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	[HA779 trade name]*
Manufacturer of Prequalified Product	Cipla Limited, Indore Unit IV Plot No. 9 and 10 Indore Special Economic Zone, Phase II, Pithampur, District Dhar, 454775, Madhya Pradesh, India
Active Pharmaceutical Ingredients (API)	Abacavir (as sulfate), dolutegravir (as sodium) and lamivudine
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of HIV infections, combinations, ATC code: J05AR02
Therapeutic indication	[HA779 trade name] is indicated for the treatment of HIV-1 infection in infants and children aged from 4 weeks and weighing 6 to 25 kg.

1. Introduction

[HA779 trade name] is indicated for the treatment of HIV-1 infection in infants and children aged from 4 weeks and weighing 6 to 25 kg.
Treatment regimens should follow most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

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 Ingredients (APIs)

Abacavir sulfate, dolutegravir sodium and lamivudine have 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 APIs, used in the manufacture of [HA779 trade name], are 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.

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

Other ingredients

Other ingredients used in the core tablet formulation include microcrystalline cellulose, sodium starch glycolate, povidone, crospovidone, strawberry cream flavour, aspartame, colloidal silicon dioxide, iron oxide red, mannitol, calcium sulphate dihydrate 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, macrogol/polyethylene glycol, talc, titanium dioxide, iron oxide yellow and iron oxide red. Magnesium stearate is from plant origin. TSE/BSE free certificate from the supplier has been provided with regard to magnesium stearate.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a pink, oval, film- coated, dispersible tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablet has 'C' debossed (stamped into) on one side and are plain on the other side. The tablets are presented in white HDPE bottles with silica gel bags and closed with white non-child resistant screw caps.

The aim of the development was to formulate an immediate release FDC dosage form, which is stable, pharmaceutically equivalent and bioequivalent to the WHO recommended comparator product Triumeq PD® (abacavir 60mg/ dolutegravir 5mg/ lamivudine 30mg) tablets for oral suspension. The excipients were chosen and finalized based on the excipients used in the comparator product and API-excipient compatibility data. The quality target product profile was defined based on the properties of the APIs, consideration of the individual product labels of the comparators and the intended patient population. The proposed formulation was developed as a film-coated bilayer dispersible tablet with abacavir sulfate and lamivudine in first layer and dolutegravir sodium in the second layer. As the proposed formulation was targeted towards the paediatric population, aspartame and strawberry cream flavour were added as sweetener and flavour, respectively, to mask the bitter taste of the APIs and to improve the taste of the formulation. Film-coating was used to improve the aesthetic properties of the tablets. Wet granulation was selected as the method of manufacture for both the layers. Various experiments were performed to select and optimize the concentration of excipients and process parameters to obtain tablets of desired characteristics. Based on the satisfactory data of optimization trials, the formula was finalized. 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 APIs (HPLC, HPLC with PDA detector) and colorants, water content (KF), dissolution (HPLC detection), uniformity of dosage units (by content uniformity), assay (HPLC), degradation products (HPLC), residual solvents, fineness of dispersion, dispersion time 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 data provided indicate that the product is suitably stable at these storage conditions. 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 90-tablet bottle pack 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 2022 according to internationally accepted guidelines:

A randomized, single dose, open label, two treatment, two-period, cross-over oral bioequivalence study between the test product, Abacavir, Dolutegravir, and Lamivudine tablet for oral suspension 60/5/30 mg (Cipla Ltd., India) and the reference product, TRIUMEQ PD (abacavir 60mg, dolutegravir 5mg and lamivudine 30mg) tablets for oral suspension of ViiV Healthcare Research Triangle Park, NC 27709 in healthy male and female of non-child bearing potential (post-menopausal or surgically sterile) human subjects under fasting conditions (study no. 22-04-052).

The objective of the study was to compare the bioavailability of the stated Abacavir/Dolutegravir/Lamivudine 60mg/5mg/30mg FDC tablet manufactured by/for Cipla Ltd., India (test drug) with the reference formulation Triumeq PD® (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 Abacavir/Dolutegravir/Lamivudine 60mg/5mg/30mg

(abacavir 60 mg + dolutegravir 5 mg + lamivudine 30 mg)
Batch no. ID20166.

Treatment R: Reference – 1 tablet Triumeq PD®

(abacavir 60 mg + dolutegravir 5 mg + lamivudine 30 mg)
Batch no. 2P3T.

The tablets were dispersed in 20 ml water and administered. A 10-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 27 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 abacavir, dolutegravir and lamivudine were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 1 ng/ mL for abacavir, 2 ng/ml for dolutegravir and 1 ng/ml for lamivudine.

The study was performed with 66 participants; data generated from a total of 65 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for abacavir, dolutegravir and lamivudine as well as statistical results are summarised in the following tables:

Abacavir

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)	0.74 ± 0.59	0.75 ± 0.50	–	–
C_{max} (ng/mL)	748 ± 266 (704)	673 ± 255 (629)	112.0	103.2 – 121.6
AUC_{0-t} (ng ·h/mL)	981 ± 384 (918)	944 ± 384 (883)	104.0	99.4 – 108.7
AUC_{0-inf} (ng ·h/mL)	985 ± 386 (922)	948 ± 385 (887)	104.0	99.4 – 108.7

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)	1.37 ± 0.86	1.06 ± 0.64	–	–
C_{max} (ng /mL)	630 ± 116 (620)	721 ± 143 (707)	87.7	85.2 – 90.3
AUC_{0-t} (ng ·h/mL)	10968 ± 2762 (10593)	11286 ± 2962 (10870)	97.5	95.6 – 99.4
AUC_{0-inf} (ng ·h/mL)	11597 ± 3177 (11133)	11864 ± 3294 (11376)	97.9	95.8 – 100.0

Lamivudine

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)	1.38 ± 0.71	1.45 ± 0.65	–	–
C_{max} (ng /mL)	378 ± 120 (359)	341 ± 110 (324)	110.8	103.8 – 118.4
AUC_{0-t} (ng ·h/mL)	1669 ± 461 (1612)	1534 ± 485 (1464)	110.1	105.3 – 115.2
AUC_{0-inf} (ng ·h/mL)	1710 ± 471 (1651)	1572 ± 493 (1502)	109.9	105.1 – 115.0

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding abacavir, dolutegravir and lamivudine. Accordingly, the test Abacavir/Dolutegravir/Lamivudine 60mg/5mg/30mg FDC tablet for oral suspension meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulation Triumeq DP® (ViiV Healthcare).

4. Summary of product safety and efficacy

[HA779 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, [HA779 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the WHO-recommended comparator product Triumeq DP® (ViiV Healthcare) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA779 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 [HA779 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA779 trade name] have been shown to be bioequivalent with Triumeq DP® (ViiV Healthcare).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA779 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 [HA779 trade name] was acceptable for the following indication: **'treatment of HIV-1 infection in infants and children aged from 4 weeks and weighing 6 to 25 kg'**, and would allow inclusion of [HA779 trade name], manufactured at Cipla Limited, Indore Unit IV, Plot No. 9 and 10 Indore Special Economic Zone, Phase II, Pithampur, District Dhar, 454775, Madhya Pradesh, India, in the list of prequalified medicinal products.