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:	ZinCfant® 20mg*
Manufacturer of the Prequalified Product:	Laboratoires Pharmaceutiques Rodael - France
Active Pharmaceutical Ingredient (API):	Zinc (as sulfate monohydrate)
Pharmaco-therapeutic group (ATC Code):	Other mineral supplements (A12CB01)
Therapeutic indication:	Zinc (as sulfate monohydrate) tablets is indicated for the treatment of acute and persistent diarrhoea in infants and children up to 5 years of age.

* Trade names are not prequalified by WHO. This is under local drug regulatory authority's responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

1. Introduction

ZinCfant® 20mg is a dispersible tablet containing 54.9 mg zinc sulfate monohydrate equivalent to 20 mg of zinc. It is indicated for the treatment of of acute and persistent diarrhoea in infants and children up to 5 years of age.

2. Assessment of Quality

Introduction

The assessment was done according to SOP 20 of the WHO Prequalification programme.

Active Pharmaceutical Ingredient (API)

Zinc sulfate exists in several hydrated forms, including the monohydrate, hexahydrate and heptahydrate. Zinc sulfate monohydrate is used in the manufacture of the dispersible tablets and is described 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 appearance, solubility, identification (zinc and sulfate), appearance of solution, pH, acidity, assay and limits for chloride, alkalies and alkaline earths, arsenic, lead and iron.

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.

Other ingredients

Other ingredients include aspartame, colloidal anhydrous silica, ethyl vanillin, magnesium stearate, maize starch and microcrystalline cellulose. Magnesium stearate is from vegetable origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Zinc (as sulfate monohydrate) 20 mg dispersible tablets are round, ivory-white tablets, flat on one side and with a score on the other side. The score-line is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies. Each tablet contains 54.9 mg zinc sulfate monohydrate equivalent to 20 mg of zinc. The tablets are packaged in white PVC/PVDC-aluminium foil blisters; 10 tablets per blister card, 10 such cards per carton.

The objective of the development programme was to obtain a stable 20 mg dispersible tablet with a score-line for subdivision, when a 10 mg dose is to be administered; that would have very rapidly disintegrating (≤ one minute) and 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/caregivers, zinc preparations should be formulated in such a way as to mask the strong bitter metallic aftertaste of zinc in order to enhance acceptability. For this product aspartame was selected as taste masker, with additionally a small amount of ethyl vanillin as a flavourant. Sufficient evidence was provided with respect to the acceptability of the product.

The manufacturing process involves two blending stages, 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. Validation data presented for production scale batches demonstrated the consistency of the process.

Specifications

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

Stability testing

Stability studies have been conducted in at 30°C/65%RH and 30°C/75%RH as long-term storage condition 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, friability and subdivision. 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 Pharmacokinetics

To support the pharmacokinetics, the absorption of zinc from ZinCfant tablets has been determined in several studies.

In a study conducted in 10 healthy, zinc replete, adult male volunteers (baseline mean plasma zinc level ±SD of 15.1 ±3.5 μmol/L) absorption of zinc from 1½ ZinCfant tablets (i.e. a 30 mg dose) was rapid, with a maximal increase in mean plasma zinc level ±SD of 11.6 ±6.0 μmol/L observed within approximately 2 hours of administration[14].

Zinc absorption from ZinCfant tablets has also been characterized over the longer term in several studies in populations of children with high prevalences of zinc deficiency.

A bioavailability study compared ZinCfant tablets and a standard zinc sulphate syrup to placebo in 451 children 6-23 months of age in Burkina Faso[15]. Infants under 1 year of age received 5 mg/kg/day and older children received 10 mg/kg/day, compared to the WHO recommended dose for diarrhoea of 10 mg/kg/day for infants younger than 6 months of age and 20 mg/day for older children. Overall baseline plasma zinc levels ±SD were 9.60 ±1.62 μmol/L; 62.7% of children had plasma zinc concentrations of <9.94 μmol/L.

Increases in plasma zinc concentrations after 21 days of supplementation were comparable in the two zinc supplemented groups, with increases of 2.58 ±2.0 μmol/L and 2.53 ±2.2 μmol/L for the ZinCfant and zinc syrup groups, respectively, compared with 0.03 ±1.7 μmol/L for children who received placebo ($p < .0001$, ANOVA, compared to placebo).

In a study conducted in Nepali children 2-35 months of age suffering from pneumonia in which ZinCfant tablets or placebo were given as an adjuvant to standard antibiotic treatment, zinc levels were measured in 206 zinc-treated and 211 placebo patients[16,17]. At baseline, the plasma zinc concentration did not differ between the zinc (mean ± SD of 8.96 ±2.9 μmol/L) and placebo (8.86 ±2.3 μmol/L) groups, and overall 70% of the children were zinc deficient. Infants less than a year of age received zinc at 10 mg/kg/day and children one year of age and older received 20 mg/kg/day for a total of 14 days. Following supplementation, plasma zinc concentrations were substantially higher in the zinc group (14.66 ±7.3 μmol/L) compared with those in the placebo group (9.26 ±2.5 μmol/L; $p=0.0001$).

Finally, in a study of Indian infants 7-120 days of age with suspected serious bacterial infections, in which ZinCfant tablets or placebo were given as an adjuvant to standard, empiric antibiotic treatment, zinc levels were obtained for 341 zinc-treated and 340 placebo-treated infants[18]. Baseline mean plasma zinc levels were 9.8 μmol/L (95% CI 7.7,12.4) in the zinc group versus 9.4 μmol/L (95% CI 7.5,11.7) for the placebo group; 43% of zinc treated infants and 46% of placebo infants were zinc deficient, as defined by a a serum zinc concentration of <9.2 μmol/L. Following administration of zinc at 10 mg/kg/day for a mean duration of approximately 5.5 days, the mean increase in serum zinc concentration from baseline (±SD) was higher in the zinc group (3.3 ±6.9 μmol/L) than in the placebo group (1.2 ±5.2 μmol/L), with a difference of 2.0 μmol/L (95% CI 1.1, 3.0; p<0.0001).

In conclusion, the increases in zinc plasma levels with ZinCfant tablets are considered comparable to those achieved with zinc oral liquid formulations.

4. Summary of Product Safety and Efficacy

Introduction

A number of clinical studies have established the value of zinc in the management of diarrhoea in children, with data supporting the efficacy of zinc supplementation in reducing the duration of acute and persistent diarrhoea in zinc deficient children. These conclusions have been supported by several meta-analyses, including a 2012 Cochrane Review[1]. There is also evidence regarding the beneficial effect of zinc on severity of diarrhoea, however this evidence is somewhat less robust, since fewer trials have reported on this parameter and different endpoints have been examined. In addition, no definitive conclusions can be drawn regarding effects on hospitalization or death, since most studies were not designed to specifically examine these outcomes, and many were conducted in hospital, where death rates were low. An epidemiological review which used hospitalization data as a proxy for mortality estimated that treatment of diarrhoea with zinc could reduce mortality due to diarrhoea by 23%, although this estimate is predicated on a number of assumptions[2].

Evidence of the efficacy and safety of zinc supplementation in the treatment of diarrhoea in children led the WHO and UNICEF to issue a joint statement in 2004 recommending the use of zinc in the clinical management of acute diarrhoea[3]. In March 2005 the WHO Expert Committee on the Use of Essential Medicines added zinc to the WHO Model List of Essential Medicines[4], and in 2007 the WHO and UNICEF published the document *Evidence for the Safety and Efficacy of Zinc Supplementation in the Management of* Diarrhoea[5].

ZinCfant® dispersible tablets are a rapidly dispersible tablet formulation of zinc sulfate monohydrate equivalent to 20 mg of elemental zinc. ZinCfant tablets are indicated for the treatment of acute and persistent diarrhoea in children and infants less than 5 years of age.

Clinical Pharmacology

Zinc is an essential trace element and the second most common trace element in the body, after iron. Zinc intake is closely related to protein intake, and thus zinc deficiency, like protein malnutrition, is common; it has been estimated that a third of the world's population is at risk of zinc deficiency. Severe zinc deficiency is associated with growth retardation, primary hypogonadism, skin disease, disturbances of taste and smell, and impaired immunity with increased susceptibility to infection.

Zinc is a component or cofactor in more than 70 important enzyme systems and plays a role in the regulation of nucleoproteins and the activity of various inflammatory cells, as well as in growth, tissue repair and wound healing, carbohydrate metabolism, and production of testicular hormones.

Pharmacodynamics

The beneficial effect of zinc in the treatment of diarrhoea may be mediated through several mechanisms. Zinc is intimately involved in immune functioning and response to infection, and deficiency is associated with impaired phagocytic function, lymphocyte depletion, and decreased immunoglobulin interleukin (IL-2) production[6-8]. Studies in developing countries, where zinc deficiency is common, have shown that zinc supplementation reduces the incidence of diarrhoeal disease and pneumonia, an effect which may persist for months following zinc discontinuation, consistent with enhancement of the immune response.[3,5] However, evidence also exists for direct inhibitory effects of zinc on enteric pathogens. Thus, zinc has been shown to block the secretory effects of cholera toxin and E. coli heat-labile enterotoxin[9], and it has demonstrated direct inhibitory effects on enteropathogenic E. coli[10].

Pharmacokinetics

Zinc is incompletely absorbed from the small bowel, with between 10 and 40% of an ingested dose absorbed[11]. Numerous dietary components can interfere with zinc absorption, particularly phytates and fibre, which bind to zinc, as well as iron and chromium, although standard iron supplements do not appear to significantly affect plasma zinc levels in healthy breastfed infants.[12] Normal plasma zinc levels range from 10.7 - 18.3 μmol/L (70 to 120 μg/dL), and deficiency is generally defined as a serum level < 9.2 μmol/L (<60 μg/dL)[13]. Approximately 60% of circulating zinc is loosely bound to albumin and 30% is more tightly bound to macroglobulin. In adults, approximately 0.5 to 1.0 mg/day is secreted in the biliary tract and excreted in the stool and 0.5 to 0.8 mg/day is excreted in the urine. The majority of zinc is stored in the liver and kidney, where it is chiefly intracellular and bound to metalloproteins.

The specific pharmacokinetic parameters of ZinCfant tablets are described in section 3 of this report.

Clinical Efficacy

The pivotal trials which established the efficacy of zinc in the treatment of acute and persistent diarrhoea in children were conducted with a variety of oral zinc solutions and syrups[19-23]. The formulations used in the studies differed in the zinc salt used (sulfate, acetate, and gluconate), excipients, and the dose of zinc administered. Little precise information is available regarding the formulations used, including excipients, which can significantly affect zinc absorption. As a result, it has not been possible to adequately characterize a comparator formulation for the purpose of demonstrating clinical non-inferiority or bioequivalence of ZinCfant tablets. Furthermore, considering the established efficacy of zinc in the treatment of diarrhoea in children, conducting a full, placebo-controlled efficacy study of ZinCfant tablets poses ethical challenges.

Consequently, for the purpose of Prequalification, evidence for the efficacy of ZinCfant tablets for the treatment of diarrhoea has been derived from data establishing that short term supplementation with ZinCfant tablets results in increases in zinc plasma levels that are comparable to those achieved in clinical trials which demonstrated efficacy with zinc oral liquid formulations.

Similar to the ZinCfant tablet pharmacokinetic studies described in Section 3, the clinical diarrhoea studies with zinc oral liquids used a variety of dosing regimens. These are briefly summarized in **Table 1**, which also displays the increases in plasma zinc levels observed following zinc supplementation. These increases were associated with efficacy, in the form of reductions in diarrhoeal duration and, in some cases, severity of diarrhoea. Taking into account the differing dosing regimens and age bands, as well as the time of zinc sampling employed across the studies, the increases in plasma zinc levels displayed in **Table 1** are considered comparable to those observed following administration of ZinCfant tablets.

Table 1. Summary of pivotal zinc oral liquid trials which reported plasma zinc results

Study	N	Age	Zinc dose (salt)	Baseline zinc (μmol/L(± SD)	Duration of Therapy	Placebo-adjusted Change in Plasma zinc
Persistent diarrhoea (> 14 d duration)						
Roy *et al*., 1998[19] (Bangladesh)	Zn: 95 Pl: 95	3-24 mos.	20 mg /d (*salt?;* t.i.d.+ vitamins)	Zn: 13.2 ± 4.9 Pl: 13.4 ± 4.5	14 days	2.0 μmol/L (p<0.03)
Penny *et al.*, 1999[20] (Peru)	Zn: 139 Pl: 136	6-36 months	20 mg /d (*gluconat*e)	Zn: 11.3 ± 2.9 Pl: 11.0 ± 2.6	14 days	5.2μmol/L (p<0.001)
Acute diarrhoea ((≤72 h duration)						
Strand *et al.,* 2002[21] (Nepal)	Zn: 447 Pl: 452	6-35 months	<12 mos: 15 mg/ d; ≥12 mos: 30 mg/d (*salt?*)	Zn: 8.7 ± 2.2 Pl: 8.6 ± 1.4	Until recovery, + 7 days (mean 10 d)	3.9 μmol/L
Bahl *et al.,* 2002[22] (India)	Zn: 404 Pl: 401	6-35 months	<12 mos: 15 mg/ d; ≥12 mos: 30 mg/d (*gluconate*)	Zn: 10.1 ± 2.1 Pl: 9.98 ± 2.0	14 days	3.70 μmol/L (95% CI 2.22, 5.18)
Bhatnagar et al., 2004[23] (India)	Zn: 132 Pl: 134	3-36 months	≤12 mos: 15 mg/ d; >12 mos: 30 mg/d (*sulfate;* t.i.d.+ vitamins)	Zn: 11.8 ± 3.8 Pl: 11.5± 3.5	14 days	1.76 μmol/L (95% CI 0.41,3.10

In summary, short term supplementation with ZinCfant tablets in children results in increases in zinc plasma levels that are comparable to those achieved in clinical trials with the syrup formulations known to be effective in treating diarrhoea.
The Prequalification Programme judges this evidence sufficient to conclude efficacy of ZinCfant tablets for the indication of treatment of acute and persistent diarrhoea in children.

Clinical Safety

ZinCfant tablets have been used in numerous clinical studies, including long-term supplementation studies[24,25] (generally at lower doses than used for diarrhoea), studies for other indications[16-18] (e.g. adjunctive treatment or prevention of pneumonia), as well as in studies in the treatment of diarrhoea in children[26-30] although the latter studies generally combined the tablets with oral rehyration solution and / or examined tolerability and acceptability.

The safety profile of ZinCfant tablets is favourable. The most common undesirable effect observed with ZinCfant® tablets is regurgitation and vomiting. This was explored in detail in a dedicated, double-blind, randomized controlled trial in 800 Bangladeshi children with diarrhoea, aged 3-59 months, which compared vomiting and regurgitation during the one hour period following administration of either a single 20 mg ZinCfant tablet, a placebo tablet, or no treatment (groups were randomized 1 :1 :1) [28]. The authors reported vomiting in 26% of children receiving the ZinCfant tablets compared to 12% for those receiving placebo, for a relative risk increase of 14% due to the ZinCfant tablets. Similarly, for regurgitation, they report regurgitation in 9.4% of children receiving the ZinCfant tablets compared to 4.2% for those receiving placebo, for a relative risk increase of 5.2%. Vomiting occurred on average within 10 minutes of zinc administration, and was a single episode in 91.2% of cases.

Children who had previously experienced episodes of vomiting prior to zinc administration were at higher risk, as were better hydrated children. It is noted that a relatively high proportion (>90%) of the hospital-treated patients had experienced previous vomiting, possibly predisposing them to presentation at the hospital. Other studies which have noted vomiting associated with zinc administration have reported that the incidence is highest following the first dose[21].

Despite theoretical concerns, there is no clear evidence that the WHO recommended 10-14 day zinc regimen for treatment of diarrhoea results in clinically significant decreases in copper levels.
Therefore, the clinical safety of ZinCfant tablets is considered acceptable when guidance and restrictions presented in the Summary of Product Characteristics are followed.

5. Benefit risk assessment and overall conclusion

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC.

Pharmacokinetics

The absorption of zinc from ZinCfant tablets has been shown in several studies. The increases in zinc plasma levels with ZinCfant tablets are considered comparable to those achieved with zinc oral liquid formulations.

Efficacy and Safety

The evidence from the submitted studies is considered adequate to establish efficacy of ZinCfant tablets for the treatment of acute and persistent diarrhoea in infants and children.
During the course of the clinical development for ZinCfant tablets, no new safety signals were observed and the general safety profile of the product was consistent with the established safety profile of zinc. ZinCfant tablets tablets are considered safe and effective when used in accordance with the guidance and restrictions presented in the Summary of Product Characteristics.

Benefit/Risk Assessment

Based on the WHO assessment of data on quality, safety and efficacy the team of assessors considered by consensus that the benefit-risk profile of ZinCfant tablets was acceptable for the following indication: “acute and persistent diarrhoea in infants and children up to 5 years of age”, and has advised that the quality, efficacy and safety of ZinCfant tablets allow inclusion of ZinCfant tablets tablets, manufactured at Laboratoires Pharmaceutiques Rodael, Bierne, France, in the list of prequalified medicinal products.

References

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