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:	[HA701 trade name][*]
Manufacturer of Prequalified Product:	Emcure Pharmaceuticals Ltd Plot No. P-1 & P-2, ITBT Park Phase II, MIDC Hinjewadi, Pune Maharashtra 411057 India
Active Pharmaceutical Ingredient (API):	Dolutegravir (as sodium)
Pharmaco-therapeutic group (ATC Code):	Antivirals for systemic use, other antivirals. (J05AX12)
Therapeutic indication:	[HA701 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

[HA701 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].

[HA701 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 [HA701 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.

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- partially hydrolysed, titanium dioxide,

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

macrogol/polyethylene glycol, talc and FD& C blue #2/Indigo carmine aluminium lake. None of the excipients used in the manufacture of the tablets are of human or animal origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a blue, round shaped, film coated tablet debossed with 'HP' on one side and '526' on the other side. The tablets are presented in white opaque, wide mouth, round HDPE bottles, each closed with white opaque polypropylene child resistant closure with heat seal liner.
The aim of the development was to formulate an immediate release tablet, which is bioequivalent to the WHO comparator product Tivicay® (dolutegravir 50mg tablets). The excipients were selected based on the excipients used in the comparator and API-excipient compatibility studies. The manufacturing process for [HA701 trade name] is a standard wet granulation process involving high shear granulation. Due to the very poor flow characteristics of the API, high shear granulation was selected as an appropriate granulation method to provide excellent flow properties. 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 UV), assay (HPLC), dissolution (HPLC detection), related substances (HPLC), uniformity of dosage units (by content uniformity), water content (KF), residual solvent, elemental impurities 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 product proved to be quite stable at these storage conditions. 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 was performed in 2016 according to internationally accepted guidelines.

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, cross-over, oral bioequivalence study of Dolutegravir 50 mg tablets of Emcure Pharmaceuticals Ltd., 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. 653/15).

The objective of the study was to compare the bioavailability of the stated Dolutegravir 50 mg tablet manufactured by/for Emcure Pharmaceuticals Ltd., 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. EM65116.
Treatment R:	Reference – 1 tablet Tivicay® (dolutegravir 50 mg) Batch no. 5ZP8846.

A 11 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 26 samples within 48h 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 36 participants; data generated from a total of 35 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)	2.25 ± 1.36	2.55 ± 1.16	-	-
C_{max} (ng/ml)	3057 ± 760 (2965)	2864 ± 773 (2774)	106.9	99.6 – 114.7
AUC_{0-t} (ng.h/ml)	52550 ± 15164 (50476)	51225 ± 15390 (49156)	102.7	95.7 – 110.2
AUC_{0-inf} (ng.h/ml)	60434 ± 18523 (57763)	58709 ± 19045 (55872)	103.4	96.2 – 111.1

*geometric mean

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® (ViiV Healthcare Research Triangle Park).

4. Summary of Product Safety and Efficacy

[HA701 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, [HA701 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the reference formulation Tivicay® (ViiV Healthcare Research Triangle Park) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [HA701 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 [HA701 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA701 trade name] has been shown to be bioequivalent with Tivicay® (ViiV Healthcare Research Triangle Park).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA701 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 [HA701 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 [HA701 trade name] allow inclusion of [HA701 trade name], manufactured at Emcure Pharmaceuticals Ltd, Plot No. P-1 & P-2, ITBT Park Phase II, MIDC, Hinjewadi, Pune, Maharashtra 411057, India in the list of prequalified medicinal products.