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	[NT022 trade name][*]
Manufacturer of Prequalified Product	Mepro Pharmaceuticals Pvt. Ltd. Unit-III, Plot No. 141/2 & 227, Haripura, Ta. Savli, Jarod, Samlaya road, Vadodara, Gujarat 391520, India
Active Pharmaceutical Ingredient (API)	Praziquantel
Pharmaco-therapeutic group (ATC Code)	Anthelmintics (P02B A01)
Therapeutic indication	[NT022 trade name] is indicated for the parasitic infections of schistosomiasis, taeniasis, neurocysticercosis, clonorchiasis, opisthorchiasis, and paragonimiasis.

1. Introduction

[NT022 trade name] is indicated for the parasitic infections of schistosomiasis, taeniasis, neurocysticercosis, clonorchiasis, opisthorchiasis, and paragonimiasis.

Detailed information on the use of this product is described in the summary of product characteristics (SmPC), which can be found in this WHOPAR.

Treatment and community prevention programmes should follow authoritative guidelines including those issued by WHO.

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)

Praziquantel 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 [NT022 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 medics regulatory authority's responsibility.

Additional user requirements for the API include tests for polymorphic form and particle size distribution, the limits of which were set on the data obtained for the API batches used in the manufacture of the FPP biobatch.

Other ingredients

Other ingredients used in the core tablet formulation include sodium lauryl sulfate, maize starch, microcrystalline cellulose, croscarmellose sodium, povidone and magnesium stearate, all being pharmacopoeial controlled. The film coat contains hypromellose, polyethylene glycol and titanium dioxide, also pharmacopoeial controlled. None of the excipients are derived from human or animal origin. TSE/BSE free certificates from the suppliers have been provided with regards to all the excipients

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white, capsule- shaped, film- coated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablets have a break line and two score lines on both sides.

The tablets are packaged in either clear colourless plastic (PVDC/PVC) on aluminium foil blister card or round, opaque white plastic (HDPE) bottle. It also contains a sachet of desiccant (drying material) and a piece of purified cotton to keep the tablets in place. The bottle has an aluminium/ plastic foil seal and a white, childproof plastic (polypropylene) screw cap.

The objective of the product development was to obtain a stable and robust formulation, bioequivalent to the WHO recommended comparator product, Biltricide® (praziquantel) 600mg tablets. The selection of excipients was based on the excipients used in the comparator product and API-excipient compatibility data. Based on the physicochemical properties of the praziquantel API, wet granulation process was selected for manufacturing of the tablets. Based on 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.

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-nitroso praziquantel on selected batches post prequalification.

Specifications

The finished product specifications are pharmacopoeial based and include tests for description, identification of API (HPLC, IR, TLC), identification of titanium oxide, uniformity of weight, average weight, disintegration time, uniformity of mass (split tablets), uniformity of dosage units (by weight variation), dissolution (UV detection), related substances (HPLC), assay (HPLC), water content (KF) and microbial limits.

Stability testing

Stability studies have been performed at 30°C/75%RH (zone IVb) as long-term storage condition and for six months at 40°C/75%RH as accelerated storage condition in the packaging proposed for marketing of the product. The data provided indicated that the tested parameters remained within acceptable limits at both storage conditions, with no obvious trend or variability. 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

The following bioequivalence study has been performed in 2023 according to internationally accepted guidelines.

An open-label, randomized, balanced, single oral dose, two-treatment, two-sequence, four-period, fully replicate crossover bioequivalence study of Praziquantel tablets 600 mg of Mepro Pharmaceuticals Pvt. Ltd with Biltricide® (praziquantel) tablets 600 mg manufactured for Bayer Healthcare, 220 Avenue de la Recherche - Parc Eurasante, 59120 Loos, France in normal healthy adult, human study participants under fed conditions (study 13153/22-23).

The objective of the study was to compare the bioavailability of the stated Praziquantel 600 mg tablet manufactured by Mepro Pharmaceuticals Pvt. Ltd, India (test drug) with the reference formulation Biltricide® 600 mg tablet (Bayer Healthcare Pharmaceuticals) 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 treatments twice in a randomized fashion:

Treatment T: Test – 1 tablet Praziquantel 600 mg (praziquantel 600 mg) Batch no. 3EX 1003.

Treatment R: Reference – 1 tablet Biltricide® 600 mg (praziquantel 600 mg) Batch no. 486019.

A 14-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 21 samples within 12 h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for praziquantel were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 3 ng/mL for praziquantel.

The study was performed with 56 participants; data generated from a total of 46 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Praziquantel

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)	2.47 ± 1.10	2.78 ± 1.18	–	–
C_{max} (ng/mL)	659 ± 487 (507)	634 ± 420 (496)	102.3	90.3 – 116.0
AUC_{0-t} (ng·h/mL)	1291 ± 912 (1004)	1273 ± 869 (1003)	100.1	92.6 – 108.3
AUC_{0-inf} (ng·h/mL)	1369 ± 968 --	1349 ± 933 --	–	

The results of the study show that preset acceptance limits of 80 – 125% are met by AUC and C_{max} values regarding praziquantel. Accordingly, the test Praziquantel 600 mg tablet meets the criteria for

bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Biltricide® 600 mg tablet (Bayer Healthcare Pharmaceuticals).

4. Summary of product safety and efficacy

[NT022 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, [NT022 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Biltricide® 600 mg tablet (Bayer Healthcare Pharmaceuticals) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [NT022 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 [NT022 trade name] is used in accordance with the SmPC.

Bioequivalence

[NT022 trade name] has been shown to be bioequivalent with Biltricide® 600 mg tablet (Bayer Healthcare Pharmaceuticals).

Efficacy and Safety

Regarding clinical efficacy and safety, [NT022 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 [NT022 trade name] was acceptable for the following indication: 'for the parasitic infections of schistosomiasis, taeniasis, neurocysticercosis, clonorchiasis, opisthorchiasis, and paragonimiasis', and would allow inclusion of [NT022 trade name], manufactured at Mepro Pharmaceuticals Pvt. Ltd. Unit-III, Plot No. 141/2 & 227, Haripura, Ta. Savli, Jarod, Samlaya road, Vadodara, Gujarat 391520, India in the list of prequalified medicinal products.