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:	[HA731 trade name][1]
Manufacturer of Prequalified Product:	Strides Pharma Science Limited Strides House, Opp IIMB, Bilekahali, Bannerghatta Road, Bangalore Karnataka, 560 076 India Tel: +91-80-67840738/290
Active Pharmaceutical Ingredient (API):	Dolutegravir (as sodium)
Pharmaco-therapeutic group (ATC Code):	Antivirals for systemic use, other antivirals. (J05AX12)
Therapeutic indication:	[HA731 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

[HA731 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.

[HA731 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 the API, used in the manufacture of [HA731 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

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

with WHO norms and standards, and assessment of the sites of API manufacture to verify compliance with WHO GMP requirements.

Additional user requirements for the critically insoluble dolutegravir sodium include tests for polymorphic form and particle size distribution, the limits of which were set on the data obtained for the API batch used in the manufacture of the FPP biobatch.

Other ingredients

Other ingredients used in the core tablet formulation include microcrystalline cellulose, 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 partially hydrolysed, titanium dioxide, macrogol/polyethylene glycol, talc and iron oxide red. 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 coloured, round shaped, biconvex film coated tablet debossed with ‘50’ on one side and plain on the other side.

The tablets are presented in round, white opaque HDPE bottles, each closed with a white opaque polypropylene, inner transparent child resistant screw cap with a heat seal liner.

The aim of the development was to formulate an immediate release dosage form, which is stable, and bioequivalent to the WHO recommended comparator product Tivicay® (Dolutegravir 50mg) tablets. The excipients are qualitatively same as for the comparator product. The quality target product profile was suitably defined and the identified critical quality attributes were found to be acceptable. Wet granulation manufacturing process was selected to improve flow properties, compressibility and dissolution of 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.

According to a risk evaluation by the applicant, the FPP appears to have no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

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

Stability testing

Stability studies have been performed at 25°C/60%RH and 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at 40°C/75%RH as accelerated condition in the packaging proposed for marketing of the product. The data showed that the results for all parameters at the storage conditions were within the acceptance criteria. 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 2018 according to internationally accepted guidelines.

An open-label, balanced, randomized, two-treatment, two-sequence, two-period, two way cross-over, single dose oral bioequivalence study comparing Dolutegravir tablets 50mg of Strides Shasun Limited, India with Tivicay® (dolutegravir) tablets 50mg of Viiv Health Care, research triangle park, NC27709, in healthy, adult, human subjects under fasting conditions (study PCLPL-082-18).

The objective of the study was to compare the bioavailability of the stated Dolutegravir 50 mg tablet manufactured by/for Strides Shasun Limited, India (test drug) with the reference formulation Tivicay® 50 mg tablet (Viiv Health Care) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, 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. 7232305.
Treatment R:	Reference – 1 tablet Tivicay® 50 mg (dolutegravir 50 mg) Batch no. 7ZP3891.

A 11 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 29 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 analyzed 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 72 participants; data generated from a total of 70 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 (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	2.53 ± 1.39	2.68 ± 1.60	-	-
C_{max} (ng/mL)	3169 ± 967 (3022)	3405 ± 1076 (3235)	93.4	85.8 – 101.6
AUC_{0-t} (ng.h/mL)	61249 ± 19053 (58237)	64684 ± 20237 (61607)	94.5	87.8 – 101.8
AUC_{0-inf} (ng.h/mL)	64762 ± 20822 --	68537 ± 22665 --	-	-

*geometric mean

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® 50 mg tablet (Viiv Health Care).

4. Summary of Product Safety and Efficacy

[HA731 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 [HA731 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Tivicay® (Viiv Health Care) for which benefits have been proven in terms of clinical efficacy.

The clinical safety [HA731 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 [HA731 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA731 trade name] has been shown to be bioequivalent with Tivicay® (Viiv Health Care).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA731 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 [HA731 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 [HA731 trade name], manufactured at Strides Pharma Science Limited KRS Gardens 36/7, Suragajakkanahalli, Indlawadi cross Anekal Taluk, Bangalore, Karnataka, 562 106, India, in the list of prequalified medicinal products.