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	[NT005 trade name]*
Manufacturer of Prequalified Product	Cipla Limited Indore (Unit-IV)
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	[NT005 trade name] is indicated for the treatment of cestode infections, lymphatic filariasis and other nematode infections

1. Introduction

[NT005 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)

The APIMF of albendazole (methyl- 5-(propylthio)-2-benzimidazolecarbamate), has been accepted through WHO's APIMF procedure. The manufacture of albendazole entails several chemical steps. The crystalline polymorphic Form- II, controlled by XRPD is consistently produced.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification (IR and TLC), assay (potentiometric), residue on ignition, organic impurities (TLC), loss on drying, related substances (HPLC), mesityl oxide content (HPLC), residual solvents (GC), appearance of solution, polymorphic identity (XRPD), formaldehyde content (GC), an o-phenylenediamine derivative (LC-MS; ≤ 37 ppm), several potentially genotoxic impurities, including nitro-anilines content (LC/GC-MS; each ≤ 1.8 ppm) and particle size distribution.

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 lactose monohydrate, corn starch, sodium starch glycolate, sodium lauryl sulphate, povidone, microcrystalline cellulose, saccharin sodium, magnesium stearate and colour FD & C yellow #6 (lake sunset yellow FCF), all with the exception of colour FD & C yellow #6 (lake sunset yellow FCF), being pharmacopoeial controlled. The colour FD

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

& C yellow #6 (lake sunset yellow FCF) is adequately controlled by in-house specifications. TSE/BSE free certificate has been provided for lactose monohydrate.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a mottled, pale orange, oblong-shaped biconvex uncoated tablet with a score line on one side and "C541" on the other side. The score line is intended for subdivision of tablet when a half doses is to be administered. The tablets are packaged in a white HDPE bottle with blue child-resistant polypropylene cap, heat seal liner and rayon sani coil.

Product development was initiated for albendazole 200 mg Tablets and accordingly the same formula was extended to obtain a dose- weight proportional formulation of albendazole 400 mg Tablets.

The aim of the formulation development strategy was to obtain a stable multisource product bioequivalent to the WHO recommended comparator product, Albenza 200 mg Tablets. The selection of the excipients was primarily based on the qualitative composition of the comparator product and API-excipient compatibility studies. A product development strategy utilizing a wet granulation process was selected to achieve and immediate release drug release profile matching with 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.

Specifications

The finished product specifications include tests for description, identification of the API (HPLC, UV) and colourant, average weight, water content (KF), friability, hardness, uniformity of dosage units (by weight variation), dissolution, disintegration time, degradation products (HPLC), assay (HPLC), 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 2017 according to internationally accepted guidelines.

An open label, balanced, randomized, two-treatment, two-sequence, four-period, single oral dose, fully replicate, bioequivalence study of albendazole tablet 400 mg of Cipla Limited, India with Albenza® (albendazole) tablets 200 mg (200 mg x 2 tablets) of Amedra Pharmaceuticals LLC, USA in healthy adult human male and female subjects under fed condition (study no. 0659-17).

The objective of the study was to compare the bioavailability of the stated albendazole 400 mg tablet manufactured by/for Cipla Limited, India (test drug) with the reference formulation Albenza® (Amedra Pharmaceuticals LLC) 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. ID71155.
Treatment R:	Reference – 2 tablets Albenza® 200 mg (albendazole 400 mg) Batch no. A6001.

A 9-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 22 samples within 48h 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 72 participants; data generated from a total of 65 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)	4.0 (1.33 – 5.0)	3.67 (1.33 – 5.0)	–	–
C_{max} (ng/mL)	84 ± 89	82 ± 79	98.3	89.6 – 107.8
AUC_{0-t} (ng·h/mL)	308 ± 368	306 ± 330	98.6	90.7 – 107.1
AUC_{0-inf} (ng·h/mL)	314 ± 368	311 ± 330		

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 Albenza® (Amedra Pharmaceuticals LLC).

4. Summary of product safety and efficacy

[NT005 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 [NT005 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Albenza® for which benefits have been proven in terms of efficacy.

The clinical safety of this product is considered acceptable when guidance and restrictions as stated in the summary of product characteristics are taken into account. 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 [NT005 trade name] is used in accordance with the SmPC.

Efficacy and Safety

Regarding clinical efficacy and safety, [NT005 trade name] is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics are taken into consideration.

Benefit Risk Assessment

Based on the WHO assessment of data on quality, safety and efficacy the team of assessors considered that the benefit–risk profile of [NT005 trade name] was acceptable for the following indication: 'for the treatment of cestode infections, lymphatic filariasis and other nematode infections' and has advised that the quality, safety and efficacy of [NT005 trade name] allow inclusion of [NT005 trade name], manufactured by Cipla Limited Indore (Unit-IV), Plot No 9, 10 & 15, Indore Special Economic Zone, Phase II, Pithampur, Dhar District, Madhya Pradesh, India, in the list of prequalified medicinal products.