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	[HA371 trade name]*
Manufacturer of Prequalified Product	Cipla Ltd, Manufacturing Division Plot No. A – 33/1/2 Patalganga Industrial Area, District – Raigad 410220 Patalganga Maharashtra India
Active Pharmaceutical Ingredient (API)	Abacavir (as sulfate)
International Nonproprietary Name	Abacavir
Pharmaco-therapeutic group (ATC Code)	Nucleoside and nucleotide reverse transcriptase inhibitors, (J05AF06)
Therapeutic indication	[HA371 trade name] is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV) infection in adults, adolescents and children.

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

1. Introduction

[HA371 trade name] is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV) infection in adults, adolescents and children. [See Part 4 Summary of Products Characteristics (SmPC), for full indications].

[HA371 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 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).

Abacavir sulfate is described in the Ph.Int. However, by the time of the submission of the dossier the monograph for abacavir sulfate was not yet included. For control of the abacavir sulfate the specifications as set by the API manufacturer were judged suitable. The critical process parameters were defined in the synthesis of abacavir sulfate and they are routinely monitored. A detailed purification procedure has been described.

Based on the results of stability testing conducted according to the requirements of WHO, a retest period of 24 months was approved for abacavir sulfate.

Other ingredients

Other ingredients used in the tablet core formulation include colloidal silicone dioxide, corn starch, hypromellose, magnesium stearate, microcrystalline cellulose and sodium starch glycolate, which are all compendial. The film coating contains hypromellose, iron oxide yellow, polyethylene glycol, polysorbate 80 and titanium dioxide.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Each tablet contains abacavir sulfate equivalent to 300mg abacavir.

[HA371 trade name] are yellow coloured, capsule shaped, biconvex film-coated tablets, plain on both sides. The tablets are packaged in a round, white opaque, induction-sealed HDPE bottle fitted with a polypropylene child-resistant closure or polypropylene screw cap and containing a silica gel desiccant (pack size: 60 tablets).

The development of the final composition of [HA371 trade name] has been described. The objective was to develop a stable product with release properties similar to that of the innovator product, Ziagen 300mg Tablets. A qualitative formulation was developed and optimised until the dissolution profiles thereof in the three BCS media were similar to that of Ziagen 300mg Tablets. The compatibility of the API with excipients was demonstrated in binary mixture studies. A wet granulation process was selected for the manufacture of the core tablets, followed by drying, compression and film coating. 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 for three commercial scale batches demonstrated the consistency of the process. The proposed specifications, analytical methods with validation, and batch quality control results ensure consistent quality for this finished pharmaceutical product.

Stability testing

Stability studies have been performed at 25°C/60%RH and 30°C/65%RH as long-term storage conditions and at accelerated conditions. The results were well within the agreed specifications at all storage conditions and a shelf-life of 24 months has been allowed for the FPP when stored not above 30°C.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2005 according to internationally accepted guidelines.

A randomized, single dose, open label, bioequivalence study, comparing Abacavir 300 mg tablets in normal healthy male subjects under fasting condition (study no. US/05/032).

The objective of the study was to compare the bioavailability of the stated abacavir 300 mg tablet manufactured by Cipla, India (test drug) with the same dose of the reference tablet (Ziagen, GlaxoSmithKline, USA) 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 – Abacavir 300 mg tablet (abacavir 300 mg) Batch no. K50904.
Treatment R:	Reference – Ziagen® tablet (abacavir 300 mg) Batch no. 5ZP3417.

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 18 samples within 24 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 abacavir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 25 ng/ml for abacavir.

The study was performed with 28 participants; data generated from a total of 28 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 (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	0.89 ± 0.63	1.04 ± 0.77	-	-
C_{max} (ng/ml)	3845 ± 935 (3737)	3777 ± 985 (3656)	102.2	92.8 – 112.7
AUC_{0-t} (ng.h/ml)	8369 ± 1893 (8134)	8237 ± 2245 (7912)	102.8	97.5 – 108.4
AUC_{0-inf} (ng.h/ml)	8457 ± 1907 (8221)	8324 ± 2254 (7999)	102.8	97.4 – 108.4

* geometric mean

Conclusion

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

4. Summary of product safety and efficacy

[HA371 trade name] has been shown to conform to the same appropriate standards of quality, efficacy and safety as those required for the innovator`s product. According to the submitted data on quality and bioavailability it is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Ziagen® 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 SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Bioequivalence

[HA371 trade name] has shown to be bioequivalent with Ziagen® (GlaxoSmithKline).

Efficacy and Safety

Regarding clinical efficacy and safety [HA371 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, bioequivalence, safety and efficacy the team of assessors considered by consensus that the benefit risk profile of [HA371 trade name] was acceptable for the following indication: **"Antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection in adults, adolescents and children."** and has advised to include, manufactured at Cipla Ltd, Manufacturing Division Plot No. A – 33/1/2, Patalganga Industrial Area, District – Raigad, 410220 Patalganga, Maharashtra,India in the list of prequalified medicinal products.