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	[HA627 trade name][1]
Manufacturer of Prequalified Product	Cipla Limited Unit II, A-42, MIDC, Patalganga, Dist: Raigad 410220, Maharashtra India
Active Pharmaceutical Ingredient (API)	Darunavir
International Nonproprietary Name	Darunavir
Pharmaco-therapeutic group(ATC Code)	Antivirals for systemic use, protease inhibitor (J05AR 14)
Therapeutic indication	[HA627 trade name], co-administered with low dose ritonavir, is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV) infection in adult and adolescent patients weighing at least 40 kg.

1. Introduction

[HA627 trade name] co-administered with low dose ritonavir, is indicated in combination with other antiretroviral medicinal products for the treatment of huma immunodeficiency virus (HIV) infection in adult and adolescent patients weighing at least 40 kg [see Part 4- Summary of Product Characteristics (SmPC), for full indications].

[HA627 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 contains 5 stereogenic carbon centres. The pharmaceutical form is [(1S,2R)-3-[[(4- aminophenyl) sulfonyl] (2-methylpropyl) amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b] furan-3-yl ester monoethanolate. Darunavir ethanolate is slightly hygroscopic.

The manufacture of the API entails several steps, is well described and renders one single isomer. The structure and absolute configuration has been confirmed with single crystal X-ray crystallography.

The API specifications include tests for description, solubility, identification (IR, HPLC), polymorphic form (IR), water content (KF), specific optical rotation, residue on ignition, heavy metals, ethanol content (GC), related substances (HPLC), assay (HPLC), particle size distribution (PSD; laser diffraction) and residual solvents (GC). The PSD limits are based on the results obtained for the API batch used in the manufacture of

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

the FPP biobatch. The related substances limits are in accordance with ICH Q3A.

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 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, talc and FD&C yellow #6/Sunset yellow FCF Aluminium Lake. None of the excipients are derived from animal origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a light orange coloured, oval shaped, biconvex, film coated tablet, debossed with 'DNV' on one side & '400' on the other side. Each tablet contains 433.648 mg darunavir ethanolate equivalent to 400 mg darunavir**.** The tablets are packaged in an HDPE bottle fitted with an HDPE non child resistant closure, and foil induction seal.

Two tablet strengths, proportionally similar in composition, were developed: 600 mg and 400 mg. The development focused on the higher strength.
The development of the final composition of the multisource product has been described. The objective was to develop a stable tablet, bioequivalent to the WHO recommended comparator product,Prezista ® tablet 600 mg, which is an immediate release solid dosage form for oral administration. Thecomparator product was characterized and on that basis a quality target product profile was defined and critical quality attributes (CQAs) identified. The composition of the final formulation is qualitatively similar to that of the comparator product. The API, darunavir ethanolate, is practically insoluble in aqueous medium over the physiological pH range and in water and therefore particle size distribution (PSD) was identified as one of the CQAs. Various trial batches with different PSD of the API were produced to determine the optimal PSD.
The dry granulation process, using roller compaction, was selected to manufacture the core tablet granules. The composition and process parameters were optimised, applying quality by design principles, to obtain 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), polymorphic form (IR) and colorants, average weight, water content (KF), uniformity of weight, uniformity of dosage units (by weight variation), disintegration time, dissolution (HPLC detection), related substances (HPLC), assay (HPLC), residual solvents, ethanol content (GC) and microbiological examination of non-sterile products. 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 with little degradation. Photo stability results revealed that the product is photo stable. 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 2014 according to internationally accepted guidelines.

Study title: Bioequivalence study comparing Darunavir (as ethanolate) 600 mg Tablets (containing darunavir ethanolate equivalent to darunavir 600 mg) of Cipla Ltd., India, with Prezista® 600 mg tablet (containing darunavir ethanolate equivalent to darunavir 600 mg) manufactured for Janssen Therapeutics, USA in normal, healthy, adult, male and female human subjects under fed conditions, co-administered with

Norvir® tablet (containing ritonavir 100 mg) of Abbott, Laboratories, USA twice daily (study no. ARL/13/213).

The objective of the study was to compare the bioavailability of the stated Darunavir (as ethanolate) 600 mg Tablets manufactured for/by Cipla 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 treatments in a randomized fashion:

Treatment T: Test – 1 tablet Darunavir 600 mg (darunavir 600 mg) Batch no. KW2703

Treatment R: Reference – 1 tablet Prezista® (darunavir 600 mg) Batch no. 13HG221

Norvir (100 mg ritonavir) was co-administered twice daily. A 16-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 24 samples within 60 hours 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 100 ng/mL for darunavir.

The study was performed with 36 participants; data generated from a total of 33 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 (*)	**Reference (R)** arithmetic mean ± SD (*)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
tmax (h)	3.92 ± 1.02	3.97 ± 1.20	-	-
Cmax (µg/mL)	8667 ± 2182 (8389)	8229 ± 2020 (7969)	105.3	99.4 – 111.5
AUC0-t (µg.h/mL)	101867 ± 40859 (93753)	101528 ± 34230 (95972)	97.7	90.1 – 105.9
AUC0-inf (µg.h/mL)	106445 ± 42430 (98116)	106585 ± 37834 (100473)	97.7	90.0 – 106.0

* geometric mean

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding darunavir. Accordingly, the test [HA627 trade name] 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 400 mg tablet strength (Cipla Ltd., India) in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the [HA627 trade name] was determined to be qualitatively essentially the same, the ratio of active ingredient and excipients between the strengths is considered essential the same and the dissolution profiles between the formulations for the API was determined the same.

4. Summary of Product Safety and Efficacy

[HA627 trade name] has been shown to conform to the same relevant standards ofquality, efficacy and safety as those required of the innovator product. According to the submitted data on quality and bioavailability [HA627 trade name] is a direct scale- down of [HA627 trade name]. The latter is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Prezista® 600 mg tablet 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 [HA627 trade name] is used in accordance with the Summary of Product Characteristics.

Bioequivalence

[HA627 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, [HA627 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 WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [HA627 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 (HIV) infection in adult and adolescent patients weighing at least 40 kg"** and would allow inclusion of [HA627 trade name] manufactured at Cipla Ltd, Unit II, A-42, MIDC, Patalganga, Dist: Raigad, 410220, Maharashtra, India in the list of prequalified medicinal products.