This part reflects the scientific knowledge and the information about this product available at the time of prequalification. Thereafter, updates may have become necessary which are included in parts 1 to 5 and, if related to pharmaceutical issues, also documented in part 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product:	Atazanavir (as sulfate)/Ritonavir 300 mg/100 mg Tablets[1]
Manufacturer of Prequalified Product:	Cipla Limited Plot No A – 42 (Unit – II) MIDC Patalganga District Raigad Maharashtra 410 220 India
Active Pharmaceutical Ingredients (APIs):	atazanavir (as sulfate), ritonavir
Pharmaco-therapeutic group (ATC Code):	Antivirals for systemic use, protease inhibitors (atazanavir: J05AE08, ritonavir: J05AE03).
Therapeutic indication:	Atazanavir (as sulfate)/Ritonavir 300 mg/100 mg Tablets is indicated for the treatment of HIV-1 infected adults and children weighing at least 30 kg, in combination with other antiretroviral medicinal products.

[1] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

1. Introduction

Atazanavir (as sulfate)/Ritonavir 300 mg/100 mg Tablets is indicated for the treatment of HIV-1 infected adults and children weighing at least 30 kg, in combination with other antiretroviral medicinal products.

Atazanavir (as sulfate)/Ritonavir 300 mg/100 mg Tablets should be prescribed 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

Atazanavir has 4 chiral centres and the all S-configuration is consistently produced. The API shows polymorphism – it has been shown by XRPD and infrared (IR) spectrophotometry that the manufacturing process consistently yields one polymorphic form (form A). Solubility data provided indicate that atazanavir sulphate is, according to the BCS, not highly soluble showing a decrease in solubility with increase in pH. The API is slightly hygroscopic.

The API specifications are regarded adequate for ensuring consistent quality and include tests for description, solubility, identification (IR, HPLC), water content (KF), specific optical rotation, residue on ignition, heavy metals, content of sulfate (potentiometric), related compounds (HPLC), assay (HPLC), formaldehyde content (GC) palladium content (ICP), residual solvents (GC), polymorphic form (XRPD) and particles size distribution (PSD). The PSD limits were set on the data obtained for the API batch used in the manufacture of the FPP biobatch. A starting material, considered a potential genotoxic impurity, is controlled at a limit of 3 ppm by means of LC-MS. The test procedures have been adequately validated.

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.

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 the API, used in the manufacture of Atazanavir (as sulfate)/Ritonavir 300 mg/100 mg Tablets, 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 inspection 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, yellow oxide of iron, magnesium stearate, colloidal silicon dioxide, anhydrous dibasic calcium phosphate, copovidone, sorbitan monolaurate and sodium stearyl fumarate. The seal coat contains hypromellose and talc, while the commercially sourced proprietary film-coating mixture contains polyvinyl alcohol partially hydrolysed, talc, titanium dioxide, polyethylene glycol, lecithin (soya) and iron oxide yellow. TSE / BSE free attestation has been provided for lactose monohydrate. None of the other excipients are derived from animal origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Atazanavir (as sulfate)/Ritonavir 300 mg/100 mg Tablets of Cipla Ltd are yellow coloured, capsule shaped, biconvex, film coated tablets debossed with "SVN" on one side and plain on other side. The tablets are packaged, together with a desiccant, in a white opaque HDPE bottle with white opaque HDPE cap or in Alu-Alu blister packs.

The objective was to develop a fixed-dose combination tablet containing 300 mg of atazanavir (as sulfate) and 100 mg of ritonavir, which is stable and bioequivalent to the co-administered WHO recommended comparator products Reyataz® 300 mg hard capsules and Norvir® 100 mg tablets, taken concomitantly. A bilayered tablet was developed, with the APIs present in separate layers. For layer identification, the atazanavir layer contains iron oxide yellow. The atazanavir layer is manufactured via a wet extruder granulation process, during which the API is converted from polymorphic form A into predominantly an amorphous form.

In order to increase the dissolution rate of the poorly water soluble ritonavir and to enhance its bioavailability from the tablet dosage form, it has to be in the form of a solid dispersion in the tablet – hot melt extrusion was selected. Excipients known to provide pharmaceutically acceptable tablets by the hot melt extrusion method, similar to those used by Norvir® 100 mg tablets, were selected for the ritonavir layer.

The core tablets are seal coated and finally film coated. The seal coat provides better adhesion of the film coat on the tablet surface. During process development, the manufacturing steps and critical process parameters that controlled each of these factors were identified.

Specifications

The finished product specifications are regarded adequate for ensuring consistent product quality and include tests for description, identification of the APIs (HPLC and TLC), average weight, water content (KF), uniformity of dosage units (by content uniformity), dissolution, degradation products (HPLC), assay (HPLC), polymorphic identification of the APIs (XRPD), residual solvents and microbiological examination of non-sterile products. The test methods have been satisfactorily described and validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH 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 showed no clear trends, except for a slight increase in water content, and the product proved to be quite stable in both packaging configurations. 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 2013 according to internationally accepted guidelines.

A randomized, balanced, open label, two-sequence, two-treatment, two-period, crossover, single dose, bioequivalence study of fixed dose combination of test product Atazanavir 300 mg + Ritonavir 100 mg tablets of Cipla Ltd., India, with reference products Reyataz® (atazanavir sulfate) capsules 300 mg of Bristol-Meyers Squibb Company, USA and Norvir® (ritonavir) tablet 100 mg of Abbott Laboratories, USA in normal, healthy, adult, male and female human subjects under fed conditions (study no. ARL/11/103).

The objective of the study was to compare the bioavailability of the stated Atazanavir/ritonavir 300/100 mg FDC tablet manufactured by/for Cipla Limited, India (test drug) with the individual reference formulations Reyataz® (Bristol-Meyers Squibb Company) and Norvir® (Abbott Laboratories) 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/ritonavir 300/100 mg
(atazanavir 300 mg + ritonavir 300 mg)
Batch no. KW3518.

Treatment R: Reference
1 capsule Reyataz®
(atazanavir sulfate 300 mg)
Batch no. 2D5002A.
1 tablet Norvir®
(ritonavir 100 mg)
Batch no. 132032E

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 26 samples within 72 h 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 60 participants; data generated from a total of 59 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)	4.63 ± 1.43	4.51 ± 1.48	-	-
C_{max} (ng/ml)	4213 ± 1174 (4029)	4465 ± 1219 (4276)	94.2	88.5 – 100.3
AUC_{0-t} (ng.h/ml)	45049 ± 13108 (43154)	45919 ± 12516 (44269)	97.5	93.2 – 102.0
AUC_{0-inf} (ng.h/ml)	48445 ± 12347 (46860)	49506 ± 11820 (48143)	97.3	93.6 – 101.3

* 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) #	4.17 ± 0.80	4.07 ± 0.89	-	-
C_{max} (ng/ml)	2020 ± 537 (1950)	2065 ± 538 (1996)	97.7	93.9 – 101.8
AUC_{0-t} (ng.h/ml)	14194 ± 4849 (13429)	14497 ± 5099 (13693)	98.1	95.4 – 100.8
AUC_{0-inf} (ng.h/ml)	14754 ± 4914 (13980)	15082 ± 5167 (14267)	98.0	95.5 – 100.5

* geometric mean; # median (range)

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 FDC tablet Atazanavir/Ritonavir 300/100 mg meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the individual references Reyataz® (Bristol-Meyers Squibb Company) and Norvir® (Abbott Laboratories).

4. Summary of Product Safety and Efficacy

Atazanavir (as sulfate)/Ritonavir 300 mg/100 mg Tablets has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator products. According to the submitted data on quality and bioavailability Atazanavir (as sulfate)/Ritonavir 300 mg/100 mg Tablets is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Reyataz® 300 mg capsules and Norvir® 100 mg tablets for which benefits have been proven in terms of virological and immunological 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 considered. 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 Atazanavir (as sulfate)/Ritonavir 300 mg/100 mg Tablets is used in accordance with the conditions as stated in the SmPC.

Bioequivalence

Atazanavir (as sulfate)/Ritonavir 300 mg/100 mg Tablets has shown to be bioequivalent with Reyataz® 300 mg capsules (atazanavir 300 mg), Bristol-Myers Squibb, USA, and Norvir® 100 mg tablets (ritonavir 100 mg) Abbott Laboratories, USA.

Efficacy and Safety

Regarding clinical efficacy and safety, Atazanavir (as sulfate)/Ritonavir 300 mg/100 mg Tablets is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics are considered.

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 Atazanavir (as sulfate)/Ritonavir 300 mg/100 mg

Tablets was acceptable for the following indication: **"treatment of HIV-1 infected adults and children weighing at least 30 kg, in combination with other antiretroviral medicinal products"**, and has advised that the quality, efficacy and safety of Atazanavir (as sulfate)/Ritonavir 300 mg/100 mg Tablets allow inclusion of Atazanavir (as sulfate)/Ritonavir 300 mg/100 mg Tablets manufactured at Cipla Ltd, Unit II, A-42, MIDC, Patalganga, District-Raigad, Maharashtra, India in the list of prequalified medicinal products.