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	[HA674 trade name][*]
Manufacturer of Prequalified Product	Micro Labs Limited (ML06) Plot No: S-155 to S-159 & N1, Phase III & Phase IV Verna Industrial Estate, Verna Goa- 403722 India Tel: +91-832-2887142 Fax: +91-832-2887143 Email: exp@microlabs.in
Active Pharmaceutical Ingredient(s) (API)	Abacavir (as sulfate)
Pharmaco-therapeutic group (ATC Code)	Nucleoside and nucleotide reverse transcriptase inhibitors (J05AF06)
Therapeutic indication	[HA722 trade name] is indicated in combination with other antiretroviral agents for the treatment of HIV infection in children weighing less than 25 kg.

1. Introduction

[HA674 trade name] is indicated in combination with other antiretroviral agents for the treatment of HIV infection in children weighing less than 25 kg. [See Part 4 Summary of Products Characteristics (SmPC), for full indications].

[HA674 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.

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

The API specifications are pharmacopoeial based and include tests for description, solubility, identification (IR, HPLC and counter ion), water content (KF), residue on ignition, heavy metals, organic impurities (HPLC), enantiomer content (chiral HPLC; ≤ 0.20%), assay (HPLC), content of sulfate (potentiometric), residual solvents (GC) and particle size. Cyclopropylamine is controlled at a limit of 30 ppm (GC).

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 dispersible tablet formulation include aspartame, colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate and strawberry flavour. BSE/TSE compliance declarations were provided for all excipients. Magnesium sulfate is of vegetable origin. The components of strawberry flavour comply with foodstuff regulations (USA and EU).

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Abacavir (as Sulfate) 60mg Dispersible Tablets are white to off white coloured, capsule shaped, biconvex uncoated tablets debossed with "C50" on one side and score-line on the other side. The score-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 in an HDPE bottle containing a desiccant (1 g silica gel bag) and purified cotton.

The development of the composition of the dispersible tablets, targeted towards the paediatric population, has been described. The aim was to develop a dispersible tablet which would be bioequivalent to the WHO recommended comparator product, Ziagen® 20 mg/ml oral solution. The excipients used in the formulation design were selected from prior knowledge with respect to their physicochemical and functional properties, supported by API-excipient compatibility studies. The QTTP provided for the dispersible tablets was considered acceptable in achieving the intended performance of the formulation. Aspartame, a sweetener commonly used in dispersible formulations, provides good taste masking properties. Strawberry flavour is a commonly used flavour in dispersible formulations.

A wet granulation process was selected to achieve good flow properties and to resolve sticking and picking issues. The formulation and process parameters were optimised to obtain a dispersible tablet with the desired characteristics as per the QTTP. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The specifications are pharmacopoeial based and include tests for description, identification (HPLC and UV), average weigh, tablet dimensions, water content (KF), uniformity of dosage units (by weight variation), dissolution (UV detection), assay (HPLC), related substances (HPLC), residual solvents (GC), disintegration (≤ 3 minutes), fineness of dispersion and microbial limits.

Stability testing

Stability studies have been conducted 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 intended for marketing of the product. The data provided show that the product is quite stable and no negative trend was observed at both storage conditions. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable. In-use stability was not required, since administration is immediately after the tablet has dispersed.

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.

Study title: An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of [HA674 trade name] of Micro Labs Ltd., India with Ziagen® (abacavir sulfate) oral solution 20 mg/ml of ViiV Healthcare Research Triangle Park, NC 27709 in healthy, adult, human subjects under fasting conditions (study no. 494-14).

The objective of the study was to compare the bioavailability of the stated [HA674 trade name] manufactured for/by Micro Labs Ltd., India (test drug) with the reference formulation Ziagen® (ViiV Healthcare Research Triangle Park) 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 – 5 tablets Abacavir 60 mg (abacavir 300 mg) Batch no. AJAG001
Treatment R:	Reference – 15 ml Ziagen® 20mg/ml oral solution (abacavir 300 mg) Batch no. B4001

An 8 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 23 samples within 12 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 10 ng/ml for abacavir.

The study was performed with 36 participants; data generated from a total of 36 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)	0.51 ± 0.23	0.62 ± 0.28	-	-
C_{max} (ng/ml)	3776 ± 919 (3673)	3527 ± 1222 (3354)	109.5	103.0 – 116.4
AUC_{0-t} (ng.h/ml)	7428 ± 1914 (7202)	7384 ± 1985 (7128)	101.0	97.3 – 104.9
AUC_{0-inf} (ng.h/ml)	7480 ± 1934 (7252)	7440 ± 2020 (7179)	101.0	97.3 – 104.9

* 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. Accordingly, the test [HA674 trade name] meets the criteria for

bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Ziagen® (ViiV Healthcare Research Triangle Park).

4. Summary of product safety and efficacy

[HA674 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the reference product. According to the submitted data on quality and bioavailability [HA674 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the reference product Ziagen® oral solution 20 mg/ml (ViiV Healthcare Research Triangle Park) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of this product is considered to be acceptable when guidance and restrictions as stated in the Summary of Product Characteristics are considered. 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 [HA674 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA674 trade name] has been shown to be bioequivalent to Ziagen® oral solution 20 mg/ml (ViiV Healthcare Research Triangle Park).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA674 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 [HA674 trade name] was acceptable for the following indication: **"in combination with other antiretroviral agents for the treatment of HIV infection in children weighing less than 25 kg"** and has advised that the quality, efficacy and safety of [HA674 trade name] are acceptable to allow inclusion of [HA674 trade name], manufactured at Micro Labs Limited (ML06), Plot no. S-155 to 159 & N1, phase III & phase IV, Verna Industrial Estate, Verna, Goa-403722, India in the list of prequalified medicinal products.