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	[HA710 trade name][*]
Manufacturer of Prequalified Product	Laurus Labs Limited (Unit -II) Plot No. 19, 20 & 21 Western Sector, APSEZ Gurajapalem Village, Rambillli Mandal, Anakapalli, Andhra Pradesh 531011 India
Active Pharmaceutical Ingredient (API)	Darunavir
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use, protease inhibitor (J05AE10)
Therapeutic indication	[HA710 trade name] co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicines for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescent patients weighing at least 40kg

1. Introduction

[HA710 trade name] co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicines for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescent patients weighing at least 40kg.

[HA710 trade name] should be initiated by a health care provider experienced in the management of HIV

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)

Darunavir has been prequalified by WHO according to WHO's *Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products* (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that darunavir, used in the manufacture of [HA710 trade name], is of good quality and manufactured in accordance with WHO good manufacturing practices. 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 assessment of the sites of API manufacture to verify compliance with WHO GMP requirements.

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

Other ingredients

Other ingredients used in the core tablet formulation include microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium and magnesium stearate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol partially hydrolysed, macrogol/PEG, titanium dioxide, talc, FD&C blue #1/Brilliant blue FCF aluminium lake and FD&C yellow #5/Tartrazine aluminium lake. BSE/TSE compliance declarations were provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a green coloured, oval shaped film coated tablet, debossed with 'DA600' on one side and plain on the other side. The tablets are packaged in a white opaque HDPE bottle with a silica gel canister and closed with a polypropylene child resistant closure with induction sealing wad.

Three tablet strengths proportionally similar in composition with regards to the core tablets were developed; 400mg, 600mg and 800mg.The development focused on the highest strength which was used in the bioequivalence study against the comparator product, Prezista® tablets of the same strength. Once the formula for the 800mg strength was finalized, the 600mg and 400mg strengths were planned using dose-proportionality approach.

The development of the final composition of the multisource product has been described. The objective was to formulate an immediate release tablet, bioequivalent to the WHO recommended comparator product, Prezista ® 800 mg Tablets. The comparator product was characterized and on that basis a quality target product profile was defined and critical quality attributes (CQAs) were identified. The manufacturing process selected for the multisource product was designed to have darunavir granulated by high shear granulation and compressed into tablets followed by film coating. The excipients were chosen and finalized based on the excipients used in the comparator product and API-excipient compatibility data. Various experiments were performed to select and optimize the concentration of excipients and other process parameters to obtain coated tablets of desired characteristics. Satisfactory in-process controls have been established.

Specifications

The finished product specifications include tests for description, identification of API (HPLC, UV) and colorants, water content (KF), uniformity of dosage units (by weight variation), dissolution (HPLC detection), related substances (HPLC), assay (HPLC), detection of amorphous nature of API (p-XRD) 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 condition and for six months at 40°C/75%RH as accelerated conditions in the packaging intended for marketing of the product. The data provided shows that the product is stable at these storage conditions. The data support the proposed shelf life at the storage conditions as stated in the SmPC.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2017/2018 according to internationally accepted guidelines:

An open label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover oral bioequivalence study of Darunavir 800mg tablets of Laurus Labs Limited, India and Prezista

(darunavir) 800 mg film-coated Tablets of Janssen-Cilag International NV, Turnhoutseweg 30, B-2340 Beerse, Belgium in healthy, adult, human subjects under fed condition (study no. 16-VIN-0521).

The objective of the study was to compare the bioavailability of the stated Darunavir 800 mg tablet manufactured by/for Laurus Labs Limited, India (test drug) with the reference formulation Prezista® (Janssen-Cilag) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fed conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T: Test – 1 tablet Darunavir 800 mg
(darunavir 800 mg)
Batch no. ADRT100317A

Treatment R: Reference – 1 tablet Prezista®
(darunavir 800 mg)
Batch no. GFZ1H00.

Ritonavir (100 mg twice daily) was administered two days prior and three days after the study products dosing in both periods. A 14-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 24 samples within 72h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for darunavir were analyzed using a validated UPLC-ESI-MS/MS method. The limit of quantification was stated to be about 50 ng/mL for darunavir.

The study was performed with 48 participants; data generated from a total of 40 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for darunavir as well as statistical results are summarised in the following table:

Darunavir

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)	3.96 ± 0.98	3.62 ± 1.13	-	-
C_{max} (µg /mL)	8.50 ± 1.65 (8.33)	8.92 ± 1.62 (8.74)	95.3	90.1 – 100.8
AUC_{0-t} (µg ·h/mL)	119 ± 46 (110)	120 ± 40 (111)	99.0	91.4 – 107.2
AUC_{0-inf} (µg ·h/mL)	123 ± 47 --	123 ± 41 --	-	-

4. Summary of product safety and efficacy

[HA711 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, [HA711 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Prezista® (Janssen-Cilag) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA711 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.

A biowaiver was granted for the additional 400 and 600 mg tablet strengths (Laurus Labs Limited, India) in accordance to the WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the Darunavir 400 and 600 mg tablets were determined to be qualitatively essentially the same, the ratio of active ingredient and excipients between the strengths was considered essentially the same and the dissolution profiles between the formulations for the API were determined the same.

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 [HA710 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA710 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

Efficacy and Safety

Regarding clinical efficacy and safety, [HA710 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 [HA710 trade name] was acceptable for the following indication: ' indicated in combination with other antiretroviral medicines for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescent patients weighing at least 40 kg', and would allow inclusion of [HA710 trade name], manufactured at Laurus Labs Limited (Unit -II), Plot No. 19, 20 & 21, Western Sector, APSEZ, Gurajapalem Village, Rambillli Mandal, Anakapalli,, Andhra Pradesh 531011,India in the list of prequalified medicinal products.