Active Pharmaceutical Ingredient (API)

Magnesium sulfate heptahydrate is a slightly hygroscopic, white or almost white, crystalline powder or brilliant colourless crystals. It is freely soluble in water. The API is manufactured from naturally occurring Kieserite (magnesium sulphate monohydrate), which is obtained from own underground salt deposits of geological origin.

The API specifications are pharmacopoeial based and include tests for appearance, identification, appearance of solution, acidity or alkalinity, elemental impurities (selenium, mercury, cadmium, lead, arsenic, cobalt, copper, lithium, nickel, antimony, vanadium – by ICP-MS), chlorides, iron, loss on drying, assay, microbial contamination and bacterial endotoxins.

Stability testing was conducted according to the requirements of WHO. The proposed re-test period is justified based on the stability results when the API is stored in the original packaging.

Other ingredients

Other ingredients include water for injections and 0.1 M sodium hydroxide and/or 0.1 M sulfuric acid for adjusting the pH to 5.5-7.0. No excipient with the risk of transmitting TSE/BSE is used.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource Magnesium Sulfate 500 mg/ml Solution for Injection is a clear colourless liquid filled in type I hydrolytic class, colourless borosilicate glass ampoules with break line or open point cut. The solution for injection is administered by the intravenous or intramuscular route. It must be diluted before intravenous use, due to its high osmolality (about 4060 mOsmol/L).

The manufacturing process 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, filling and sealing of the ampoules. Finally steam sterilization by autoclaving of the filled ampoules is performed. The headspace of the ampoules is replaced with nitrogen during the filling process to prevent oxidation of the API. Satisfactory operating parameters and in-process controls have been defined at each stage of manufacture. Process validation have been conducted on 3 consecutive batches.

Specifications

The finished product specifications are pharmacopoeial based and include tests for description, identification, clarity, colour, pH, extractable volume, particulate contamination (visible and sub-visible particles), sterility, bacterial endotoxins and assay.

Stability testing

Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term storage condition and for six months at 40°C/75%RH as accelerated conditions. The product proved to be quite stable at both long term and accelerated storage conditions with no apparent negative trend. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of Bio-Equivalence

The applicant requests a biowaiver 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 sulphate 500 mg/ml (solution for injection, Fresenius Kabi, US). The composition of the proposed product is the same i.e. it contains 500 mg/ml magnesium sulphate and sulfuric acid and/or sodium hydroxide for pH adjustment.
As the proposed product meets the biowaiver requirements described above, a biowaiver can be granted.

4. Summary of Product Safety and Efficacy

Magnesium sulfate-Kalceks has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator product. According to the submitted data on quality Magnesium sulfate-Kalceks is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Magnesium sulphate 500 mg/ml (solution for injection, Fresenius Kabi, US) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of this product is considered to be acceptable when guidance and restrictions as stated in the Summary of Product Characteristics are taken into account. Reference is made to the SmPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality

Physicochemical and biological aspects relevant to the uniform pharmaceutical characteristics have been investigated and are controlled in a satisfactory way. The quality of this product is considered to lead to an acceptable clinical performance when Magnesium sulfate-Kalceks is used in accordance with the conditions as stated in the SmPC.

Bioequivalence

N/A

Efficacy and Safety

Regarding clinical efficacy and safety Magnesium sulfate-Kalceks is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics are taken into consideration.

Benefit Risk Assessment

Based on WHO's assessment of data on quality, safety and efficacy the team of assessors considered that the benefit risk profile of Magnesium sulfate-Kalceks was acceptable for the following: **"treatment of women with eclampsia, prevention of eclampsia in women with severe pre-eclampsia and prevention of cerebral palsy in the infant in women at risk of imminent preterm birth before 32 weeks of gestation."** and has advised that the quality, efficacy and safety of Magnesium sulfate-Kalceks are acceptable to allow inclusion of Magnesium sulfate-Kalceks, manufactured at HBM Pharma s.r.o, Sklabinska 30, 036 80 Martin, Slovakia in the list of prequalified medicinal products.