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:	[HA635 trade name][*]
Manufacturer of Prequalified Product:	Mylan Laboratories Limited F-4 & F-12, Malegaon M.I.D.C. Sinnar, Nashik Dist. – 422 113 Maharashtra State India
Active Pharmaceutical Ingredient (API):	Abacavir (as sulfate) / Lamivudine/
Pharmaco-therapeutic group (ATC Code):	Antivirals for treatment of HIV infections, combinations (J05AR02)
Therapeutic indication:	[HA635 trade name] is indicated in combination with other antiretroviral agents for the treatment of Human Immunodeficiency Virus (HIV) infection in adults, adolescents and children weighing at least 25 kg.

1. Introduction

[HA635 trade name] is indicated in the treatment of HIV, as detailed in the summary of product characteristics.

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)

Based on scientific principles the WHO Prequalification Team – Medicines has identified abacavir (as sulfate) (up to 600 mg oral dose) and lamivudine (up to 300 mg oral dose) as BCS class 3 APIs. Abacavir sulfate and lamivudine are thus highly soluble in aqueous medium over the pH range 1.0 – 6.8.

Abacavir sulfate and lamivudine 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 these two APIs, used in the manufacture of [HA635 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 inspection 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 microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate and magnesium stearate, all being pharmacopoeia-controlled. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, macrogol/PEG, iron oxide yellow, polysorbate and FD&C Yellow #6/Sunset Yellow FCF aluminium lake. BSE/TSE compliance declarations were provided.

Finished pharmaceutical product (FPP)
Pharmaceutical development and manufacture
The multisource product is a yellow-coloured, biconvex, film-coated tablet, debossed with "M157" on one side and plain on the other side. The tablets are packaged in an HDPE bottle with a screw cap. The objective was to develop a stable, fixed-dose combination, essentially similar in formulation and bioequivalent to the WHO comparator product, Epzicom®. The tablets have been developed as an immediate release solid dosage form for oral administration. The qualitative formulation was developed and each excipient was selected for its intended use based on optimization studies. The dry granulation process was selected as the manufacturing process as this is the simplest and most preferred technique for the tablet manufacturing and involves lesser unit operations. All the critical steps of the manufacturing process were optimized. Appropriate in-process controls were set to ensure batch-to-batch reproducibility. The multisource product showed very rapidly dissolving dissolution properties, similar to the comparator product.

Product specifications

The finished product specifications include tests for description, identification of the APIs (HPLC and TLC) and colorants, dissolution (HPLC), uniformity of dosage units (by content uniformity), related substances (HPLC), assay (HPLC), loss on drying, tablet thickness 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 conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. The product proved to be quite stable at these storage conditions, with very little degradation. 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 2007 according to internationally accepted guidelines.

Study Title: A randomized, open label, two-period, two-treatment, two-sequence, single dose, crossover bioequivalence study comparing fixed dose combination of abacavir sulfate 600 mg and lamivudine 300 mg tablets manufactured by Matrix Laboratories Limited, India with Epzicom® (containing fixed dose combination of abacavir sulfate/lamivudine) 600 mg /300 mg tablets manufactured by GlaxoSmithKline, USA in normal, healthy, adult, human subjects under fasting condition (study no. US/AHD/07/040).

The objective of the study was to compare the bioavailability of the stated abacavir/lamivudine 600 mg /300 mg FDC tablets manufactured for/by Matrix Laboratories Ltd., India (test drug) with the reference formulation Epzicom® (GlaxoSmithKline) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following treatments in a randomized fashion:

Treatment T: Test – 1 tablet [HA635 trade name]
(Abacavir [as sulfate] 600 mg + Lamivudine 300 mg)
Batch no. 1002505

Treatment R: Reference – 1 tablet Epzicom®
(Abacavir [as sulfate] 600 mg + Lamivudine 300 mg)
Batch no. R307336

An 8-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 20 samples within 36 hours post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for abacavir and lamivudine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 100 ng/mL for abacavir and about 80 ng/mL for lamivudine.

The study was performed with 28 participants; data generated from a total of 24 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for abacavir and lamivudine as well as statistical results are summarized in the following table:

Abacavir

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)	1.63 ± 0.49	1.50 ± 0.84	-	-
C_{max} (ng/ml)	5766 ± 1887 (5474)	6011 ± 1784 (5801)	94.4	86.4 – 103.0
AUC_{0-t} (ng.h/ml)	17094 ± 5078 (16308)	16737 ± 4142 (16423)	100.4	91.8 – 109.9
AUC_{0-inf} (ng.h/ml)	17548 ± 5186 (16742)	17045 ± 4127 (16562)	101.1	92.5 – 110.5

* geometric mean

Lamivudine

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)	2.25 ± 0.69	2.04 ± 0.70	-	-
C_{max} (ng/ml)	2660 ± 653 (2570)	2773 ± 749 (2660)	96.6	89.0 – 105.0
AUC_{0-t} (ng.h/ml)	13043 ± 3366 (12596)	13359 ± 4194 (12671)	99.4	89.8 – 110.0
AUC_{0-inf} (ng.h/ml)	13989 ± 3881 (13435)	14016 ± 4334 (13305)	101.0	91.1 – 111.9

* geometric mean

Conclusions

The results of the study show that the pre-set acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding abacavir and lamivudine. Accordingly, the test FDC tablet abacavir (as sulfate)/lamivudine 600 mg/300 mg meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Epzicom® (GlaxoSmithKline).

4. Summary of Product Safety and Efficacy

[HA635 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, [HA635 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the reference reference Epzicom® (GlaxoSmithKline), for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [HA635 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 [HA635 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA635 trade name] has been shown to be bioequivalent with reference Epzicom® (GlaxoSmithKline).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA635 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 [HA635 trade name] was acceptable for the following indication**: "in combination with other antiretroviral agents for the treatment of Human Immunodeficiency Virus (HIV) infection in adults, adolescents and children weighing at least 25 kg"** and has advised that the quality, efficacy and safety of [HA635 trade name] allow inclusion of [HA635 trade name], manufactured at Mylan Laboratories Limited, F-4 & F-12, Malegaon M.I.D.C., Sinnar, Nashik Dist. – 422 113, Maharashtra State, India, in the list of prequalified medicinal products.