LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Tenofovir disoproxil Teva
(tenofovir disoproxil)

SE/H/1432/01/DC

This module reflects the scientific discussion for the approval of Tenofovir disoproxil Teva. The procedure was finalised on 2015-07-14. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Tenofovir disoproxil Teva, 245 mg, film-coated tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Teva Sweden AB, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, DE, DK, ES, FI, FR, IE, IS, IT, LU, LV, NL, PT, UK as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Viread, 245 mg, film-coated tablets authorised in EU (centrally authorised product) since 2002, with Gilead Sciences International Ltd as marketing authorisation holder. The member state of source for the reference product used in the bioequivalence study is Germany.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Tenofovir disoproxil is a water soluble ester prodrug which is rapidly absorbed and converted in vivo to tenofovir. The oral bioavailability of tenofovir from tenofovir disoproxil in fasted patients was approximately 25%. Following an oral dose of tenofovir disoproxil maximal plasma concentrations of tenofovir occur within one hour of dosing in the fasted state and within two hours when taken with food. Administration of tenofovir disoproxil with a high fat meal enhanced the oral bioavailability, with an increase in tenofovir AUC by approximately 40% and C_{max} by approximately 14%. However, administration of tenofovir disoproxil with a light meal did not have a significant effect on the pharmacokinetics of tenofovir. According to the SmPC of the originator the product should be administered with food. The pharmacokinetics of tenofovir were independent of tenofovir disoproxil dose over the dose range 75 to 600 mg and were not affected by repeated dosing at any dose level. 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. Following oral administration the terminal half-life of tenofovir is approximately 12 to 18 hours.

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 24 healthy volunteers, comparing Tenofovir disoproxil (as phosphate), 245 mg, film-coated tablets with Viread (tenofovir disoproxil [as fumarate]), 245 mg, film-coated tablets under fed conditions. Blood samples were collected pre-dose and up to 72 hours post-dose. The study design is considered acceptable. Serum concentrations of tenofovir were determined with an adequately validated LC/MS/MS method. It is agreed to base bioequivalence on the active metabolite tenofovir since the prodrug tenofovir disoproxil is rapidly converted to tenofovir following absorption. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%. The applied product contains a different salt of the prodrug tenofovir disoproxil compared to the originator (phosphate instead of fumarate). For a generic product it is acceptable to use different salts provided that they do not differ significantly in properties with regard to efficacy and safety. In this case, since bioequivalence has been demonstrated for the active metabolite and since phosphate salts are commonly used in general, no concern is raised regarding the change in salt.

Based on the submitted bioequivalence study, Tenofovirdisoproxil Teva is considered bioequivalent with Viread.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, 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 Teva.

Safety specification

Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks	• Renal Toxicity • Bone events due to proximal renal tubulopathy/loss of bone mineral density • Post-treatment hepatic flares in HBV monoinfected and HIV/HBV co-infected patients • Interaction with didanosine • Pancreatitis • Lactic acidosis and severe hepatomegaly with steatosis • Lipodystrophy
Important potential risks	• Development of resistance during long-term exposure in HBV infected patients
Missing information	• Safety in children (including long-term safety) • Safety in pregnancy • Safety in patients with renal impairment • Safety in elderly patients • Safety in lactation • Safety in black HBV infected patients • Safety in HBV infected patients with decompensated liver disease and CPT score > 9 (including long term safety) • Safety in liver transplant recipients infected with HBV

Risk minimisation measures

Summary of Safety Concerns and Planned Risk Minimisation Activities as proposed/ approved in RMP

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Renal toxicity	**Labelling:** • section 4.2 Posology and method of administration, Renal impairment • section 4.4 Special warnings and precautions for use, Renal and bone effects in adult/paediatric population • section 4.8 Undesirable effects Prescription only medicine; initiated by a physician experienced in the management of HIV infection and/or treatment of chronic hepatitis B.	*Educational initiatives distributed to prescribers:* • HIV renal educational brochure, including the creatinine clearance slide ruler/calculator • HBV renal educational brochure, including the creatinine clearance slide ruler/calculator • HIV paediatric educational brochure • HBV paediatric educational brochure
Bone events due to proximal renal tubulopathy/loss of bone mineral density	**Labelling:** • section 4.4 Special warnings and precautions for use, Renal and bone effects in adult/paediatric population • section 4.8 Undesirable effects Prescription only medicine; initiated by a physician experienced in the management of HIV infection and/or treatment of chronic hepatitis B.	Not applicable
Post-treatment hepatic flares in HBV monoinfected and HIV/HBV Co-infected patients	**Labelling:** • section 4.2 Posology and method of administration, Hepatic impairment • section 4.4 Special warnings and precautions for use, Liver disease: Flares after treatment discontinuation • section 4.8 Undesirable effects, Exacerbations of hepatitis after discontinuation of treatment Prescription only medicine; initiated by a physician experienced in the management of HIV infection and/or treatment of chronic hepatitis B.	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Interaction with didanosine	**Labelling:** • section 4.4 Special warnings and precautions for use, Co-administration of other medicinal products • section 4.5 Interaction with other medicinal products and other forms of interaction, Concomitant use not recommended • section 4.8 Undesirable effects, Interaction with didanosine Prescription only medicine; initiated by a physician experienced in the management of HIV infection and/or treatment of chronic hepatitis B.	Not applicable
Pancreatitis	**Labelling:** Pancreatitis associated with the interaction with didanosine is described in: • section 4.4 Special warnings and precautions for use • section 4.5 Interaction with other medicinal products and other forms of interaction • section 4.8 Undesirable effects Prescription only medicine; initiated by a physician experienced in the management of HIV infection and/or treatment of chronic hepatitis B.	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Lactic acidosis and severe hepatomegaly with steatosis	**Labelling:** • section 4.4 Special warnings and precautions for use, **Boxed warning** of a class effect of nucleoside analogues • section 4.5 Interaction with other medicinal products and other forms of interaction, Didanosine • section 4.8 Undesirable effects, frequency rare Prescription only medicine; initiated by a physician experienced in the management of HIV infection and/or treatment of chronic hepatitis B.	Not applicable
Lipodystrophy	**Labelling:** • section 4.4 Special warnings and precautions for use, Lipodystrophy • section 4.8 Undesirable effects, Lipids, lipodystrophy and metabolic abnormalities Prescription only medicine; initiated by a physician experienced in the management of HIV infection and/or treatment of chronic hepatitis B.	Not applicable
Development of resistance during long-term exposure in HBV infected patients	**Labelling:** • section 5.1 Pharmacodynamic properties, Data pertaining to HBV: Resistance Prescription only medicine; initiated by a physician experienced in the management of HIV infection and/or treatment of chronic hepatitis B.	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Safety in children (including long-term safety)	**Labelling:** • section 4.2 Posology and method of administration, Paediatric population • section 4.4 Special warnings and precautions for use, Renal and bone effects in paediatric population • section 4.8 Undesirable effects, Paediatric population Prescription only medicine; initiated by a physician experienced in the management of HIV infection and/or treatment of chronic hepatitis B.	*Educational initiatives distributed to prescribers:* • HIV paediatric educational brochure • HBV paediatric educational brochure
Safety in pregnancy	**Labelling:** • section 4.6 Fertility, pregnancy and lactation Prescription only medicine; initiated by a physician experienced in the management of HIV infection and/or treatment of chronic hepatitis B.	Not applicable
Safety in patients with renal impairment	**Labelling:** • section 4.2 Posology and method of administration, Renal impairment • section 4.4 Special warnings and precautions for use, Renal and bone effects in adult/paediatric population *See above safety concern "Renal toxicity".* Prescription only medicine; initiated by a physician experienced in the management of HIV infection and/or treatment of chronic hepatitis B.	*Educational initiatives distributed to prescribers::* • HIV renal educational brochure, including the creatinine clearance slide ruler/calculator • HBV renal educational brochure, including the creatinine clearance slide ruler/calculator • HIV paediatric educational brochure • HBV paediatric educational brochure

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Safety in elderly patients	**Labelling:** • section 4.2 Posology and method of administration, Special populations: Elderly • section 4.4 Special warnings and precautions for use, Elderly • section 4.8 Undesirable effects, Other special populations: Elderly Prescription only medicine; initiated by a physician experienced in the management of HIV infection and/or treatment of chronic hepatitis B.	Not applicable
Safety in lactation	**Labelling:** • section 4.6 Fertility, pregnancy and lactation; Breastfeeding Prescription only medicine; initiated by a physician experienced in the management of HIV infection and/or treatment of chronic hepatitis B.	Not applicable
Safety in black HBV infected patients	In the absence of specific safety signals relating to use in black HBV infected patients the applicant does not propose any risk minimisation activities at this time.	Not applicable
Safety in HBV infected patients with decompensated liver disease and CPT score >9 (including long-term safety)	**Labelling:** • section 4.4 Special warnings and precautions for use Prescription only medicine; initiated by a physician experienced in the management of HIV infection and/or treatment of chronic hepatitis B.	Not applicable
Safety in liver transplant recipients infected with HBV	In the absence of specific safety signals relating to use in liver transplant recipients infected with HBV, the applicant does not propose any risk minimisation activities at this time.	Not applicable

Summary of the RMP

The MAH has satisfactory responded to the questions raised and updated the RMP accordingly. The RMP is approved

V. USER CONSULTATION

The 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. The language used for the purpose of user testing the 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

The quality of the generic product, Tenofovir disoproxil Teva, is found adequate. There are no objections to approval of Tenofovir disoproxil Teva, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable.
The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Tenofovir disoproxil Teva, 245 mg, film-coated tablet was positively finalised on 2015-07-14.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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