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	[HA793 trade name][*]
Manufacturer of Prequalified Product	Micro Labs Limited Plot No S-155 to S-159 & N1 Phase III & Phase IV, Verna Industrial Estate, Verna, Goa, 403 722 India
Active Pharmaceutical Ingredient(s) (API)	Dolutegravir (as sodium)
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use, other antivirals (J05AJ03)
Therapeutic indication	[HA793 trade name] is indicated, in combination with other antiretroviral medicines, for the treatment of human immunodeficiency virus (HIV) infection in children at least 4 weeks of age or older and weighing at least 3 kg. [HA793 trade name] may also be used in these patients as part of a regimen for post-exposure prophylaxis to HIV.

1. Introduction

[HA793 trade name] is indicated, in combination with other antiretroviral medicines, for the treatment of human immunodeficiency virus (HIV) infection in children at least 4 weeks of age or older and weighing at least 3 kg.

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

[HA793 trade name] may also be used in these patients 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

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

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 [HA793 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 microcrystalline cellulose, mannitol, sodium starch glycolate, povidone, silicified microcrystalline cellulose, calcium sulfate dihydrate, crospovidone, sucralose, strawberry flavour and sodium stearyl fumarate, all being controlled by acceptable specifications. The commercially sourced proprietary film-coating mixture contains hypromellose and macrogol/polyethylene glycol. None of the excipients are derived from human or animal origin. TSE/BSE free certificates have been provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off white, round, film-coated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablet has 'I' and 'I' debossed (stamped into) and separated by a break line in one side and is plain on the other side. The tablets are packaged in round, opaque white plastic (HDPE) bottles. Each bottle also contains a canister of desiccant (drying material). Each bottle has an aluminium/plastic foil seal and a white, childproof plastic (polypropylene) screw cap.

The development strategy was to formulate a dispersible oral tablet, which is stable, robust and bioequivalent to the WHO comparator product Tivicay PD (Dolutegravir 5mg) tablets for oral suspension. The excipients were selected based on the qualitative composition of the comparator product and API-excipient compatibility data. Based on the available literature on the comparator product, a wet granulation manufacturing process was selected for 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 of the API (HPLC and UV-PDA detection), water content (KF), disintegration time, fineness of dispersion, assay (HPLC), dissolution (HPLC detection), uniformity of dosage units (by content uniformity), related substances (HPLC), residual solvents, 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 storage condition in the packaging proposed for

marketing of the product. The product proved to be quite stable at these storage conditions with no apparent negative trend. 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 2024 according to internationally accepted guidelines:

An open-label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, two-way crossover oral bioequivalence study of Dolutegravir dispersible tablets 10 mg (test) of Micro Labs Limited, India and Tivicay PD (dolutegravir) tablets for oral suspension 5 mg [2 × 5 mg] (reference), manufactured for ViiV Healthcare, Research Triangle Park, NC 27709 in healthy adult human male subjects under fasting conditions (study no. ML-CPU-053-22).

The objective of the study was to compare the bioavailability of the stated Dolutegravir 10 mg dispersible tablet manufactured by/for Micro Labs Limited, India (test drug) with the reference Tivicay PD 5 mg tablet for oral suspension (ViiV Healthcare) 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 10 mg (dolutegravir 10 mg) Batch no. WDAG001.
Treatment R:	Reference – 2 tablets Tivicay PD (dolutegravir 10 mg) Batch no. M39B.

The tablets were dispersed in 5 mL water (+ 10 mL of rinsing water) and administered. 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 h 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 5 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 tables:

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)	1.71 ± 0.93	1.55 ± 1.00	–	–
C_{max} (ng /mL)	1133 ± 219 (1110)	1127 ± 214 (1104)	100.5	95.8 – 105.5
AUC_{0-t} (ng·h/mL)	18954 ± 4325 (18437)	18889 ± 4095 (18396)	100.2	97.2 – 103.3
AUC_{0-inf} (ng·h/mL)	19836 ± 5076 (19192)	19870 ± 4949 (19222)	99.9	96.8 – 102.9

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 10 mg dispersible tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulation Tivicay PD tablet for oral suspension (ViiV Healthcare).

4. Summary of product safety and efficacy

[HA793 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, [HA793 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Tivicay PD tablet for oral suspension (ViiV Healthcare) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA793 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 [HA793 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA793 trade name] has been shown to be bioequivalent with Tivicay PD tablet for oral suspension (ViiV Healthcare).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA793 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 [HA793 trade name] was acceptable for the following indication: 'in combination with other antiretroviral medicines, for the treatment of human immunodeficiency virus (HIV) infection in children at least 4 weeks of age or older and weighing at least 3 kg ', and would allow inclusion of [HA793 trade name], manufactured at Micro Labs Limited, Plot No S-155 to S-159 & N1, Phase III & Phase IV, Verna Industrial Estate, Verna, Goa, 403 722, India in the list of prequalified medicinal products.