Public Assessment Report

Decentralised Procedure

Abacavir/Lamivudine Vale 600 mg/300 mg Film-coated Tablets

(Abacavir sulfate and lamivudine)

Procedure No: UK/H/6260/001/DC

UK Licence Number: PL 20692/0136

Vale Pharmaceuticals Ltd
LAY SUMMARY
Abacavir/Lamivudine Vale 600 mg/300 mg Film-coated Tablets
(Abacavir sulfate and lamivudine)

This is a summary of the Public Assessment Report (PAR) for Abacavir/Lamivudine Vale 600 mg/300 mg Film-coated Tablets (PL 20692/0136; UK/H/6260/001/DC). It explains how Abacavir/lamivudine Vale 600 mg/300 mg film-coated tablets was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Abacavir/lamivudine Vale 600 mg/300 mg film-coated tablets.

For ease of reading, this product will be referred to as Abacavir/Lamivudine throughout this Lay Summary.

For practical information about using Abacavir/Lamivudine, patients should read the package leaflet or contact their doctor or pharmacist.

What is Abacavir/Lamivudine and what is it used for?
Abacavir/Lamivudine is a ‘generic medicine’. This means that Abacavir/Lamivudine is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Kivexa 600mg/300mg film-coated tablets (ViiV Healthcare UK Limited, UK).

Abacavir/Lamivudine is used to treat HIV (human immunodeficiency virus) infection in adults, adolescents and children weighing at least 25 kg.

How does Abacavir/Lamivudine work?
Abacavir/Lamivudine contains two active ingredients that are used to treat HIV infection: abacavir and lamivudine. These belong to a group of anti-retroviral medicines called nucleoside analogue reverse transcriptase inhibitors (NRTIs).

Abacavir/Lamivudine does not completely cure HIV infection; it reduces the amount of virus in the body, and keeps it at a low level. It also increases the CD4 cell (a type of white blood cells that are important in helping the body to fight infection) count in the blood. Not everyone responds to treatment with Abacavir/Lamivudine in the same way. The patient’s doctor will monitor the effectiveness of their treatment.

How is Abacavir/Lamivudine used?
The pharmaceutical form of this medicine is a film-coated tablet, and the route of administration is oral (by mouth). The whole tablet must be swallowed with some water. Abacavir/Lamivudine can be taken with or without food.

The patient must always take this medicine exactly as their doctor has told them. The patient should check with their doctor or pharmacist if they are not sure.

The recommended dose of Abacavir/Lamivudine for adults, adolescents and children weighing 25 kg or more is one tablet once a day.

The patient should stay in regular contact with their doctor.

Abacavir/Lamivudine helps to control the patient’s condition. The patient needs to keep taking it every day to stop their illness getting worse. The patient may still develop other infections and illnesses linked to HIV infection.
The patient should keep in touch with their doctor and must not stop taking Abacavir/Lamivudine without advice from their doctor.

The patient should read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

For further information on how Abacavir/Lamivudine is used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

**What benefits of Abacavir/Lamivudine have been shown in studies?**
Because Abacavir/Lamivudine is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine Kivexa 600mg/300mg film-coated tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Abacavir/Lamivudine?**
Because Abacavir/Lamivudine is a generic medicine and is bioequivalent to the reference medicine Kivexa 600mg/300mg film-coated tablets, its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Abacavir/Lamivudine, see section 4 of the package leaflet available on the MHRA website.

**Why was Abacavir/Lamivudine approved?**
It was concluded that, in accordance with EU requirements, Abacavir/Lamivudine has been shown to have comparable quality and to be bioequivalent to Kivexa 600mg/300mg film-coated tablets. Therefore, the MHRA decided that, as for Kivexa 600mg/300mg film-coated tablets; the benefits are greater than the risks and recommended that it can be approved for use.

**What measures are being taken to ensure the safe and effective use of Abacavir/Lamivudine?**
A risk management plan (RMP) has been developed to ensure that Abacavir/Lamivudine is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Abacavir/Lamivudine including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

**Other information about Abacavir/Lamivudine**
Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Italy, Ireland, Latvia, Lithuania, Luxemburg, Norway, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, The Netherlands and the UK agreed to grant a Marketing Authorisation for Abacavir/Lamivudine on 01 September 2017. A Marketing Authorisation was granted in the UK on 31 October 2017.

The full PAR for Abacavir/Lamivudine follows this summary.

This summary was last updated in December 2017.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Vale Pharmaceuticals Ltd, a marketing authorisation for the medicinal product Abacavir/lamivudine Vale 600 mg/300 mg film-coated tablets (PL 20692/0136; UK/H/6260/001/DC). The product is a prescription-only medicine (POM), indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection in adults, adolescents and children weighing at least 25 kg.

Before initiating treatment with abacavir, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin. Abacavir should not be used in patients known to carry the HLA-B*5701 allele.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Italy, Latvia, Lithuania, Luxemburg, Norway, Poland, Portugal, Romania, Republic of Ireland, Slovak Republic, Slovenia, Spain, Sweden and The Netherlands as Concerned Member States (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for this application is Kivexa 600mg/300mg film-coated tablets, which was first authorised to the marketing authorisation holder (MAH) ViiV Healthcare UK Limited, UK on 17 December 2004 via the centralised procedure (EU/1/04/298/001-003).

Abacavir and lamivudine are nucleoside reverse transcriptase inhibitors (NRTIs), and are potent selective inhibitors of HIV-1 and HIV-2 (LAV2 and EHO) replication. Both abacavir and lamivudine are metabolised sequentially by intracellular kinases to the respective 5'-triphosphate (TP) which are the active moieties.

Lamivudine-TP and carbovir-TP (the active triphosphate form of abacavir) are substrates for and competitive inhibitors of HIV reverse transcriptase (RT). However, their main antiviral activity is through incorporation of the monophosphate form into the viral DNA chain, resulting in chain termination. Abacavir and lamivudine triphosphates show significantly less affinity for host cell DNA polymerases.

No antagonistic effects were seen in vitro with lamivudine and other antiretrovirals (tested agents: didanosine, nevirapine and zidovudine). The antiviral activity of abacavir in cell culture was not antagonised when combined with the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine, emtricitabine, stavudine, tenofovir or zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, or the protease inhibitor (PI) amprenavir.

To support the application the applicant has submitted two bioequivalence studies comparing the applicant’s test product Abacavir/lamivudine 600 mg/300 mg film-coated tablets with the reference product Kivexa 600 mg/300 mg, Film-coated Tablets (ViiV Healthcare UK Limited, UK) in healthy adult human volunteers, under fasting conditions. The first study did not show bioequivalence between the test and reference product. Therefore, the applicant conducted a second bioequivalence study which was considered acceptable. The bioequivalence study was conducted in line with current Good Clinical Practice (GCP).

With the exception of the bioequivalence studies, no new non-clinical or clinical data were submitted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.
The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

All involved Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 208 – 01 September 2017). After a subsequent national phase, the UK granted a Marketing Authorisation (PL 20692/0136) for this product on 31 October 2017.
II QUALITY ASPECTS
II.1 Introduction
The product is presented as film-coated tablets and each tablet contains 600 mg of abacavir (as abacavir sulfate) and 300 mg lamivudine as the active ingredients. Other ingredients consist of the pharmaceutical excipients microcrystalline cellulose, crospovidone, magnesium stearate, silica, colloidal anhydrous and talc making up the tablet core and the tablet-coating is composed of Opadry 13B58894 white (hypromellose, titanium dioxide (E171), macrogol and polysorbate 80).

All excipients comply with their respective European Pharmacopoeia monographs with the exception of Opadry 13B58894 white which complies with an inhouse specification. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients contain materials of animal or human origin. Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

The finished product is packaged in:
1. polyvinylchloride (PVC)/polyvinylidenechloride (PVDC)/Aluminium foil blister pack perforated unit dose blister packs with a pack size of 30, 30x1 (perforated unit dose blisters), 90 tablets or multipack size 90 (3 packs of 30) tablets.
2. high density polyethylene (HDPE) bottle with white opaque polypropylene child-resistant closure and aluminium induction sealing liner wad, with a pack size of 30 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substances
1. Lamivudine
INN: Lamivudine
Chemical name: 2R-cis)-4- Amino-1- [2-(hydroxymethyl)-1, 3- oxathiolan - 5- yl]-2(1H)-pyrimidinone, ii. (-)-2’-deoxy-3’-thiacytidine, iii.3’-thia-2’, 3’-dideoxycytidine.

Structure:

![Lamivudine Structure](image_url)

Molecular formula: C₈H₁₁N₃O₃S
Molecular weight: 229.3 g/mol
Description: White or almost white powder.
Solubility: Soluble in water, sparingly soluble in methanol and slightly soluble in ethanol.

Lamivudine is the subject of a European Pharmacopoeia monograph.
All aspects of the manufacture and control of the active substance, lamivudine, are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

2. Abacavir sulfate
INN: Abacavir sulfate
Chemical name: \[(1S,4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopent-2-ene-1-yl]-methanol, sulfuric acid

Structural formula:

![Structural formula of Abacavir sulfate]

Molecular formula: \(C_{28}H_{38}N_{12}O_{6}S\)
Molecular mass: 670.7 g/mol
Appearance: White or almost white powder.
Solubility: Soluble in water. Practically insoluble in ethanol and in methylene chloride.

Abacavir sulfate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, abacavir sulfate, are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious film-coated tablets containing abacavir sulfate equivalent to 600 mg abacavir and 300 mg lamivudine per tablet, that are generic versions of the reference product Kivexa 600mg/300mg film-coated tablets (ViiV Healthcare UK Limited, UK). A satisfactory account of the pharmaceutical development has been provided.

Comparative in-vitro dissolution and impurity profiles have been provided for the proposed and originator products.

Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of the product, together with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale batch size and has shown satisfactory results.

Finished Product Specification
The proposed finished product specification is acceptable. The test methods that have been adequately validated have been described. Batch data complying with the release specifications have been provided. Certificates of Analysis have been provided for all working standards used.
Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for blister and bottle with no special temperature storage conditions. The product must be stored in the original package in order to protect it from light.

Suitable post approval stability commitments to continue stability testing on batches of finished product have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS
III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of abacavir sulfate and lamivudine are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
There are no toxicological concerns with impurities and residual solvent levels in the the drug substance or drug product specifications proposed.

III.5 Ecotoxicity/environmental risk assessment (ERA)
No environmental risk assessment has been conducted and an acceptable justification for its absence has been provided in line with EMEA/CHMP/SWP/4447/00 corr 2. It is anticipated that sales of the proposed product will replace those of similar marketed products, and it is unlikely that an increase in environmental exposure to the active substance will occur on marketing of the proposed product.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS
IV.1 Introduction
The clinical pharmacology of abacavir sulfate and lamivudine is well-known. With the exception of data from the bioequivalence studies detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for this application.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of abacavir sulfate and lamivudine.
The first bioequivalence study submitted by the applicant was not considered acceptable. Therefore, a second study was conducted to show bioequivalence between the test and reference products. Based on the data provided, Abacavir/lamivudine Vale 600 mg/300 mg film-coated tablets can be considered bioequivalent to Kivexa 600/300mg film-coated tablets (ViiV Healthcare UK Limited, UK).

**IV.2 Pharmacokinetics**

In support of this application, the applicant submitted the following two bioequivalence studies:

**STUDY 1**

An open label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period crossover oral bioequivalence study of the applicant’s test product Abacavir/Lamivudine 600 mg/300 mg film-coated tablets versus the reference product Kivexa 600/300mg film-coated tablets (ViiV Healthcare UK Limited, UK) in healthy, adult, subjects under fasting conditions.

Blood samples were collected for plasma levels before dosing and up to and including 24 hours after each administration. The washout period between the treatment phases was 8 days. The pharmacokinetic results are presented below:

**Results**

Summary of pharmacokinetic parameters, ratios and 90% Confidence Interval for abacavir

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± S.D. (Median)</th>
<th>Range</th>
<th>[Geometric Mean Ratio]</th>
<th>P-value of F Ratio (formulation difference)</th>
<th>90% Geometric CI Two one-sided t-test (Schuirmann) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (mg/ml)</td>
<td>8369.77 ± 2815.0137 [7673.822]</td>
<td>7623.87 ± 1946.0698 [7482.191]</td>
<td>4051.90 to 1503.01</td>
<td>4536.33 to 13409.18</td>
<td>106.45 %</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>1.166 ± 0.6094</td>
<td>1.279 ± 0.5362</td>
<td>0.33 to 2.00</td>
<td>0.33 to 2.50</td>
<td>[n/c]</td>
</tr>
<tr>
<td>AUCtot (hr*mg/ml)</td>
<td>23804.559 ± 7204.8240 [23785.961]</td>
<td>22509.564 ± 5482.2045 [22548.579]</td>
<td>13192.91 to 4884.63</td>
<td>13915.46 to 37002.34</td>
<td>104.45 %</td>
</tr>
<tr>
<td>AUCinf (hr*mg/ml)</td>
<td>24034.960 ± 7370.8752 [23962.461]</td>
<td>22756.284 ± 5555.9993 [22722.448]</td>
<td>13385.52 to 2004.58</td>
<td>13082.26 to 37462.20</td>
<td>104.36 %</td>
</tr>
<tr>
<td>t1/2 (hr)</td>
<td>1.624 ± 0.2228 [1.557]</td>
<td>1.721 ± 0.3230 [1.615]</td>
<td>1.13 to 2.08</td>
<td>1.35 to 2.62</td>
<td>[n/c]</td>
</tr>
<tr>
<td>Ke (1/hr)</td>
<td>0.4346 ± 0.00857 [0.4451]</td>
<td>0.4141 ± 0.00582 [0.4293]</td>
<td>0.334 to 0.612</td>
<td>0.265 to 0.512</td>
<td>[n/c]</td>
</tr>
<tr>
<td>AUC_NonF abs</td>
<td>0.984 ± 0.4478 [0.870]</td>
<td>1.066 ± 0.4372 [0.976]</td>
<td>0.39 to 2.32</td>
<td>0.56 to 2.56</td>
<td>[n/c]</td>
</tr>
</tbody>
</table>

Summary of pharmacokinetic parameters, ratios and 90% Confidence Interval for lamivudine

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± S.D. (Median)</th>
<th>Range</th>
<th>[Geometric Mean Ratio]</th>
<th>P-value of F Ratio (formulation difference)</th>
<th>90% Geometric CI Two one-sided t-test (Schuirmann) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (mg/ml)</td>
<td>3077.132 ± 498.7687 [3191.357]</td>
<td>2728.971 ± 773.4966 [2806.478]</td>
<td>1768.65 to 4345.47</td>
<td>1470.70 to 3998.31</td>
<td>114.35 %</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>2.043 ± 0.6986</td>
<td>2.206 ± 0.6543</td>
<td>0.83 to 4.00</td>
<td>1.00 to 4.00</td>
<td>[n/c]</td>
</tr>
<tr>
<td>AUCtot (hr*mg/ml)</td>
<td>18331.833 ± 5201.5326 [17311.722]</td>
<td>16040.346 ± 4022.2047 [16913.571]</td>
<td>9031.91 to 33799.29</td>
<td>7903.70 to 26189.07</td>
<td>110.32 %</td>
</tr>
<tr>
<td>AUCinf (hr*mg/ml)</td>
<td>18411.525 ± 5372.0242 [17810.127]</td>
<td>17149.163 ± 4083.0029 [17276.369]</td>
<td>9970.67 to 8239.38</td>
<td>5599.41 to 26717.93</td>
<td>109.76 %</td>
</tr>
<tr>
<td>t1/2 (hr)</td>
<td>4.989 ± 0.7595 [4.849]</td>
<td>5.323 ± 0.7069 [5.334]</td>
<td>3.60 to 7.23</td>
<td>4.21 to 7.28</td>
<td>[n/c]</td>
</tr>
<tr>
<td>Ke (1/hr)</td>
<td>0.1419 ± 0.02061 [0.1429]</td>
<td>0.1377 ± 0.03184 [0.1324]</td>
<td>0.096 to 0.192</td>
<td>0.095 to 0.165</td>
<td>[n/c]</td>
</tr>
<tr>
<td>AUC_NonF abs</td>
<td>2.595 ± 0.1715 [2.092]</td>
<td>3.075 ± 1.4000 [2.381]</td>
<td>1.27 to 0.11</td>
<td>1.51 to 2.86</td>
<td>[n/c]</td>
</tr>
</tbody>
</table>

*Statistically Significant

n/c: not calculated

**Note:** The table values for abacavir and lamivudine are presented separately due to the different units and scales used in their calculations.
Study 1 did not demonstrate bioequivalence between the reference and test products, as the confidence limits for \( C_{\text{max}} \) were slightly outside the acceptance range of 80.00 to 125.00% (90% CI: 103.75, 126.03). While suggestive of higher levels on the test product compared to the reference it is likely that with a larger sample size bioequivalence would have been demonstrated. There were also two subjects with extreme values which could have affected the results for \( C_{\text{max}} \). The result of study 1 prompted the applicant to conduct a second study with a larger sample size.

**STUDY 2**

This was an open-label, balanced, randomised, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study of Abacavir Sulphate and Lamivudine 600/300mg film coated tablets with KIVEXA® 600/300mg film coated tablets (ViiV healthcare UK Limited), in normal healthy adult human subjects under fasting conditions.

Blood samples were collected for plasma levels before dosing and up to and including 24 hours after each administration. The washout period between the treatment phases was 7 days. The pharmacokinetic results are presented below.

**Results**

**Table 1: Pharmacokinetic Data (Mean ± SD) Test vs Reference (n=37) for Abacavir**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± S.D. [Median]</th>
<th>Range</th>
<th>Arithmetic Mean Ratio [Geometric Mean Ratio] (%)</th>
<th>P-value of F Ratio (formulation difference)</th>
<th>90% Geometric CI Two one-sided t-test (Schuirmann) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( T_{\text{max}} ) (h)</td>
<td>0.93 ± 0.557 [0.49]</td>
<td>1.13 ± 0.475 [1.25]</td>
<td>0.33 ± 2.50</td>
<td>0.33 ± 2.00</td>
<td>n/c</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/mL)</td>
<td>6514.909 ± 1533.8367 [6257.622]</td>
<td>6270.797 ± 1264.5004 [6217.568]</td>
<td>3961.171 ± 10269.620</td>
<td>3841.886 ± 8701.902</td>
<td>104.9</td>
</tr>
<tr>
<td>AUC0-t (ng.h/mL)</td>
<td>17944.73 ± 3909.4517 [17641.576]</td>
<td>18014.545 ± 3286.134 [17942.800]</td>
<td>12321.842 ± 25250.399</td>
<td>11996.986 ± 26240.092</td>
<td>99.8</td>
</tr>
<tr>
<td>AUC0-inf (ng.h/mL)</td>
<td>18203.177 ± 3257.3025 [17776.642]</td>
<td>18252.768 ± 3266.474 [18180.344]</td>
<td>12091.417 ± 25883.352</td>
<td>12110.147 ± 26735.211</td>
<td>99.8</td>
</tr>
<tr>
<td>Kel (h⁻¹)</td>
<td>0.406 ± 0.0693 [0.416]</td>
<td>0.402 ± 0.0653 [0.414]</td>
<td>0.243 ± 0.534</td>
<td>0.253 ± 0.512</td>
<td>n/c</td>
</tr>
<tr>
<td>fs (%)</td>
<td>1.702 ± 0.3563 [1.667]</td>
<td>1.776 ± 0.3508 [1.675]</td>
<td>1.297 ± 2.848</td>
<td>1.354 ± 2.744</td>
<td>n/c</td>
</tr>
<tr>
<td>(%AUC0-t/AUC0-inf)*100</td>
<td>98.738 ± 0.636 [98.679]</td>
<td>98.724 ± 0.5158 [98.941]</td>
<td>98.193 – 99.317</td>
<td>97.262 – 99.355</td>
<td>n/c</td>
</tr>
</tbody>
</table>

n/c: not calculated

**Table 2: Pharmacokinetic Data (Mean ± SD) Test vs Reference (n=37) for Lamivudine**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± S.D. [Median]</th>
<th>Range</th>
<th>Arithmetic Mean Ratio [Geometric Mean Ratio] (%)</th>
<th>P-value of F Ratio (formulation difference)</th>
<th>90% Geometric CI Two one-sided t-test (Schuirmann) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( T_{\text{max}} ) (h)</td>
<td>1.71 ± 0.729 [1.75]</td>
<td>1.86 ± 0.834 [1.75]</td>
<td>0.67 ± 4.00</td>
<td>0.83 ± 4.00</td>
<td>n/c</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (mg/mL)</td>
<td>2734.846 ± 708.9800 [2647.769]</td>
<td>2587.603 ± 593.8602 [2607.729]</td>
<td>1672.043 ± 4965.958</td>
<td>1096.891 ± 3932.704</td>
<td>105.0</td>
</tr>
<tr>
<td>AUC0-t (mg.h/mL)</td>
<td>14966.328 ± 3028.929 [14366.448]</td>
<td>13733.371 ± 2890.7309 [13588.461]</td>
<td>8338.848 ± 21077.999</td>
<td>8254.146 ± 20308.017</td>
<td>103.8</td>
</tr>
<tr>
<td>AUC0-inf (mg.h/mL)</td>
<td>14589.311 ± 3033.581 [14063.335]</td>
<td>14033.917 ± 2876.1602 [13825.197]</td>
<td>8533.806 ± 23132.542</td>
<td>9098.113 ± 20228.192</td>
<td>103.7</td>
</tr>
<tr>
<td>Kel (h⁻¹)</td>
<td>0.149 ± 0.0278 [0.142]</td>
<td>0.148 ± 0.0294 [0.146]</td>
<td>0.112 ± 0.206</td>
<td>0.086 ± 0.291</td>
<td>n/c</td>
</tr>
<tr>
<td>fs (%)</td>
<td>4.771 ± 0.751 [4.870]</td>
<td>4.830 ± 0.805 [4.741]</td>
<td>2.011 ± 8.169</td>
<td>2.385 ± 8.054</td>
<td>n/c</td>
</tr>
<tr>
<td>(%AUC0-t/AUC0-inf)*100</td>
<td>97.908 ± 0.7873 [98.026]</td>
<td>97.735 ± 1.0254 [98.013]</td>
<td>95.322 – 98.900</td>
<td>91.630 – 98.937</td>
<td>n/c</td>
</tr>
</tbody>
</table>

n/c: not calculated

Study 2 successfully demonstrated bioequivalence of the Test and Reference products. The limits of the 90% confidence interval for AUC0-t and \( C_{\text{max}} \) were within the acceptance range for bioequivalence of 80.00 to 125.00%.
**Conclusion**
As stated in the CHMP guideline on the investigation of bioequivalence "The existence of a study which demonstrates bioequivalence does not mean that those which do not can be ignored". When bioequivalence is in doubt, an analysis based on the pooled data could be requested. However, this is not the case here. The results from study 1 are generally consistent with those from study 2 and it seems likely that with a larger sample size study 1 would have been positive. An analysis based on the pooled data from the two studies would lead to narrow confidence intervals and would clearly be positive. Therefore, the results from study 2 supported by study 1, demonstrated that the test product, Abacavir/lamivudine Vale 600 mg/300 mg film-coated tablets is bioequivalent to the reference product Kivexa film-coated tablets (ViiV Healthcare UK Limited, UK).

**IV.3 Pharmacodynamics**
No new pharmacodynamic data were submitted and none were required for applications of this type.

**IV.4 Clinical efficacy**
No new efficacy data were submitted and none were required for applications of this type.

**IV.5 Clinical safety**
No new safety data were submitted and none are required.

**IV.6 Risk Management Plan (RMP) and Pharmacovigilance System**
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Abacavir/lamivudine Vale 600 mg/300 mg film-coated tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:
<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
</table>
| ABC Hypersensitivity Reaction (including reduced vigilance following HLA-B*5701 testing) | • Sections 4.3, 4.4 and 4.8 of the SPC contain adequate warning on this risk  
• Product is a prescription-only medicine (POM) and should be prescribed by a physician experienced in the management of HIV | Educational material for HCPs in the form of slide set (to cover the key elements as stated in Annex II for Kivexa: major symptoms associated with ABC HSR, pharmacogenetic testing (HLA-B*5701 testing), management of ABC HSR reaction and hypersensitivity case studies. In line with the reference product, this shall be reviewed annually)  
Patient alert card included with the product in the packaging |
| Use in patients with moderate/severe hepatic impairment | • Sections 4.2, 4.4, 4.8 and 5.2 of the SPC contain adequate warnings on this risk  
• Product is a prescription-only medicine (POM) and should be prescribed by a physician experienced in the management of HIV | None |
<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic cardiac events</td>
<td>• Sections 4.4 contains relevant information regarding the association between abacavir/lamivudine and ischaemic cardiac events such as myocardial infarction. • Product is a prescription-only medicine (POM) and should be prescribed by a physician experienced in the management of HIV</td>
<td>None</td>
</tr>
<tr>
<td>Risk of shorter time to virological failure</td>
<td>• Sections 4.4 and 5.1 of the SPC contain sufficient information regarding virological failure PIL does not include any information about this risk. • Product is a prescription-only medicine (POM) and should be prescribed by a physician experienced in the management of HIV</td>
<td>None</td>
</tr>
<tr>
<td>Drug interaction with ribavirin</td>
<td>• Sections 4.4 and 4.5 of the SPC contain sufficient information regarding this risk. • Product is a prescription-only medicine (POM) and should be prescribed by a physician experienced in the management of HIV</td>
<td>None</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
<tr>
<td>----------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------</td>
</tr>
</tbody>
</table>
| Drug interaction with tenofovir disoproxil fumarate | - Sections 4.4 and 5.1 of the SPC includes information regarding drug interaction of abacavir/lamivudine with tenofovir disoproxil fumarate.  
- Product is a prescription-only medicine (POM) and should be prescribed by a physician experienced in the management of HIV. | None |
| Use in pregnancy and breastfeeding                  | - Sections 4.6 and 5.3 of the SmPC clearly contain information on the non-availability of data from the use of abacavir/lamivudine during pregnancy and lactation.  
- Product is a prescription-only medicine (POM) and should be prescribed by a physician experienced in the management of HIV. | None |
<p>| Carcinogenicity and long term use                   | - Section 5.3 of the SmPC contains relevant information on carcinogenicity and long-term use.        | None |</p>
<table>
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<tr>
<th>Safety concern</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Product is a prescription-only medicine (POM) and should be prescribed by a physician experienced in the management of HIV</td>
<td></td>
</tr>
</tbody>
</table>

Additional risk minimisation measures have been proposed for the safety concern of “Abacavir Hypersensitivity Reaction”. No risk minimisation measures for missing information was required.

IV.7 Discussion on the clinical aspects
The grant of a marketing authorisation is recommended for this application.

V User consultation
User-testing of the patient information leaflet (PIL) for Abacavir/Lamivudine Vale 600 mg/300 mg Film-coated Tablets (PL 20692/0136) has been accepted based on the bridging report provided by the applicant making reference to the successful user-testing of the PIL for Kivexa® 600/300mg film-coated tablets (EU/1/04/298/001-003) as the ‘parent PIL’.

VI Overall conclusion, benefit/risk assessment and recommendation
The quality of the product is acceptable and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with abacavir sulfate and lamivudine is considered to have demonstrated the therapeutic value of the compounds. The benefit-risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved text labelling for this medicine is as follows:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BLISTER CARTON

1. NAME OF THE MEDICINAL PRODUCT
Abacavir/lamivudine Vale 600 mg/300 mg Film-coated Tablets
abacavir/lamivudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each film-coated tablet contains abacavir sulfate equivalent to 600 mg of abacavir and 300 mg lamivudine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS
Film-coated tablet
30 tablets
30x1 tablets (in perforated unit dose blisters)
90 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION
Read the package leaflet before use.
For oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN
Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
Remove enclosed Alert Card, it contains important safety information.
WARNING! In case of any symptoms suggesting hypersensitivity reactions, contact your doctor IMMEDIATELY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vale Pharmaceuticals Ltd.
1B Gurtnafleur Business Park
E91 F9W8 Gurtnafleur, Clonmel, Co. Tipperary
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

PL 20692/0136

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Abacavir/Lamivudine Vale
<table>
<thead>
<tr>
<th>17.</th>
<th>UNIQUE IDENTIFIER – 2D BARCODE</th>
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</thead>
<tbody>
<tr>
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<td>2D barcode carrying the unique identifier included</td>
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</table>

<table>
<thead>
<tr>
<th>18.</th>
<th>UNIQUE IDENTIFIER – HUMAN READABLE DATA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PC:</td>
</tr>
<tr>
<td></td>
<td>SN:</td>
</tr>
<tr>
<td></td>
<td>NN:</td>
</tr>
</tbody>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BLISTER CARTON - OUTER - MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Abacavir/Lamivudine Vale 600 mg/300 mg Film-coated Tablets
abacavir/lamivudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains abacavir sulfate equivalent to 600 mg of abacavir and 300 mg lamivudine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
Multipack: 90 (3 packs of 30) tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Each carton contains an Alert Card with important safety information.
Remove this card and keep it with you at all times.

WARNING! In case of any symptoms suggesting hypersensitivity reactions, contact your doctor IMMEDIATELY.
8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vale Pharmaceuticals Ltd.
1B Guiltmengl Business Park
E91 F9W8 Guiltmengl, Clonmel, Co. Tipperary
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

PL 20692/0136

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Abacavir/Lamivudine Vale
17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BLISTER CARTON - INNER - MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Abacavir/Lamivudine Vale 600 mg/300 mg Film-coated Tablets
abacavir/lamivudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains abacavir sulfate equivalent to 600 mg of abacavir and 300 mg lamivudine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
30 tablets. Components of a multipack cannot be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Remove enclosed Alert Card, it contains important safety information.
WARNING! In case of any symptoms suggesting hypersensitivity reactions, contact your doctor IMMEDIATELY
8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vale Pharmaceuticals Ltd.
1B Gurtnafeur Business Park
E91 F9W8 Gurtnafeur, Clonmel, Co. Tipperary
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

PL 20692/0136

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE
2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT
Abacavir/Lamivudine Vale 600 mg/300 mg Film-coated Tablets
abacavir/lamivudine

2. NAME OF THE MARKETING AUTHORITY\$ATION HOLDER
Vale Pharmaceuticals Ltd.

3. EXPIRY DATE
EXP

4. BATCH NUMBER
Lot

5. OTHER
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND IMMEDIATE PACKAGING

BOTTLE CARTON AND LABEL

1. NAME OF THE MEDICINAL PRODUCT

Abacavir/Lamivudine Vale 600 mg/300 mg Film-coated Tablets

abacavir/lamivudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains abacavir sulfate equivalent to 600 mg of abacavir and 300 mg lamivudine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

30 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

[CARTON only]

Remove enclosed Alert Card, it contains important safety information.
WARNING! In case of any symptoms suggesting hypersensitivity reactions, contact your doctor IMMEDIATELY

[LABEL only]

The carton contains an Alert Card with important safety information. Remove this card and keep it with you at all times.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

Do not use this medicine after 90 days of first opening the bottle.

Date opened: __________

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vale Pharmaceuticals Ltd.
1B Gurttafleur Business Park
EI 9F 8Gurttafleur, Clonmel, Co. Tipperary
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

PL 20692/0136

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM
### 15. INSTRUCTIONS ON USE

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Abacavir/Lamivudine Vale

### 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

### 18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:
Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/non approval</th>
<th>Assessment report attached Y/N (version)</th>
</tr>
</thead>
</table>