

This part reflects the scientific knowledge and the information about this product available at the time of prequalification. Thereafter, updates may have become necessary which are included in parts 1 to 5 and, if related to pharmaceutical issues, also documented in part 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product:	Praziquantel Tablets 600 mg ¹
Manufacturer of Prequalified Product:	Macleods Pharmaceuticals Limited Block: N-2, Village Theda P.O. LodhiMajra Tehsil Baddi Dist.: Solan Himachal Pradesh, 174101 India
Active Pharmaceutical Ingredient (API):	Praziquantel
International Nonproprietary Name:	Praziquantel
Pharmaco-therapeutic group (ATC Code):	Anthelminthics for schistosoma infections (P02BA01)
Therapeutic indication:	Praziquantel Tablets 600 mg is indicated for large scale preventive chemotherapy interventions for the control of schistosoma infections.

¹Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

1. Introduction

Praziquantel Tablets 600 mg is indicated for large scale preventative chemotherapy interventions for the control of schistosoma infection in adults and children (see Part 4 for full indications).

Praziquantel Tablets 600 mg should be initiated by a healthcare provider experienced in the management of schistosoma infection.

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)

A CEP (Certificate of Suitability) issued by the EDQM was submitted, ensuring good manufacturing control and applicability of the Ph.Eur. monograph to control the quality of the API. The FPP manufacturer's API specifications include particle size distribution and polymorphic form (with XRPD), which are regarded critical quality attributes due to the BCS low solubility of praziquantel across the physiological pH. The acceptance criteria for these two parameters were derived from the information of the API lot used in the FPP biobatch.

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 packaging.

Other ingredients

Other ingredients used in the core tablet formulation include microcrystalline cellulose, pregelatinized starch, sodium lauryl sulfate, povidone and magnesium stearate. The commercially sourced proprietary film-coating mixture contains hypromellose, polyethylene glycol and titanium dioxide. None of the excipients used in the manufacture of the tablets are of human or animal origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off white, capsule shaped, film coated tablet with breaklines on both sides. The breaklines are intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies. The tablets are packaged in HDPE bottles or clear film PVC/PVdC-Alu blisters.

The aim was to develop an immediate release tablet dosage form for oral administration. The WHO recommended comparator product, Biltricide® 600 mg, was characterised in support of setting the quality target product profile. The selection of suitable excipients for development was based on the desired process and product attributes, supported by API-excipient compatibility studies. Physicochemical characterization of the critically insoluble API included parameters such as assay, particle size and flow properties.

It was observed that the API material selected for the development has very poor flow properties, thus direct compression was not considered feasible. A wet granulation, organic solvent based, approach has been employed to improve flowability. Various studies were performed to optimize the concentration of excipients and process parameters to obtain a product of desired characteristics, including dissolution profile similarity with the comparator product. Satisfactory in-process controls have been established.

Specifications

The product specifications include tests for description, identification of the API (HPLC, TLC) and colorant, average weight, loss on drying, dissolution (HPLC detection), uniformity of dosage units (by weight variation), related substances (HPLC), assay (HPLC), residual solvents (GC) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been performed at 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at 40°C/75%RH as accelerated conditions in the packaging proposed for marketing of the product. The data showed that the FPP is quite stable at both storage conditions in all packaging configurations, with only a slight increase of total degradation products. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable. The in-use storage periods as indicated in the product information for the bottle packs are 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 2015 according to internationally accepted guidelines.

Study title: Bioequivalence study of single dose of Praziquantel tablets USP 600 mg manufactured by Macleods Pharmaceuticals Ltd., India in comparison with Biltricide® (praziquantel) tablets 600 mg manufactured by Bayer HealthCare Pharmaceuticals Inc. USA in healthy, adult, human subjects under fed condition (study no. BEQ-1531-PRAZ-2015).

The objective of the study was to compare the bioavailability of the stated Praziquantel 600 mg tablet manufactured for/by Macleods Pharmaceuticals Ltd., India (test drug) with the reference formulation Biltricide® (Bayer HealthCare Pharmaceuticals Inc.) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, four-period, crossover replicate 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. BPB7503B
- Treatment R: Reference – 1 tablet Biltricide®
(praziquantel 600 mg)
Batch no. AHOO3NP

A minimum of at least 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 24 samples within 15 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 90 participants; data generated from a total of 50 subjects completing all four periods 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 (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t _{max} (h)	2.33 ± 0.78	2.33 ± 0.77	-	-
C _{max} (ng/ml)	545 ± 381 (410)	590 ± 384 (461)	89.1	81.3 – 97.7
AUC _{0-t} (ng.h/ml)	1362 ± 950 (1011)	1486 ± 1087 (1124)	90.0	83.7 – 96.7
AUC _{0-inf} (ng.h/ml)	1416 ± 995 (NA [#])	1540 ± 1141 (NA [#])	--	--

* geometric mean; # not analyzed

Conclusion

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 is therefore bioequivalent to the reference Biltricide[®] (Bayer HealthCare Pharmaceuticals Inc.).

4. Summary of Product Safety and Efficacy

Praziquantel Tablets 600 mg has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the reference product. According to the submitted data on quality and bioavailability Praziquantel Tablets 600 mg is pharmaceutically and therapeutically equivalent and thus interchangeable with the reference product Biltricide[®](Bayer HealthCare Pharmaceuticals Inc) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of this product is considered to be acceptable when guidance and restrictions as stated in the Summary of Product Characteristics are considered. 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 Praziquantel Tablets 600 mg is used in accordance with the Summary of Product Characteristics.

Bioequivalence

Praziquantel Tablets 600 mg has been shown to be bioequivalent with Biltricide[®] (Bayer Healthcare Pharmaceuticals Inc, Germany).

Efficacy and Safety

Regarding clinical efficacy and safety, Praziquantel Tablets 600 mg 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 WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of Praziquantel Tablets 600 mg was acceptable for the following indication: **“large scale preventive chemotherapy interventions for the control of schistosoma infection in adults and children over 6 years ”** and has advised that the quality, efficacy and safety of Praziquantel Tablets 600 mg allow inclusion of Praziquantel Tablets 600 mg, manufactured at Macleods Pharmaceuticals Limited, Block no. 2, Village Theda, P.O. LodhiMajra, Tehsil Baddi, Dist.Solan, Himachal Pradesh, 174101, India in the list of prequalified medicinal products.