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:	[HA467 trade name]*
Manufacturer of Prequalified Product:	Matrix Laboratories Limited F-4, F-12, Malegaon M.I.D.C Sinnar 422113 Nashik Maharashtra India
Active Pharmaceutical Ingredient (API):	Ritonavir
Pharmaco-therapeutic group (ATC Code):	Antiviral for systemic use, protease inhibitor (J05AE03).
Therapeutic indication:	[HA467 trade name] is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infected patients (adults and children of 2 years of age and older).

1. Introduction

[HA467 trade name] is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infected patients (adults and children of 2 years of age and older).

2. Assessment of Quality

The assessment was done according to SOP 20 of the WHO Prequalification programme.

Active pharmaceutical ingredients (API)

Ritonavir is a class 4/2 API according to Biopharmaceutics Classification System (WHO Technical Report Series 937, Annex 8: *Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms*).

Ritonavir is described in the Ph.Int, Ph.Eur. and USP. The API is obtained from within the Mylan group of companies and the APIMF has been accepted through WHO's APIMF procedure. Ritonavir has four chiral centres, is practically insoluble in water and is known to exhibit polymorphism. The manufacture of ritonavir entails several steps and is stereoselective producing the desired stereoisomer. The manufacturing process has been validated in all respects and found to be consistent. Polymorphic Form II is consistently produced through control of the final recrystallisation step, which includes seeding. The

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.
** Previously known as Matrix Laboratories Limited.

API is adequately controlled by its set of quality specifications which is pharmacopoeial based, with additional in-house specifications including residual solvents.

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.

Other ingredients

Other ingredients used in the core tablet formulation include colloidal silicon dioxide, copovidone, sodium chloride, sodium stearyl fumarate, sorbitan monolaurate, all being compendial controlled. The film coating contains colloidal anhydrous silica, hypromellose, hydroxypropyl cellulose, iron oxide yellow, polyethylene glycol, polysorbate 80, talc and titanium dioxide.

Finished pharmaceutical product (FPP)

[HA467 trade name] tablets are yellow-coloured, capsule-shaped, film-coated tablets debossed with "M163" on one side and plain on the other side. The tablets are packaged in white opaque HDPE bottle with white opaque cap with inbuilt desiccant (30 tablets and 120 tablets per bottle).

The development of the final composition of [HA467 trade name] has been described. The objective was to develop a tablet formulation, which will have a good stability when stored at room temperature and which is bioequivalent to the comparator product, Norvir® 100 mg soft capsules (the development started and the dossier was submitted before approval of Norvir® 100 mg film-coated tablets by the US-FDA or EMA). In order to increase the dissolution rate of the poorly 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. A solvent evaporation technique was employed to manufacture the solid dispersion (ritonavir premix) in a surfactant-polymer matrix. The premix and excipients are sifted, blended together and compressed. The tablets are finally coated. The formulation was optimized by experimenting with difference amounts of the excipients with dissolution as the primary criterion. The critical steps of the manufacturing process were optimized and appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data presented on three primary batches demonstrated the consistency of the process and the quality of the product.

The finished product specifications include appropriate tests for description, identification of the API (HPLC and TLC) and of titanium dioxide, dissolution (2-point), uniformity of dosage units (by content uniformity), related substances (HPLC), assay (HPLC), water (KF) and microbial limits. The ritonavir premix specifications include *inter alia* a test to ensure the absence of crystalline ritonavir by XRPD and a test for residual solvents (GC).

Stability testing

Stability studies have been performed on three primary batches at 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at accelerated conditions. The data showed a slight increase for some of the degradation products, though within the agreed limits. 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 Bio-Equivalence

The following bioequivalence study has been performed in 2008 according to internationally accepted guidelines.

Open label, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, crossover comparative oral bioavailability study of [HA467 trade name] of Mylan Laboratories Limited, India and

Norvir® (ritonavir) 100 mg soft gelatin capsules of Abbott Laboratories, North Chicago, IL 60064, USA, in normal, healthy, adult, human subjects under fed condition with a 200 mg dose i.e. 2X100 mg tablets of Test and 200 mg dose i.e. 2X100 mg capsules of Reference products (study no. 235-08).

The objective of the study was to compare the bioavailability of the stated [HA467 trade name] tablet manufactured by Mylan Laboratories Ltd. India (test drug) with the same dose of the reference formulation (Norvir® 100 mg capsule, Abbott) 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 – 2 x [HA467 trade name]
(ritonavir 200 mg)
Batch no. 1005474.

Treatment R: Reference – 2 x Norvir® 100 mg capsule
(ritonavir 200 mg)
Batch no. 526442E21.

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 19 samples within 36 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 ritonavir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 50 ng/ml for ritonavir.

The study was performed with 44 participants; data generated from a total of 44 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 (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	5.2 ± 1.7	5.6 ± 2.4	-	-
C_{max} (ng/ml)	3089 ± 1105 (2876)	3045 ± 1259 (2801)	102.7	90.2 – 117.0
AUC_{0-t} (ng.h/ml)	22019 ± 7915 (20705)	22276 ± 8494 (20876)	99.2	92.4 – 106.5
AUC_{0-inf} (ng.h/ml)	22816 ± 7993 (21531)	23187 ± 8774 (21768)	98.9	92.5 – 105.7

* geometric mean

Conclusions

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 [HA467 trade name] tablet meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Norvir® 100 mg capsule (Abbott).

4. Summary of Product Safety and Efficacy

[HA467 trade name] tablets have been shown to conform to the same appropriate standards of quality, efficacy and safety as those required of the reference product. According to the submitted data on quality and bioavailability it is pharmaceutically and therapeutically equivalent and thus interchangeable with the reference product Norvir®, 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 presented in the Summary of Product Characteristics are taken into consideration. Reference is made to the SPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Bioequivalence

Bioequivalence is established between [HA467 trade name] 100 mg tablets and Norvir® (Abbott Laboratories).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA467 trade name] is considered effective and safe to use when the guidance and restrictions presented in the Summary of Product Characteristics are taken into consideration.

Benefit Risk Assessment

Based on the WHO assessment of data on quality and bioequivalence the team of assessors considered by consensus that the benefit risk profile of [HA467 trade name] was acceptable for the following indication: “in combination with other antiretroviral agents for the treatment of HIV-1 infected patients (adults and children of 2 years of age and older),” and has advised to include [HA467 trade name], manufactured at Mylan Laboratories Limited, F-4, F-12, Malegaon M.I.D.C, Sinnar, Nashik 422113, Maharashtra, India, in the list of prequalified medicinal products.