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	[HA725 trade name]*
Manufacturer of Prequalified Product	MSN Laboratories Private Limited Formulations Division, Unit-II Survey Nos. 1277, 1319 to 1324 Nandigama (Village & Mandal) Rangareddy District Telangana – 509228 India
Active Pharmaceutical Ingredient(s) (API)	Darunavir
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use, protease inhibitors (J05AE10)
Therapeutic indication	[HA725 trade name] is indicated in combination with other antiretroviral medicines for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents weighing at least 35 kg.

1. Introduction

[HA725 trade name] is indicated in the treatment of HIV, as detailed in the summary of product characteristics.

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. Darunavir is produced in the amorphous form and it is slightly hygroscopic.

The manufacture of the API entails several steps and is well described. The structure and absolute configuration have been confirmed by FT-IR, 1H-NMR, 13C-NMR, mass spectral data, TGA analysis and single crystal x-ray crystallography respectively. The manufacturer consistently produces the amorphous (non -crystalline) form, which is routinely controlled by PXRD in the specifications of the API.

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

The API specifications include tests for description, solubility, identification (IR and HPLC), water determination (by KF), residue on ignition, related substances (HPLC), assay (HPLC), residual solvents (GC), polymorphic identification (PXRD), microbial limits 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.

Other ingredients

Other ingredients used in the core tablet formulation include silicified microcrystalline cellulose, crospovidone, hydroxypropyl cellulose, sodium chloride, silica colloidal anhydrous, magnesium stearate and polacrilin potassium, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol -part hydrolyzed, titanium dioxide, macrogol/PEG, talc, iron oxide yellow and iron oxide red. None of the excipients used in the manufacture of the tablets are of human or animal origin. BSE/TSE compliance declarations were provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a brown coloured, oval shaped, biconvex film-coated tablet, debossed with 'D' on one side and '800' on the other side. The tablets are packaged in a white, opaque HDPE container closed with a white, opaque polypropylene child-resistant closure with wad having induction sealing liner.

Three tablet strengths proportionally similar in composition with regards to the core tablets were developed; 400 mg, 600 mg and 800 mg. 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 800 mg strength was finalized, the 600 mg and 400 mg strengths were planned using dose-proportionality approach.

The development of the final composition of the multisource product has been described. The objective was to develop a solid oral dosage form which is stable, pharmaceutically equivalent and bioequivalent to the WHO recommended comparator product, Prezista® (darunavir 800 mg) tablets. Based on available literature and comparator product characterization, dry granulation was selected for the manufacture of the finished pharmaceutical product. 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 appears to have no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications include tests for description, identification of API (TLC and HPLC) and colorants, average mass, uniformity of dosage units (by mass variation), determination of water (KF), dissolution (HPLC detection), assay (HPLC), related substances (HPLC), polymorphic identification (PXRD) 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 indicates 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, cross-over, single oral dose, bioequivalence study of [HA725 trade name] of MSN Laboratories Private Limited, India comparing with Prezista (darunavir) 800 mg film-coated tablets of Janssen-Cilag International NV, Belgium along with co-administration of Norvir (ritonavir) 100 mg film-coated tablets of AbbVie Ltd, United Kingdom in healthy, adult, human subjects, under fed conditions. (Study no. 062-BE-2017).

The objective of the study was to compare the bioavailability of the stated [HA725 trade name] manufactured by/for of MSN Laboratories Private 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, single dose, 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 [HA725 trade name] (darunavir 800 mg) Batch no. DT1709051A.
Treatment R:	Reference – 1 tablet Prezista® 800 mg (darunavir 800 mg) Batch no. HBZ0C00.

Ritonavir (Norvir® 100 mg twice daily) 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 25 samples within 72 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 50 ng/mL for darunavir.

The study was performed with 52 participants. Data generated from a total of 50 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)	3.63 ± 1.09	4.33 ± 0.98	–	–
C_{max} (µg/mL)	11.4 ± 2.2 (11.2)	10.6 ± 2.2 (10.4)	107.6	104.4 – 110.9
AUC_{0-t} (µg·h/mL)	135 ± 47 (128)	129 ± 44 (121)	105.5	101.5 – 109.7
AUC_{0-inf} (µg·h/mL)	139 ± 49 --	131 ± 46 --	–	–

The results of the study show that the preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values 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-Cilag).

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

4. Summary of product safety and efficacy

[HA725 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, [HA725 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 [HA725 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 [HA725 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA725 trade name] has been shown to be bioequivalent with Prezista® (Janssen-Cilag).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA725 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 [HA725 trade name] was acceptable for the following indication: ' in combination with other antiretroviral medicines for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents weighing at least 35 kg', and would allow inclusion of [HA725 trade name], manufactured at MSN Laboratories Private Limited, Formulations Division, Unit-II, Survey Nos. 1277, 1319 to 1324, Nandigama (Village & Mandal), Rangareddy District, Telangana – 509228, India in the list of prequalified medicinal products.