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	[HA494 trade name][*]
Manufacturer of Prequalified Product	Strides Arcolab Limited Bilekahalli, Bannerghatta Road Bangalore -560076, India
Active Pharmaceutical Ingredient(s) (API)	abacavir (as sulfate)
Pharmaco-therapeutic group (ATC Code)	Nucleoside reverse transcriptase inhibitor (J05AF06)
Therapeutic indication	[HA494 trade name] is indicated for the treatment of HIV infection in combination with other antiretroviral agents

1. Introduction

[HA494 trade name] is indicated in combination with another antiretroviral agent for the treatment of Human Immunodeficiency Virus (HIV).

[HA494 trade name] should be prescribed by a physician 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 is a class 3 API according to the 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). The API is thus BCS highly soluble.

The APIMF of abacavir sulfate, (1S,4R)-4-[2-amino-6(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol hemisulfate, 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 the starting material. The reactions involved in the conversion of the starting material to the API do not involve the chiral centres and hence the original chirality of the starting material is retained in the final API. The

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

enantiomer (1R,4S configuration) of the API is controlled at not more than 0.3%. The critical process parameters were defined in the synthesis of abacavir sulfate and they are routinely monitored. The API specifications include tests for description, solubility, identification, water, specific optical rotation, sulphated ash, heavy metals, related substances (HPLC), assay, enantiomeric purity (chiral HPLC), residual solvents, particle size distribution and bulk density.

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, magnesium stearate, microcrystalline cellulose and sodium starch glycolate. Magnesium stearate is from vegetable origin. The film coating contains hypromellose, iron oxide yellow, macrogol 400 and titanium dioxide.

Finished pharmaceutical product (FPP)

Each tablet contains abacavir sulfate equivalent to 300mg abacavir. Abacavir (as sulfate) 300mg Tablets are dark yellow coloured, film-coated, biconvex, capsules shaped tablets, with “AB” embossed on one side and a break-line on the other side. The break-line is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies. The tablets are packaged PVC-aluminium blister cards and HDPE bottles with child resistant caps or screw caps.

Pharmaceutical development and manufacture

The development of the final composition of Abacavir (as sulfate) 300mg Tablets has been described. The objective was to develop a stable product, pharmaceutically equivalent and bioequivalent to the comparator product, Ziagen® 300mg Tablets, which is an immediate release solid dosage form for oral administration. The choice of excipients and process (direct compression) was based on the available information on the comparator product. The comparator product was also investigated for various parameters, including impurity profile and in vitro dissolution profiles in BCS related media. The latter profiles were targeted in the optimisation studies.

Process validation has been conducted on three batches, including the batches used in the bioequivalence studies and stability studies. Satisfactory in-process controls have been established.

Specifications

The finished product specifications include tests for description, identification (HPLC and UV), average weight, tablet dimensions, loss on drying, disintegration time, uniformity of dosage unity (mass variation), dissolution, related substances (HPLC), assay (HPLC), residual solvents and microbial limits.

Stability testing

Stability studies have been performed at 25°C/60%RH, 30°C/65%RH and 30°C/75%RH as long-term storage conditions and for six months at accelerated conditions in all packaging configurations. The product proved to be quite stable at both long-term and accelerated storage conditions. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

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

A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of [HA494 trade name] of Strides Arcolab Limited., Bangalore – 560 076 and Ziagen® (abacavir sulfate) tablets 300mg of GlaxoSmithKline, Research Triangle Park, NC 27709 in healthy human adult male subjects under fasting conditions (study no. 08-VIN-103).

The objective of the study was to compare the bioavailability of the stated [HA494 trade name] manufactured by Strides Arcolab Limited, India (test drug) with the same dose of the reference formulation Ziagen® 300 mg tablet (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 two treatments in a randomized fashion:

Treatment T: Test – [HA494 trade name]
(Abacavir (as sulfate) 300 mg tablet)
Batch no. 7505632.
Treatment R: Reference – Ziagen® 300 mg tablet
(abacavir 300 mg)
Batch no. 7ZP4773.

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 24 h post dose) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax for bioequivalence evaluation. Drug concentrations for abacavir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 30 ng/mL for abacavir.

The study was performed with 32 participants; data generated from a total of 31 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Abacavir

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)	0.6 ± 0.4	0.6 ± 0.4	–	–
C_{max} (ng/mL)	3424 ± 1225 (3225)	3493 ± 1403 (3247)	99.3	90.9-108.5
AUC_{0-t} (ng·h/mL)	6915 ± 2262 (6584)	6976 ± 2424 (6597)	99.8	95.7-104.2
AUC_{0-inf} (ng·h/mL)	7013 ± 2276 (6683)	7070 ± 2443 (6690)	99.9	65.8-104.2

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and Cmax values regarding abacavir. Accordingly, the test [HA494 trade name] meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Ziagen® 300 mg tablet (GlaxoSmithKline).

4. Summary of product safety and efficacy

[HA494 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, [HA494 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Ziagen® 300 mg tablet (GlaxoSmithKline) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA494 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 [HA494 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA494 trade name] has been shown to be bioequivalent with Ziagen® 300 mg tablet (GlaxoSmithKline).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA494 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 [HA494 trade name] was acceptable for the following indication: indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV) infection in adults, adolescents and children, and would allow inclusion of [HA494 trade name], manufactured at Strides Arcolab Limited, Bilekahalli, Bannerghatta Road, Bangalore -560076, India in the list of prequalified medicinal products.