Public Assessment Report

Decentralised Procedure

Tenofovir disoproxil Aristo 245 mg film-coated tablets

(Tenofovir disoproxil phosphate)

Procedure No: UK/H/6267/001/DC

UK Licence No: PL 40546/0009

Aristo Pharma GmbH
LAY SUMMARY

Tenofovir disoproxil Aristo 245 mg film-coated tablets
(Tenofovir disoproxil)

The product may be referred to as ‘Tenofovir disoproxil Aristo’ in this Lay Summary.

This is a summary of the Public Assessment Report (PAR) for Tenofovir disoproxil Aristo 245 mg film-coated tablets (PL 40546/0009; UK/H/6267/001/DC). It explains how the application for Tenofovir disoproxil Aristo was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Tenofovir disoproxil Aristo.

For practical information about using Tenofovir disoproxil Aristo, patients should read the package leaflet or contact their doctor or pharmacist.

What is Tenofovir disoproxil Aristo and what is it used for?
Tenofovir disoproxil Aristo is a ‘generic’ medicine. This means that Tenofovir disoproxil Aristo is similar to a reference medicine already authorised in the European Union (EU) called Viread film coated tablets (Gilead Sciences International Limited, UK). Viread film coated tablets may be referred to as ‘Viread’ in this Lay Summary.

Tenofovir disoproxil Aristo is a treatment for HIV (Human Immunodeficiency Virus) infection. The tablets are suitable for:
- adults
- adolescents aged 12 to less than 18 years who have already been treated with other HIV medicines which are no longer fully effective due to development of resistance, or have caused side effects.

Tenofovir disoproxil Aristo is also a treatment for chronic hepatitis B, an infection with HBV (hepatitis B virus). The tablets are suitable for:
- adults
- adolescents aged 12 to less than 18 years.

The patient does not have to have HIV to be treated with tenofovir disoproxil for HBV.

This medicine is not a cure for HIV infection.

How does Tenofovir disoproxil Aristo work?
Tenofovir disoproxil Aristo contains the active substance tenofovir disoproxil (as tenofovir disoproxil phosphate). This active substance is an antiretroviral or antiviral medicine which is used to treat HIV or HBV infection or both. Tenofovir is a nucleotide reverse transcriptase inhibitor, generally known as an NRTI and works by interfering with the normal working of enzymes (in HIV reverse transcriptase; in hepatitis B DNA polymerase) that are essential for the viruses to reproduce themselves. In HIV tenofovir disoproxil should always be used combined with other medicines to treat HIV infection.

How is Tenofovir disoproxil Aristo used?
Tenofovir disoproxil Aristo is available as film-coated tablets and is taken by mouth (orally).

Tenofovir disoproxil Aristo can only be obtained with a prescription. The tablets should be taken exactly as told by the doctor or pharmacist. The patient should check with the doctor or pharmacist if not sure.
The recommended dose is:
- Adults: 1 tablet each day with food (for example, a meal or a snack).
- Adolescents aged 12 to less than 18 years who weigh at least 35 kg: 1 tablet each day with food (for example, a meal or a snack).

If the patient has particular difficulty swallowing, he/she can use the tip of a spoon to crush the tablet. Then the patient should mix the powder with about 100 ml (half a glass) of water, orange juice or grape juice and drink immediately.

While taking Tenofovir disoproxil Aristo the patient may still develop infections or other illnesses associated with HIV infection. The patient can also pass on HIV or HBV to others, so it is important to take precautions to avoid infecting other people.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

**What benefits of Tenofovir disoproxil Aristo has been shown in studies?**
As Tenofovir disoproxil Aristo is a generic medicine, studies have been limited to tests to determine that Tenofovir disoproxil Aristo is bioequivalent to the reference medicine Viread (Gilead Sciences International Limited, UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Tenofovir disoproxil Aristo?**
Because Tenofovir disoproxil Aristo is a generic medicine and bioequivalent to the reference medicine Viread (Gilead Sciences International Limited, UK), the possible side effects are taken as being the same as those of the reference medicine.

For the full list of all side effects reported with Tenofovir disoproxil Aristo, see section 4 of the package leaflet.

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

**Why is Tenofovir disoproxil Aristo approved?**
It was concluded that, in accordance with EU requirements, Tenofovir disoproxil Aristo has been shown to have comparable quality and to be bioequivalent to Viread (Gilead Sciences International Limited, UK). Therefore, the view was that, as for Viread (Gilead Sciences International Limited, UK), the benefits outweigh the identified risks.

**What measures are being taken to ensure the safe and effective use of Tenofovir disoproxil Aristo?**
A Risk Management Plan has been developed to ensure that Tenofovir disoproxil Aristo 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 Tenofovir disoproxil Aristo, 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 and healthcare professionals will be monitored and reviewed continuously as well.

**Other information about Tenofovir disoproxil Aristo**
Austria, Germany, Spain, Italy, the Netherlands and the UK agreed to grant a Marketing Authorisation for Tenofovir disoproxil Aristo on 19 March 2017. A Marketing Authorisation was granted in the UK on 04 April 2017.

The full PAR for Tenofovir disoproxil Aristo follows this summary.
For more information about treatment with Tenofovir disoproxil Aristo, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in June 2017.
SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

<table>
<thead>
<tr>
<th></th>
<th>Introduction</th>
<th>Page 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Quality aspects</td>
<td>Page 7</td>
</tr>
<tr>
<td>III</td>
<td>Non-clinical aspects</td>
<td>Page 10</td>
</tr>
<tr>
<td>IV</td>
<td>Clinical aspects</td>
<td>Page 11</td>
</tr>
<tr>
<td>V</td>
<td>User consultation</td>
<td>Page 14</td>
</tr>
<tr>
<td>VI</td>
<td>Overall conclusion, benefit/risk assessment and recommendation</td>
<td>Page 14</td>
</tr>
<tr>
<td></td>
<td>Annex 1 - Table of content of the PAR update for MRP and DCP</td>
<td>Page 23</td>
</tr>
</tbody>
</table>
I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Tenofovir disoproxil Aristo 245 mg film-coated tablets (PL 40546/0009; UK/H/6267/001/DC) could be approved. The product may be referred to as ‘Tenofovir disoproxil Aristo tablets’ in this Scientific Discussion.

Tenofovir disoproxil Aristo tablets are a Prescription Only Medicine (POM) and are indicated in the following:

- **HIV-1 infection**
  Tenofovir disoproxil Aristo tablets are indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected adults.

  In adults, the demonstration of the benefit of tenofovir disoproxil in HIV-1 infection is based on results of one study in treatment-naïve patients, including patients with a high viral load (> 100,000 copies/ml) and studies in which tenofovir disoproxil phosphate was added to stable background therapy (mainly tritherapy) in antiretroviral pre-treated patients experiencing early virological failure (< 10,000 copies/ml, with the majority of patients having < 5,000 copies/ml).

  Tenofovir disoproxil Aristo tablets are also indicated for the treatment of HIV-1 infected adolescents, with NRTI resistance or toxicities precluding the use of first line agents, aged 12 to < 18 years.

  The choice of tenofovir disoproxil to treat antiretroviral-experienced patients with HIV-1 infection should be based on individual viral resistance testing and/or treatment history of patients.

- **Hepatitis B infection**
  Tenofovir disoproxil Aristo tablets are indicated for the treatment of chronic hepatitis B in adults with:
  - compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.
  - evidence of lamivudine-resistant hepatitis B virus
  - decompensated liver disease.

  Tenofovir disoproxil Aristo 245 mg tablets are indicated for the treatment of chronic hepatitis B in adolescents 12 to < 18 years of age with:
  - compensated liver disease and evidence of immune active disease, i.e. active viral replication, persistently elevated serum ALT levels and histological evidence of active inflammation and/or fibrosis

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Austria, Germany, Spain, Italy and the Netherlands as Concerned Member States (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of the originator medicinal product Viread film coated tablets (Gilead Sciences International, Limited, UK), which was first authorised on 05 February 2002 in the Community via the Centralised Procedure (EU/1/01/200/001). Viread film coated tablets may be referred to as ‘Viread’ in this Scientific Discussion.

The active substance in Tenofovir disoproxil Aristo tablets, is tenofovir disoproxil (as tenofovir disoproxil phosphate) while that in the originator product is tenofovir disoproxil, as tenofovir disoproxil
Tenofovir disoproxil Aristo 245 mg film-coated tablets

UK/H/6267/001/DC

fumarate. The applicant has presented data to support the claim that the active substance tenofovir disoproxil in tenofovir disoproxil fumarate and tenofovir disoproxil phosphate is interchangeable.

Tenofovir disoproxil is absorbed and converted to the active substance tenofovir, which is a nucleoside monophosphate (nucleotide) analogue. Tenofovir is then converted to the active metabolite, tenofovir diphosphate, an obligate chain terminator, by constitutively expressed cellular enzymes. Tenofovir diphosphate has an intracellular half-life of 10 hours in activated and 50 hours in resting peripheral blood mononuclear cells (PBMCs). Tenofovir diphosphate inhibits HIV-1 reverse transcriptase and the HBV polymerase by direct binding competition with the natural deoxyribonucleotide substrate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of cellular polymerases α, β, and γ. At concentrations of up to 300 µmol/l, tenofovir has also shown no effect on the synthesis of mitochondrial DNA or the production of lactic acid in \textit{in vitro} assays.

One bioequivalence study comparing the applicant’s test product Tenofovir Disoproxil Phosphate Tablets 300 mg (equivalent to Tenofovir Disoproxil 245 mg) with the reference product Viread (Tenofovir Disoproxil) 245 mg Tablets (Gilead Sciences International, Limited, UK), under fed conditions. It is stated that the bioequivalence study was conducted in accordance with Good Clinical Practice (GCP) and the Declaration of Helsinki.

With the exception of the bioequivalence study, no new non-clinical or clinical studies were conducted, which is acceptable given that the subject of this application is a generic medicinal product of an originator product that have been licensed for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place 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 manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

Austria, Germany, Spain, Italy, the Netherlands and the UK considered that the application could be approved at the end of procedure (Day 210) on 19 March 2017. After a subsequent national phase, a Marketing Authorisation was granted in the UK to Aristo Pharma GmbH on 04 April 2017, respectively.

II QUALITY ASPECTS

II.1 Introduction

The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Tenofovir disoproxil Aristo tablets are blue, oval, biconvex film-coated tablets debossed with “T1” on one side and plain on the other side.

Each film-coated tablet contains 245 mg of tenofovir disoproxil (as tenofovir disoproxil phosphate).
The product also contains pharmaceutical excipients in the tablet core and coating, namely microcrystalline cellulose, croscarmellose sodium, stearic acid, lactose monohydrate, hypromellose (E464), titanium dioxide (E171), triacetin and indigo carmine aluminium lake (E132). Appropriate justification for the inclusion of each excipient has been provided.

The finished product is supplied in white high density polyethylene (HDPE) bottles each with a child-resistant closure containing 30 film-coated-tablets or 90 film-coated tablets. The neck of each bottle is sealed with a tamper evident laminate film. Each bottle contains two silica gel desiccants.

The product is available in pack sizes of 30 film-coated tablets and multipacks containing 90 (3 packs of 30) film-coated tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for the primary packaging materials have been provided. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

II.2 DRUG SUBSTANCE

Tenofovir disoproxil phosphate

INN: Tenofovir disoproxil phosphate

Structural formula:

![Structural formula of Tenofovir disoproxil phosphate]

Molecular formula: \(C_{19}H_{33}N_{5}O_{14}P_{2}\)

\(M_r: 617.44\)

Appearance: White to off white powder.

Solubility: Slightly soluble in methanol.

Tenofovir disoproxil phosphate was not the subject of a European Pharmacopoeia monograph at the time of assessment.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.
An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards used.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 MEDICINAL PRODUCT
Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious, stable film-coated tablets, each containing 245 mg of tenofovir disoproxil (as tenofovir disoproxil phosphate), which were bioequivalent to Viread film coated tablets (Gilead Sciences International Limited, UK). Suitable pharmaceutical development data have been provided for this application.

Comparative in-vitro dissolution profiles have been provided for this product and the reference product. The dissolution profiles were satisfactory.

With the exception of indigo carmine aluminium lake (E132), all excipients comply with their respective European Pharmacopoeia monographs. Indigo carmine aluminium lake (E132) is in compliance with the current EU Directive concerning the use of colouring agents.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material, other than calf rennet, is used during the production of lactose monohydrate.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. The manufacturing process has been validated with pilot-scale batches and has shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation studies on future full-scale production batches.

Control of Finished Product
The finished product specification is acceptable. Test methods have been described and have been validated adequately. Batch data have been provided that complies with the release specification. 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 finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years, with special storage instructions of ‘Store below 25°C.’ has been accepted.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.
Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study. The bioequivalence study is discussed in Section IV, Clinical Aspects.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that a Marketing Authorisation is granted for this application, from a quality point of view.

III NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of tenofovir disoproxil are well known. No new non-clinical data have been submitted for this application and none are required given the clinical data study and the pharmaceutical comparative data that have been submitted.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

The Applicant proposes a change in salt from the fumarate to the phosphate. The Applicant provides no new in vivo non-clinical data in support of this change of salt, however provides clinical data to support the change. It is acceptable that no non-clinical in vivo work has been conducted, given the clinical studies with the Applicant’s product and the pharmaceutical comparative exercise that has been conducted.

III.2 Pharmacology
No new data have been submitted and none are required for an application of this type. Refer to Section III.1, Introduction, above.

III.3 Pharmacokinetics
No new data have been submitted and none are required for an application of this type. Refer to Section III.1, Introduction, above.

III.4 Toxicology
The in silico toxicity of tenofovir disoproxil phosphate and tenofovir disoproxil fumarate using structural alert software (Derek Nexus) was examined.

The Applicant adequately discussed the clinical relevance of the endpoints the Derek Nexus screen showed. It is agreed that that nephrotoxicity, hepatotoxicity and cutaneous signals reported in the Derek Nexus study are known effects associated with the use of tenofovir disoproxil and are adequately addressed in the product literature.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of already authorised product, it is not expected that environmental exposure of tenofovir disoproxil will increase following approval of the Marketing Authorisation for the proposed product. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

III.6 Discussion of the non-clinical aspects
It is recommended that a Marketing Authorisation is granted, from a non-clinical point of view.
IV. CLINICAL ASPECTS

IV.1 Introduction.
The clinical pharmacology of tenofovir disoproxil is well-known.

With the exception of data from the bioequivalence study detailed in Section IV.2, Pharmacokinetics below, no new pharmacokinetic data is provided or required for this application.

IV.2 Pharmacokinetics
Tenofovir disoproxil is a water soluble ester prodrug which is rapidly converted in vivo to tenofovir and formaldehyde. Tenofovir is converted intracellularly to tenofovir monophosphate and to the active component, tenofovir diphosphate.

Absorption: Following oral administration of tenofovir disoproxil fumarate to HIV infected patients, tenofovir disoproxil fumarate is rapidly absorbed and converted to tenofovir. Administration of multiple doses of tenofovir disoproxil fumarate with a meal to HIV infected patients resulted in mean (% CV) tenofovir Cmax, AUC0-t, and Cmin values of 326 (36.6%) ng/ml, 3,324 (41.2%) ng·h/ml and 64.4 (39.4%) ng/ml, respectively. Maximum tenofovir concentrations are observed in serum within one hour of dosing in the fasted state and within two hours when taken with food. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted patients was approximately 25%. Administration of tenofovir disoproxil fumarate with a high fat meal enhanced the oral bioavailability, with an increase in tenofovir AUC by approximately 40% and Cmax by approximately 14%. Following the first dose of tenofovir disoproxil fumarate in fed patients, the median Cmax in serum ranged from 213 to 375 ng/ml. However, administration of tenofovir disoproxil fumarate with a light meal did not have a significant effect on the pharmacokinetics of tenofovir.

Distribution: Following intravenous administration the steady-state volume of distribution of tenofovir was estimated to be approximately 800 ml/kg. After oral administration of tenofovir disoproxil fumarate, tenofovir is distributed to most tissues with the highest concentrations occurring in the kidney, liver and the intestinal contents (preclinical studies). In vitro protein binding of tenofovir to plasma or serum protein was less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 µg/ml.

Biotransformation: In vitro studies have determined that neither tenofovir disoproxil fumarate nor tenofovir are substrates for the CYP450 enzymes. Moreover, at concentrations substantially higher (approximately 300-fold) than those observed in vivo, tenofovir did not inhibit in vitro drug metabolism mediated by any of the major human CYP450 isoforms involved in drug biotransformation (CYP3A4, CYP2D6, CYP2C9, CYP2E1, or CYP1A1/2). Tenofovir disoproxil fumarate at a concentration of 100 µmol/l had no effect on any of the CYP450 isoforms, except CYP1A1/2, where a small (6%) but statistically significant reduction in metabolism of CYP1A1/2 substrate was observed. Based on these data, it is unlikely that clinically significant interactions involving tenofovir disoproxil fumarate and medicinal products metabolised by CYP450 would occur.

Elimination: Tenofovir is primarily excreted by the kidney by both filtration and an active tubular transport system with approximately 70-80% of the dose excreted unchanged in urine following intravenous administration. Total clearance has been estimated to be approximately 230 ml/h/kg (approximately 300 ml/min). Renal clearance has been estimated to be approximately 160 ml/h/kg (approximately 210 ml/min), which is in excess of the glomerular filtration rate. This indicates that active tubular secretion is an important part of the elimination of tenofovir. Following oral administration the terminal half-life of tenofovir is approximately 12 to 18 hours.

Studies have established the pathway of active tubular secretion of tenofovir to be influx into proximal tubule cell by the human organic anion transporters (hOAT) 1 and 3 and efflux into the urine by the multidrug resistant protein 4 (MRP 4).
Linearity/non-linearity: The pharmacokinetics of tenofovir were independent of tenofovir disoproxil fumarate dose over the dose range 75 to 600 mg and were not affected by repeated dosing at any dose level.

In support of the application, the applicant submitted the following bioequivalence study:

**An open-label, randomised, two-treatment, two-sequence, two-period, single-dose, crossover, bioequivalence study** comparing the test product Tenofovir Disoproxil Fumarate Tablets 300 mg (equivalent to Tenofovir Disoproxil 245 mg) versus the reference product Viread (Tenofovir Disoproxil) 245 mg Tablets (Gilead Sciences International Limited, UK) in healthy human male volunteers under fed conditions.

Subjects were administered a single oral dose of either the test or reference product with 240 ml of water at room temperature after a standard high fat, high calorie breakfast after an overnight fast. Blood sampling was performed pre-dose and up to 72 hours post dose in each treatment period. A washout period of 7 days was kept between each consecutive dosing period. The pharmacokinetic results are presented below for the analyte, tenofovir:

<table>
<thead>
<tr>
<th>Variable</th>
<th>point estimator</th>
<th>confidence intervals</th>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(0-t) (ratio test/reference)</td>
<td>93.85%</td>
<td>89.95% - 97.92%</td>
<td>8.77%</td>
</tr>
<tr>
<td>Cmax (ratio test/reference)</td>
<td>91.55%</td>
<td>84.74% - 98.91%</td>
<td>16.04%</td>
</tr>
</tbody>
</table>

AUC<sub>0-t</sub> area under the plasma concentration-time curve from time zero to t hours
C<sub>max</sub> maximum plasma concentration
CV coefficient of variation

**Bioequivalence Discussion and Conclusion**

The Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr*) defines the confidence limits for ratio of geometric means for acceptance of bioequivalence as 80.00% to 125.00% for C<sub>max</sub> and AUC values. The results indicate that the bioequivalence criteria are met for tenofovir as the AUC(0-t) and C<sub>max</sub> values lie within acceptance limits. Hence, the data from this study support the claim that the applicant’s test product is bioequivalent to the reference product, Viread 245 mg Tablets (Gilead Sciences International Limited, UK), under fed conditions.

**IV.3 Pharmacodynamics**

The clinical pharmacodynamics properties of tenofovir disoproxil are well-known. No new pharmacodynamic data were submitted and none are required for an application of this type.

**IV.4 Clinical Efficacy**

The clinical efficacy of tenofovir disoproxil is well-known. No new efficacy data are presented or are required for an application of this type.

**IV.5 Clinical Safety**

No new safety data were submitted and none are required for an application of this type. No new or unexpected safety issues arose during the bioequivalence study.
IV.6 Risk Management Plan

The 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 Tenofovir disoproxil Aristo tablets.

A summary of safety concerns is listed in the table below:

<table>
<thead>
<tr>
<th>Table 1: Summary of Safety Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Important identified risk(s)</strong></td>
</tr>
<tr>
<td>1. Post-treatment hepatic flares in HBV mono-infected and HIV/HBV co-infected patients</td>
</tr>
<tr>
<td>2. Renal toxicity</td>
</tr>
<tr>
<td>3. Bone events due to proximal renal tubulopathy/loss of bone mineral density (BMD)</td>
</tr>
<tr>
<td>4. Drug interaction with didanosine</td>
</tr>
<tr>
<td>5. Pancreatitis</td>
</tr>
<tr>
<td><strong>Important potential risk(s)</strong></td>
</tr>
<tr>
<td>1. Development of resistance during long-term exposure in HBV infected patients</td>
</tr>
<tr>
<td><strong>Missing information</strong></td>
</tr>
<tr>
<td>1. Safety in children (including long-term safety)</td>
</tr>
<tr>
<td>2. Safety in elderly patients</td>
</tr>
<tr>
<td>3. Safety in pregnancy</td>
</tr>
<tr>
<td>4. Safety in lactation</td>
</tr>
<tr>
<td>5. Safety in patients with renal impairment</td>
</tr>
<tr>
<td>6. Safety in black HBV infected patients</td>
</tr>
<tr>
<td>7. Safety in HBV infected patients with decompensated liver disease and CPT score &gt;9 (including long-term safety)</td>
</tr>
<tr>
<td>8. Safety in liver transplant recipients infected with HBV</td>
</tr>
</tbody>
</table>

Routine pharmacovigilance activities are planned for all safety concerns which are considered acceptable.

Routine risk minimisation activities are planned for all safety concerns. Additional risk minimisation measures are planned for the safety concerns of ‘Renal toxicity’, ‘Safety in children (including long term safety)’ and ‘Safety in patients with renal impairment’ in the form of the distribution of the following educational material:

- HIV renal educational brochure, including the creatinine clearance slide ruler
- HBV renal educational brochure, including the creatinine clearance slide ruler
- HIV paediatric educational brochure
- HBV paediatric educational brochure

IV.7 Discussion of the clinical aspects

It is recommended that a Marketing Authorisation is granted, from a clinical point of view.

V. USER CONSULTATION

A package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The language used for the purpose of user testing the package information leaflet (PIL) was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.
VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The important quality characteristics of Tenofovir disoproxil Aristo tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type. As the pharmacokinetics, pharmacodynamics and toxicology of tenofovir disoproxil are well-known, no additional data were required.

EFICACY
Bioequivalence has been demonstrated between the applicant’s test product and the reference product Viread 245 mg Tablets (Gilead Sciences International Limited, UK), under fed conditions.

SAFETY
No new data were submitted and none are required for an application of this type. As the safety profile of tenofovir disoproxil is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with tenofovir disoproxil is considered to have demonstrated the therapeutic value of the compound. The product is bioequivalent to the marketed reference product. The overall benefit/risk assessment is therefore considered to be positive.

RECOMMENDATION
The grant of a Marketing Authorisation is recommended.
In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website. The current labelling is presented below:
Annex 1 - 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

<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>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>