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	[HA809 trade name][*]
Manufacturer of Prequalified Product	Micro Labs Limited (ML06) 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)	Abacavir (as sulfate), dolutegravir (as sodium) and lamivudine
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of HIV infections, combinations, ATC code: J05AR13
Therapeutic indication	[HA809 trade name] is indicated for the treatment of HIV infection in babies and children over 4 weeks of age who weigh between 3 kg and 25 kg.

1. Introduction

[HA809 trade name] is indicated for the treatment of HIV infection in infants and children over 4 weeks of age who weigh between 3 kg and 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 [HA809 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.

Additional user requirements for these APIs include test for 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 Microcrystalline cellulose, sodium starch glycolate, sucralose, crospovidone, strawberry flavour, sodium stearyl fumarate, mannitol, povidone and acesulfame potassium, all with the exception of strawberry flavour, being pharmacopoeial controlled. Strawberry flavour is adequately controlled by in-house specifications. 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, oval, film-coated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablets have ‘E71’ debossed (stamped into) one side and are plain on the other side. The tablets are packaged in a round, opaque, white plastic (HDPE) bottle with a canister 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, Triumeq PD (Abacavir sulfate/Dolutegravir sodium/ Lamivudine 60mg/5mg/30mg tablets for oral suspension). The comparator product was characterized and on that basis a quality target product profile was defined; critical quality attributes were also identified. The selection of the excipients was primarily based on the qualitative composition of the comparator product and API-excipient compatibility studies. The sweetener and flavouring agent were included to improve the taste of the paediatric formulation. Based on the physical characteristics of the APIs, wet granulation manufacturing process was selected to achieve free flowing granules with increased compressibility. The tablets were compressed as bilayer using abacavir sulfate and lamivudine lubricated blend as a first layer and dolutegravir lubricated blend as a second layer. 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 description, identification of APIs (HPLC and HPLC; by PDA detector), water content (KF), disintegration time, fineness of dispersion, assay (HPLC), dissolution (HPLC detection), uniformity of dosage units (by content uniformity), related substances (HPLC), residual solvent, average weight, elemental impurities 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. The in-use storage period as indicated in the product information for the 180-tablet bottle pack is supported by stability data.

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:

This is a randomized, open label, balanced, two treatment, two period, two sequence, two-way cross-over, oral bioequivalence study of Abacavir, Dolutegravir and Lamivudine tablets for oral suspension 60mg/5mg/30mg of Micro Labs Ltd., India comparing with Triumeq PD (abacavir, dolutegravir and lamivudine) tablets for oral suspension 60mg/5mg/30mg manufactured for ViiV Healthcare, RTP, NC 27709 in healthy males and healthy females not of reproductive potential subjects under fasting conditions (study no. 115-24).

The objective of the study was to compare the bioavailability of the stated Abacavir/Dolutegravir/Lamivudine 60mg/5mg/30mg FDC tablet manufactured by/for Micro Labs 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. CVAG001

Treatment R: Reference – 1 tablet Triumeq PD®

(abacavir 60 mg + dolutegravir 5 mg + lamivudine 30 mg)
Batch no. FH8N.

The dispersible tablets were dispersed in 20 ml water (+ 30 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 29 samples within 72h post dose) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax 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 8 ng/ml for abacavir, 5 ng/ml for dolutegravir and 4 ng/ml for lamivudine.

The study was performed with 36 participants; data generated from a total of 34 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)	0.67 ± 0.57	0.53 ± 0.33	-	-
C_{max} (ng/mL)	650 ± 315 (590)	690 ± 330 (615)	96.0	84.0 – 109.7
AUC_{0-t} (ng ·h/mL)	869 ± 371 (803)	866 ± 383 (809)	99.2	92.2 – 106.8
AUC_{0-inf} (ng ·h/mL)	891 ± 375 (826)	890 ± 387 (834)	99.1	92.2 – 106.5

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)	0.78 ± 0.58	0.76 ± 0.48	-	-
C_{max} (ng /mL)	781 ± 181 (762)	800 ± 193 (779)	97.9	93.1 – 102.8
AUC_{0-t} (ng ·h/mL)	10685 ± 2064 (10510)	10802 ± 2138 (10613)	99.0	96.7 – 101.5
AUC_{0-inf} (ng ·h/mL)	11211 ± 2380 (10992)	11329 ± 2411 (11099)	99.0	96.5 – 101.6

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)	1.46 ± 0.83	1.41 ± 0.83	-	-
C_{max} (ng /mL)	339 ± 127 (317)	323 ± 110 (306)	103.6	95.2 – 112.8
AUC_{0-t} (ng ·h/mL)	1557 ± 416 (1501)	1482 ± 338 (1445)	103.9	98.3– 109.8
AUC_{0-inf} (ng ·h/mL)	1634 ± 426 (1579)	1556 ± 344 (1520)	103.9	98.5 – 109.5

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^{PD} (ViiV Healthcare).

4. Summary of product safety and efficacy

[HA809 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, [HA809 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 [HA809 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 [HA809 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA809 trade name] have been shown to be bioequivalent with Triumeq DP® (ViiV Healthcare).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA809 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 [HA809 trade name] was acceptable for the following indication: **' the treatment of HIV infection in infants and children aged from 4 weeks and weighing 3 to 25 kg '**, and would allow inclusion of [HA809 trade name], manufactured at Micro Labs Limited (ML06), 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.