### SCIENTIFIC DISCUSSION

This part reflects the scientific knowledge and the information about this product available at the time of prequalification. Thereafter, updates may have become necessary which are included in parts 1 to 5 and, if related to pharmaceutical issues, also documented in part 8 of this WHOPAR.

<table>
<thead>
<tr>
<th>Name of the Finished Pharmaceutical Product:</th>
<th>Abacavir Sulfate 20 mg/ml oral solution*</th>
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</thead>
<tbody>
<tr>
<td>Manufacturer of Prequalified Product:</td>
<td>Hetero Labs Limited</td>
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<td></td>
<td>Unit-III, # 22-110</td>
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<td></td>
<td>I.D.A., Jeedimetla</td>
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<td></td>
<td>Hyderabad</td>
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<td>Zip Code: 500 055</td>
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<td></td>
<td>Andhra Pradesh</td>
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<td></td>
<td>India</td>
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<tr>
<td>Active Pharmaceutical Ingredient (API):</td>
<td>Abacavir (as sulfate)</td>
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<tr>
<td>Pharmaco-therapeutic group (ATC Code):</td>
<td>Nucleoside reverse transcriptase inhibitors (J05AF06)</td>
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<tr>
<td>Therapeutic indication:</td>
<td>Abacavir Sulfate 20 mg/ml oral solution is indicated in combination with other antiretroviral agents for the treatment of HIV infection in children</td>
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</table>

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority’s (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.
1. Introduction

Abacavir Sulfate 20 mg/ml oral solution is indicated in combination with other antiretroviral agents for the treatment of Human Immunodeficiency Virus (HIV) infection in children.

Abacavir Sulfate 20 mg/ml oral solution should be prescribed by a physician experienced in the management of HIV infection.

2. Assessment of Quality

The assessment was done according to SOP 20 of the WHO Prequalification programme.

Active Pharmaceutical Ingredient (API)

Based on scientific principles, the WHO Prequalification of Medicines Programme (PQP) has identified abacavir (as sulfate) (up to 600mg oral dose) as a BCS class 3 AP, eligible for BCS-based biowaiver applications. The API is thus BCS highly soluble.

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, content of sulfate (potentiometric), organic impurities (HPLC), assay (HPLC), enantiomeric content (chiral HPLC; \( \leq 0.20\% \)), residual solvents and microbial limits.

Stability testing was conducted according to the requirements of WHO. The proposed re-test period of 24 months is justified based on the stability results when the API is stored not above 30ºC in the original packing material.

Other ingredients

Other ingredients used in the oral solution formulation include banana flavour, citric acid, methyl parahydroxybenzoate, propyl parahydroxybenzoate, propylene glycol, purified water, saccharin sodium, sodium citrate, sorbitol liquid (non-crystallising) and strawberry flavour.

Finished Pharmaceutical Product (FPP)

The oral solution is a clear to opalescent, yellowish, strawberry-banana flavoured liquid, presented in a 250 ml HDPE bottle closed with child resistant PP cap with induction sealing FSE wad or expanded PE wad. The pack size is 240 ml. A 10 ml oral dosing syringe, duly calibrated, is provided for accurate dosage measurement.

Pharmaceutical development and manufacture

The development of the final composition of the oral solution has been described. As part of the predevelopment studies the comparator product has characterized for its chemical and physical characteristics, including its pH as a CQA, as well as packaging. The selection of the excipients was based on the qualitative composition of the comparator product (Ziagen® 20 mg/ml oral solution). The amount of sorbitol was comparable to that of the comparator product as reported in its SmPC – this has been regarded essential for considering a biowaiver. Several batches were produced to optimize the formulation and manufacturing process. The oral solution contains methyl- and propyl hydroxybenzoate as preservatives, which were shown to be effective to control the growth of
microorganisms throughout the shelf life.

The manufacturing process consists of conventional preparation of the solution, adjustment of pH and volume, filtration and bottle filling. The critical steps were identified and appropriate in-process controls set. Validation data demonstrated the consistency of the process and the quality of the product.

**Specifications**
The finished product specifications include appropriate tests for description, identification of the API (TLC, HPLC) and sulfates, uniformity of mass of delivered dose, pH, related compounds (HPLC), assay (HPLC), content of preservatives (HPLC) and microbial limits. The test methods have been satisfactorily described and validated.

**Stability testing**
Stability studies have been performed at 25°C/60%RH and 30°C/75%RH as long-term storage conditions and for 6 months at accelerated conditions in the packaging proposed for marketing of the product. The data showed that the product is quite stable at all storage conditions, with a slight increase in degradation products with time, and little to no change in preservative content. The data support the proposed shelf life and storage conditions as defined in the SmPC.

**Conclusions**
The quality part of the dossier is accepted.

### 3. Assessment of Bioequivalence

A biowaiver was granted for Abacavir Sulfate 20 mg/ml oral solution manufactured by Hetero Labs Ltd., India, in accordance to the WHO guideline. In comparison with the innovator Ziagen oral solution, 20 mg/ml (GlaxoSmithKline), the test product was determined to be qualitatively essentially the same and quantitatively comparable regarding excipients which may affect absorption of abacavir.

### 4. Summary of Product Safety and Efficacy

Abacavir Sulfate 20 mg/ml oral solution has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator product. Abacavir Sulfate 20 mg/ml oral solution fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

The clinical safety of this product is considered to be 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 Abacavir Sulfate 20 mg/ml oral solution is used in accordance with the SmPC.
Bioequivalence

Abacavir Sulfate 20 mg/ml oral solution fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance. Hence, Abacavir Sulfate 20 mg/ml oral solution and Ziagen® 20 mg/ml oral solution (GlaxoSmithKline) can be considered bioequivalent.

Efficacy and Safety

Regarding clinical efficacy and safety Abacavir Sulfate 20 mg/ml oral solution 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's assessment of data on quality, safety and efficacy the team of assessors considered that the benefit-risk profile of Abacavir Sulfate 20 mg/ml oral solution was acceptable for the following indication: “antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection in children” and has advised that the quality, efficacy and safety of Abacavir Sulfate 20 mg/ml oral solution allow inclusion of Abacavir Sulfate 20 mg/ml oral solution, manufactured at Hetero Labs Ltd., Unit III Jeedimetla, Hyderabad, 500 055 Andhra Pradesh, India, in the list of prequalified medicinal products.