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.

**SCIENTIFIC DISCUSSION**

<table>
<thead>
<tr>
<th>Name of the Finished Pharmaceutical Product:</th>
<th>AVIRODAY-EM *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer of Prequalified Product:</td>
<td>Shasun Pharmaceuticals Limited Unit – II, R.S No. 32-34, Shasun Road Periyakalapet Pondicherry – 605014, INDIA</td>
</tr>
<tr>
<td>Active Pharmaceutical Ingredients(APIs):</td>
<td>Efavirenz, Emtricitabine, Tenofovir disoproxil fumarate.</td>
</tr>
<tr>
<td>Pharmaco-therapeutic group (ATC Code):</td>
<td>Antivirals for treatment of HIV infections, combinations (emtricitabine, tenofovir disoproxil fumarate and efavirenz: J05AR06)</td>
</tr>
<tr>
<td>Therapeutic indication:</td>
<td>AVIRODAY-EM is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents from 10 years of age and weighing at least 35 kg</td>
</tr>
</tbody>
</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

AVIRODAY-EM is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents from 10 years of age and weighing at least 35 kg.

AVIRODAY-EM 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)

Efavirenz

Efavirenz is a class 4/2 API according to 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). Data provided in the dossier show that efavirenz is practically insoluble in aqueous medium over the pH range 1.2 to 8.0.

Efavirenz is manufactured in several steps from a commercially available starting material. It can exist in a number of crystalline forms, which were characterised by X-ray powder diffraction (XRPD). XRPD and DSC demonstrated that Form I is consistently produced.

The API specifications, which are pharmacopoeial based, include tests for description, solubility, identification (IR and HPLC), polymorphic form (XRPD), differential scanning calorimetry, specific optical rotation, water content, residue on ignition, heavy metals, completeness of solution, organic impurities (HPLC), assay (HPLC), limit of efavirenz, enantiomer (chiral HPLC; ≤ 0.2%), particle size distribution, residual solvents and determination of metal impurities (ICP-MS).

Stability testing was conducted according to the requirements of WHO. The proposed re-test period is justified based on the stability results when the efavirenz is stored in the original packing material.

Emtricitabine

Based on scientific principles the WHO Prequalification of Medicines Programme (PQP) has identified emtricitabine (up to 200 mg oral dose) as a BCS class 1 API. Emtricitabine is thus highly soluble according to the BCS.

Emtricitabine, 4-amino-5-fluoro-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-2(1H)-pyrimidinone, has two chiral centres. The desired stereochemistry is built into the key intermediate in the multi-step synthesis process, with L-menthol as the starting material for synthesis. Emtricitabine is known to exhibit polymorphism. Form I is consistently produced.

The API specifications include tests for description, solubility, identification (IR and HPLC), polymorphic identity (XPRD), loss on drying, specific optical rotation, residue on ignition, heavy metals, chloride content (potentiometric), organic impurities (HPLC), assay (HPLC), residual solvents, particle size distribution and content of alkyl methane sulfonates (LC/MS/MS; each individual ≤ 7.5 ppm).

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.
Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets (Sun Pharmaceuticals Ltd), HA527

Tenofovir disoproxil fumarate
Tenofovir disoproxil fumarate (TDF) is the salt of tenofovir disoproxil with fumaric acid. Tenofovir disoproxil is a diester pro-drug of the purine based nucleotide analogue, tenofovir. The pro-drug has increased oral bioavailability compared to tenofovir. TDF is a BCS Class 3 API, i.e. of high solubility and low permeability.

TDF, (R)-9-(2-phosphonomethoxypropyl)adenine disoproxil fumarate, is manufactured in several steps from adenine via (R)-9-(2-hydroxypropyl)adenine. The specifications and test methods for the isolated intermediates are considered to be satisfactory. The structure and stereochemistry of TDF were confirmed by the route of synthesis and spectrometric data.

The specifications for TDF include tests for description, solubility, identification of the API (IR, HPLC), fumaric acid (HPLC) and of the polymorphic form (XRPD), clarity of solution, water content (KF), heavy metals, melting point (DSC), related compounds (HPLC), enantiomeric impurity (chiral HPLC; ≤ 0.15%), assay and fumaric acid content (HPLC), residual solvents and particle size. The specifications also control the mutagenic 9-propenyladenine, which is a synthesis related substance, at ≤ 5 ppm. This is in accordance with the requirement of Tenofovir disoproxil fumarate Ph.Int.

TDF is known to exhibit polymorphism and exists in two forms, namely a low melting form (m.p. 112-114°C) and a high melting form (m.p. 114-118°C). The high melting form, controlled by XRPD and melting point, is consistently produced. The test methods have been adequately validated.

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 packaging.

Other ingredients
Other ingredients used in the core tablet formulation include microcrystalline cellulose, croscarmellose sodium, red iron oxide, hydroxypropyl cellulose, sodium lauryl sulfate and magnesium stearate. Magnesium stearate is of vegetable origin. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol (part-hydrolysed), titanium dioxide, polyethylene glycol and talc.

Finished Pharmaceutical Product (FPP)

Pharmaceutical development and manufacture
Each tablet contains 600 mg of efavirenz, 200 mg of emtricitabine and 300 mg of TDF equivalent to 245 mg of tenofovir disoproxil or 136 mg of tenofovir.

The multisource product is a white to off-white, capsule shaped film coated tablet debossed with ‘RF21’ on one side and plain on the other side. The tablets are packaged in an HDPE bottle with child resistant polypropylene closure with heat seal liner. The bottle also contains a desiccant sachet.

The objective of the development programme was to obtain a stable, robust, immediate-release FDC tablet that is bioequivalent to the WHO comparator product, Atripla®. Similar to the comparator product, a bilayer tablet containing the BCS low soluble efavirenz in one layer and the BCS highly soluble emtricitabine and TDF in the other layer was developed. The selection of excipients was based on their suitability to achieve the desired tablet characteristics, information of the qualitative composition of the comparator product and compatibility with the APIs.

Efavirenz and TDF are high dose, low density APIs with poor flow properties therefore needs densification to achieve satisfactory flow properties. Furthermore TDF is sensitive towards hydrolysis. It was accordingly decided to prepare the efavirenz blend by a wet granulation process and the
emtricitabine/TDF blend via a dry granulation process and compress into bilayer tablets. To protect the product from moisture a silica gel desiccant is included in the bottle packs. The process parameters were optimised to obtain tablets of desired characteristics. Satisfactory in-process controls have been established.

**Specifications**

The finished product specifications include tests for description, identification of the APIs (HPLC and TLC) and colorants, average weight, uniformity of dosage units (by content uniformity), water content (KF), dissolution (HPLC detection), related substances (HPLC), assay (HPLC) and microbial limits. The test methods have been satisfactorily validated.

**Stability testing**

Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. Slight degradation was observed for TDF, though the degradants remained within acceptable limits. 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 2010/2011 according to internationally accepted guidelines.

An open label, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, crossover bioequivalence study comparing fixed dose combination tablets of efavirenz 600 mg, emtricitabine 200 mg & tenofovir disoproxil fumarate 300 mg of Ranbaxy Laboratories Limited with Atripla® tablets (containing efavirenz 600 mg, emtricitabine 200 mg & tenofovir disoproxil fumarate 300 mg) of Bristol Myers Squibb & Gilead Sciences, Inc. in healthy, adult, human subjects under fasting condition (study no. 1017/10).

The objective of the study was to compare the bioavailability of the stated Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600/200/300mg FDC tablet manufactured by Ranbaxy Laboratories Ltd., India (test drug) with the reference formulation Atripla® (Bristol-Myers Squibb and Gilead Sciences) 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 – 1 tablet Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600/200/300mg (efavirenz 600 mg + emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg) Batch no. 10EL001A.
- **Treatment R**: Reference – 1 tablet Atripla® (efavirenz 600 mg + emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg) Batch no. V0259A003.
A 35 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 31 samples within 72 h post dose) were taken during each study period to obtain bioavailability characteristics AUC, \( C_{\text{max}} \) and \( t_{\text{max}} \) for bioequivalence evaluation. Drug concentrations for efavirenz, emtricitabine and tenofovir were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 10 ng/ml for efavirenz as well as for emtricitabine and tenofovir.

The study was performed with 52 participants; data generated from a total of 45 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for efavirenz, emtricitabine and tenofovir as well as statistical results are summarised in the following tables:

### Efavirenz

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Test formulation (T) arithmetic mean ± SD (*)</th>
<th>Reference (R) arithmetic mean ± SD (*)</th>
<th>log-transformed parameters</th>
<th>Ratio T/R (%)</th>
<th>Conventional 90% CI (ANOVA Log)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( t_{\text{max}} ) (h)</td>
<td>3.16 ± 1.31</td>
<td>3.36 ± 1.27</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/ml)</td>
<td>2576 ± 602 (2518)</td>
<td>2844 ± 678 (2762)</td>
<td>91.3</td>
<td>85.4 – 97.5</td>
<td></td>
</tr>
<tr>
<td>AUC0-72h (ng.h/ml)</td>
<td>58412 ± 13808 (56814)</td>
<td>61877 ± 16471 (59727)</td>
<td>94.6</td>
<td>90.0 – 99.5</td>
<td></td>
</tr>
</tbody>
</table>

* geometric mean

### Emtricitabine

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Test formulation (T) arithmetic mean ± SD (*)</th>
<th>Reference (R) arithmetic mean ± SD (*)</th>
<th>log-transformed parameters</th>
<th>Ratio T/R (%)</th>
<th>Conventional 90% CI (ANOVA Log)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( t_{\text{max}} ) (h)</td>
<td>1.69 ± 0.89</td>
<td>1.76 ± 0.56</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/ml)</td>
<td>2427 ± 513 (2376)</td>
<td>2444 ± 503 (2397)</td>
<td>99.1</td>
<td>94.5 – 104.0</td>
<td></td>
</tr>
<tr>
<td>AUC0-t (ng.h/ml)</td>
<td>13070 ± 2192 (12900)</td>
<td>12916 ± 2095 (12755)</td>
<td>101.0</td>
<td>97.9 – 104.3</td>
<td></td>
</tr>
<tr>
<td>AUC0-inf (ng.h/ml)</td>
<td>13353 ± 2207 (13184)</td>
<td>13176 ± 2106 (13016)</td>
<td>101.2</td>
<td>98.2 – 104.3</td>
<td></td>
</tr>
</tbody>
</table>

* geometric mean

### Tenofovir

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Test formulation (T) arithmetic mean ± SD (*)</th>
<th>Reference (R) arithmetic mean ± SD (*)</th>
<th>log-transformed parameters</th>
<th>Ratio T/R (%)</th>
<th>Conventional 90% CI (ANOVA Log)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( t_{\text{max}} ) (h)</td>
<td>1.25 ± 0.68</td>
<td>1.03 ± 0.45</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/ml)</td>
<td>350 ± 101 (337)</td>
<td>349 ± 83 (339)</td>
<td>99.3</td>
<td>92.2 – 107.0</td>
<td></td>
</tr>
<tr>
<td>AUC0-t (ng.h/ml)</td>
<td>2425 ± 538 (2369)</td>
<td>2465 ± 572 (2397)</td>
<td>98.8</td>
<td>93.8 – 104.1</td>
<td></td>
</tr>
<tr>
<td>AUC0-inf (ng.h/ml)</td>
<td>2811 ± 581 (2753)</td>
<td>2860 ± 618 (2791)</td>
<td>97.6</td>
<td>93.1 – 102.4</td>
<td></td>
</tr>
</tbody>
</table>

* geometric mean
The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C\text{max} values regarding efavirenz, emtricitabine and tenofovir. Accordingly, the test FDC tablet Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600/200/300mg meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Atripla\textregistered (Bristol-Myers Squibb/Gilead Sciences Inc.).

4. Summary of Product Safety and Efficacy

AVIRODAY-EM has been shown to conform to the same relevant standards of quality, efficacy and safety as those required for the innovator product. According to the submitted data on quality and bioavailability AVIRODAY-EM is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Atripla\textsuperscript{TM} tablet (Bristol-Myers Squibb and Gilead Sciences Inc, U.S.A.) 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 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 AVIRODAY-EM is used in accordance with the conditions as stated in the SmPC.

Bioequivalence

AVIRODAY-EM has shown to be bioequivalent with Atripla\textsuperscript{TM} tablet (Bristol-Myers Squibb and Gilead Sciences Inc, U.S.A.).

Efficacy and Safety

Regarding clinical efficacy and safety, AVIRODAY-EM 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 WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of AVIRODAY-EM was acceptable for the following indication: “treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents from 10 years of age and weighing at least 35 kg” and has advised that the quality, efficacy and safety of AVIRODAY-EM allow inclusion of AVIRODAY-EM, manufactured at Shasun Pharmaceuticals Limited, Unit – II, R.S No. 32-34, Shasun Road, Peryakalapet, Pondicherry – 605014, India in the list of prequalified medicinal products.