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**

<table>
<thead>
<tr>
<th>Name of the Finished Pharmaceutical Product:</th>
<th>Praziquantel 600mg Tablets ¹*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer of Prequalified Product:</td>
<td>Cipla Limited C/O Meditab Specialities Goa 352, Kundaim Industrial Estate Kundaim Goa 403115 India</td>
</tr>
<tr>
<td>Active Pharmaceutical Ingredient (API):</td>
<td>Praziquantel</td>
</tr>
<tr>
<td>International Nonproprietary Name:</td>
<td>Praziquantel</td>
</tr>
<tr>
<td>Pharmaco-therapeutic group (ATC Code):</td>
<td>Anthelminthics for schistosoma infections (P02BA01)</td>
</tr>
<tr>
<td>Therapeutic indication:</td>
<td>Praziquantel 600mg Tablets is indicated for large scale preventive chemotherapy interventions for the control of schistosoma infections in adults and children in highly endemic areas.</td>
</tr>
</tbody>
</table>

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

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

Praziquantel 600mg Tablets should be initiated by a health care provider experienced in the management of schistosoma infections.

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 user requirements 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.

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, corn starch, croscarmellose sodium, povidone, sodium lauryl sulfate and magnesium stearate. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide and macrogol. None of the excipients are derived from animal origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to orange tinged, film coated, capsule shaped tablet with two scores and central breakline on both sides. The tablet is coded with “C” and “L” on one side. The breaklines are intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies. The scores are non-functional. The tablets are packaged in an HDPE bottle with HDPE screw cap, having 2 silica gel bags of 1gm and Rayon Sani coil. The product is hygroscopic, though the API is not moisture sensitive, hence the inclusion of a desiccant.

The development of the final composition of Praziquantel 600mg Tablets has been described. The formulation strategy was aimed at developing a product comparable with the comparator product, Biltricide® 600 mg. The comparator product was profiled and used to determine the quality target product profile and critical quality attributes. The selection of the excipients was based on prior knowledge with respect to their physicochemical and functional properties, the qualitative composition of the comparator product and compatibility with the API. The wet granulation process was selected for manufacture of the core tablets. Various experiments were performed to optimize the concentration of excipients and process parameters to obtain a product of desired characteristics. Satisfactory in-process controls have been established.
Specifications

The product specifications are pharmacopoeial based and include tests for description, identification of API (HPLC, TLC) and colorant, average weight, disintegration time, water content, degradation products (HPLC), assay (HPLC), dissolution (HPLC), uniformity of dosage units (by weight variation), residual solvents and microbiological examination of non-sterile products.

Stability testing

Stability studies have been performed 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 data showed that the FPP is quite stable at both storage conditions, with no negative trends observed for the parameters tested. 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 for the bulk packs (500 tablets) 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 2014 according to internationally accepted guidelines.

Study Title: A randomized, open label, balanced, two treatment, four period, two sequence, single dose, crossover, fully replicated, bioequivalence study of Praziquantel 600 mg × 2 tablets (1200 mg dose) of Cipla Ltd., India with Biltricide® (praziquantel) 600 mg × 2 tablets (1200 mg dose) of Bayer Healthcare Pharmaceuticals Inc, Germany in healthy adult human subjects, under fed conditions (study no. 054-14).

The objective of the study was to compare the bioavailability of the stated Praziquantel 600 mg tablet manufactured for/by Cipla 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, 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 Praziquantel 600 mg (praziquantel 1200 mg) 
  Batch no. KT4231.

- **Treatment R:** Reference – 2 tablets Biltricide® (praziquantel 1200 mg) 
  Batch no. 286812

A 7 day wash-out period was observed between administration in each period. 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 10 ng/ml for praziquantel.

The study was performed with 60 participants; data generated from a total of 50 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.
Arithmetic mean values of the pharmacokinetic variables for praziquantel are summarised in the following table:

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Test formulation (T) arithmetic mean ± SD</th>
<th>Reference (R) arithmetic mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>2.44 ± 1.74</td>
<td>2.55 ± 1.36</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>1363 ± 880</td>
<td>1372 ± 962</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng.h/ml)</td>
<td>2790 ± 1535</td>
<td>2982 ± 1864</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (ng.h/ml)</td>
<td>2938 ± 1607</td>
<td>3098 ± 1936</td>
</tr>
</tbody>
</table>

Geometric mean values of the pharmacokinetic variables for praziquantel and the 90% confidence intervals are summarised in the following table:

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Test formulation (T) Geometric mean</th>
<th>Reference (R) Geometric mean</th>
<th>Ratio (90% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>1069</td>
<td>1218</td>
<td>87.8 (76.4 – 101.0)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng.h/ml)</td>
<td>2350</td>
<td>2613</td>
<td>89.9 (82.7 – 97.9)</td>
</tr>
</tbody>
</table>

**Conclusion**

The results of the study show that preset acceptance limits of 80 -125 % are met for AUC values regarding praziquantel. Based upon the observed intra-subject variability for C<sub>max</sub> of the Reference in this study of 58.4% and applying the widened acceptance range of 69.8 – 143.2%, bioequivalence is also considered proven for C<sub>max</sub>. Accordingly, the test tablet Praziquantel 600 mg 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 600mg Tablets has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator product. According to the submitted data on quality and bioavailability Praziquantel 600mg Tablets is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Biltricide® for which benefits have been proven in terms of clinical efficacy.

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 600mg Tablets is used in accordance with the Summary of Product Characteristics.
Bioequivalence

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

Efficacy and Safety

Regarding clinical efficacy and safety, Praziquantel 600mg Tablets 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 600mg Tablets was acceptable for the following indication: “large scale preventive chemotherapy interventions for the control of schistosoma infection in adults and children in highly endemic areas” and has advised that the quality, efficacy and safety of Praziquantel 600mg Tablets allow inclusion of Praziquantel 600mg Tablets, manufactured for/by Cipla Limited C/O Meditab Specialities Goa, 352, Kundaim Industrial Estate, Kundaim Goa, 403115, India in the list of prequalified medicinal products.