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	[HA741 trade name][*]
Manufacturer of Prequalified Product	Cipla Limited
Active Pharmaceutical Ingredient(s) (API)	Ritonavir
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use, protease inhibitors (ATC code: J05AE03)
Therapeutic indication	[HA741 trade name] is indicated as a pharmacokinetic enhancer for protease inhibitors when these are used in combination therapy with other antiretroviral agents for the treatment of HIV-1 infected patients.

1. Introduction

[HA741 trade name] is indicated as a pharmacokinetic enhancer for protease inhibitors when these are used in combination therapy with other antiretroviral agents for the treatment of HIV-1 infected patients.

Consideration should be given to official treatment guidelines for HIV-1 infection (e.g. those of the WHO).

Therapy 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)

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 [HA741 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 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 colloidal silicon dioxide, anhydrous dibasic calcium phosphate, copovidone, sorbitan monolaurate and sodium stearyl fumarate. The seal

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

coat contains hypromellose, while the commercially sourced proprietary film-coating mixture contains titanium dioxide, hypromellose, macrogol/polyethylene glycol and polysorbate 80. None of the excipients are derived from animal origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white-coloured, oval-shaped, shallow, film-coated tablet debossed with "25" on one side and plain on the other side. The tablets are packaged in a white opaque HDPE bottle with white opaque non-CRC HDPE cap.

Three strengths of Ritonavir Tablets proportionally similar in composition and manufactured from a common blend were developed: 100 mg, 50 mg and 25 mg. The development focused on the highest strength, which was used in the BE study against the comparator product, Norvir® tablets of the same strength. Once the formula for the 100 mg strength was finalized, the 50 mg and 25 mg strengths were planned using dose-proportionality approach.

The aim of the product development was to obtain a stable and robust formulation of ritonavir tablets, bioequivalent to the WHO-recommended comparator product Norvir® 100 mg tablets.

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.

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.

Formulation trials were performed to optimize the concentration of excipients and process parameters, resulting in a product with the desired physicochemical characteristics including dissolution profile similarity with the comparator product. Satisfactory in-process controls have been established.

Specifications

The finished product specifications are pharmacopoeial based and include tests for identification of the API (HPLC and TLC), assay (HPLC), dissolution (2-point), organic impurities (HPLC), description, average weight, water content (KF), uniformity of dosage units (by content uniformity), polymorphic (amorphous) identification of the API (XRPD), limit on crystalline ritonavir (XRPD), residual solvents (GC) 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 all the parameters meet their acceptance criteria at both long-term and accelerated storage conditions in the proposed packaging configuration. 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 2011 according to internationally accepted guidelines.

A randomized, balanced, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Ritonavir 100 mg tablets of Cipla Ltd., India with Norvir® tablets (containing ritonavir 100 mg) of Abbott Laboratories, USA, in normal, healthy, adult, male and female human subjects under fed conditions (study no. ARL/11/228).

The objective of the study was to compare the bioavailability of the stated Ritonavir 100 mg tablet manufactured by/for Cipla Ltd., India (test drug) with the reference formulation Norvir® (Abbott Laboratories) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, 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 – 2 tablets Ritonavir 100 mg (ritonavir 200 mg) Batch no. KW1140.

Treatment R: Reference – 2 tablets Norvir® 100 mg (ritonavir 200 mg) Batch no. 903692E21.

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 22 samples within 24h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for ritonavir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 51 ng/ml for ritonavir.

The study was performed with 42 participants; data generated from a total of 39 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

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)	4.16 ± 1.05	4.45 ± 1.00	–	–
C_{max} (ng/mL)	2903 ± 914 (2788)	2787 ± 859 (2675)	104.2	97.6 – 111.3
AUC_{0-t} (ng·h/mL)	19620 ± 7548 (18414)	19240 ± 7418 (17982)	102.4	97.8 – 107.2
AUC_{0-inf} (ng·h/mL)	20632 ± 8125 (19294)	20392 ± 8114 (18956)	101.8	97.3 – 106.5

Conclusion

The results of the study show that preset acceptance limits of 80–125% are met by both AUC and C_{max} values regarding ritonavir. Accordingly, the test Ritonavir 100 mg tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Norvir® (Abbott Laboratories).

A biowaiver was granted for the additional 25 mg tablet strength (Cipla Ltd., India) in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the Ritonavir 25 mg tablet was determined to be qualitative essential the same, the ratio of active

ingredient and excipients between the strengths was considered essentially the same and the dissolution profiles between the formulations for the API were determined to be the same.

4. Summary of product safety and efficacy

[HA741 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, [HA741 trade name] is a direct scale-down of Ritonavir 100 mg tablets of Cipla Ltd. The latter is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Norvir® (Abbott Laboratories) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [HA741 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 [HA741 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA741 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

Efficacy and Safety

Regarding clinical efficacy and safety, [HA741 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 [HA741 trade name] was acceptable for the following indication: 'as a pharmacokinetic enhancer for protease inhibitors when these are used in combination therapy with other antiretroviral agents for the treatment of HIV-1 infected patients', and would allow inclusion of [HA741 trade name], manufactured at Cipla Limited, Plot No A – 42 (Unit – II), MIDC Patalganga, District Raigad, Maharashtra 410 220, India, in the list of prequalified medicinal products.