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	[HA718 trade name]*
Manufacturer of Prequalified Product	Laurus Labs Limited (Unit -2) Plot No. 19, 20 & 21 Western Sector, APSEZ, Atchutapuram Mandal Visakhapatnam- District -531011 Andhra Pradesh India
Active Pharmaceutical Ingredient(s) (API)	Dolutegravir (as sodium)
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use, other antivirals. (J05AX12)
Therapeutic indication	[HA718 trade name] is indicated, in combination with other antiretroviral medicines, for the treatment of human immunodeficiency virus (HIV) infection in adults and adolescents weighing at least 40 kg.

1. Introduction

[HA718 trade name] is indicated, in combination with other antiretroviral medicines, for the treatment of human immunodeficiency virus (HIV) infection in adults and adolescents weighing at least 40 kg.

[HA718 trade name] should be prescribed 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 [HA718 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.

* 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 mannitol, microcrystalline cellulose, 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 and sunset yellow FCF (E 110). 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 light orange, round-shaped, biconvex, film-coated tablet debossed with 'LA54' on one side and plain on the other side. The tablets are presented in white opaque HDPE bottles with polypropylene child resistant closures and induction sealing wad.

The aim of the development was to formulate an immediate release tablet, which is bioequivalent to the WHO comparator product Tivicay® (dolutegravir 50 mg tablets). The excipients were selected based on the excipients used in the comparator and API-excipient compatibility studies. Due to the very poor flow characteristics of the API, it was not feasible to manufacture the tablets by direct compression. Wet granulation was therefore selected as a way to improve the density of the API followed by drying and compression into tablets. 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, UV) and colorants, water content (KF), uniformity of dosage units (by content), dissolution (UV detection), related substances (HPLC), assay (HPLC) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been performed at 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 data showed some slight degradation for tablets in pack sizes of 30 under accelerated stability condition though the degradation products remained within acceptable limits. Based on the available stability data, the proposed shelf-life and storage conditions of the unopened bottles as stated in the SmPC are acceptable. The in-use storage period after first opening of the bottle of pack size of 90 tablets is based on in-use stability data.

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.

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, cross-over, oral bioequivalence study compared [HA718 trade name] of Laurus Labs Limited, India, with Tivicay® (dolutegravir) 50 mg tablets of ViiV Healthcare, Research Triangle Park, NC 27709, in healthy adult human subjects under fasting conditions (study no. 690-17).

The objective of the study was to compare the bioavailability of [HA718 trade name] of Laurus Labs Limited, India, with the reference formulation Tivicay® (ViiV Healthcare, 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 randomised fashion:

Treatment T: Test – 1 tablet [HA718 trade name] (dolutegravir 50 mg) Batch no. ADTG200217.

Treatment R: Reference – 1 tablet Tivicay® (dolutegravir 50 mg) Batch no. 7ZP3891.

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 23 samples within 72 hours 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 analysed using a validated LC-MS/MS method. The limit of quantification was stated to be about 20 ng/mL for dolutegravir.

The study was performed with 60 participants. Data generated from a total of 56 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)	2.33 (0.67 – 9.00)	2.00 (0.33 – 4.50)	–	–
C_{max} (ng/mL)	2994 ± 850 (2872)	3075 ± 919 (2941)	97.7	91.5 – 104.2
AUC_{0-t} (ng·h/mL)	52361 ± 18269 (49362)	54074 ± 20031 (50874)	97.0	92.1 – 102.2
AUC_{0-inf} (ng·h/mL)	55008 ± 20285 (51544)	56540 ± 21675 (52990)	97.3	92.4 – 102.4

Conclusions:

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 [HA718 trade name] meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Tivicay® (ViiV Healthcare, Research Triangle Park).

4. Summary of product safety and efficacy

[HA718 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, [HA718 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Tivicay® (ViiV Healthcare, Research Triangle Park) for which benefits have been proven in terms of clinical efficacy.

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 [HA718 trade name] is used in accordance with the SmPC

Bioequivalence

[HA718 trade name] has shown to be bioequivalent to Tivicay® (ViiV Healthcare, Research Triangle Park).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA718 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 WHO's assessment of data on quality, bioequivalence, safety and efficacy, the team of assessors considered that the benefit–risk profile of [HA718 trade name] was acceptable for the following indication: "**in combination with other antiretroviral medicines, for the treatment of human immunodeficiency virus (HIV) infection in adults and adolescents weighing at least 40 kg**" and would allow inclusion of [HA718 trade name], manufactured at Laurus Labs Limited (Unit-II), Plot No. 19, 20 & 21, Western Sector, APSEZ, Atchutapuram Mandal, Visakhapatnam- District - 531011, Andhra Pradesh, India, in the list of prequalified medicinal products.