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:	[HA678 trade name][*]
Manufacturer of Prequalified Product:	Mylan Laboratories Limited Plot no: 11-12 & 13, Indore SEZ Pharma Zone, Phase-II, Sector-III Pithampur –454775 Dist. Dhar, Madhya Pradesh India
Active Pharmaceutical Ingredient (API):	Dolutegravir (as sodium)
Pharmaco-therapeutic group (ATC Code):	Antivirals for systemic use, other antivirals. (J05AX12)
Therapeutic indication:	[HA678 trade name] is indicated in combination with other antiretroviral medicines for the treatment of human immunodeficiency virus (HIV) infected adults and adolescents weighing at least 40kg.

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

1. Introduction

[HA678 trade name] is indicated in combination with other antiretroviral medicines for the treatment of human immunodeficiency virus (HIV) infected adults and adolescents weighing at least 40kg.

[HA678 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 sodium 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 dolutegravir sodium, used in the manufacture of Dolutegravir (as sodium) 50mg Tablets, is of good quality and manufactured in accordance with WHO good manufacturing practices (GMP). 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.

The API is slightly hygroscopic. It is practically insoluble across the physiological pH range, therefore the FPP manufacturer controls particle size and polymorphic form in the API specifications.

Other ingredients

Other ingredients used in the core tablet formulation include mannitol, povidone, sodium starch glycolate, microcrystalline cellulose 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, macrogol/polyethylene glycol, talc, titanium dioxide, red iron oxide red and black iron oxide. 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 pink, film-coated, round, biconvex, beveled edge tablet debossed with **M** on one side of the tablet and **DT5** on the other side. The tablets are presented in PVC/ACLAR blisters and HDPE bottles closed with blue opaque polypropylene caps.

The tablets have been developed as immediate release solid dosage form for oral administration. The excipients selected are qualitatively the same as included in the WHO recommended comparator product, Tivicay® 50 mg tablets. Dolutegravir sodium has very poor flow properties, hence direct compression process was not considered for manufacture of the tablets. In order to ensure content uniformity and considering the poor solubility of Dolutegravir sodium active pharmaceutical ingredient, an aqueous wet granulation process was selected. The critical steps of the manufacturing process have been optimized. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications include tests for description, identification (HPLC and TLC), colour identifications, dissolution (HPLC detection), uniformity of dosage units (by content uniformity), assay (HPLC), related substances (HPLC), water content (KF) 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 results for all parameters at these storage conditions were within agreed acceptance criteria and no negative or atypical trends were observed. 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 2016 according to internationally accepted guidelines.

An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study of Dolutegravir tablets 50 mg of Mylan Laboratories Limited, India with Tivicay® (dolutegravir) tablets 50 mg of GlaxoSmithKline, Research Triangle Park, NC 27709, for ViiV Healthcare, RTP, NC 27709 in normal healthy adult human subjects under fasting conditions (study no. C14349).

The objective of the study was to compare the bioavailability of the stated Dolutegravir 50 mg tablet manufactured by/for Mylan Laboratories Limited, India (test drug) with the reference formulation Tivicay® (GlaxoSmithKline) 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. 2010882.
Treatment R:	Reference – 1 tablet Tivicay® (dolutegravir 50 mg) Batch no. 4ZP4087.

A 4-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 24 samples within 72h 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 50 ng/mL for dolutegravir.

The study was performed with 44 participants; data generated from a total of 41 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)	2.50 ± 1.51	2.68 ± 1.24	-	-

C_{max} (µg/mL)	2.32 ± 0.65 (2.23)	2.47 ± 0.82 (2.32)	96.3	87.9 – 105.5
AUC_{0-t} (µg.h/mL)	42.5 ± 14.3 (39.8)	45.9 ± 18.4 (41.8)	95.1	87.3 – 103.6
AUC_{0-inf} (µg.h/mL)	45.7 ± 15.4 (42.8)	48.5 ± 19.7 (44.2)	96.8	89.5– 104.7

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® (GlaxoSmithKline).

4. Summary of Product Safety and Efficacy

[HA678 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 [HA678 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 [HA678 trade name] is considered to be acceptable when guidance and restrictions presented 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 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 [HA678 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA678 trade name] has shown to be bioequivalent with Tivicay® (GlaxoSmithKline).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA678 trade name] 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 the WHO assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit risk profile of [HA678 trade name] was acceptable for the following indication: **"in combination with other antiretroviral medicines for the treatment of human immunodeficiency virus (HIV) infected adults and adolescents weighing at least 40kg"** and has advised that quality, efficacy and safety of [HA678 trade name] allow inclusion of [HA678 trade name], manufactured at Mylan Laboratories Limited Plot no: 11-12 & 13, Indore SEZ, Pharma Zone, Phase-II, Sector-III Pithampur –454775 Dist. Dhar, Madhya Pradesh, India, in the list of prequalified medicinal products.