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	[HA749 trade name][*]
Manufacturer of Prequalified Product	Shanghai Desano Bio-Pharmaceutical Co Ltd 1479 Zhangheng Road China (Shanghai) Pilot Free Trade Zone Shanghai 201203 P.R. China
Active Pharmaceutical Ingredient(s) (API)	Atazanavir (as sulfate)/ritonavir
Pharmaco-therapeutic group (ATC Code)	Antivirals, protease inhibitors J05AE08 (atazanavir), J05AE03 (ritonavir)
Therapeutic indication	[HA749 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

[HA749 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. Detailed information on the use of this product is described in the summary of product characteristics (SmPC).

[HA749 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)

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 [HA749 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:

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

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, partially pregelatinized starch, crospovidone, calcium silicate, ferric oxide yellow, magnesium stearate, copovidone, colloidal silicon dioxide, sorbitan monolaurate, dicalcium phosphate anhydrous and sodium stearyl fumarate, all being conventional pharmaceutical ingredients complying with the requirements of the pharmacopoeia. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol partially hydrolysed, talc, macrogol, titanium dioxide and iron oxide yellow. TSE/BSE free certificates from the suppliers have been provided with regards to all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a pale yellow to yellow colored, capsule shaped, biconvex, film coated tablet debossed with 'D09' on one side and plain surface on the other side. The tablets are presented in white opaque HDPE bottles; each with an oxygen-absorbing pouch and a polypropylene closure. Each closure consists of a polypropylene liner and a saf-cap.

The strategy of the product development was to formulate an immediate release oral tablet dosage form, which is stable, robust and bioequivalent to the individual WHO recommended comparator products, Reyataz® (atazanavir sulfate) 300 mg capsules and Novir (ritonavir) 100 mg tablets. The excipients were selected based on the excipients used in the comparator products and API-excipient compatibility data. The formulation was developed by preparation of the atazanavir sulfate part separately through wet granulation and use of hot melt extrusion for the ritonavir part and then both blends are compressed with a double-layer compression machine and film-coated. 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.

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 the APIs (HPLC and UV), average weight, assay (HPLC), dissolution (HPLC detection), uniformity of dosage units (by content uniformity), related substances (HPLC), water content, p-XRD and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been performed 30°C/75%RH (zone IVb) as long-term storage condition and for six months at 40°C/75%RH as accelerated condition in the packaging proposed for marketing of the product. The data provided indicated that the product is stable at these storage conditions with no apparent negative trend. 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 of Atazanavir Sulfate/Ritonavir tablets 300/100 mg of Shanghai Desano Bio-Pharmaceutical Co., Ltd with Reyataz® (atazanavir sulfate) capsules 300 mg of Bristol-Myers Squibb Company, Princeton, NJ 08543, USA and Norvir® (ritonavir) tablets 100 mg AbbVie Inc., N. Chicago, IL 60064, USA in normal healthy adult human subjects under fed conditions (study no. C17393).

The objective of the study was to compare the bioavailability of the stated Atazanavir sulfate/Ritonavir 300mg/100mg tablet manufactured by/for Shanghai Desano Bio-Pharmaceutical Co., Ltd (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. BSE17001.

Treatment R: Reference
– 1 tablet Reyataz® (atazanavir sulfate 300 mg) Batch no. JN0452.
– 1 tablet Norvir® (ritonavir 100 mg) Batch no. 1089793.

A 8 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 24 samples within 48h 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 5 ng/mL for ritonavir.

The study was performed with 18 participants; data generated from a total of 17 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)	2.77 ± 0.67	3.24 ± 0.86	-	-
C_{max} (ng/mL)	4813 ± 684 (4744)	5243 ± 1203 (5110)	92.8	82.9 – 103.9
AUC_{0-t} (ng·h/mL)	47488 ± 9037 (46284)	50740 ± 9534 (49800)	92.9	85.3 – 101.3
AUC_{0-inf} (ng·h/mL)	50087 ± 9870 (48747)	53441 ± 10170 (52422)	93.0	85.4 – 101.3

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)	4.00 ± 0.47	3.84 ± 0.74	-	-
C_{max} (ng/ml)	2262 ± 504 (2198)	2389 ± 515 (2347)	93.7	87.1 – 100.7
AUC_{0-t} (ng·h/mL)	14999 ± 3888 (14479)	14925 ± 3776 (14527)	99.7	94.2 – 105.5
AUC_{0-inf} (ng·h/mL)	15075 ± 3904 (14554)	15016 ± 3781 (14620)	99.5	94.2 – 105.2

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 [HA749 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

[HA749 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, [HA749 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Reyataz® Bristol-Myers Squibb Company) and Norvir® (AbbVie Inc.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA749 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 [HA749 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA749 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, [HA749 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 [HA749 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 [HA749 trade name], manufactured at Shanghai Desano Bio-Pharmaceutical Co Ltd, 1479 Zhangheng Road China (Shanghai) Pilot Free Trade Zone, Shanghai 201203, P.R. China in the list of prequalified medicinal products.