This part outlines the scientific assessment and knowledge about this product at the time of prequalification. Updates to this information are included in parts 1 to 5 and 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product:	[RH086 trade name][*]
Manufacturer of Prequalified Product:	Joint Stock Company "Halychpharm" 6/8, Opryshkivska Str, Lviv, 79024, Ukraine
Active Pharmaceutical Ingredient (API):	Magnesium sulfate heptahydrate
Pharmaco-therapeutic group (ATC Code):	B05XA05
Therapeutic indication:	• 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

1. Introduction

[RH086 trade name] is indicated for the prevention of eclampsia in women with severe pre-eclampsia, treatment of women with eclampsia and prevention of cerebral palsy in the infant of women at risk of imminent preterm birth before 32 weeks of gestation.
[See Part 4 Summary of Products Characteristics (SmPC), for full indications].

[RH086 trade name] should be initiated by a health care provider experienced in the management of HIV infection.

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)

A CEP (Certificate of Suitability) issued by the EDQM was submitted for magnesium sulfate heptahydrate ensuring good manufacturing control and applicability of the Ph.Eur monograph to control the quality of the API.

Other ingredients

Other ingredients include water for injections and 0.1M sodium hydroxide and/or 0.5M sulfuric acid for adjusting the pH to 7.2-7.8. No excipient with the risk of transmitting TSE/BSE is used.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a clear colourless solution filled in type I hydrolytic, colourless borosilicate glass ampoules with an open point cut or colour breaking circle. 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 –

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

including the steps of preparation of the solution with adjustment of pH, pre- and sterile filtration, filling of the solution in ampoules and sealing. Finally steam sterilization by autoclaving of the filled ampoules is performed. 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 appearance, identification, clarity, colour, particulate contamination (visible and sub-visible particles), pH, extractable volume, 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 Bioequivalence

The applicant requested a biowaiver as per WHO Technical Report Series, No. 1003 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). The proposed product is also a solution for injection, i.e. Magnesium sulphate 500 mg/ml. The formulations contain comparable excipients.
As the proposed product met the biowaiver requirements described above, a biowaiver was granted.

4. Summary of Product Safety and Efficacy

[RH086 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. According to the submitted data on quality and bioavailability, [RH086 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the reference formulation Magnesium sulphate 500 mg/ml, solution for injection (Fresenius Kabi) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [RH086 trade name] is considered acceptable when guidance and restrictions stated in the Summary of Product Characteristics (SmPC) are considered. Refer 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 [RH086 trade name] is used in accordance with the SmPC.

Bioequivalence

N/A

Efficacy and Safety
Regarding clinical efficacy and safety, [RH086 trade name] is considered effective and safe to use when the guidance and restrictions in the SmPC 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 [RH086 trade name] was acceptable for the following indication**: "the prevention of eclampsia in women with severe pre-eclampsia, treatment of women with eclampsia and prevention of cerebral palsy in the infant of women at risk of imminent preterm birth before 32 weeks of gestation"** and has advised that the quality, efficacy and safety of [RH086 trade name] allow inclusion of [RH086 trade name], manufactured at Joint Stock Company "Halychpharm" 6/8, Opryshkivska Str, Lviv, 79024, Ukraine in the list of prequalified medicinal products.