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	[HA772 trade name][*]
Manufacturer of Prequalified Product	Laurus Labs Limited, (Unit-II), Plot No:19, 20 & 21, Western Sector, APSEZ, Atchutapuram Mandal, Visakhapatnam-District-531011, Andhra Pradesh, India
Active Pharmaceutical Ingredients (API)	Atazanavir (as sulfate)/ritonavir
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use, protease inhibitors ATC codes: J05AE08 (atazanavir), J05AE03 (ritonavir)
Therapeutic indication	[HA772 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

[HA772 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.

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-dioxo-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.

[*] 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, HPLC, sulfates), water content (KF), residue on ignition, sulfate content, specific optical rotation, enantiomer content (chiral HPLC), related substances (HPLC), assay (HPLC), residual solvents (GC), polymorphic form (p-XRD), BOC-hydrazine content (LC-MS; ≤ 21.9ppm), BOC-epoxide content (LC-MS; ≤ 3.3ppm), palladium content (AAS or ICPMS; ≤10ppm), nickel content (AAS or ICPMS; ≤ 20ppm) 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 has been prequalified by WHO according to WHO's *Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products* (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that daclatasvir dihydrochloride, used in the manufacture of [HA772 trade name], is of good quality and manufactured in accordance with WHO Good Manufacturing Practices.

API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and assessment of the sites of API manufacture to verify compliance with WHO GMP requirements.

Other ingredients

Other ingredients used in the core tablet formulation include lactose monohydrate, crospovidone, magnesium stearate, copovidone, sorbitan monolaurate, colloidal silicon dioxide, calcium hydrogen phosphate, iron oxide yellow and sodium stearyl fumarate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, macrogol/PEG and iron oxide yellow. Lactose monohydrate is from bovine origin. BSE/TSE compliance declarations were provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a yellow, oval-shaped, film-coated tablet debossed with "L61" on one side and plain on the other. The tablets are packaged in an opaque, white plastic (HDPE) bottle. It also contains a canister (1g or 2g silica gel) of desiccant (drying material). The bottle has a white childproof plastic (polypropylene) screw cap with induction sealing wad.

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 excipients were chosen and finalized based on the excipients used in the comparator products and API-API and API-excipient compatibility data. Wet granulation was selected for the manufacture of atazanavir layer and hot melt extrusion process was used for the ritonavir layer; the 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) and colourants, water content (KF), uniformity of dosage units (by content uniformity),

dissolution (HPLC detection), assay (HPLC), related substances (HPLC), 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, with slight increase of related substance, in particular for atazanavir – though within agreed levels. 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 after first opening of the 90-tablet bottle pack is based on in-use stability data.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2021 according to internationally accepted guidelines:

An open label, balanced, randomized, two-treatment, two-sequence, four-period, single-dose, full replicate, crossover oral bioequivalence study of [HA772 trade name] of Laurus Labs Limited, India with REYATAZ® (atazanavir) capsules 300 mg (Reference 1) of Bristol-Myers Squibb Company Princeton, NJ 08543 USA, Norvir® (ritonavir) tablets 100 mg (Reference 2) of AbbVie Inc. N. Chicago, IL 60064 USA in normal, healthy, adult, human subjects under fed conditions (study no. 21-018).

The objective of the study was to compare the bioavailability of the stated [HA772 trade name] manufactured by/for Laurus Labs 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, fully replicate, crossover study in healthy subjects under fed conditions. Each subject was assigned to receive each of the following two treatments twice in a randomized fashion:

Treatment T:	Test – 1 tablet [HA772 trade name] (atazanavir sulfate 300 mg + ritonavir 100 mg) Batch no. E2100421.
Treatment R:	Reference– 1 tablet Reyataz® (atazanavir sulfate 300 mg) Batch no. LM3048A1. – 1 tablet Norvir® (ritonavir 100 mg) Batch no. 1123530.

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 27 samples within 72h 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 30 ng/mL for atazanavir and 10 ng/mL for ritonavir.

The study was performed with 36 participants; data generated from a total of 36 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 (geometric mean)		**Reference (R)** arithmetic mean ± SD (geometric mean)		**log-transformed parameters**	
					Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
	T1	T2	R1	R2		
t_{max} (h)	3.11 ± 0.86	3.30 ± 0.95	3.30 ± 0.80	3.32 ± 0.88	–	–
C_{max} (ng/mL)	4902 ± 1091 (4741)	4850 ± 1025	5398 ± 1153 (4897)	4809 ± 1258	96.8	91.6 – 102.3
AUC_{0-t} (ng·h/mL)	42405 ± 10881 (40688)	41892 ± 10517	46530 ± 10939 (42856)	42864 ± 11847	94.9	90.8 – 99.3
AUC_{0-inf} (ng·h/mL)	43899 ± 11145 --	43148 ± 10747	47940 ± 11258 --	44168 ± 11972	-	-

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)
	T1	T2	R1	R2		
t_{max} (h)	4.30 ± 0.26	4.32 ± 0.34	3.91 ± 0.71	3.91 ± 0.81	-	-
C_{max} (ng/mL)	1870 ± 693 (1712)	1784 ± 590	2141 ± 509 (2001)	2012 ± 509	85.5	81.7 – 89.5
AUC_{0-t} (ng·h/mL)	11910 ± 5316 (10389)	11221 ± 4831	13312 ± 5434 (11970)	12798 ± 4934	86.8	83.4 – 90.3
AUC_{0-inf} (ng·h/mL)	12081 ± 5327 --	11396 ± 4848	13478 ± 5462 --	12972 ± 4959	-	-

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 [HA772 trade name] 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

[HA772 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, [HA772 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator products Reyataz® (Bristol-Myers Squibb Company) and Norvir® (Abbvie Inc.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA772 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 [HA772 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA772 trade name] has been shown to be bioequivalent with Reyataz® (Bristol-Myers Squibb Company) and Norvir® (Abbvie Inc.).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA772 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 [HA772 trade name] was acceptable for the following indication: 'treatment of HIV-1 infected adults and children weighing at least 25 kg, in combination with other antiretroviral medicinal products', and would allow inclusion of [HA772 trade name], manufactured at Laurus Labs Limited, (Unit-II), Plot No:19, 20 & 21, Western Sector, APSEZ, Atchutapuram Mandal, Visakhapatnam-District-531011, Andhra Pradesh, India in the list of prequalified medicinal products.