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	[HA757 trade name]*
Manufacturer of Prequalified Product	Hetero Labs Limited Unit - III (Formulations), Plot no 22 - 110, I.D.A Jeedimetla, Hyderabad, Telangana, India Phone: 91-40-23096171/72/73/74
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	[HA757 trade name] is indicated for the treatment of human immunodeficiency virus infection in paediatric patients, adults and adolescents.

1. Introduction

[HA757 trade name] is indicated for the treatment of human immunodeficiency virus infection in paediatric, adults and adolescents patients. [See Part 4 Summary of Products Characteristics (SmPC), for full indications]. [HA757 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

Darunavir ethanolate is an off-white to cream hygroscopic powder. It has poor solubility across the physiological pH range and therefore considered critically insoluble according to the WHO PQT/MED's classification.

The APIMF of darunavir ethanolate has been accepted through WHO's APIMF procedure. Details pertaining to manufacturing process development of darunavir ethanolate API has been provided in

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

the restricted part of the API master file. The manufacturer consistently produces crystalline polymorphic form A, which is routinely controlled by p-XRD in the specifications of the API.

The API specifications include tests for description, solubility, identification (IR, HPLC and p-XRD), water content (KF), residue on ignition, related substances (HPLC), enantiomeric purity (HPLC), ethanol content (GC), assay (HPLC), residual solvents (GC), several characterised genotoxic impurities (GC or LC-MS, limits in line with ICH M9) 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. Crystalline polymorphic form II, characterised by the p-XRD pattern, is consistently produced.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification (IR, HPLC), polymorphic form (p-XRD), heavy metals, water content (KF), residue on ignition, related substances (HPLC), assay (HPLC), specific optical rotation, residual solvents (GC), microbial limits and genotoxic impurity (by UFLC-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 packing material.

Other ingredients

Other ingredients used in the core tablet formulation include crospovidone, hypromellose, silicified microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, copovidone, sorbitan monolaurate, dibasic calcium phosphate, microcrystalline cellulose, corn starch, mannitol and sodium stearyl fumarate, all being controlled by acceptable specifications. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, macrogol/polyethylene glycol, hydroxypropyl cellulose, iron oxide yellow, talc, colloidal anhydrous silica and polysorbate. None of the excipients are derived from human or animal origin. TSE/BSE free certificates have been provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a yellow, capsule-shaped, film-coated tablet. It is biconvex (rounded on top and bottom) with a bevelled edge. The tablet has 'H' debossed (stamped into) one side and 'D46' on the other side. The tablets are packaged in a round, opaque white plastic (HDPE) bottle. The bottle also contains a canister of desiccant (drying material) and a piece of purified cotton to keep the tablets in place. The bottle has an aluminium/ plastic foil seal and a white, childproof plastic (polypropylene) screw cap.

Two strengths of darunavir (as ethanolate)/ ritonavir film-coated tablets proportionally similar in composition were developed: 800mg/100mg and 400mg/50mg. The higher strength was used in the BE study against the individual WHO recommended comparator products, Prezista® (darunavir)

tablets 800 mg of Janssen Therapeutics, NJ 08560 and Norvir® (ritonavir) tablets 100 mg of AbbVie Inc., USA.

The development of the final composition of the multisource product has been described. The objective was to develop a stable, robust, immediate release tablet, bioequivalent to the individual WHO recommended comparator products. The comparator products were characterized and on that basis a quality target product profile was defined and critical quality attributes were identified. The selection of excipients was based on the excipients used in the comparator products, previous formulation experience and API-excipient compatibility data. The method of manufacture was to prepare a darunavir ethanolate blend separately by wet granulation process and a ritonavir layer blend by hot melt extrusion process. Both blends were then compressed into bi-layer tablets. Based on the satisfactory data of optimization trials, the formulation was finalized resulting in a product matching the quality target product profile. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

A risk assessment has been performed and a risk for nitrosamine impurities has been identified within the FPP manufacture. Confirmatory testing has been performed and N-nitroso-ritonavir impurity was identified. A test for this impurity has been included in the FPP specifications.

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), polymorphic form of APIs (p-XRD), ethanol content (GC), content of N-nitroso ritonavir (LC-MS/MS; ≤ 0.88ppm). 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 40°C/75%RH as accelerated storage conditions in the packaging intended for marketing of the product. The data provided indicate that, though there was a slight increase in the content of water, the product was stable at both storage conditions. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable. The in-use storage period as indicated in the product information for the 180-tablet bottle pack is supported by stability data.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2019 according to internationally accepted guidelines.

An open-label, balanced, randomized, two treatment, two sequence, two period, two way cross-over, single oral dose bioequivalence study of Darunavir and Ritonavir tablets 800 mg/100 mg of Hetero Labs Limited, India with Prezista® (darunavir) tablets 800 mg of Janssen Therapeutics, NJ 08560 and Norvir® (ritonavir) tablets 100 mg of AbbVie Inc., USA, in normal, healthy, adult, human subjects under fed conditions (study no. BE/19/100).

The objective of the study was to compare the bioavailability of the stated Darunavir/Ritonavir 800/100 mg FDC tablet manufactured by/for Hetero Labs Limited, India (test drug) with the same dose of the reference formulations Prezista® (Janssen Therapeutics) 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 treatments in a randomized fashion:

Treatment T: Test – 1 tablet Darunavir/Ritonavir 800/100 mg

(darunavir 800 mg + ritonavir 100 mg)
Batch no. E182176A.

Treatment R: Reference

- 1 tablet Prezista®
(darunavir 800 mg)
Batch no. 17NG996
- 1 tablet Norvir®
(ritonavir 100 mg)
Batch no. 1089793

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 28 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 and ritonavir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 126 ng/ml for darunavir and to be about 20 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 of darunavir and ritonavir.

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 (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	4.15 ± 0.62	4.20 ± 0.65	-	-
C_{max} (ng/ml)	8404 ± 2339 (8085)	8159 ± 2135 (7887)	102.5	97.3 – 108.0
AUC_{0-t} (ng.h/ml)	92793 ± 32338 (86819)	93753 ± 32018 (88271)	98.4	91.8 – 105.4
AUC_{0-inf} (ng.h/ml)	97451 ± 31759 --	99410 ± 34326 --	-	-

* geometric mean

Ritonavir

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	4.44 ± 0.52	4.46 ± 0.30	-	-
C_{max} (ng/ml)	822 ± 359 (737)	822 ± 375 (742)	99.4	90.7 – 108.9
AUC_{0-t} (ng.h/ml)	5592 ± 2361 (5049)	5805 ± 2347 (5314)	95.0	88.3 – 102.2
AUC_{0-inf} (ng.h/ml)	5953 ± 2389 --	6185 ± 2387 --	-	-

* 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 and ritonavir. Accordingly, the test FDC tablet Darunavir/Ritonavir 800/100 mg meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the references Prezista® (Janssen Therapeutics) and Norvir® (Abbvie Inc.).

A biowaiver was granted for the additional strength FDC tablet Darunavir/Ritonavir 400/50 mg (Hetero Labs Limited, India) in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the Darunavir/Ritonavir 400/50 mg FDC tablet were determined to be qualitative essential 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 APIs were determined the same.

Summary of product safety and efficacy

[HA757 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. A biowaiver was granted for the additional strength [HA757 trade name] in accordance to WHO guideline. Therefore the clinical safety of [HA757 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.

4. 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 [HA757 trade name] is used in accordance with the SmPC.

Bioequivalence

The test FDC tablet Darunavir/Ritonavir 800/100 mg has been shown to be bioequivalent with references Prezista® (Janssen Therapeutics) and Norvir® (Abbvie Inc.) and a biowaiver granted for [HA757 trade name]. In comparison with the strength of the test product used in the bioequivalence study, the [HA757 trade name] tablet were determined to be qualitatively essential the same with comparable dissolution profiles.

Efficacy and Safety

Regarding clinical efficacy and safety, [HA757 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 [HA757 trade name] was acceptable for the for the treatment of HIV/AIDS, and would allow inclusion of [HA757 trade name], manufactured at at Hetero Labs Limited Unit - III (Formulations Hyderabad, Telangana, India, Pin Code - 500 055 in the list of prequalified medicinal products.