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	[HA708 trade name][*]
Manufacturer of Prequalified Product	Sun Pharmaceutical Industries Limited Village Ganguwala Paonta Sahib District Sirmour Himachal Pradesh 173 025 India
Active Pharmaceutical Ingredient(s) (API)	Dolutegravir (as sodium)
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use, other antivirals. (J05AJ03)
Therapeutic indication	[HA708 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

[HA708 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 [See Part 4 Summary of Products Characteristics (SmPC), for full indications].

[HA708 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 [HA708 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

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

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

Other ingredients

Other ingredients used in the core tablet formulation include mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, sodium stearyl fumarate, talc and magnesium stearate, 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, iron oxide yellow 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 light brown to brown film coated, capsule shaped tablet debossed with "RL75" on one side and break line on the other side. The break line is intended for subdivision of tablets when half a tablet dose is to be administered as supported by divisibility studies. The tablets are presented in white, opaque HDPE bottles with white opaque polypropylene screw/child resistant closures.

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 50mg) Tablets. The excipients were selected based on the excipients used in the comparator product and excipient compatibility data. Wet granulation was selected as the literature-standard manufacturing process for dolutegravir granules. 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 IR) and colorants, uniformity of dosage units (by content uniformity), loss on drying, sub-division of tablet, 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 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. 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 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 2018 according to internationally accepted guidelines.

Single dose two way crossover bioequivalence study on dolutegravir tablets 50 mg in healthy adult human subjects under fasting condition (study no. DLG_50T_0600_17).

The objective of the study was to compare the bioavailability of the stated Dolutegravir 50 mg tablet manufactured by/for Sun Pharmaceuticals Industries Limited, India (test drug) 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 randomized fashion:

Treatment T: Test – 1 tablet dolutegravir 50 mg (dolutegravir 50 mg) Batch no. 2889198.
Treatment R: Reference – 1 tablet Tivicay® (dolutegravir 50 mg) Batch no. 6ZP6123.

A 7-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, Cmax and tmax 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 40 ng/ml for dolutegravir.

The study was performed with 42 participants; data generated from a total of 38 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)	2.10 ± 1.20	2.42 ± 1.40	–	–
C_{max} (ng/mL)	2667 ± 638 (2587)	2551 ± 725 (2441)	106.0	98.4 – 114.2
AUC_{0-t} (ng·h/mL)	39166 ± 12770 (37093)	38873 ± 13139 (36475)	101.7	94.0 – 110.0
AUC_{0-inf} (ng·h/mL)	40808 ± 13097 (38735)	40582 ± 13653 (38107)	101.7	94.1 – 109.8

The results of the study show that the 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® (ViiV Healthcare Research Triangle Park).

4. Summary of product safety and efficacy

[HA708 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, [HA708 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.

The clinical safety of [HA708 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 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 [HA708 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA708 trade name] has been shown to be bioequivalent with Tivicay® (ViiV Healthcare Research Triangle Park).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA708 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's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [HA708 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 has advised that the quality, efficacy and safety of [HA708 trade name] allow inclusion of [HA708 trade name], manufactured at Sun Pharmaceutical Industries Limited, Village Ganguwala, Paonta Sahib, District Sirmour, Himachal Pradesh, 173 025, India in the list of prequalified medicinal products.