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** | [NT011 name]* |
| **Manufacturer of Prequalified Product** | Hetero Labs Limited, Unit-V<br>Survey No. 439, 440, 441 & 458,<br>TSIIC-Formulation SEZ, Polepally Village,<br>Jadcherla (Mandal), Mahaboob Nagar District<br>Telangana State – 509 301,<br>India |
| **Active Pharmaceutical Ingredients (APIs)** | Praziquantel |
| **Pharmaco-therapeutic group (ATC Code)** | P02BA01 |
| **Therapeutic indication** | [NT011 trade name] is indicated for the treatment of schistosoma infections. |

### 1. Introduction

[NT011 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 Ingredients (APIs)

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 [NT011 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, microcrystalline cellulose and magnesium stearate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains hydroxypropyl methylcellulose,

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

titanium dioxide, macrogol/ PEG and sodium lauryl sulfate. 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 orange tinged, oblong, film-coated tablet with three scores on one side and two scores on the other side. The tablet is debossed with "P8" on one side and "H" on the other side. The scores are intended for subdivision of tablets when either half or quarter tablet doses are to be administered, as supported by divisibility data. The tablets are packaged in cold form PVC/Alu/OPA-Alu blisters and 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 600mg) tablets. The selection of the excipients was primarily based on the qualitative composition of the comparator product and API-excipient compatibility studies. Based on the flow properties of the API, selected excipients and literature, wet granulation manufacturing process was selected for the FPP. 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.

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 are pharmacopoeial based and include tests for description, identification (HPLC and TLC), average weight, water content (KF), dissolution (UV detection), uniformity of dosage units (by weight variation), related substances (HPLC), assay (HPLC) 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 2020 according to internationally accepted guidelines.

An open label, balanced, randomized, single oral dose, two-treatment, two-sequence, four-period, fully replicate, cross over oral bioequivalence study of Praziquantel tablets 600 mg of Hetero Labs Limited, India with BILTRICIDE® (praziquantel) tablet 600 mg of Bayer Healthcare Pharmaceuticals Inc. USA in normal healthy, adult, human subjects under fed condition (study 072-20).

The objective of the study was to compare the bioavailability of the stated Praziquantel 600 mg tablet manufactured by/for Hetero Labs Limited, 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. PQL19003.
Treatment R: Reference – 1 tablet Biltricide® 600 mg (praziquantel 600 mg) Batch no. 9420423.

A 8 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 23 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 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 64 participants; data generated from a total of 63 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 (*) | Reference (R) arithmetic mean ± SD (*) | log-transformed parameters | |
|---|---|---|---|---|
| | | | Ratio T/R (%) | Conventional 90% CI (ANOVAlog) |
| $t_{max}$ (h) | 2.40 ± 1.04 | 2.56 ± 1.15 | - | - |
| $C_{max}$ (ng/ml) | 773 ± 641 (527) | 663 ± 540 (477) | 110.4 | 96.9 – 125.7 |
| $AUC_{0-t}$ (ng.h/ml) | 1328 ± 1082 (892) | 1226 ± 969 (859) | 103.8 | 94.3 – 114.3 |
| $AUC_{0-inf}$ (ng.h/ml) | 1407 ± 1154 -- | 1300 ± 1035 -- | - | - |

*geometric mean

The results of the study show that preset acceptance limits of 80 – 125% are met by AUC and widened acceptance limits are met by $C_{max}$ 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

[NT011 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the WHO recommended comparator product. According to the submitted data on quality and bioavailability, [NT011 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the WHO recommended comparator product Biltricide® 600 mg tablet (Bayer Healthcare Pharmaceuticals) 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 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 [NT011 trade name] is used in accordance with the SmPC.

**Bioequivalence**

[NT011 trade name] has been shown to be bioequivalent to Biltricide® 600 mg tablet (Bayer Healthcare Pharmaceuticals).

**Efficacy and Safety**

Regarding clinical efficacy and safety, [NT011 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's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit-risk profile of [NT011 trade name] was acceptable for the following indication: **"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*)"** and has advised that the quality, efficacy and safety of [NT011 trade name] allow inclusion of [NT011 trade name], manufactured at Hetero Labs Limited, Unit-V, Survey No. 439, 440, 441 & 458, TSIIC-Formulation SEZ, Polepally Village, Jadcherla (Mandal), Mahaboob Nagar District, Telangana State – 509 301, India in the list of prequalified medicinal products.