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

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|---|---|
| **Name of the Finished Pharmaceutical Product:** | [HA698 trade name][1] |
| **Manufacturer of Prequalified Product:** | Sun Pharmaceutical Industries Limited<br>Village Ganguwala<br>Paonta Sahib,<br>District Sirmour<br>Himachal Pradesh-173025<br>India |
| **Active Pharmaceutical Ingredient (API):** | Abacavir (as sulfate)/Lamivudine |
| **Pharmaco-therapeutic group (ATC Code):** | Antivirals for treatment of HIV infections, combinations (J05AR02) |
| **Therapeutic indication:** | [HA698 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

[HA698 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. [HA698 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)

*Abacavir sulfate*

Based on scientific principles WHO PQTm has identified abacavir (as sulfate) (up to 600 mg oral dose) as a BCS class 3 API. The API is thus highly soluble over the pH range 1 to 6.8.

The APIMF of abacavir sulfate, (1S,4R)-4-[2-Amino-6(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol sulfate (2:1), has been accepted through WHO's APIMF procedure. The manufacture of abacavir sulfate, which contains two chiral carbon atoms, entails several chemical steps. The desired stereochemistry at the chiral centres (1S,4R) is built into a starting material. The reactions involved in the conversion of this starting material to the API do not involve the chiral centres and hence the original chirality of the starting material is retained throughout the synthesis.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification (IR, HPLC and test for sulfate), water content (KF), residue on ignition, heavy metals,

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

organic impurities (HPLC), enantiomer content (HPLC; ≤ 0.30%), assay (HPLC), residual solvents (GC) and content of sulfate (potentiometric).

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.

*Lamivudine*

Lamivudine 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 lamivudine, used in the manufacture of [HA698 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 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, microcrystalline cellulose, sodium starch glycolate, colloidal anhydrous silica and magnesium stearate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, macrogol, FD&C yellow #6/sunset yellow FCF aluminium lake and polysorbate 80. BSE/TSE compliance declarations were provided

## Finished pharmaceutical product (FPP)

*Pharmaceutical development and manufacture*

The multisource product is anorange-coloured, capsule-shaped, film-coated tablet, debossed with RF-90 on one side and plain on other side. The tablets are packaged in a white opaque HDPE bottle having a polypropylene child resistant closure or screw closure with induction seal liner.

The objective of the product development was to obtain a formulation bioequivalent to the WHO recommended comparator product, Kivexa® Tablets. The excipients selected were with reference to the comparator product. Compatibility studies which were conducted showed that the APIs were compatible with the selected excipients. Formulation trials were performed to optimise the concentration of excipients and process parameters. Dry granulation was selected as the manufacturing process. Satisfactory in-process controls have been established.

*Specifications*

The finished product specifications include tests for description, identification of APIs (HPLC and IR) and colorants, water (KF), uniformity of dosage units (by content uniformity for lamivudine, weight variation for abacavir), dissolution (HPLC detection), related substances (HPLC), assay (HPLC), and microbial limits.

*Stability testing*

Stability studies have been performed at 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 product proved to be quite stable, with no significant change or negative trend observed. 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 2016 according to internationally accepted guidelines.

A randomized, open label, balanced, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Abacavir and Lamivudine tablets, 600 mg/300 mg of Sun Pharmaceutical Industries Limited, India and Kivexa® tablets (containing 600 mg of abacavir as abacavir sulfate and 300 mg lamivudine) of ViiV Healthcare UK Limited, in 36 healthy adult subjects under fasting condition (study no. PKD_15_326).

The objective of the study was to compare the bioavailability of the stated Abacavir/Lamivudine 600 mg/300 mg FDC tablet manufactured by/for Sun Pharmaceutical Industries Limited, India (test drug) with the reference formulation Kivexa®(ViiV Healthcare Ltd.) and to assess bioequivalence. The comparison was performed as a single center, open label, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

| | |
|---|---|
| Treatment T: | Test – 1 tablet Abacavir/Lamivudine 600 mg/300mg (abacavir 600 mg + lamivudine 300 mg) Batch no. 2743236. |
| Treatment R: | Reference– 1 tablet Kivexa® (abacavir 600 mg + lamivudine 300 mg) Batch no. L93M |

A 6 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 24 samples within 36 hour 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 10 ng/mL for abacavir as well as for lamivudine.

The study was performed with 36 participants; data generated from a total of 29 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 summarised in the following tables:

**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) | 1.37 ± 0.67 | 1.20 ± 0.66 | - | - |
| $C_{max}$ (ng/mL) | 6784 ± 1679 (6592) | 6724 ± 1465 (6579) | 100.2 | 94.8 – 105.9 |
| $AUC_{0-t}$ (ng.h/mL) | 19094 ± 4144 (18679) | 18559 ± 4101 (18172) | 102.8 | 100.8 – 104.8 |
| $AUC_{0-inf}$ (ng.h/mL) | 19168 ± 4143 (18755) | 18626 ± 4118 (18238) | 102.8 | 100.9 – 104.9 |

* 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) | 1.94 ± 0.76 | 1.89 ± 0.70 | - | - |
| $C_{max}$ (ng/mL) | 2974 ± 1128 (2734) | 3281 ± 1111 (3063) | 89.3 | 80.7 – 98.7 |
| $AUC_{0-t}$ (ng.h/mL) | 15861 ± 4799 (14954) | 16594 ± 4822 (15763) | 94.9 | 87.1 – 103.3 |
| $AUC_{0-inf}$ (ng.h/mL) | 16079 ± 4800 (15187) | 16808 ± 4818 (15990) | 95.0 | 87.3 – 103.3 |

* geometric mean

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and $C_{max}$ values regarding abacavir and lamivudine. Accordingly, the test Abacavir/Lamivudine 600 mg/300 mg FDC tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulation Kivexa® (ViiV Healthcare UK Ltd.).

## 4. Summary of product safety and efficacy

[HA698 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 [HA698 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Kivexa® for which benefits have been proven in terms of virological and immunological efficacy.

The clinical safety of this product is considered acceptable when guidance and restrictions as stated in the summary of product characteristics are taken into account. 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 [HA698 trade name] is used in accordance with the SmPC.

### Bioequivalence

[HA698 trade name] has been shown to be bioequivalent with Kivexa® (ViiV Healthcare UK Ltd.).

### Efficacy and Safety

Regarding clinical efficacy and safety, [HA698 trade name]is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics are taken into consideration.

### Benefit Risk Assessment

Based on the WHO assessment of data on quality, safety and efficacy the team of assessors considered that the benefit–risk profile of [HA698 trade name]was acceptable for the following indication: **"in combination with other antiretroviral agents for the treatment of HIV infection in adults, adolescents and children weighing at least 25 kg."** and has advised that the quality, safety and

efficacy of [HA698 trade name] allow inclusion of[HA698 trade name], manufactured at Sun Pharmaceutical Industries limited, Village Ganguwala, Paonta Sahib, District Sirmour, Himachal Pradesh, India, in the list of prequalified medicinal products.