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	HA720 name][*]
Manufacturer of Prequalified Product	Lupin Limited (Unit 1) Plot No. 6A, Sector-17 Special Economic Zone MIHAN Notified Area Nagpur Maharashtra-441108 India
Active Pharmaceutical Ingredients (APIs)	Atazanavir (as sulfate) and ritonavir
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of HIV infections, combinations, (J05AR)
Therapeutic indication	[HA720 trade name] is indicated for the treatment of HIV-1 infected adults and children weighing at least 25 kg, in combination with other antiretroviral medicinal products

1. Introduction

[HA720 trade name] is indicated for indicated for the treatment of HIV-1 infected adults and children weighing at least 25 kg, in combination with other antiretroviral medicinal products.

[HA720 trade name] should be prescribed by a health care provider experienced in the management of tuberculosis 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 Ingredients (APIs)

Atazanavir

Atazanavir sulfate is a white to pale yellow crystalline powder. The pharmaceutical form is (3S,8S,9S,12S)-3,12-bis(1,1-dimethylethyl)-8-hydroxy-4,11-diozo-9-(phenylmethyl)-6- [[4-(2-pyridinyl) phenyl] methyl]-2,5,6,10,13-pentaazatetradecanedioic acid dimethyl ester, sulfate. Atazanavir sulfate is slightly hygroscopic and practically insoluble in water.

From the chemical structure of Atazanavir sulfate it is evident that it has four chiral centres which result in total of 16 possible stereo-isomers. Atazanavir is the SSSS isomer, it has S configuration in all of its four chiral centers.

The manufacture of the API entails several steps and is well described. The manufacturer consistently produces 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, sulfates), specific optical rotation, water content (KF), sulfated ash, sulfate content, enantiomer content (chiral

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

HPLC), related substances (HPLC), assay (HPLC), residual solvents (GC), polymorphic form (p-XRD), palladium content (ICPMS; ≤10ppm), nickel content (ICPMS; ≤ 20ppm), BOC-epoxide content (LC-MS; ≤ 3.3ppm), BOC-hydrazine content (LC-MS; ≤ 21.9ppm), 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.

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 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), 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; ≤ 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 lactose monohydrate, crospovidone, microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, copovidone, sorbitan monolaurate and sodium stearyl fumarate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains hypromellose and macrogol/PEG. BSE/TSE compliance declarations were provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a bilayer, capsule shaped, biconvex, film-coated tablet having one layer with white to pale yellow colour and the other white to off-white colour, plain on both the sides. A thin line on the tablet side may be visible.

The tablets are packaged in a white opaque, round, HDPE bottle with a polypropylene non-child resistant closure and heat seal liner. The bottle also contains a 2g activated silica gel sachet.

The development of the final composition of the multisource product has been described. The objective was to develop a fixed dose bilayer formulation of atazanavir (as sulfate) / ritonavir 300 mg /100 mg film-coated tablets bioequivalent to the individual WHO recommended comparator products, Reyataz® (atazanavir sulfate) capsules 300 mg and Novir (ritonavir) 100 mg tablets. The comparator products were characterized and on that basis a quality target product profile was defined and critical quality attributes were identified. The excipients were chosen and finalized based on the excipients used in the comparator products and API-excipient compatibility data. Based on literature search and comparator product characterization, wet granulation was selected for the manufacture of atazanavir 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. 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 (HPLC and TLC), water content (KF), dissolution (HPLC detection), uniformity of dosage units (content uniformity), assay (HPLC), related substances (HPLC), residual solvents (GC), polymorphic form identification (p-XRD, for both APIs) 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. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

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:

A randomized, open label, balanced, two treatment, two period, two sequence, single dose, crossover oral bioequivalence study comparing Test product (T) Atazanavir sulfate and Ritonavir tablets 300 mg/100 mg manufactured by Lupin Limited, India with Reference product (R): Reyataz® (atazanavir sulfate) capsules 300 mg (R1) manufactured by Bristol-Myers Squibb Company, Princeton, NJ 084543, USA + Norvir® (ritonavir) tablets 100 mg (R2) manufactured by Abbvie Inc. North Chicago, IL 60064, USA in normal, healthy, adult, male, human subjects under fed conditions (study no. ARL/17/130).

The objective of the study was to compare the bioavailability of the stated Atazanavir sulfate/Ritonavir 300mg/100mg tablet manufactured by/for Lupin Limited, India (test drug) with the reference formulations Reyataz® (Bristol-Myers Squibb Company) 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 – 1 tablet Atazanavir sulfate/Ritonavir 300mg/100mg (atazanavir sulfate 300 mg + ritonavir 100 mg) Batch no. M790975.
Treatment R:	Reference – 1 tablet Reyataz® (atazanavir sulfate 300 mg) Batch no. HL0513. – 1 tablet Norvir® (ritonavir 100 mg) Batch no. 1083125.

A 8 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 19 samples within 36h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for atazanavir and ritonavir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 50 ng/ml for atazanavir and 10 ng/ml for ritonavir.

The study was performed with 36 participants; data generated from a total of 34 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Atazanavir

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)	2.59 ± 0.69	2.75 ± 0.70	-	-
C_{max} (ng/ml)	6211 ± 1435 (6050)	6563 ± 1683 (6364)	95.1	89.9 – 100.5
AUC_{0-t} (ng.h/ml)	59130 ± 14708 (57435)	61574 ± 15536 (59749)	96.1	91.4 – 101.0
AUC_{0-inf} (ng.h/ml)	66317 ± 15677 --	68877 ± 17885 --	-	-

* 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)	4.10 ± 0.55	3.19 ± 0.89	-	-
C_{max} (ng/ml)	3194 ± 1112 (3004)	3345 ± 1502 (3090)	97.2	90.8 – 104.0
AUC_{0-t} (ng.h/ml)	20700 ± 7027 (19435)	21016 ± 8697 (19364)	100.4	94.9 – 106.2
AUC_{0-inf} (ng.h/ml)	20975 ± 7103 --	21288 ± 8773 --	-	-

* 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 atazanavir and ritonavir. Accordingly, the test Atazanavir sulfate/Ritonavir 300 mg/100 mg tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulations Reyataz® Bristol-Myers Squibb Company) and Norvir® (AbbVie Inc.).

4. Summary of Product Safety and Efficacy

[HA720 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the WHO recommended comparator products. According to the submitted data on quality and bioavailability, [HA720 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the WHO recommended comparator products Reyataz® and Norvir® for which benefits have been proven in terms of clinical efficacy.
The clinical safety of this product is considered to be acceptable when guidance and restrictions as stated in the Summary of Product Characteristics are taken into account. Reference is made 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 [HA720 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA720 trade name] has been shown to be bioequivalent to Reyataz® Bristol-Myers Squibb Company) and Norvir® (AbbVie Inc.).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA720 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 the WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit-risk profile of [HA720 trade name] was acceptable for the following indication: **"the treatment of HIV-1 infected adults and children weighing at least 25 kg, in combination with other antiretroviral medicinal products"** and has advised that the quality, efficacy and safety of [HA720 trade name] allow inclusion of [HA720 trade name], manufactured at Lupin Limited (Unit 1), Plot No. 6A, Sector-17, Special Economic Zone, MIHAN Notified Area Nagpur, Maharashtra-441108, India in the list of prequalified medicinal products.