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	[NT013 trade name]*
Manufacturer of Prequalified Product	Merck S. A. de C.V.
Active Pharmaceutical Ingredient(s) (API)	Praziquantel
Pharmaco-therapeutic group (ATC Code)	Anthelmintics (P02B A01)
Therapeutic indication	[NT013 trade name] is used for the following parasitic infections: schistosomiasis, taeniasis, neurocysticercosis and foodborne trematodiasis.

1. Introduction

[NT013 trade name] is used for the following parasitic infections: schistosomiasis, taeniasis, neurocysticercosis and foodborne trematodiasis.

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 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 [NT013 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.

Other ingredients

Other ingredients used in the core tablet formulation include pregelatinized starch, povidone, sodium lauryl sulfate, crospovidone, microcrystalline cellulose and magnesium stearate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains

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

hydroxypropyl methylcellulose, partially hydrolysed polyvinyl alcohol, titanium dioxide, macrogol/ PEG, talc and artificial blackberry flavour. Magnesium stearate is of vegetable origin. TSE/BSE free certificate has been provided for magnesium stearate.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white, oblong, film-coated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablet has 'MERCK' debossed (stamped into) one side and 'PZ' and 'QL' on the other side, either side of a break line. The break line can be used to divide the tablet into equal doses. The tablets are packaged in HDPE bottles.

The objective of the formulation development strategy was to obtain a stable multisource product bioequivalent to the WHO recommended comparator product, Biltricide® (praziquantel 600 mg) tablets. The quality target product profile was defined and critical quality attributes were satisfactorily identified. The selection of the excipients was made based on experience with the uncoated formulation for donation to WHO as well as the physicochemical characteristics of the API and API-excipient compatibility studies. Due to the low density and extremely poor flow of the API, a wet granulation process was selected for the FPP manufacture to ensure the homogeneity during mixing stages and to improve powder flow characteristics for the compression process. The manufacturing process ran as intended during the process performance qualification with all in-process specifications being met. Satisfactory in-process controls have been established.

According to a risk evaluation by the applicant, the FPP appears to have no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications include tests for appearance, identification (HPLC and IR), assay (HPLC), related substances (HPLC), dissolution (UV detection), content uniformity, weight variation, water determination (KF), disintegration, hardness 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. 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.

A Phase I, open-label, randomized, 4-period, crossover, fully replicated, reference-scaled, single centre study to assess the bioequivalence of a single oral dose of 1200 mg of the coated Cesol tablet formulation versus comparator Biltricide® in healthy male volunteers (study MS200585_0004).

The objective of the study was to compare the bioavailability of the stated [NT013 trade name] manufactured by/for Merck Healthcare KGaA, Germany (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 – 2 tablets [NT013 trade name]
(praziquantel 1200 mg)
Batch no. 016565 / M91895-LP/A.
Treatment R: Reference – 2 tablets Biltricide® 600 mg
(praziquantel 1200 mg)
Batch no. 314419.

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 12h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for the enantiomers (R)-praziquantel and (S)-praziquantel were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be 5 ng/mL for (R)-praziquantel and (S)-praziquantel respectively.

The study was performed with 36 participants; data generated from a total of 35 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)	2.10 ± 0.94	2.31 ± 1.02	-	-
C_{max} (ng/mL)	632 ± 629 (434)	674 ± 730 (436)	99.6	85.1 – 116.7
AUC_{0-t} (ng·h/mL)	1320 ± 1329 (914)	1428 ± 1608 (914)	100.0	89.1 – 112.2
AUC_{0-inf} (ng·h/mL)	1373 ± 1396 --	1484 ± 1668 --	-	-

The results of the study show that preset acceptance limits of 80 – 125% are met by AUC and Cmax values regarding praziquantel. Accordingly, the test [NT013 trade name] 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

[NT013 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, [NT013 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 [NT013 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 [NT013 trade name] is used in accordance with the SmPC.

Bioequivalence

[NT013 trade name] has been shown to be bioequivalent with Biltricide® 600 mg tablet (Bayer Healthcare Pharmaceuticals).

Efficacy and Safety

Regarding clinical efficacy and safety, [NT013 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 [NT013 trade name] was acceptable for the following indication: ‘schistosomiasis, taeniasis, neurocysticercosis and foodborne trematodiasis’, and would allow inclusion of [NT013 trade name], manufactured at Merck S. A. de C.V., Calle 5, No. 7, Fraccionamiento Industrial Alce Blanco, Naucalpan de Juárez, C.P. 53370, Mexico in the list of prequalified medicinal products.