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	[HA742 trade name][*]
Manufacturer of Prequalified Product	Sun Pharmaceutical Industries Limited Village Ganguwala, Paonta Sahib District Sirmour – 173025 Himachal Pradesh India
Active Pharmaceutical Ingredient(s) (API)	Atazanavir (as sulfate)/ritonavir
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use, protease inhibitors J05AE08 (atazanavir), J05AE03 (ritonavir)
Therapeutic indication	[HA742 trade name] is indicated for the treatment of HIV-infected adults and children weighing at least 25 kg, in combination with other antiretroviral medicinal products.

1. Introduction

[HA742 trade name] is indicated for the treatment of HIV-infected adults and children weighing at least 25 kg, in combination with other antiretroviral medicinal products.

Treatment regimens should follow most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

[HA742 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 Ingredients (APIs)

Atazanavir sulfate and ritonavir have 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 the APIs, used in the manufacture of [HA742 trade name], are 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.

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

Other ingredients

Other ingredients used in the core tablet formulation include lactose monohydrate, crospovidone, calcium silicate, iron oxide yellow, magnesium stearate, copovidone, sorbitan monolaurate, colloidal silicon dioxide, anhydrous dibasic calcium phosphate 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 80. Lactose monohydrate and magnesium stearate are of bovine and vegetable origin, respectively. 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, film-coated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablet has "R180" debossed (stamped into) one side and is plain on the other side. The tablets are packaged in an opaque, white plastic (HDPE) bottle. The bottle has a plain aluminium foil induction seal and an opaque, white plastic (polypropylene) screw cap

The objective was to develop a fixed dose bilayer formulation of [HA742 trade name] 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 bilayered 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 N-nitrosamine impurities and hence no risk was identified, though the manufacturer undertook to conduct confirmatory testing for potential N-nitrosamines on selected batches post prequalification.

Specifications

The finished product specifications include tests for description, identification of APIs (HPLC and HPLC-PDA detector) and colourants, polymorphic form identification of ritonavir (p-XRD), uniformity of dosage units (by content uniformity), water content (KF), dissolution (HPLC detection), related substances (HPLC), assay (HPLC) 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 30°C/75%RH as 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 increases in water content and related substances 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 bottle 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 2018 according to internationally accepted guidelines:

Single dose two-way crossover bioequivalence study on fixed dose combination tablets of [HA742 trade name] in healthy adult human subjects under fed condition (study no. AZRN_300-100T_0719_18).

The objective of the study was to compare the bioavailability of the stated [HA742 trade name] manufactured by/for Sun Pharmaceutical Industries 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 twice in a randomized fashion:

Treatment T: Test – 1 tablet [HA742 trade name]
(atazanavir sulfate 300 mg + ritonavir 100 mg)
Batch no. 3000029.

Treatment R: Reference
– 1 tablet Reyataz® (atazanavir sulfate 300 mg)
Batch no. AAZ4389.
– 1 tablet Norvir® (ritonavir 100 mg)
Batch no. 1091095.

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 29 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 10 ng/ml for atazanavir and 4 ng/ml for ritonavir.

The study was performed with 56 participants; data generated from a total of 52 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)
t_{max} (h)	2.82 ± 0.95	3.52 ± 0.85	–	–
C_{max} (ng/mL)	5022 ± 1229 (4848)	5219 ± 1133 (5093)	94.9	89.2 – 100.9
AUC_{0-t} (ng·h/mL)	45264 ± 10650 (43864)	50857 ± 10522 (49746)	88.3	84.2 – 92.7
AUC_{0-inf} (ng·h/mL)	47581 ± 11627 (45988)	53576 ± 11607 (52288)	88.5	84.2 – 92.9

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)	3.88 ± 0.85	3.88 ± 0.70	–	–
C_{max} (ng/mL)	2107 ± 582 (2025)	2180 ± 622 (2095)	96.4	92.3 – 100.8
AUC_{0-t} (ng·h/mL)	13919 ± 4647 (13165)	13960 ± 4587 (13207)	99.7	96.8 – 102.7
AUC_{0-inf} (ng·h/mL)	14011 ± 4647 (13254)	14045 ± 4612 (13288)	99.8	96.9 – 102.8

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and Cmax values regarding atazanavir and ritonavir. Accordingly, the test [HA742 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

[HA742 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, [HA742 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 [HA742 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 [HA742 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA742 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, [HA742 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 [HA742 trade name] was acceptable for the following indication: 'treatment of HIV-infected adults and children weighing at least 25 kg, in combination with other antiretroviral medicinal products', and would allow inclusion of

[HA742 trade name], manufactured at Sun Pharmaceutical Industries Limited, Sun House, 201 B/1, Western Express Highway, Goregaon (East), Mumbai – 400063, India in the list of prequalified medicinal products.