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	[NT008 trade name]*
Manufacturer of Prequalified Product	Medopharm Private Limited Unit II, No 50, Kayarambedu Village Guduvanchery- 603 202 Tamilnadu, India.
Active Pharmaceutical Ingredient (API)	Praziquantel
Pharmaco-therapeutic group (ATC Code)	Anthelminthics for schistosoma infections (P02BA01)
Therapeutic indication	[NT008 trade name] is indicated for elimination of schistosoma infections through mass drug administration programmes.

1. Introduction

[NT008 trade name] is indicated in adults and children for the elimination through mass drug administration programmes of schistosoma infections due to various types of blood fluke worms (*Schistosoma mansoni, Schistosoma haematobium, Schistosoma japonicum, Schistosoma mekongi, Schistosoma intercalatum*) following the recommendations of the WHO Global Programme to Eliminate Schistosomiasis.

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 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 [NT008 trade name], is of good quality and manufactured in accordance with WHO Good Manufacturing Practices (GMP). 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. Additional user requirements for the BCS low soluble praziquantel include tests for polymorphic form and particle size distribution, the limits of which were set on the data 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.

Other ingredients

Other ingredients used in the core tablet formulation include microcrystalline cellulose, maize starch, croscarmellose sodium, sodium lauryl sulphate, povidone and magnesium stearate, all being pharmacopoeial controlled. The film-coating mixture contains hydroxypropyl methylcellulose, titanium dioxide and propylene glycol. All the excipients used are well known and widely used as pharmaceutical excipients in oral solid formulations and comply with the relevant pharmacopoeial monographs. None of the excipients are of animal or human origin. TSE/BSE free certificates have been provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off-white, oblong, film coated tablet with three scores on both sides. The scores are intended for subdivision of tablets when either half or quarter tablet doses are to be administered. The tablets are packaged in a low-density polyethylene bag. Each sealed bag is then packed together with a 1g silica gel desiccant packet in a white HDPE rectangular rib jar sealed with aluminium tagger foil with a HDPE white cap.

The aim of the formulation development strategy was to obtain a stable multisource product bioequivalent to the WHO recommended comparator product, Biltricide 600mg Tablets. The selection of the excipients was primarily based on the qualitative composition of the comparator product and API-excipient compatibility studies. Due to the hygroscopic nature of the API, the manufacturing process was by non-aqueous granulation and coating. 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 (TLC, IR, HPLC and melting point), average weight, uniformity of dosage units (by mass variation), tablet dimensions (length, width and thickness), disintegration time, water content (KF), average weight of tablet quarters, uniformity of mass of tablet quarters dissolution (UV detection), assay (HPLC), related substances (HPLC), residual solvents (GC) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 25°C/60%RH, 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 2019 according to internationally accepted guidelines.

Study title:

Randomised, open label, balanced, two-treatment, two-sequence, four-period, single oral dose, crossover, fully replicated, bioequivalence study of Praziquantel 600 mg tablet of Medopharm Private Limited, India with Biltricide® (praziquantel) tablets 600 mg, manufactured for Bayer Healthcare

Pharmaceuticals Inc., Wayne, NJ 07470, manufactured in Germany in healthy adult human subjects under fed conditions (study no. PRAZ/2018/1621).

The objective of the study was to compare the bioavailability of the stated praziquantel 600-mg tablet [NT008 trade name] manufactured for/by Medopharm Private Limited, India (test drug) with the reference formulation Biltricide® 600 mg (Bayer Healthcare Pharmaceuticals Inc.) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, fully replicated 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 [NT008 trade name]
(praziquantel 600 mg)
Batch no. : 218070003

Treatment R: Reference
– 1 tablet Biltricide® 600 mg
(praziquantel 600 mg)
Batch no. 254117

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 20 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 analysed using a validated LC-MS/MS method. The limit of quantification was stated to be about 5 ng/ml for praziquantel.

The study was performed with 68 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 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)#	2.0 (0.75 – 4.2)	2.0 (0.63 – 5.5)	-	-
C_{max} (ng/ml)	410 ± 315 (275)	464 ± 445 (272)	101.2	89.5 – 114.3
AUC_{0-t} (ng.h/ml)	945 ± 762 (630)	999 ± 900 (603)	104.5	95.9 – 113.9
AUC_{0-inf} (ng.h/ml)	1037 ± 883	1077 ± 981	-	-

#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 praziquantel. Accordingly, the test praziquantel 600-mg tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and [NT008 trade name] is therefore bioequivalent to the reference Biltricide® (Bayer Healthcare Pharmaceuticals Inc.).

4. Summary of product safety and efficacy

[NT008 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, [NT008 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Biltricide® (Bayer Healthcare Pharmaceuticals Inc.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [NT008 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 [NT008 trade name] is used in accordance with the SmPC.

Bioequivalence

[NT008 trade name] has been shown to be bioequivalent to the reference Biltricide® (Bayer Healthcare Pharmaceuticals Inc.).

Efficacy and Safety

Regarding clinical efficacy and safety, [NT008 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 [NT008 trade name] was acceptable for the following indication: 'elimination through mass drug administration programmes of schistosoma infections due to various types of blood fluke worms (*Schistosoma mansoni, Schistosoma haematobium, Schistosoma japonicum, Schistosoma mekongi, Schistosoma intercalatum*)', and would allow inclusion of [NT008 trade name], manufactured at Medopharm Private Limited, Unit II, No 50, Kayarambedu Village, Guduvanchery 603 202, Tamilnadu, India, in the list of prequalified medicinal products.