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	[DI005 trade name][*]
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited Block N2 (Unit No.VI), Village Theda P. O. Lodhi Majra Tehsil Baddi , Dist. Solan Himachal Pradesh, INDIA
Active Pharmaceutical Ingredient(s) (API)	Zinc (as sulfate monohydrate)
Pharmaco-therapeutic group (ATC Code)	Other mineral supplements (A12CB01)
Therapeutic indication	[DI005 trade name] is indicated for the treatment of acute and persistent diarrhoea in infants and children aged up to 5 years.

1. Introduction

[DI005 trade name] is indicated for the treatment of acute and persistent diarrhoea in infants and children aged up to 5 years.

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)

Zinc sulfate can exist in several hydrated forms, including the monohydrate, hexahydrate and heptahydrate. Zinc sulfate monohydrate is used in the manufacture of the dispersible tablets and is describe in the Ph.Int, Ph.Eur and the USP.

The API is obtained from zinc oxide, by treatment with sulfuric acid, followed by several purification steps. The in-process controls are regarded adequate for controlling the quality of the API.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification (zinc and sulfate), acidity, alkalies and alkaline earths, arsenic, lead, iron and assay.

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 packing material.

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

Other ingredients

Other ingredients include aspartame, microcrystalline cellulose, colloidal silicon dioxide, crospovidone, Trusil orange ASV flavour and magnesium stearate. Magnesium stearate is of vegetable origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Zinc (as sulfate monohydrate) 20 mg dispersible tablets are white to off-white, circular flat, bevelled, uncoated, flavoured tablets with break-line on one side and plain surface on the other side. The breakline is intended for subdivision of tablets when half a tablet dose is to be administered as supported by divisibility studies, conducted during development and during shelf life. Each tablet contains 54.89 mg zinc sulfate monohydrate equivalent to 20 mg of zinc. The tablets are packaged in PVC/PVdC aluminium blisters.

The objective of the development programme was to obtain a stable 20 mg dispersible tablet that would comply with the pharmacopoeial requirements of zinc sulfate dispersible tablets, being very rapidly disintegrating (≤ one minute) and with acceptable taste properties. These properties are required by the 2007 WHO publication entitled Production of Zinc tablets and Zinc Oral Solutions: Guidelines for Programme Managers and Pharmaceutical Manufacturers to be used in infant treatment programmes. Since adherence to the treatment regimen will be affected if the product is not acceptable to infants, young children and their mothers, zinc preparations should be formulated in such a way as to mask the strong bitter metallic aftertaste of zinc in order to enhance acceptability. The excipients selection was based on compatibility results and the suitability of excipients to achieve the quality target product profile. Aspartame was selected as taste masker, with additionally a small amount of Trusil Orange ASV as flavouring agent. Sufficient evidence was provided with respect to the acceptability of the product in accordance with the above mentioned guidance.

The manufacturing process involves conventional steps of blending, lubrication and direct compression, followed by packaging of the tablets into the blisters. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications are pharmacopoeial based and include tests for description, identification (zinc and sulfate), average weight, friability, hardness, disintegration time (≤ 60 seconds), fineness of dispersion, uniformity of dosage units (by content uniformity), assay, water content, subdivision of tablets and microbial limits.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. The tablets showed minor changes with respect to some physical parameters, including hardness. These changes were considered not to be of particular concern. The disintegration time remained within specification at all storage conditions. 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

No bioequivalence study has been performed. As zinc sulphate is selected by the WHO being eligible for a biowaiver, a request for a biowaiver has been made. In accordance with the WHO guidance and criteria for zinc sulphate tablets, supporting data have been provided regarding lack of excipient

interaction on absorption and in vitro dissolution and solubility data. It has been sufficiently shown that the Zinc (as sulfate) dispersible tablets 20 mg (Macleods Pharmaceuticals Limited, India) completely dissolve in 5 mL of water within 1 minute at room temperature. Accordingly, the test tablet Zinc (as sulfate) Dispersible tablets 20 mg (Macleods Pharmaceuticals Limited, India) meets the criteria for a biowaiver in accordance with the WHO guidance and criteria for zinc sulphate tablets.

4. Summary of product safety and efficacy

[DI005 trade name] has been shown to conform to appropriate standards of quality, efficacy and safety.

The clinical safety of this product is considered to be acceptable when guidance and restrictions presented in the Summary of Product Characteristics are taken into consideration. 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 [DI005 trade name] is used in accordance with the SmPC.

Bioequivalence

[DI005 trade name] (Macleods Pharmaceuticals Limited, India) meets the criteria for a biowaiver in accordance with the WHO guidance and criteria for zinc sulphate tablets.

Efficacy and Safety

Regarding clinical efficacy and safety, [DI005 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, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [DI005 trade name] was acceptable for the following indication: ' the treatment of acute and persistent diarrhoea in infants and children aged up to 5 years ', and would allow inclusion of [DI005 trade name], manufactured at Macleods Pharmaceuticals Limited, Block N2 (Unit No.VI), Village Theda, P. O. Lodhi Majra, Tehsil -Baddi, Dist. Solan, Himachal Pradesh, India in the list of prequalified medicinal products.