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	[HA794 trade name]*
Manufacturer of Prequalified Product	RV Lifesciences Limited Plot No. H-19, MIDC, Waluj Chhatrapati Sambhajinagar – 431133 Maharashtra State India
Active Pharmaceutical Ingredient(s) (API)	Dolutegravir (as sodium)
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use, integrase inhibitors (J05AJ03)
Therapeutic indication	[HA794 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.

1. Introduction

[HA794 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.

Treatment regimens should follow most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

[HA794 trade name] may also be used as part of a regimen for post-exposure prophylaxis to HIV. For use of antiretroviral agents for post-exposure prophylaxis the most recent official guidelines, e.g. those by WHO, should be consulted.

Treatment with [HA794 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 [HA794 trade name], is of good quality and manufactured in

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

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.

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

Other ingredients

Other ingredients used in the core tablet formulation include mannitol, microcrystalline cellulose, sodium starch glycolate, povidone and sodium stearyl fumarate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol- partially hydrolysed, titanium dioxide, macrogol/polyethylene glycol, talc and iron oxide yellow. None of the excipients are derived from human or animal origin. 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 yellow, round, film-coated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablets have ‘A’ debossed (stamped into) one side and ‘21’ on the other side. The tablets are packaged in either aluminium foil on aluminium foil blister card or round, opaque white plastic (HDPE) bottle. The bottle also contains a sachet of desiccant (drying material). The bottle has an aluminium/ plastic foil seal and a white, childproof plastic (polypropylene) screw cap.

The objective of the product development was to obtain a stable and robust formulation, bioequivalent to the WHO recommended comparator product, Tivicay (Dolutegravir sodium 50 mg film-coated tablets). The selection of excipients was based on the comparator product information, compatibility study, experience with similar kind of dosage form and prior knowledge on excipients. The dolutegravir sodium API is cohesive and displays poor flowability that may produce tablets with high weight variability and content variability. Therefore, direct compression was avoided, rather an aqueous wet granulation process was selected for the development. Based on 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 appearance, identification of API (HPLC and HPLC with PDA detection), average mass of tablets, uniformity of mass, water content (KF), disintegration time, dissolution (HPLC detection), assay (HPLC), uniformity of dosage units (by content uniformity), related substances (HPLC), API polymorphic form (pXRD) and microbial limits.

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 storage condition in the packaging proposed for marketing of the product. The data provided indicated that the tested parameters remained within acceptable limits at both storage conditions, with no obvious trend or variability. 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 2023 according to internationally accepted guidelines.

An open label, balanced, randomized, two-treatment, two-period, two-sequence, two-way cross-over, single oral dose, bioequivalence study of [HA794 trade name] of RV Lifesciences Limited, Mumbai comparing with Tivicay (dolutegravir) 50 mg film-coated tablets of ViiV Healthcare BV, Netherlands in healthy, adult, human, subjects under fasting conditions (study 015-BE-2023).

The objective of the study was to compare the bioavailability of the stated [HA794 trade name] manufactured by/for RV Lifesciences Limited, India (test drug) with the reference formulation Tivicay® 50 mg tablet (Viiv Healthcare) 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 [HA794 trade name] (dolutegravir 50 mg) Batch no. RV23068A.
Treatment R:	Reference – 1 tablet Tivicay® 50 mg (dolutegravir 50 mg) Batch no. 7PE0.

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 19 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 19 ng/mL for dolutegravir.

The study was performed with 56 participants; data generated from a total of 53 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)**	2.00 (0.50 – 5.00)	2.50 (0.50 – 5.00)	–	–
C_{max} (ng/mL)	3199 ± 998 (3059)	3030 ± 734 (2950)	103.7	97.0 – 110.9
AUC_{0-t} (ng·h/mL)	63926 ± 20582 (60687)	62442 ± 18801 (59659)	101.7	95.2 – 108.7
AUC_{0-inf} (ng·h/mL)	67647 ± 23007 --	65674 ± 20351 --	–	–

**median (range)

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and Cmax values regarding dolutegravir. Accordingly, the test [HA794 trade name] 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 Healthcare).

4. Summary of product safety and efficacy

[HA794 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, [HA794 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Tivicay® 50 mg tablets (Viiv Healthcare) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA794 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 [HA794 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA794 trade name] has been shown to be bioequivalent with Tivicay® 50 mg tablets (Viiv Healthcare).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA794 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 [HA794 trade name] was acceptable for the following indication: '[HA794 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', and would allow inclusion of [HA794 trade name], manufactured at RV Lifesciences Limited, Plot No. H-19, MIDC, Waluj, Chhatrapati Sambhajinagar – 431133, Maharashtra State, India in the list of prequalified medicinal products.