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	[HA719 trade name]*
Manufacturer of Prequalified Product	Hetero Labs Limited, Unit III Plot No. 22-110, IDA, Jeedimetla, Hyderabad Ranga Reddy District Telangana, 500 055 India. Phone: 91-40-23096171/72/73/74 Fax: 91-40-23095105, 23097756, 23140376
Active Pharmaceutical Ingredient(s) (API)	Darunavir (as ethanolate), ritonavir
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use, protease inhibitors (darunavir: J05AR14, ritonavir: J05AE03)
Therapeutic indication	[HA719 trade name] is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents weighing at least 40 kg.

1. Introduction

[HA719 trade name] is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents weighing at least 40 kg. [See Part 4 Summary of Products Characteristics (SmPC), for full indications].

[HA719 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

Darunavir ethanolate 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.

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

The manufacture of the API entails several steps, is well described and renders a pure enantiomer. The structure and absolute configuration have been confirmed with single crystal X-ray crystallography. The manufacturer consistently produces crystalline polymorphic form A, which is routinely controlled by XRD in the specifications of the API.

The API specifications include tests for description, solubility, identification (IR, HPLC and XRPD), water content (KF), residue on ignition, related substances (HPLC), ethanol content (GC), assay (HPLC), residual solvents (GC), several characterised genotoxic impurities (GC or LC-MS, limits in line with ICH M9), specific optical rotation and particle size distribution (PSD). The PSD limits are based on the results obtained for the API batch used in the manufacture of 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.

Ritonavir

Ritonavir is described in the Ph.Int, Ph.Eur and USP. The API has four chiral centres, is practically insoluble in water and is known to exhibit polymorphism, with various crystal forms. The manufacture of ritonavir entails several steps and stereo selectively produces the desired stereoisomer. Polymorphic form I, characterised by the XRPD pattern, is consistently produced.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification (IR, HPLC), polymorphic form (XRPD), water content (KF), residue on ignition, related substances (HPLC), assay (HPLC), specific optical rotation, residual solvents (GC), microbial limits and genotoxic impurities (UFLC-MS; ≤ 1.25ppm and GC-MS; ≤ 1.25ppm).

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 silicified microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate, copovidone, sorbitan monolaurate, dibasic calcium phosphate anhydrous and sodium stearyl fumarate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, macrogol/PEG, hydroxypropyl cellulose, iron oxide yellow, talc, colloidal anhydrous silica and polysorbate. BSE/TSE compliance declarations were provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a yellow, capsule shaped, bevel edged, biconvex film coated tablets debossed with 'H' on one side and 'D8' on the other side. The tablets are packaged in either a white opaque, heavy weight HDPE container with a desiccant canister and closed with a polypropylene child resistant cap with pulp liner or a white opaque, heavy weight HDPE container with a desiccant canister and purified cotton and closed with a polypropylene child resistant closure with pulp liner.

The development of the final composition of the multisource product has been described. The objective was to develop a fixed dose bilayer formulation of darunavir (as ethanolate) / ritonavir 400mg /50mg tablets bioequivalent to the individual WHO recommended comparator products, Prezista ® (darunavir) 800 mg tablets and Novir (ritonavir) 100mg tablets. The comparator products were characterized and on that basis a quality target product profile was defined and critical quality attributes were identified. Based on literature search and comparator product characterization, direct compression was selected for the manufacture of darunavir layer and hot melt extrusion process was used for the ritonavir layer; both blends were then compressed into bi-layer tablets followed by film coating. The excipients were chosen and finalized based on the excipients used in the comparator products 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.

According to a risk evaluation by the applicant, the FPP has no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications include tests for description, identification of APIs (TLC and HPLC), average weight, water content (KF), dissolution (HPLC detection), uniformity of dosage units (content uniformity), related substances (HPLC), assay (HPLC), ethanol content (GC), detection of ritonavir crystalline polymorphic forms I and II (XRD) 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 2018 according to internationally accepted guidelines:

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover bioequivalence study of fixed dose combination of Darunavir and Ritonavir tablet 400/50 mg (2 tablets) of Hetero Labs Limited, India comparing with Prezista® (darunavir) tablet 800 mg of Janssen Ortho LLC, Gurabo, PR 00778 and Norvir® (ritonavir) tablet 100 mg of Abbvie Inc. North Chicago, IL 60064 USA, in normal, healthy, adult, human subjects under fed condition (study no. 0906-17).

The objective of the study was to compare the bioavailability of the stated Darunavir/Ritonavir 400mg/50mg tablet manufactured by/for Hetero Lab. Limited, India (test drug) with the reference formulations Prezista® (Janssen Ortho LLC.) and Norvir® (Abbvie Inc.) 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 – 2 tablets Darunavir/Ritonavir 400mg/50mg
	(darunavir 800 mg + ritonavir 100 mg)
	Batch no. E161210.
Treatment R:	Reference
	– 1 tablet Prezista®
	(darunavir 800 mg)
	Batch no. 16GG597.
	– 1 tablet Norvir®
	(ritonavir 100 mg)
	Batch no. 1059108.

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 26 samples within 72h post dose) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax for bioequivalence evaluation. Drug concentrations for darunavir and ritonavir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 40 ng/ml for darunavir and 2.5 ng/ml for ritonavir.

The study was performed with 54 participants; data generated from a total of 53 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

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)	4.33 (1.67 – 4.67)	4.33 (2.00 – 4.68)	–	–
C_{max} (ng/mL)	8872 ± 2250 (8619)	7967 ± 2060 (7698)	112.0	107.7 – 116.4
AUC_{0-t} (ng·h/mL)	92947 ± 33693 (87734)	85279 ± 32767 (79834)	109.9	105.2 – 114.8
AUC_{0-inf} (ng·h/mL)	94972 ± 34187 (89683)	87029 ± 32684 (81757)	109.7	105.2 – 114.4

Ritonavir

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)	4.35 (1.33 – 6.00)	4.33 (2.33 – 6.00)	–	–
C_{max} (ng/mL)	681 ± 225 (646)	656 ± 265 (602)	107.4	100.7 – 114.6
AUC_{0-t} (ng·h/mL)	5459 ± 2362 (5036)	5345 ± 2341 (4871)	103.4	98.8 – 108.2
AUC_{0-inf} (ng·h/mL)	5523 ± 2387 (5096)	5406 ± 2367 (4929)	103.4	98.8 – 108.2

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding darunavir and ritonavir. Accordingly, the test Darunavir (as ethanolate) /Ritonavir 400mg/50mg tablets meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulations Prezista® (Janssen Ortho LLC) and Norvir® (AbbVie Inc.).

4. Summary of product safety and efficacy

[HA719 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, [HA719 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator products Prezista® (Janssen Ortho LLC) and Norvir® (AbbVie Inc.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA719 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.

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 [HA719 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA719 trade name] has been shown to be bioequivalent with Prezista® (Darunavir 800 mg) and Norvir® (Ritonavir 100 mg).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA719 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 [HA719 trade name] was acceptable for the following indication: ' treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents weighing at least 40 kg', and would allow inclusion of [HA719 trade name], manufactured at Hetero labs Limited, Unit – III, # 22 – 110, IDA, Jeedimetla, Hyderabad, Pin code – 500 055, Telangana, India in the list of prequalified medicinal products.