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	[HA353 trade name]*
Manufacturer of Prequalified Product	Cipla Ltd 289 JBB Marg Mumbai Central Mumbai 400 008 India Phone: +91 22 23082891, 23095521 Fax: +91 22 23070013, 23070393, 23070385 Email: ciplaexp@cipla.com
Active Pharmaceutical Ingredient(s) (API)	Lamivudine
Pharmaco-therapeutic group (ATC Code)	Nucleoside and nucleotide reverse transcriptase inhibitors, ATC Code J05AF05
Therapeutic indication	[HA353 trade name] is indicated for the treatment of HIV-1 infection in adults, adolescents and children (weighing over 14 kg), in combination with other antiretroviral agents.

1. Introduction

[HA353 trade name] is indicated for the treatment of HIV-1 infection in adults, adolescents and children (weighing over 14 kg), in combination with other antiretroviral agents. [HA353 trade name] is not indicated for use in patients with clinically significant hypersensitivity to lamivudine or to any of the components contained in the formulation. It is recommended that therapy is given only by a physician experienced in the management of HIV infection.

2. Assessment of quality

The assessment was done according to SOP 20 of the WHO Prequalification programme.

Active pharmaceutical Ingredient (API)

Lamivudine is a class 1 API according to Biopharmaceutics Classification System (WHO Technical Report Series 937, Annex 8: Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms). It is thus highly soluble in aqueous medium over the pH range 1–6.8.

Lamivudine API is described in the Ph.Int., Ph.Eur. and the USP, and is considered well-established in the Prequalification Programme.

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

The API is adequately controlled by its set of quality specifications which is pharmacopoeial based, with additional in-house specifications including polymorphic identity (Form II), tapped density, particle size and residual solvents.

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 packing material

Other ingredients

Other ingredients used in the core tablet formulation include corn starch, magnesium stearate, microcrystalline cellulose and sodium starch glycollate. The film coating contains hydroxypropyl methylcellulose 2910, propylene glycol 6000 (macrogol) and titanium oxide. Assurance by means of a certificate was provided that magnesium stearate is BSE/TSE free.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

[HA353 trade name] are white capsule-shaped, biconvex film-coated tablets with "LVR" debossed on one side and central break-line on the other side. The break-line is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies. The tablets are packaged in a cylindrical, white opaque HDPE bottle with continuous thread with a polyethylene screw cap (pack size: 30 or 60 tablets).

The development of the final composition of [HA353 trade name] has been described. The objective was to develop a stable product, essentially similar in composition and bioequivalent to the comparator product, Epivir® 150 mg film-coated tablets. The wet granulation method was selected for manufacture of the core tablets. The multisource product showed dissolution profiles similar to that of the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data presented for three production scale batches demonstrated the consistency of the process.

Cipla's [HA353 trade name] is proportionally similar in composition to its Lamivudine 300 mg Tablets, which was shown to be bioequivalent to Epivir® 300 mg film-coated tablets. Comparative dissolution studies were conducted between Cipla's 300 mg tablets and 150 mg tablets in the three BCS media according to the requirements of WHO's Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability (WHO Technical Report Series 937, Annex 7). Based on the similarity of the dissolution profiles, a biowaiver was allowed for [HA353 trade name]. Both strengths showed very rapidly dissolving dissolution properties.

Specifications

The finished product specifications are regarded adequate for ensuring consistent quality of this FPP and include tests for description, identification of the API (HPLC and UV), average weight, uniformity of weight, hardness, disintegration time, dissolution, related substances (HPLC) and assay (HPLC). Batch analysis data confirm consistency and uniformity of manufacture and indicate that the process is under control.

Stability testing

Stability studies have been conducted on three primary batches at 30ºC/65%RH as long-term storage conditions and for six months at accelerated conditions. The product proved to be quite stable at both these storage conditions. Based on the available stability data, the proposed shelf-life and storage conditions as stated in the SPC are acceptable.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

Cipla's product [HA353 trade name] is proportionally similar in composition to its Lamivudine 300 mg Tablets, which was shown to be bioequivalent to Epivir® 300 mg film-coated tablets. Comparative dissolution studies were conducted between Cipla's Lamivudine 300 mg tablets and [HA353 trade name] in the three BCS media according to the requirements of WHO's Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability (WHO Technical Report Series 937, Annex 7). Based on the similarity of the dissolution profiles, a biowaiver was allowed for [HA353 trade name]. Both strengths showed very rapidly dissolving dissolution properties.

4. Summary of product safety and efficacy

[HA353 trade name] has been shown to conform to the same appropriate standards of quality, efficacy and safety as those required of the innovator product. According to the submitted data on quality and bioavailability it is pharmaceutically and therapeutically equivalent and thus interchangeable with the individual reference Epivir® 150 mg tablets, for which benefits have been proven in terms of virological and immunological efficacy.

The clinical safety of this product is considered to be acceptable when guidance and restrictions presented in the Summary of Product Characteristics are taken into consideration. Reference is made to the SmPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Bioequivalence

[HA353 trade name] has shown to be bioequivalent to the reference formulation, Epivir® tablets (GlaxoSmithKline).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA353 trade name] is considered effective and safe to use when the guidance and restrictions presented 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 [HA353 trade name] was acceptable for the following indication: treatment of HIV-1 infection in adults, adolescents and children (weighing over 14 kg), in combination with other antiretroviral agents, and would allow inclusion of [HA353 trade name], manufactured at Cipla Ltd, Unit III, IV, VII, Verna Industrial Estate, Verna Salcete, 403 722 Goa, India and Meditab Specialities Pvt. Ltd., 352 Kundaim Industrial Estate, Kundaim 403 115, Goa, India in the list of prequalified medicinal products in the list of prequalified medicinal products.