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	[DI011 trade name][*]
Manufacturer of Prequalified Product	Ipca Laboratories Limited Plot No. 255/1. Village Athal Silvassa 396 230, Dadra and Nagar Haveli (U.T,) India.
Active Pharmaceutical Ingredient(s) (API)	Zinc (as sulfate monohydrate)
Pharmaco-therapeutic group (ATC Code)	Other mineral supplements (A12CB01).
Therapeutic indication	[DI011 trade name] is indicated for the treatment of acute and persistent diarrhoea in infants and children aged up to 5 years

1. Introduction

[DI011 trade name] is indicated for the treatment of acute and persistent diarrhea in infants and children aged up to 5 years.

[See Part 4 Summary of Products Characteristics (SmPC), for full indications].

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 [DI011 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, crospovidone, aspartame, sucralose, orange flavour, colloidal silicon dioxide and magnesium stearate. Magnesium stearate is of vegetable origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Zinc (as sulfate monohydrate) 20mg dispersible tablets are white to off-white, round, flat, bevel edge, uncoated, dispersible tablets with a break-line on one side and debossed with 'C70' on the other side. 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 tablet contains 54.9 mg zinc sulfate monohydrate equivalent to 20 mg of zinc. The tablets are packaged in either PVdC/PVC – aluminium blisters or Alu-Alu 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 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), similar WHO prequalified products and API-excipient compatibility studies. Sucralose and aspartame were used as sweeteners and orange 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 sifting, blending, pre-lubrication, lubrication and direct compression, followed by packaging of the tablets into the 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.

Specifications

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

[DI011 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.

[DI011 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 [DI011 trade name] is used in accordance with the SmPC.

Bioequivalence

[DI011 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, [DI011 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 [DI011 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 [DI011 trade name], manufactured at Ipca Laboratories Limited, Plot No. 255/1. Village Athal, Silvassa 396 230, Dadra and Nagar Haveli (U.T,), India in the list of prequalified medicinal products.