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	[HA685 trade name][*]
Manufacturer of Prequalified Product	Mylan Laboratories Limited (FDF Unit – 2) Plot No. H-12 and H-13 MIDC, Waluj Industrial Area Aurangabad – 431136 Maharashtra India
Active Pharmaceutical Ingredient(s) (API)	Darunavir
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use, protease inhibitor (J05AE10)
Therapeutic indication	[HA685 trade name] co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescent patients weighing at least 40 kg

1. Introduction

[HA685 trade name] co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescent patients weighing at least 40 kg. [See Part 4 Summary of Products Characteristics (SmPC), for full indications].

[HA685 trade name] should be initiated by a health care provider experienced in the management of HIV infection.

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 ethanolate 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 ethanolate, used in the manufacture of [HA685 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

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

(APIMF) to verify compliance with WHO norms and standards, and assessment of the sites of API manufacture to verify compliance with WHO GMP requirements.

Other ingredients

Other ingredients used in the core tablet formulation include hypromellose, silicified microcrystalline cellulose, crospovidone, colloidal silicon dioxide and magnesium stearate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol part hydrolysed, titanium dioxide, macrogol/PEG and talc. Magnesium stearate is from plant origin. BSE/TSE compliance declarations were provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off-white, film coated, oval shaped, biconvex tablet, debossed with 'M' on one side and 'DE6' on the other side. The tablets are packaged in a round blue opaque HDPE bottle with a desiccant and closed with a blue opaque polypropylene cap.

Two tablet strengths proportionally similar in composition were developed; 600 mg and 800 mg. The development focused on the higher strength which was used in the bioequivalence study.

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 composition of the final formulation is qualitatively similar to that of the comparator product. Considering the poor flow property and poor solubility of darunavir ethanolate, wet granulation process was selected as the manufacturing process to improve the blend flow. The dried granules are compressed into tablets followed by film coating. 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), dissolution (UV detection), uniformity of dosage units (by mass variation), related substances (HPLC), assay (HPLC), water content (KF), ethanol content (GC) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage condition and for six months at 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 2016 according to internationally accepted guidelines.

An open-label, balanced, randomized, two-treatment, two-sequence, two-period, cross-over, single dose, oral bioequivalence study of Darunavir (as ethanolate) tablets 800 mg (Test) of Mylan Laboratories Limited, India and Prezista® (darunavir) tablets 800 mg (Reference) of Janssen Therapeutics, Division of Janssen Products, LP, Titusville NJ 08560 with co-administration of Norvir® (ritonavir) tablets

100 mg of AbbVie Inc., North Chicago, IL 60064 USA in healthy, adult, human subjects under fed conditions(study no. 017-16).

The objective of the study was to compare the bioavailability of the stated Darunavir 800 mg tablet manufactured by/for Mylan Laboratories Limited, India (test drug) with the reference formulation Prezista® (Janssen Therapeutics) 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. 2011145.
Treatment R: Reference – 1 tablet Prezista® (darunavir 800 mg) Batch no. 15LG822.

Ritonavir (100 mg) was administered two days prior and two days after the study products dosing in both periods. A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 23 samples within 72 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 darunavir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 150 ng/mL for darunavir.

The study was performed with 48 participants; data generated from a total of 45 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) #	4.00 (1.67 – 5.00)	4.00 (1.33 – 5.00)	–	–
C_{max} (µg/mL)	9.93 ± 1.50 (9.83)	9.12 ± 1.74 (8.94)	110.0	105.7 – 114.4
AUC_{0-t} (µg·h/mL)	132 ± 47 (125)	120 ± 38 (113)	110.3	104.7 – 116.1
AUC_{0-inf} (µg·h/mL)	140 ± 52 (132)	127 ± 40 (120)	110.2	104.6 – 116.1

median (range)

The results of the study show that preset acceptance limits of 80 – 125 % are met by both AUC and Cmaxvalues regarding darunavir. Accordingly, the test Darunavir 800 mg tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Prezista® (Janssen Therapeutics).

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

4. Summary of product safety and efficacy

[HA685 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. [HA685 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

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 [HA685 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA685 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, [HA685 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 [HA685 trade name] was acceptable for the following indication: 'co-administered with low dose ritonavir, in combination with other antiretroviral medicinal products 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 [HA685 trade name], manufactured at Mylan Laboratories Limited (FDF Unit – 2),Plot No. H-12 and H-13,MIDC, Waluj Industrial Area, Aurangabad – 431136, Maharashtra, India in the list of prequalified medicinal products.