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	[DI013 trade name]*
Manufacturer of Prequalified Product	The ACME Laboratories Limited, Solid Dosages Unit, Dhulivita, Dhamrai, Dhaka-1350, Bangladesh.
Active Pharmaceutical Ingredient(s) (API)	Zinc (as sulfate monohydrate)
Pharmaco-therapeutic group (ATC Code)	Mineral supplements (A12CB01)
Therapeutic indication	[DI013 trade name] is indicated for the treatment of acute and persistent diarrhoea in infants and children aged up to 5 years.

1. Introduction

[DI013 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 monohydrate has been prequalified by WHO according to WHO's *Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products* (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that the API, used in the manufacture of [DI013 trade name], is of good quality and manufactured in accordance with WHO Good Manufacturing Practices. API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and assessment of the sites of API manufacture to verify compliance with WHO GMP requirements.

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

Other ingredients

Other ingredients include microcrystalline cellulose, maize starch, aspartame, colloidal silicon dioxide, vanilla flavour and magnesium stearate. None of the excipients are of animal or human origin. TSE/BSE free certificates have been provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off-white coloured, round-shaped, flat, dispersible tablet, one face is plain and the other face has a break-line; the tablets may have brown specks. The break-line 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 dispersible tablet contains 54.9 mg zinc sulfate monohydrate equivalent to 20 mg of zinc. The tablets are packaged in white opaque PVC/PVdC-aluminium blisters.

The objective of the development programme was to obtain a stable and optimized formulation of Zinc (as sulfate monohydrate) 20 mg dispersible tablets that would comply with the pharmacopoeial requirements of zinc (as 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 or caregivers, zinc preparations should be formulated as palatable and in such a way as to mask the strong bitter metallic aftertaste of zinc in order to enhance acceptability. The excipients selected were based on the excipients used in the WHO comparator product ZinCfant® 20mg Tablets (M/S Laboratories Pharmaceutiques Rodael, Fierne, France) and API-excipient compatibility studies. Aspartame was used as a sweetener and vanilla flavour was added as a 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 pre-blending, blending, lubrication and direct compression, followed by packaging of the tablets into blisters. Based on the satisfactory data of optimization trials, the formulation was finalized resulting in a product matching the quality target product profile. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.According to a risk evaluation by the applicant, the FPP has no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications are pharmacopoeial based and include tests for description, identification (zinc and sulfate), average weight, uniformity of weight (whole and split tablets), friability, hardness, thickness, loss on drying, dispersion time in 5mL water, disintegration time (≤ 60 seconds), fineness of dispersion, content uniformity (whole and split tablets), assay 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

[DI013 trade name] meets the criteria for a biowaiver in accordance with the WHO guidance and criteria for zinc sulfate tablets.

4. Summary of product safety and efficacy

WHO zinc recommendations for treatment of acute paediatric diarrhoea are based on studies demonstrating that administration of supplemental zinc results in a shorter duration of diarrhoea, reduces the number of stools and stool output, reduces the risk of persistent diarrhoea, and may reduce the risk of subsequent illness and increase weight gain. [DI013 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 [DI013 trade name] is used in accordance with the SmPC.

Bioequivalence

[DI013 trade name] meets the criteria for a biowaiver in accordance with the WHO guidance and criteria for zinc sulfate tablets.

Efficacy and Safety

Regarding clinical efficacy and safety, [DI013 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 the WHO assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [DI013 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 has advised that the quality, efficacy and safety of [DI013 trade name], allow inclusion of [DI013 trade name], manufactured at The ACME Laboratories Limited, Solid Dosages Unit, Dhulivita, Dhamrai, Dhaka-1350, Bangladesh, in the list of prequalified medicines.