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:	[HA751 trade name][1]
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, 403 722, India
Active Pharmaceutical Ingredient (API):	Dolutegravir (as sodium)
Pharmaco-therapeutic group **(ATC Code):**	Antivirals for systemic use, other antivirals. (J05AX12)
Therapeutic indication:	[HA751 trade name] is indicated in combination with other antiretroviral medicines for the treatment of human immunodeficiency virus (HIV) infection in patients weighing at least 20kg.

1. Introduction

[HA751 trade name] is indicated in combination with other antiretroviral medicines for the treatment of human immunodeficiency virus (HIV) infection in patients weighing at least 20 kg.

[HA751 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)

Dolutegravir has been prequalified by WHO according to WHO's *Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products* (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that the API, used in the manufacture of [HA751 trade name], is of good quality and manufactured in accordance with WHO Good Manufacturing Practices. API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and assessment of the sites of API manufacture to verify compliance with WHO GMP requirements.

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

Other ingredients

Other ingredients used in the core tablet formulation include microcrystalline cellulose, D-mannitol, sodium starch glycolate, povidone and sodium stearyl fumarate, all being conventional pharmaceutical ingredients complying with the requirements of the pharmacopoeia. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol, titanium dioxide, macrogol/polyethylene glycol, talc, FD&C blue #2/ indigo carmine aluminium lake and D&C yellow #10 aluminium lake. TSE/BSE free certificates from the suppliers have been provided with regards to all the excipients.

Finished Pharmaceutical Product (FPP)

Pharmaceutical development and manufacture

The multisource product is a green coloured, round shaped, biconvex, film coated tablet debossed with 'C' on one side and '90' on the other side (with approximate dimensions of 9.10 mm in diameter and 4.60 mm in thickness). The tablets are presented in round, white opaque HDPE bottles with white, round polypropylene child resistant closures with head induction foil inner seals

The development strategy was to formulate an immediate release oral tablet dosage form, which is stable, robust and bioequivalent to the WHO comparator product Tivicay® (Dolutegravir 50 mg) Tablets. The excipients were selected based on the excipients used in the comparator product and API-excipient compatibility data. Based on the available literature on the comparator product, a wet granulation manufacturing process was selected for the finished pharmaceutical product. Based on the satisfactory data of optimization trials, the formulation was finalized resulting in a product matching the quality target product profile. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications include tests for description, identification of the API (HPLC and UV-PDA detection), water content (KF), uniformity of dosage units (by content uniformity), dissolution (HPLC detection), related substances (HPLC), assay (HPLC), residual solvents, elemental impurities and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been performed 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 proposed for marketing of the product. The product proved to be quite stable at these storage conditions with no apparent negative trend. 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 2017 according to internationally accepted guidelines.

A randomized, open-label, balanced, two-treatment, two-period, two-sequence, single-dose, two-way crossover, oral bioequivalence study of Dolutegravir (as sodium) Tablets 50 mg manufactured by Micro Labs Limited, India and TIVICAY® (dolutegravir) Tablets 50 mg manufactured by GlaxoSmithKline, Research Triangle Park, NC 27709, made in Japan, manufactured for ViiV Healthcare Research Triangle Park, NC 27709, in healthy, adult, human subjects under fasting conditions (study no. 052-17).

The objective of the study was to compare the bioavailability of the stated Dolutegravir (as sodium) 50 mg tablet manufactured by/for Micro Labs Limited, India (test drug) with the reference formulation Tivicay® (GSK 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 two treatments in a randomized fashion:

Treatment T: Test – 1 tablet Dolutegravir 50 mg (dolutegravir 50 mg) Batch no. OAAG001.

Treatment R: Reference – 1 tablet Tivicay® (dolutegravir 50 mg) Batch no. 5ZP1936.

A 3 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 25 samples within 48h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for dolutegravir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 30 ng/mL for dolutegravir.

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 dolutegravir as well as statistical results are summarised in the following table:

Dolutegravir

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (geometric mean)	Reference (R) arithmetic mean ± SD (geometric mean)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	2.61 ± 1.25	2.36 ± 1.02	-	-
C_{max} (ng/mL)	2700 ± 968 (2484)	2792 ± 792 (2577)	96.4	84.5 – 109.9
AUC_{0-t} (ng.h/mL)	41441 ± 18178 (37474)	41150 ± 14264 (38557)	97.2	86.5 – 109.2
AUC_{0-inf} (ng.h/mL)	46093 ± 22267 (40995)	45795 ± 16942 (42523)	96.4	86.1 – 107.9

Conclusion

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding dolutegravir. Accordingly, the test Dolutegravir 50 mg tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Tivicay® (GSK Research Triangle Park).

4. Summary of Product Safety and Efficacy

[HA751 trade name] 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 [HA751 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Tivicay® (GlaxoSmithKline) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [HA751 trade name] is considered acceptable when guidance and restrictions stated in the summary of product characteristics (SmPC) are considered. Refer 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 clinical performance of the product 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 [HA751 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA751 trade name] has been shown to be bioequivalent with Tivicay® (GlaxoSmithKline).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA751 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 assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit-risk profile of [HA751 trade name] was acceptable for the following indication: **"in combination with other antiretroviral medicines for the treatment of human immunodeficiency virus (HIV) infection in patients weighing at least 20kg"** and would allow inclusion of [HA751 trade name], manufactured at Micro Labs Limited (ML06), Plot No S-155 to S-159 & N1, Phase III & Phase IV, Verna Industrial Estate, Verna, Goa, 403 722, India, in the list of prequalified medicinal products.