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	[NT021 trade name]*
Manufacturer of Prequalified Product	Ipca Laboratories Limited
Active Pharmaceutical Ingredient(s) (API)	Albendazole
Pharmaco-therapeutic group (ATC Code)	Anthelminthics for treatment of trematodes, nematodes and cestodes causing the infections (P02CA03)
Therapeutic indication	[NT021 trade name] is indicated for the treatment of cestode infections, lymphatic filariasis and other nematode infections

1. Introduction

[NT021 trade name] is indicated for the treatment of cestode infections, lymphatic filariasis and other nematode infections

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)

Active pharmaceutical Ingredient (API)

Albendazole 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 [NT021 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 inspection of the sites of API manufacture to verify compliance with WHO GMP requirements.

Data provided in the dossier show that albendazole is of BCS low solubility across the physiological pH range, hence particle size distribution (PSD) and polymorphism are considered critical parameters and form part of the FPP manufacturer's API specifications.

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

Other ingredients

Other ingredients used in the tablet formulation include lactose monohydrate, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, povidone, sodium lauryl sulphate, saccharin sodium, trusil vanilla flavour, trusil orange flavour and magnesium stearate, all with the exception of the flavourants trusil vanilla and trusil orange, being pharmacopoeial controlled. Trusil vanilla and trusil orange flavours are adequately controlled by in-house specifications. Lactose monohydrate is of bovine origin. TSE/BSE free certificates from the suppliers have been provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is an off- white, oval, uncoated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablets have a break line on one side and are plain on the other side. The score line is intended for subdivision of tablet when a half a tablet dose is to be administered as supported by divisibility data. The tablets are packaged in clear colourless plastic (PVDC/PVC) on aluminium foil blister cards and round, opaque white plastic (HDPE) bottles. Each bottle has an aluminium/plastic foil seal and a white plastic (polypropylene) screw cap.

The aim of the formulation development strategy was to obtain a stable multisource product bioequivalent to the WHO recommended comparator product, Eskazole 400mg Tablets. The selection of the excipients was primarily based on the qualitative composition of the comparator product and API-excipient compatibility studies. Regarding the manufacturing process, wet granulation was selected to achieve the quality target product profile. Various experiments were performed to select and optimize the concentration of excipients and other process parameters to obtain tablets of desired characteristics, including dissolution profile similarity with the comparator product. Satisfactory in-process controls have been established.

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 of the API (HPLC, UV), average weight, weight of 20 tablets, uniformity of dosage units (by mass variation), disintegration time, friability, assay (HPLC), dissolution (HPLC detection), related substances (HPLC), residual solvents, water content (KF), hardness, polymorphic identity and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. The product proved to be quite stable at these storage conditions, with little degradation observed. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable. The in-use storage period as indicated in the product information is supported by stability data.

Conclusion

The quality part of the dossier is accepted.

.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2022 according to internationally accepted guidelines.

Single dose oral bioequivalence study of Albendazole tablets 400 mg and Eskazole® 400 mg tabletten albendazol in healthy adult human subjects under fed conditions (study no. C1B02168).

The objective of the study was to compare the bioavailability of the stated Albendazole 400 mg tablet manufactured by/for Ipca, India (test drug) with the reference formulation Eskazole® (GSK) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, randomized, fully replicate crossover study in healthy subjects under fed conditions. Each subject was assigned to receive each of the following two treatments twice in a randomized fashion:

Treatment T: Test – 1 tablet Albendazole 400 mg
(albendazole 400 mg)
Batch no. JWQ0320019.

Treatment R: Reference – 1 tablet Eskazole® 400 mg
(albendazole 400 mg)
Batch no. AW2H.

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 21 samples within 18h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for albendazole were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 0.25 ng/ml for albendazole.

The study was performed with 56 participants; data generated from a total of 55 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for albendazole as well as statistical results are summarised in the following table:

Albendazole

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	3.17 ± 1.43	3.12 ± 1.36	-	-
C_{max} (ng/ml)	40.3 ± 39.4 (22.8)	38.0 ± 44.5 (21.3)	107.3	92.3 – 124.8
AUC_{0-t} (ng.h/ml)	148 ± 148 (81)	137 ± 158 (76)	106.0	91.9 – 122.2
AUC_{0-inf} (ng.h/ml)	152 ± 152 --	141 ± 161 --	-	-

*geometric mean; #median (range)

The results of the study show that acceptance limits are met by both AUC and C_{max} values regarding albendazole. Accordingly, the test Albendazole 400 mg tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Eskazole® (GSK).

Summary of product safety and efficacy

[NT021 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, [NT021 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Eskazole® (GSK). for which benefits have been proven in terms of clinical efficacy. The clinical safety of [NT021 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.

4. 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 [NT021 trade name] is used in accordance with the SmPC.

Bioequivalence

[NT021 trade name] has been shown to be bioequivalent with Eskazole® (GSK).

Efficacy and Safety

Regarding clinical efficacy and safety, [NT021 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 [NT021trade name] was acceptable for the following indication: ‘for the treatment of cestode infections, lymphatic filariasis and other nematode infections’, and would allow inclusion of [NT021 trade name], manufactured at Ipca Laboratories Limited, Plot no. 255/1, Village Athal, Silvassa 396 230, U.T. of Dadra and Nagar Haveli and Daman and Diu, India in the list of prequalified medicinal products.