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**

| Name of the Finished Pharmaceutical Product: | Darunavir (as ethanolate) 800mg Tablets* |
| Manufacturer of Prequalified Product: | Cipla Limited  
Unit –II, A-42, MIDC  
Patalganga: 410220  
District: Raigad, Maharashtra  
India |
| Active Pharmaceutical Ingredient (API): | Darunavir |
| Pharmaco-therapeutic group (ATC Code): | Antivirals for systemic use, protease inhibitor (J05AR 14) |
| Therapeutic indication: | Darunavir (as ethanolate) 800 mg Tablets co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescent patients weighing at least 40 kg. |

* 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
Darunavir (as ethanolate) 800 mg Tablets co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescent patients weighing at least 40 kg. [See Part 4 Summary of Products Characteristics (SmPC), for full indications].

Darunavir (as ethanolate) 800 mg Tablets 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)
Darunavir contains 5 stereogenic carbon centres. The pharmaceutical form is [(1S,2R)-3-[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carboxylic acid (3R,3aS,6aR)-6-hexahydrofuran-3-yl ester monoethanolate. Darunavir ethanolate is slightly hygroscopic.

The manufacture of the API entails several steps, is well described and renders one single isomer. The structure and absolute configuration has been confirmed with single crystal X-ray crystallography.

The API specifications include tests for description, solubility, identification (IR, HPLC), polymorphic form (IR), water content (KF), specific optical rotation, residue on ignition, heavy metals, ethanol content (GC), related substances (HPLC), assay (HPLC), particle size distribution (PSD; laser diffraction) and residual solvents (GC). The PSD limits are based on the results obtained for the API batch used in the manufacture of the FPP biobatch. The related substances limits are in accordance with ICH Q3A.

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 hydroxypropyl methylcellulose, silicified microcrystalline cellulose, crospovidone, colloidal silicon dioxide and magnesium stearate, all being pharmacopeial controlled. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol part hydrolysed, titanium dioxide, macrogol/PEG, talc and iron oxide red. None of the excipients are derived from animal origin.

Finished pharmaceutical product (FPP)
Pharmaceutical development and manufacture
The multisource product is a dark red coloured, oval shaped, biconvex, film coated tablet, debossed with ‘DNV’ on one side and with ‘800’ on the other side. Each tablet contains 867.297 mg darunavir ethanolate equivalent to 800 mg darunavir. The tablets are packaged in a white HDPE bottle fitted with a white CRC polypropylene cap.

The development of the final composition of the multisource product has been described. The objective was to develop a stable tablet, bioequivalent to the WHO recommended comparator product, Prezista® tablet 800 mg, which is an immediate release solid dosage form for oral administration. The comparator product was characterized and on that basis a quality target product profile was defined and critical quality attributes (CQAs) identified. The composition of the final formulation is qualitatively similar to that of the comparator product. The API, darunavir ethanolate, is practically insoluble in aqueous medium over the physiological pH range and in water and therefore particle size distribution (PSD) was identified as one of the CQAs.
Wet granulation using fluid bed equipment was selected as the manufacturing process. The composition and process parameters were optimised, applying quality by design principles, to obtain tablets of desired characteristics. Satisfactory in-process controls have been established.

**Specifications**

The finished product specifications include tests for description, identification of API (HPLC, UV) and colorants, average weight, water content (KF), uniformity of weight, disintegration time, uniformity of dosage units (by weight variation), dissolution (HPLC detection), related substances (HPLC), assay (HPLC), residual solvents, ethanol content (GC), polymorphic identification (IR) and microbiological examination of non-sterile products. The test procedures have been adequately validated.

**Stability testing**

Stability studies have been conducted at 30°C/75%RH as long-term storage condition and for six months at accelerated conditions in the packaging intended for marketing of the product. The data provided shows that the product is stable with little degradation at the accelerated conditions. Photo stability results revealed that the product is photo stable. The data support the proposed shelf life at the storage conditions as stated in the SmPC.

**Conclusion**

The quality part of the dossier is accepted.

### 3. Assessment of Bio-Equivalence

The following bioequivalence study has been performed in 2015 according to internationally accepted guidelines.

A randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study of Darunavir ethanolate tablets 800 mg of Cipla Ltd., India with Prezista® (darunavir) tablets 800 mg of Janssen Therapeutics, USA, co-administration with Norvir® (ritonavir) tablet 100 mg of Abbvie Inc, USA twice daily, in normal, healthy, adult, human subjects under fed condition (study no. ARL/14/528).

The objective of the study was to compare the bioavailability of the stated Darunavir 800 mg tablet manufactured by/for Cipla Limited, India (test drug) with the reference formulation Prezista® (Janssen Therapeutics) and to assess bioequivalence. Ritonavir 100 mg twice daily was administered for 5 days. Darunavir was co-administered at day 3. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fed conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

**Treatment T:**
- Test – 1 tablet Darunavir 800 mg (darunavir 800 mg)
  - Batch no. PB50069.

**Treatment R:**
- Reference – 1 tablet Prezista® (darunavir 800 mg)
  - Batch no. 14GG213.

A 13 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 25 samples within 72 hours 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 darunavir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 100 ng/ml for darunavir.

The study was performed with 36 participants; data generated from a total of 33 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.
Arithmetic mean and geometric mean values of the pharmacokinetic variables for darunavir as well as statistical results are summarised in the following table:

<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 Ratio T/R (%)</th>
<th>Conventional 90% CI (ANOVAlog)</th>
</tr>
</thead>
<tbody>
<tr>
<td>t_{max} (h)</td>
<td>3.69 ± 1.35</td>
<td>3.65 ± 1.31</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C_{max} (µg/ml)</td>
<td>8.89 ± 2.04 (8.69)</td>
<td>8.35 ± 1.86 (8.15)</td>
<td>106.6</td>
<td>101.3 – 112.2</td>
</tr>
<tr>
<td>AUC_{0-1} (µg.h/ml)</td>
<td>127 ± 41 (121)</td>
<td>115 ± 37 (110)</td>
<td>110.3</td>
<td>103.2 – 117.8</td>
</tr>
<tr>
<td>AUC_{0-inf} (µg.h/ml)</td>
<td>132 ± 43 (126)</td>
<td>119 ± 39 (114)</td>
<td>110.6</td>
<td>103.3 – 118.4</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_{max} values regarding darunavir. Accordingly, the test Darunavir 800 mg tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Prezista® (Janssen Therapeutics, USA).

4. Summary of Product Safety and Efficacy
Darunavir (as ethanolate) 800 mg Tablets 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, Darunavir (as ethanolate) 800 mg Tablets is pharmaceutically and therapeutically equivalent and thus interchangeable with the WHO recommended comparator product Prezista® 800mg tablets 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 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 Darunavir (as ethanolate) 800 mg Tablets is used in accordance with the SmPC.

Bioequivalence
Darunavir (as ethanolate) 800 mg Tablets has shown to be bioequivalent with Prezista® [darunavir as ethanolate] 800 mg tablets, Janssen Therapeutics, USA.

Efficacy and Safety
Regarding clinical efficacy and safety, Darunavir (as ethanolate) 800 mg Tablets is considered effective and safe to use when the guidance and restrictions 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 Darunavir (as ethanolate) 800 mg Tablets was
acceptable for the following indication: “co-administered with low dose ritonavir, in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescent patients weighing at least 40 kg” and has advised that the quality, efficacy and safety of Darunavir (as ethanolate) 800 mg Tablets allow inclusion of Darunavir (as ethanolate) 800 mg Tablets, manufactured at Cipla Limited, Unit – II, A-42, MIDC, Patalganga 410220, District Raigad, Maharashtra, India in the list of prequalified medicinal products.