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** | [HA790 trade name]* |
| **Manufacturer of Prequalified Product** | Lupin Limited<br>Plot No. 6A1, 6A2, Sector–17<br>Special Economic Zone<br>MIHAN Notified Area<br>Nagpur<br>Maharashtra – 441108<br>India |
| **Active Pharmaceutical Ingredient(s) (API)** | Abacavir (as sulfate)/dolutegravir (as sodium)/lamivudine |
| **Pharmaco-therapeutic group (ATC Code)** | Antivirals for treatment of HIV infections, combinations, (J05AR02) |
| **Therapeutic indication** | [HA790 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

[HA790 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.

[HA790 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 Ingredients (APIs)

*Dolutegravir sodium*

Dolutegravir sodium is a white to light yellow powder. The structure is characterized by FT-IR, UV, 1H-NMR, 13C-NMR, mass spectrometry and elemental analysis. The API is BCS critically insoluble. The API possesses two chiral centres and exhibits isomerism. The manufacturer consistently produces the crystalline anhydrous form and in the micronized grade. The polymorphic form- I which is obtained by the FPP manufacturer is confirmed by p-XRD.

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

The specifications for dolutegravir sodium include tests for description, solubility, identification (IR and HPLC), polymorphic identity (p-XRD), water content (KF), sodium content, enantiomer content (HPLC), assay (HPLC), organic impurities (HPLC), residual solvents (GC and GC-MS), particle size distribution, methanesulfonates (methyl, ethyl and propyl; by GC-MS ≤ 14.2ppm) and microbial limits.

Stability testing was conducted according to the requirements of WHO. The proposed re-test period is justified based on the stability results when the API is stored in the original packaging.

*Abacavir and lamivudine*

Abacavir 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 [HA790 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.

## Other ingredients

Other ingredients used in the core tablet formulation include mannitol, microcrystalline cellulose, sodium starch glycolate, povidone, silicified microcrystalline cellulose, crospovidone, strawberry flavour, colloidal silicon dioxide, yellow iron oxide, acesulfame potassium, sucralose, and sodium stearyl fumarate, all being controlled by acceptable specifications.

The strawberry flavour contains flavouring substances, maize maltodextrin, triethyl citrate and propylene glycol. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol-partially hydrolysed, titanium dioxide, macrogol/polyethylene glycol, talc, red iron oxide and black iron oxide. None of the excipients are derived from human or animal origin. TSE / BSE free certificates have been provided for the excipients.

## Finished pharmaceutical product (FPP)

*Pharmaceutical development and manufacture*

The multisource product is a pink to light pink, oval, film-coated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablets have 'E06' debossed (stamped into) one side and 'LU' on the other side. The tablets are packaged in a round, opaque white plastic (HDPE) bottle. Each bottle also contains a canister of desiccant (drying material). The bottle has an aluminium/plastic foil seal and a white non-child resistant plastic (polypropylene) screw. The bottle may include a 40 mL dosing-cup.

The objective of the development programme was to obtain a stable, robust, immediate-release FDC tablet that is bioequivalent to the WHO recommended comparator product, Triumeq$^{PD}$ [abacavir (as sulfate) /dolutegravir (as sodium) /lamivudine 60 mg/5 mg/30 mg tablets]. The selection of excipients was based on characterisation of the comparator product, compatibility with the APIs and previous formulation experience. The composition included sweeteners and flavouring agents to improve the palatability of the formulation. Wet granulation was selected for the manufacturing of the dispersible film-coated bilayer tablets. In this formulation dolutegravir granules and lamivudine were blended and compressed together in one layer while abacavir was in the other layer. Formulation trials were performed to optimise the concentration of excipients and process parameters. Satisfactory in-process controls have been established.

According to a risk assessment by the applicant, the potential presence of N-nitroso abacavir impurity was declared, however confirmatory test results for the FPP did not find detectable levels of the impurity.

*Specifications*

The finished product specifications include tests for description, identification of the APIs (HPLC and HPLC with PDA/DAD detector), water content (KF), dissolution (HPLC detection), uniformity of dosage units (by content uniformity), assay (HPLC), degradation products (HPLC), limit of enantiomers of abacavir, dolutegravir and lamivudine (HPLC), residual solvents, disintegration time, fineness of dispersion, elemental impurities and microbial limits. The test methods have been satisfactorily validated.

*Stability testing*

Stability studies have been conducted at 30ºC/75%RH as long-term storage conditions and for six months at 40°C/75%RH as accelerated conditions in the packaging proposed for marketing of the product. The product proved to be quite stable data with all parameters well within the agreed limits at both storage conditions. 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 after first opening of the bottles 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 2022/2023 according to internationally accepted guidelines:

An open label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period crossover oral bioequivalence study comparing [HA790 trade name] manufactured by Lupin Limited, India with Triumeq$^{PD}$ (abacavir, dolutegravir and lamivudine) tablets for oral suspension 60 mg/5 mg/30 mg manufactured by GlaxoSmithKline Research Triangle Park, NC 27709 manufactured for ViiV Healthcare Research Triangle Park, NC 27709 in healthy, adult, human subjects under fasting conditions (study no. LBC-22-110).

The objective of the study was to compare the bioavailability of the stated [HA790 trade name] FDC tablet for oral suspension manufactured by/for Lupin Limited, India (test drug) with the reference FDC tablet for oral suspension 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 [HA790 trade name]<br>(abacavir 60 mg + dolutegravir 5 mg + lamivudine 30 mg)<br>Batch no. M290188 |
| Treatment R: | Reference – 1 tablet Triumeq$^{PD}$<br>(abacavir 60 mg + dolutegravir 5 mg + lamivudine 30 mg)<br>Batch no. 2P3T |

The dispersible tablet was dispersed in 20 mL water (+ 15 mL of rinsing water) and administered. A 11-day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 23 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 2 ng/mL for abacavir, 3 ng/mL for dolutegravir and 5 ng/mL for lamivudine.

The study was performed with 66 participants; data generated from a total of 60 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) | 0.66 ± 0.47 | 0.72 ± 0.58 | – | – |
| $C_{max}$ (ng/mL) | 543 ± 255 (486) | 514 ± 235 (463) | 104.8 | 94.3 – 116.5 |
| $AUC_{0-t}$ (ng·h/mL) | 747 ± 307 (695) | 741 ± 278 (692) | 100.3 | 94.7 – 106.3 |
| $AUC_{0-inf}$ (ng·h/mL) | 753 ± 308 (701) | 747 ± 278 (698) | 100.4 | 94.8 – 106.3 |

**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) | 0.86 ± 0.51 | 0.90 ± 0.62 | – | – |
| $C_{max}$ (ng/mL) | 758 ± 117 (749) | 801 ± 140 (790) | 94.8 | 91.6 – 98.1 |
| $AUC_{0-t}$ (ng·h/mL) | 11019 ± 2230 (10779) | 11260 ± 2177 (11048) | 97.6 | 95.6 – 99.6 |
| $AUC_{0-inf}$ (ng·h/mL) | 11578 ± 2614 (11275) | 11774 ± 2498 (11511) | 97.9 | 95.8 – 100.1 |

**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) | 1.20 ± 0.55 | 1.41 ± 0.70 | – | – |
| $C_{max}$ (ng/mL) | 282 ± 75 (272) | 274 ± 77 (264) | 103.2 | 96.9 – 109.8 |
| $AUC_{0-t}$ (ng·h/mL) | 1217 ± 287 (1183) | 1157 ± 290 (1122) | 105.4 | 100.2– 111.0 |
| $AUC_{0-inf}$ (ng·h/mL) | 1278 ± 293 (1244) | 1213 ± 298 (1177) | 105.7 | 100.8 – 111.0 |

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and Cmax values regarding abacavir, dolutegravir and lamivudine. Accordingly, the test,

[HA790 trade name] 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

[HA790 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, [HA790 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Triumeq[PD] (ViiV Healthcare) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA790 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 [HA790 trade name] is used in accordance with the SmPC.

### Bioequivalence

[HA790 trade name] has been shown to be bioequivalent with Triumeq[PD] (ViiV Healthcare).

### Efficacy and Safety

Regarding clinical efficacy and safety, [HA790 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 [HA790 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 [HA790 trade name], manufactured at Lupin Limited, Plot No. 6A1, 6A2, Sector–17, Special Economic Zone, MIHAN Notified Area, Nagpur, Maharashtra – 441108, India in the list of prequalified medicinal products.