LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Tenovelb

(tenofovir disoproxil fumarate)

SE/H/1709/01/DC
2017-0377

This module reflects the scientific discussion for the approval of Tenovelb. The procedure was finalised on 2018-05-31. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Tenovelb, 245mg, film-coated tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, axunio Pharma GmbH, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and FR, ES, IT, UK and DE as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Viread, 245mg, film-coated tablets authorised in union since 2002 with Gilead Sciences Int. Ltd. as marketing authorisation holder.

The reference product used in the bioequivalence study is Viread, 245mg, film-coated tablets authorised in union since 2002 with Gilead Sciences Int. Ltd. as marketing authorisation holder.

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 fumarate is a water soluble ester prodrug which is rapidly absorbed and converted *in vivo* to tenofovir and formaldehyde. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted patients was approximately 25%. Following an oral dose of tenofovir disoproxil fumarate 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 fumarate 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 fumarate 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. In exceptional circumstances the originator product can also be administered following disintegration of the tablet in at least 100 ml of water, orange juice or grape juice. 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. 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 36 healthy male volunteers, comparing Tenofovir disoproxil, 245 mg, film coated tablets with Viread, 245 mg, film coated tablets under fed conditions. The study was conducted between 28 Jan 2016 and 11 Feb 2016. Blood samples were collected pre-dose and up to 72 hours post-dose. The study design is considered acceptable. Plasma concentrations of tenofovir were determined with an adequately validated LC/MS/MS method. It is agreed to base bioequivalence on 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%.

Table: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for tenofovir, n=36.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	3021.52 ± 570.8646	330.68 ± 93.9842	1.50 (0.50 – 5.00)
Reference	3033.65 ± 701.0706	341.18 ± 109.6846	1.63 (0.50 – 4.00)
***Ratio (90% CI)**	100.53 (97.26 -103.90)	98.15 (92.41 -104.23)	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

The reference product Viread can in exceptional circumstance also be administered following disintegration of the tablet in at least 100 ml of water, orange juice or grape juice but no bioequivalence study was performed with these additional modes of administration. However a waiver for further bioequivalence studies is acceptable since the following conditions are met:

- successful bioequivalence with uncrushed products;
- BCS classification of the drug substance as class 1 or 3;
- comparative evaluation of excipients, particularly regarding potentially surface active excipients;
- comparative multimedia in-vitro dissolution;
- comparative disintegration testing.

In conclusion bioequivalence has been shown.

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 Tenovelb.

Safety specification

Table: 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 ofbone mineral density • Post-treatment hepatic flares in HBV monoinfected and HIV-1/HBV coinfected patients • Interaction with didanosine • Pancreatitis
Important potential risks	• Development ofresistance during long-term exposure in HBV infected patients
Missing information	• Safety in children (including long-term safety) • Safety in elderly patients • Safety in pregnancy • Safety in lactation • Safety in black HBV infected patients • Safety in patients with renal impairment • 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

Assessor's comment: The summary safety concerns is updated according to the recent RMP for Viread which is endorsed.

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Table: Summary of Safety Concerns and Planned Risk Minimisation Activities

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Renal Toxicity	*SmPC Section 4.2* Posology and method of administration: • Statement that tenofovir is eliminated by renal excretion and the exposure to tenofovir increases in patients with renal dysfunction. *Adults* • Statements that tenofovir should only be used in patients with moderate and severe renal impairment (creatinine clearance < 50 ml/min) if the potential benefits of treatment are considered to outweigh the potential risks. • Statements indicating that long-term safety data has not been evaluated in patients with mild renal impairment (creatinine clearance 50-80 ml/min) and limited data from clinical studies support once daily dosing of 245 mg tenofovir disoproxil. • Recommendations for administration of a reduced daily dose of tenofovir in patients with creatinine clearance <50 ml/min, including hemodialysis	*HIV* HIV renal educational brochure (including creatinine clearance slide ruler) for prescribers of adult patients HIV educational brochure for prescribers of tenofovir to pediatric patients *HBV* HBV renal educational brochure (including creatinine clearance slide ruler) for prescribers of

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	patients. • Guidance that for patients with moderate renal impairment (creatinine clearance 30-49 ml/min) where administration of a lower dose is not possible of tenofovir, prolonged dose intervals using the 245 mg tablets may be used. • Guidance that for patients with severe renal impairment (creatinine clearance < 30 ml/min), and hemodialysis patients, if no alternative treatment available, prolonged dose intervals using the 245 mg tablets may be used. <u>*Paediatric population*</u> • Statement that tenofovir is not recommended in pediatric patients with renal impairment. *SmPC Section 4.4 Special warnings and precautions for use:* • Warning that concomitant administration of several products containing tenofovir should not take place. <u>*Adults*</u> • Statement that tenofovir is principally eliminated via the kidney and that renal failure, renal impairment, elevated creatinine, hypophosphatemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir. • Warning that bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy; if bone abnormalities are suspected then appropriate consultation should be obtained. • Recommendation that renal function (creatinine clearance and serum phosphate) is assessed in all patients prior to initiating therapy with tenofovir disoproxil fumarate and that it is also monitored after two to four weeks of treatment, after three months of treatment and every three to six months thereafter in patients without renal risk factors. In patients at risk for renal impairment, a more frequent monitoring of renal function is required. • Recommendation to measure serum potassium, and blood and urine glucose levels within one week if serum phosphate is < 1.5 mg/dl (0.48 mmol/l) or creatinine clearance is decreased to < 50 ml/min; consideration should be given to interrupting tenofovir DF in patients with creatinine clearances < 50 ml/min or decreases in serum phosphate to <1.0 mg/dl (0.32 mmol/1). Interrupting treatment with tenofovir disoproxil fumarate should also be considered in case of progressive decline of renal function when no other cause has been identified. • Recommendation that tenofovir DF should be avoided with concurrent or recent use of a nephrotoxic medicinal product. If concomitant use of tenofovir DF and nephrotoxic agents is unavoidable, renal function should be monitored weekly.	adult patients HBV Educational brochure for prescribers of tenofovir to pediatric patients

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• Recommendation against the concomitant use of tenofovir DF and medicinal products that are secreted by the same renal pathway including the transport proteins human organic anion transporter (hOAT) 1 and 3 or multidrug resistant protein 4 (MRP 4), e.g. cidofovir, a known nephrotoxic medicinal product; if such use is unavoidable, renal function should be monitored weekly. • Statement that cases of acute renal failure after initiation of high dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) have been reported in patients treated with tenofovir disoproxil fumarate and with risk factors for renal dysfunction. If tenofovir disoproxil fumarate is co-administered with an NSAID, renal function should be monitored adequately. • Statement that a higher risk of renal impairment has been reported in patients receiving tenofovir disoproxil fumarate in combination with a ritonavir or cobicistat boosted protease inhibitor. A close monitoring of renal function is required in these patients. In patients with renal risk factors, the coadministration of tenofovir disoproxil fumarate with a boosted protease inhibitor should be carefully evaluated. • Statement that renal safety with tenofovir has only been studied to a very limited degree in adult patients with impaired renal function (creatinine clearance < 80 ml/min). • Warning that tenofovir DF should only be used in patients with creatinine clearance < 50 ml/min, including hemodialysis patients, if the potential benefits of treatment are considered to outweigh the potential risks. • Warning that in in patients with severe renal impairment (creatinine clearance < 30 ml/min) and in patients who require haemodialysis use of tenofovir disoproxil fumarate is not recommended. If no alternative treatment is available, the dosing interval must be adjusted and renal function should be closely monitored. *Paediatric population* • Statement that there are uncertainties associated with the long term effects of bone and renal toxicity in pediatric patients and the reversibility of renal toxicity cannot be fully ascertained. Therefore, a multidisciplinary approach is recommended for these patients to assess the benefit/risk balance of treatment, decide the appropriate monitoring during treatment and consider the need for supplementation. • Statement indicating that renal adverse reactions consistent with proximal renal tubulopathy have been reported in HIV-1 infected pediatric patients aged 2 to <12 years in clinical study GS-US-104-0352. • Recommendation that renal function should be	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	evaluated prior to treatment, and monitored during treatment as in adults. • Recommendation to measure serum potassium and blood and urine glucose levels in any pediatric patient within one week if serum phosphate is < 3.0 mg/dl (0.96 mmol/l); consideration should be given to interrupting tenofovir DF if renal abnormalities are suspected. • Warning that the use of tenofovir DF is not recommended in pediatric patients with renal impairment. *SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction* • An interaction statement that tenofovir DF is primarily eliminated by the kidneys and therefore coadministration of tenofovir DF with medicinal products that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir DF and/or the coadministered products. • Recommendation that use of tenofovir DF should be avoided with concurrent or recent use of nephrotoxic medicinal products. • Recommendation that as tacrolimus can also affect renal function, close monitoring is undertaken when it is coadministered with tenofovir DF. • Recommendation that patients receiving tenofovir concomitantly with ledipasvir/sofosbuvir (LDV/SOF) should be monitored for adverse reactions associated with tenofovir DF. *SmPC Section 4.8 Undesirable effects:* • Statement to indicate that rare events of renal impairment, renal failure and proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently leading to fractures) have been reported with the use of tenofovir DF. • Statement recommending that renal function is monitored in patients receiving tenofovir, as tenofovir may cause renal damage. • Statement that proximal renal tubulopathy generally resolved or improved after tenofovir disoproxil fumarate discontinuation. However, in some patients, declines in creatinine clearance did not completely resolve despite tenofovir disoproxil fumarate discontinuation. Patients at risk of renal impairment (such as patients with baseline renal risk factors, advanced HIV disease, or patients receiving concomitant nephrotoxic medications) are at increased risk of experiencing incomplete recovery of renal function despite tenofovir disoproxil fumarate	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	discontinuation. • The following ADRs are listed in the tabulated summary of adverse reactions: increased creatinine, proximal renal tubulopathy including Fanconi syndrome, acute renal failure, renal failure, acute tubular necrosis, nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus. • The following ADRs are listed in the tabulated summary of adverse reactions as adverse reactions that may occur as a consequence of proximal renal tubulopathy: hypophosphatemia, hypokalemia, rhabdomyolysis, muscular weakness, osteomalacia (manifested as bone pain and infrequently contributing to fractures), myopathy. • Recommendation that renal function is closely monitored in patients with renal impairment, since tenofovir DF has been associated with renal toxicity. <u>*Paediatric population*</u> • Statements that the adverse reactions in HBV and HIV-1 infected pediatric patients were consistent with those observed in clinical studies of tenofovir DF in adults. • A statement that of 89 patients (2 to < 12 years) who received tenofovir disoproxil fumarate in study GS-US-104-0352 (median exposure 104 weeks), 4 patients discontinued from the study due to adverse reactions consistent with proximal renal tubulopathy. • Recommendation not to use tenofovir DF in pediatric patients with renal impairment.	
Bone events due to proximal renal tubulopathy/loss of hone mineral density	*SmPC Section 4.4 Special warnings and precautions for use:* <u>*Adults*</u> • Statement that in HIV infected patients from a 144-week controlled clinical study that compared tenofovir DF with stavudine in combination with lamivudine and efavirenz in ART-naive adult patients, small decreases in BMD of the hip and spine were observed in both treatment groups. Decreases in BMD of spine and changes in bone biomarkers from baseline were significantly greater in the tenofovir DF treatment group at 144 weeks. Decreases in BMD of hip were significantly greater in this group until 96 weeks. However, there was no increased risk of fractures or evidence for clinically relevant bone abnormalities over 144 weeks. • Warning that bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy and that if bone abnormalities are suspected then appropriate consultation should be obtained. <u>*Paediatric population*</u> • Statement that tenofovir DF may cause a reduction in BMD and the effects of tenofovir DF-associated changes in BMD on long-term bone health and future	none

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	fracture risk are currently unknown. • Statement that there are uncertainties associated with the long term effects of bone and renal toxicity in pediatric patients and the reversibility of renal toxicity cannot be fully ascertained. Therefore, a multidisciplinary approach is recommended for these patients to assess the benefit/risk balance oftreatment, decide the appropriate monitoring during treatment and consider the need for supplementation. • Recommendation that if bone abnormalities are detected or suspected in pediatric patients, consultation with an endocrinologist and/or nephrologist should be obtained. *SmPC Section 4.8 Undesirable effects:* *Adults* • Statement to indicate that rare events of renal impairment, renal failure and proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have been reported. • Osteomalacia (manifested as bone pain and infrequently contributing to fractures) is included as an ADR in the tabulated summary of adverse reactions. *Pediatrics* • Statement that reductions in BMD have been reported in HIV-1 infected pediatric and adolescent patients who received tenofovir DF. • Statement that reductions in BMD have been observed in HBV infected adolescents who received tenofovir DF. *SmPC section 5.1 Pharmacodynamic properties:* *Pediatrics* • Statements that small decreases in BMD Z-scores have been observed following treatment with tenofovir DF in HIV infected pediatric and adolescent patients and HBV infected adolescents.	
Post-treatment hepatic flares in HBV monoinfected and HIV-1/HBV coinfected patients	*SmPC section 4.2 Posology and method of administration:* • Statement that if tenofovir DF is discontinued in patients with chronic hepatitis B (CHB) with or without HIV coinfection, these patients should be closely monitored for evidence of exacerbation of hepatitis. *SmPC section 4.4 Special warnings and precautions for use:* • Warning about the risk of exacerbation of hepatitis following discontinuation of HBV treatment, guidance that these patients should be closely monitored with both clinical and laboratory follow up for at least 6 months after stopping treatment, and guidance that, if appropriate, resumption of anti-HBV therapy may be warranted.	none

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• Recommendation that treatment is not discontinued in patients with advanced liver disease or cirrhosis since post-treatment exacerbation of hepatitis may lead to hepatic decompensation. • Warning that due to the risk of development of HIV resistance, tenofovir DF should only be used as part of an appropriate antiretroviral combination regimen in HIV/HBV coinfected patients. • Warning that patients coinfected with HIV/HBV with pre-existing liver dysfunction, have an increased frequency ofliver function abnormalities during cART and should be monitored; ifthere is evidence ofworsening liver disease in such patients, interruption or discontinuation of treatment must be considered. *Section 4.8 Undesirable effects:* • Statement indicating that discontinuation of therapy may be associated with exacerbations of hepatitis in HBV infected patients.	
Interaction with didanosine	*SmPC section 4.4 Special warnings and precautions for use:* • Warning that coadministration of tenofovir DF and didanosine is not recommended since exposure to didanosine is significantly increased following coadministration with tenofovir DF that may increase the risk of didanosine-related adverse reactions. *SmPC section 4.5 Interaction with other medicinal products and other forms of interaction:* • Warning that the coadministration of tenofovir DF and didanosine is not recommended. *SmPC Section 4.8 Undesirable effects:* Statement regarding the risk of lactic acidosis and pancreatitis associated with the interaction between tenofovir DF and tenofovir DF may cause a reduction in BMD didanosine.	none
Pancreatitis	*SmPC sections 4.4, 4.5 and 4.8:* • Warning statements regarding the risk of pancreatitis associated with the interaction between tenofovir DF and didanosine. *SmPC Section 4.8 Undesirable effects:* • 'Pancreatitis' is included as an ADR in the tabulated summary of adverse reactions.	none
Development of resistance during long-term exposure in HBV infected patients	*SmPC section 5.1 Pharmacodynamic properties* • No HBV mutations associated with tenofovir disoproxil fumarate resistance have been identified.	none

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Safety in children (including long-term safety)	*SmPC section 4.2 Posology and method of administration:* • Statement that in HIV-1 infected adolescents aged 12 to <18 years and weighing ≥35 kg, the recommended dose of tenofovir DF is 245 mg once daily, orally with food. • Statement that reduced doses of tenofovir disoproxil are used for treatment of HIV-1 infected paediatric patients aged 2 to <12 years. • Statement that in adolescents with CHB aged 12 to < 18 years and weighing ≥35 kg, the recommended dose of tenofovir DF is 245 mg once daily, orally with food. The optimal duration of treatment is currently unknown. • Statement that no data are available on the safety and efficacy oftenofovir DF in HIV-1 infected children under 2 years of age or HBV infected children aged 2 to < 12 years, or weighing < 35 kg. • Statement that tenofovir DF is not recommended in pediatric patients with renal impairment. *SmPC section 4.4 Special warnings and precautions for use:* • Statement that there are uncertainties associated with the long term effects of bone and renal toxicity in pediatric patients and the reversibility of renal toxicity cannot be fully ascertained. Therefore, a multidisciplinary approach is recommended for these patients to assess the benefit/risk balance of treatment, decide the appropriate monitoring during treatment and consider the need for supplementation. • Statement indicating that renal adverse reactions consistent with proximal renal tubulopathy have been reported in HIV-1 infected pediatric patients aged 2 to < 12 years in clinical study GS-US-104-0352. • Recommendation to monitor renal function (creatinine clearance and serum phosphate) as in adults. • Recommendation to measure serum potassium and blood and urine glucose levels in any pediatric patient within one week if serum phosphate is < 3.0 mg/dl (0.96 mmol/l); consideration should be given to interrupting tenofovir DF if renal abnormalities are suspected. • Warning that the use of tenofovir DF is not recommended in pediatric patients with renal impairment. • Statement that tenofovir DF may cause a reduction in BMD and the effects of tenofovir DF-associated changes in BMD on long-term bone health and future fracture risk are currently unknown. • Recommendation that if bone abnormalities are detected or suspected in pediatric patients, consultation with an endocrinologist and/or	none

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	nephrologist should be obtained. *SmPC Section 4.8 Undesirable effects:* • Statement that reductions in BMD have been reported in HIV-1 infected pediatric and adolescent patients who received tenofovir DF. • Statement that reductions in BMD have been observed in HBV infected adolescents who received tenofovir DF. • Recommendation that tenofovir DF is not used in pediatric patients with renal impairment. *SmPC section 5.1 Pharmacodynamic properties:* • Statements that small decreases in BMD Z-scores have been observed following treatment with tenofovir DF in HIV infected pediatric and adolescent patients and HBV infected adolescents.	
Safety in elderly patients	*SmPC section 4.2 Posology and method of administration:* • Statement indicating that no data are available on which to make a dose recommendation for elderly patients (> 65 years). *SmPC section 4.4 and 4.8:* • Statement indicating that tenofovir DF has not been studied in elderly patients (> 65 years). • Statement that elderly patients are more likely to have decreased renal function; therefore caution should be exercised when treating elderly patients with tenofovir DF.	none
Safety in pregnancy	*SmPC Section 4.6 Fertility, pregnancy and lactation* <u>Pregnancy</u> • Statement that a moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformations or foetal/neonatal toxicity associated with tenofovir DF. • Statement that animal studies do not indicate reproductive toxicity. • Statement that the use of tenofovir DF may be considered during pregnancy, if necessary.	none
Safety in lactation	*SmPC Section 4.6 Fertility, pregnancy and lactation:* • Statement indicating that tenofovir has been shown to be excreted in human milk. • Statement that there is insufficient information on the effects of tenofovir in newboms/infants; therefore tenofovir DF should not be used during breast-feeding. • Recommendations that HIV and HBV infected women	none

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	do not breast-feed their infants in order to avoid transmission of HIV and HBV to the infant.	
Safety in black HBV infected patients	Data from HIV infected patients do not suggest additional risks for black patients, no additional specific warnings are considered necessary for this population at this time.	none
Safety in patients with renal impairment	*SmPC section 4.2 Posology and method of administration:* • Statement that tenofovir is eliminated by renal excretion and the exposure to tenofovir increases in patients with renal dysfunction. <u>*Adults*</u> • Statements that tenofovir DF should only be used in patients with moderate and severe renal impairment (creatinine clearance < 50 ml/min) ifthe potential benefits of treatment are considered to outweigh the potential risks. • Statements indicating that long-term safety data has not been evaluated in patients with mild renal impairment (creatinine clearance 50-80 ml/min) and limited data from clinical studies support once daily dosing of 245 mg tenofovir disoproxil. • Recommendations for administration of a reduced daily dose of tenofovir in patients with creatinine clearance <50 ml/min, including hemodialysis patients. • Guidance that for patients with moderate renal impairment (creatinine clearance 30-49 ml/min) where administration of a lower dose is not possible, prolonged dose intervals using the 245 mg film-coated tablets may be used. • Guidance that for patients with severe renal impairment (creatinine clearance < 30 ml/min), and hemodialysis patients, where adequate dose adjustment cannot be applied and with no alternative treatment available, prolonged <lose intervals using the 245 mg film coated tablets may be used. <u>*Pediatrics*</u> • Statement that tenofovir DF is not recommended in pediatric patients with renal impairment. *SmPC section 4.4 Special warnings and precautions for use:* <u>*Adults*</u> • Statement that renal safety with tenofovir has only been studied to a very limited degree in adult patients with impaired renal function (creatinine clearance < 80 ml/min). • Warning that tenofovir DF should only be used in patients with creatinine clearance < 50 ml/min, including hemodialysis patients, ifthe potential benefits of treatment are considered to outweigh the potential risks. • Warning that in in patients with severe renal impairment (creatinine clearance < 30 ml/min) and in patients who require haemodialysis use of tenofovir	none

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	disoproxil fumarate is not recommended. If no alternative treatment is available, the dosing interval must be adjusted and renal function should be closely monitored. *Pediatrics* • Warning that the use of tenofovir DF is not recommended in pediatric patients with renal impairment. *SmPC Section 4.8 Undesirable effects:* • Recommendation that renal function is closely monitored in patients with renal impairment, since tenofovir DF has been associated with renal toxicity. Recommendation that tenofovir DF is not used in pediatric patients with renal impairment.	
Safety in HBV infected patients with decompensated liver disease and CPT score > 9 (including long-term safety)	*SmPC section 4.4 Special warnings and precautions for use:* • Statement that there are limited data on the safety and efficacy of tenofovir DF in HBV infected patients with decompensated liver disease and who have a CPT score >9. • Warning that these patients may be at higher risk of experiencing serious hepatic or renal adverse reactions. • Recommendation to closely monitor hepatobiliary and renal parameters. • Warning that liver flares are especially serious, and sometimes fatal in patients with decompensated liver disease.	none
Safety in liver transplant recipients infected with HBV	*SmPC section 4.4 Special warnings and precautions for use:* Statement indicating that safety and efficacy data are very limited in liver transplant patients.	none

Assessor's comment: The proposed risk minimisation measures are endorsed.

Summary of the RMP

The RMP is approved.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to the content of an already approved generic product (SE/H/1432/001/DC). Regarding the corporate layout a bridging to the generic product approved within procedure BE/H/0196/01-02/DC was made. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Tenovelb, is found adequate. There are no objections to approval of Tenovelb, 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

Regarding Article 21a of Directive 2001/83/EC, as amended, additional Risk Minimisation Measures are in place for this generic product, consisting of educational material.

The educational material for Tenovelb should be the same as those proposed for the reference medicinal product Viread. The educational material as well as the need for its distribution should be reviewed by the national competent authorities prior to the actual launch of the tenofovir-containing product onto the market.

The educational material should contain the following key elements:

The Marketing Authorisation Holder (MAH) shall ensure that all physicians who are expected to prescribe/use Tenofovir in adults and/or paediatric patients are provided with a physician educational pack containing the Summary of Product Characteristics and an appropriate educational brochure, as detailed below:

- 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

The HIV and HBV renal educational brochures should contain the following key messages:

- That there is an increased risk of renal disease in HIV and HBV infected patients associated with tenofovir disoproxil-containing products

 That Tenofovir should only be used in patients with impaired renal function if the potential benefits of treatment are considered to outweigh the potential risks
 The importance of dose interval adjustment using Tenofovir 245 mg film-coated tablets, in adult patients with creatinine clearance of 30-49 ml/min
 For patients with severe renal impairment (creatinine clearance < 30 ml/min), prolonged dose intervals using Tenofovir 245 mg film-coated tablets may be used
 That use of Tenofovir should be avoided with concomitant or recent use of nephrotoxic medicinal products. If Tenofovir is used with nephrotoxic medicinal products, renal function should be closely monitored according to the recommended schedule
 That patients should have their baseline renal function assessed prior to initiating Tenofovir therapy
 The importance of regular monitoring of renal function during Tenofovir therapy
 Recommended schedule for monitoring renal function considering the presence or absence of additional risk factors for renal impairment
 That if serum phosphate is < 1.5 mg/dl or creatinine clearance decreases during therapy to < 50 ml/min then renal function should be re-evaluated within one week. If creatinine clearance is confirmed as < 50 ml/min or serum phosphate decreases to < 1.0 mg/dl then consideration should be given to interrupting Tenofovir therapy. Interrupting treatment with Tenofovir should also be considered in case of progressive decline of renal function when no other cause has been identified.
 Instructions on the use of the creatinine clearance slide ruler

The HIV and HBV paediatric educational brochures should contain the following key messages:

 That a multidisciplinary approach is recommended for the management of paediatric patients
 That there is an increased risk of renal disease in HIV and HBV infected patients associated with tenofovir disoproxil-containing products
 That Tenofovir is not recommended for use in paediatric patients with renal impairment
 That use of Tenofovir should be avoided with concomitant or recent use of nephrotoxic medicinal products. If Tenofovir is used with nephrotoxic medicinal products, renal function should be closely monitored according to the recommended schedule
 That patients should have their baseline renal function assessed prior to initiating Tenofovir therapy
 The importance of regular monitoring of renal function during Tenofovir therapy
 Recommended schedule for monitoring renal function considering the presence or absence of additional risk factors for renal impairment
 That if serum phosphate is confirmed to be < 3.0 mg/dl (0.96 mmol/l) in any paediatric patient receiving tenofovir disoproxil, renal function should be re-evaluated within one week. If renal abnormalities are detected or suspected then consultation with a nephrologist should be obtained to consider interruption of Tenofovir treatment. Interrupting treatment with Tenofovir should also be considered in case of progressive decline of renal function when no other cause has been identified.
 That Tenofovir may cause a reduction in BMD and the effects of Tenofovir associated changes in BMD on long term bone health and future fracture risk are currently unknown in paediatric patients
 That if bone abnormalities are detected or suspected then consultation with an endocrinologist and/or nephrologist should be obtained.

VII. APPROVAL

The Mutual recognition/Decentralised procedure for Tenovelb, 245mg, film-coated tablet was positively finalised on 2018-05-31.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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