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	[NT014 trade name]*
Manufacturer of Prequalified Product	Mepro Pharmaceuticals Pvt. Ltd. Unit-II, Q Road, Phase-IV, G.I.D.C, Wadhwan Dist: Surendranagar, Gujarat 363035, India
Active Pharmaceutical Ingredient (API)	Albendazole
Pharmaco-therapeutic group (ATC Code)	Anthelminthics for treatment of trematodes, nematodes and cestodes causing the infections (P02CA03)
Therapeutic indication	[NT014 trade name] is indicated for the treatment of cestode infections, lymphatic filariasis and other nematode infections

1. Introduction

[NT014 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)

Data provided in the dossier show that albendazole is a white or slightly yellowish powder. Albendazole is practically insoluble in water, hence particle size distribution (PSD) and polymorphism are considered critical parameters and form part of the FPP manufacturer's API specifications.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification (IR), appearance of solution, related substances (HPLC), loss on drying, sulfated ash, assay (potentiometric titration), residual solvents (GC), melting point, polymorphic identity (p-XRD), diamine of albendazole content (LC-MS; ≤ 1.8 ppm) and particle size distribution. The PSD limits are based on the results obtained for the API batch used in the manufacture of the FPP biobatch.

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

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 used in the tablet formulation include sodium starch glycolate, microcrystalline cellulose, sodium lauryl sulphate, maize starch, colloidal anhydrous silica, aspartame, mixed fruit flavour, purified talc and magnesium stearate, all with the exception of mixed fruit flavour, being pharmacopoeial controlled. The mixed fruit flavour is adequately controlled by in-house specifications. TSE/BSE free certificate has been provided for the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off-white, oblong, uncoated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablet has a break line on one side and is plain on the other side. The break line is intended for subdivision of tablet when a half dose is to be administered. The tablets are packaged in a round, white plastic (HDPE) bottle. The bottle has an aluminium tagger seal and a round, white childproof plastic (polypropylene) cap.

The aim of the formulation development strategy was to obtain a stable multisource product bioequivalent to the WHO recommended comparator product, Eskazole (Albendazole 400 mg tablets). The selection of the excipients was primarily based on the available literature, qualitative composition of the comparator product and API-excipient compatibility studies. The flavouring agent and sweetener were used to improve the taste of the chewable tablets. A wet granulation manufacturing process was selected to achieve an immediate release tablet with release profile similar to that of the comparator product. 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 N-nitrosamine impurities and hence no risk was identified, though the manufacturer undertook to conduct confirmatory testing for potential N-nitrosamines on selected batches post prequalification.

Specifications

The finished product specifications include tests for description, identification of the API (HPLC, UV), uniformity of weight, average weight, disintegration time, uniformity of mass (subdivided tablets), hardness, friability, water content (KF), related substances (HPLC), dissolution (UV detection), assay (HPLC), polymorphic quantification (p-XRD) 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 2020 according to internationally accepted guidelines.

An open label, balanced, randomized, two-treatment, four-period, two-sequence, single oral dose, full replicate bioequivalence study of Albendazole 400 mg chewable tablets of Mepro Pharmaceuticals Pvt. Ltd., India with Eskazole 400 mg (chewable) tablets of Aspen Pharmacare Australia Pty. Ltd. in normal, healthy adult human subjects under fed condition (study no. 0639-19).

The objective of the study was to compare the bioavailability of the stated Albendazole 400 mg chewable tablet manufactured by Mepro Pharmaceuticals Pvt. Ltd., India (test drug) with the reference formulation Eskazole® (Aspen Pharmacare Australia Pty Ltd.) 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 chewable tablet Albendazole 400 mg (albendazole 400 mg) Batch no. AB20201.

Treatment R: Reference – 1 tablet Eskazole® 400 mg (albendazole 400 mg) Batch no. 373899.

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 23 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 0.3 ng/mL for albendazole.

The study was performed with 77 participants; data generated from a total of 69 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 (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h) #	4.33 (0.67 – 6.00)	4.33 (1.33 – 6.00)	–	–
C_{max} (ng/mL)	116 ± 95 (79)	110 ± 93 (75)	104.8	94.2 – 116.6
AUC_{0-t} (ng·h/mL)	404 ± 335 (278)	361 ± 313 (247)	112.2	101.8 – 123.8
AUC_{0-inf} (ng·h/mL)	420 ± 347 (289)	377 ± 326 (259)	111.8	101.7 – 123.0

#median (range)

The results of the study show that preset acceptance limits of 80 -125 % 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® (Aspen Pharmacare Australia Pty Ltd.).

4. Summary of product safety and efficacy

[NT014 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, [NT014 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Eskazole® (Aspen Pharmacare Australia Pty Ltd.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [NT014 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.

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 [NT014 trade name] is used in accordance with the SmPC.

Bioequivalence

[NT014 trade name] has been shown to be bioequivalent with Eskazole® (Aspen Pharmacare Australia Pty Ltd.).

Efficacy and Safety

Regarding clinical efficacy and safety, [NT014 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 [NT014 trade name] was acceptable for the following indication: ' for the treatment of cestode infections, lymphatic filariasis and other nematode infections ', and would allow inclusion of [NT014 trade name], manufactured at Mepro Pharmaceuticals Pvt. Ltd. Unit-II, Q Road, Phase-IV, G.I.D.C, Wadhwan , Dist: Surendranagar, Gujarat 363035, India in the list of prequalified medicinal products.