COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Emtricitabine/Tenofovirdisoproxil Glenmark 200 mg/245 mg film-coated tablets (emtricitabine and tenofovir disoproxil phosphate)

NL/H/4882/001/DC

Date: 1 March 2023

This module reflects the scientific discussion for the approval of Emtricitabine/Tenofovirdisoproxil Glenmark 200 mg/245 mg film-coated tablets. The procedure was finalised in the United Kingdom (UK/H/6333/001/DC). After a transfer in 2019, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

Emtricitabine/tenofovir disoproxil Glenmark 200 mg/245 mg Film-coated Tablets

(Emtricitabine and tenofovir disoproxil phosphate)

Procedure No: UK/H/6333/001/DC

UK Licence No: PL 25258/0210

Glenmark Pharmaceuticals Europe Limited

LAY SUMMARY

Emtricitabine/tenofovir disoproxil Glenmark 200 mg/245 mg Film-coated Tablets (Emtricitabine and tenofovir disoproxil phosphate)

This is a summary of the public assessment report (PAR) for Emtricitabine/tenofovir disoproxil Glenmark 200 mg/245 mg Film-coated Tablets (UK/H/6333/001/DC; PL 25258/0210). This product will be referred to as Emtricitabine/tenofovir disoproxil tablets in this lay summary for ease of reading.

This summary explains how Emtricitabine/tenofovir disoproxil tablets were assessed and their authorisation recommended as well as the conditions of use. It is not intended to provide practical advice on how to use Emtricitabine/tenofovir disoproxil tablets.

For practical information about using Emtricitabine/tenofovir disoproxil tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Emtricitabine/tenofovir disoproxil tablets and what are they used for?
Emtricitabine/tenofovir disoproxil tablets are a 'generic medicine'. This means that Emtricitabine/tenofovir disoproxil tablets are similar to a 'reference medicine' already authorised in the EU called Truvada 200mg/245mg film-coated tablets (Gilead Sciences Int. Ltd, UK).

Emtricitabine/tenofovir disoproxil tablets are used to treat Human Immunodeficiency Virus (HIV-1) Infection in adults aged 18 years and over.

Emtricitabine/tenofovir disoproxil tablets should always be used combined with other medicines to treat HIV infection.

Emtricitabine/tenofovir disoproxil tablets can be administered in place of emtricitabine and tenofovir disoproxil used separately at the same doses.

People who are HIV positive can still pass on HIV when taking this medicine, although this risk is lowered by effective antiretroviral therapy. Patients must discuss with their doctor the precautions needed to avoid infecting other people.

This medicine is not a cure for HIV infection. While taking this medicine patients may develop infections or other illnesses associated with HIV infection.

Emtricitabine/tenofovir disoproxil tablets are also used to reduce the risk of getting HIV-1 infection, when used as a daily treatment, together with safer sex practices.

How do Emtricitabine/tenofovir disoproxil tablets work?
Emtricitabine/tenofovir disoproxil tablets contain the active ingredients, emtricitabine and tenofovir disoproxil. These active ingredients are antiretroviral medicines which are used to treat HIV infection. Emtricitabine is nucleoside reverse transcriptase inhibitor and tenofovir is a nucleotide reverse transcriptase inhibitor. This medicine works by interfering with the normal working of an enzyme (reverse transcriptase) that is essential for the virus to reproduce itself.

How are Emtricitabine/tenofovir disoproxil tablets used?
Emtricitabine/tenofovir disoproxil tablets are taken by mouth.

The recommended dose of Emtricitabine/tenofovir disoproxil tablets to treat HIV or to reduce the risk of getting HIV is:

- Adults: one tablet each day, taken with food.

If patients have difficulty swallowing they can use the tip of the spoon to crush the tablet. Then mix the powder with about 100 ml (half a glass) of water, orange juice or grape juice and drink immediately.

Patients should always take the dose recommended by a doctor. This is to make sure that this medicine is fully effective, and to reduce the risk of developing resistance to the treatment. Patients must not change the dose unless the doctor tells them.

If patients are being treated for HIV infection a doctor will prescribe Emtricitabine/tenofovir disoproxil tablets with other antiretroviral medicines. Patients must refer to the patient information leaflets of the other antiretrovirals for guidance on how to take those medicines.

If patients are taking Emtricitabine/tenofovir disoproxil tablets to reduce the risk of getting HIV, they should take this medicine every day, not just when they think they have been at risk of HIV infection.

Patients must ask a doctor if they have any questions about how to prevent getting HIV or prevent spreading HIV to other people.

Emtricitabine/tenofovir disoproxil tablets can only be obtained on prescription from a doctor.

For further information on how Emtricitabine/tenofovir disoproxil tablets are used, please see the Summary of Product Characteristics and package leaflet available on the MHRA website.

How have Emtricitabine/tenofovir disoproxil tablets been studied?
Because Emtricitabine/tenofovir disoproxil tablets are a generic medicine, studies have been limited to tests to determine that it is bioequivalent to the reference medicine, Truvada 200mg/245mg film- coated tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the benefits and risks of Emtricitabine/tenofovir disoproxil tablets?
Because Emtricitabine/tenofovir disoproxil tablets is a generic medicine and is bioequivalent to the reference medicine, 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.

Why are Emtricitabine/tenofovir disoproxil tablets approved?
It was concluded that, in accordance with EU requirements, Emtricitabine/tenofovir disoproxil tablets has been shown to have comparable quality and to be bioequivalent to Truvada 200mg/245mg film-coated tablets. Therefore, the member states involved in the procedure concluded that, as for Truvada 200mg/245mg film- coated tablets, the benefits are greater than its risk and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Emtricitabine/tenofovir disoproxil tablets?
A risk management plan has been developed to ensure that Emtricitabine/tenofovir disoproxil tablets are used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the leaflet for Emtricitabine/tenofovir disoproxil tablets, 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 as well.

Other information about Emtricitabine/tenofovir disoproxil tablets

Germany, Spain, The Netherlands and the UK agreed to grant a Marketing Authorisation for Emtricitabine/tenofovir disoproxil tablets on 13 June 2017. A Marketing Authorisation was granted in the UK on 04 July 2017.

This summary was last updated in September 2017.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMS) considered that the application for Emtricitabine/tenofovir disoproxil Glenmark 200 mg/245 mg Film-coated Tablets (UK/H/6333/001/DC; PL 25258/0210), is approvable.

This product is a prescription only medicine (POM), indicated for:

- *Treatment of HIV-1 infection:* indicated in antiretroviral combination therapy for the treatment of HIV-1 infected adults

- *Pre-exposure prophylaxis (PrEP):* indicated in combination with safer sex practices for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in adults at high risk

The application was submitted using the Decentralised Procedure (DCP) with the UK as the RMS and Germany, Spain and The Netherlands as CMSs. The application was submitted under Article 10.1 of Directive 2001/83/EC, as amended. The applicant has cross referred to Truvada 200mg/245mg film-coated tablets, first authorised on 21 February 2005 via the Centralised Procedure (EU/1/04/305/001-02). The reference product contains tenofovir disoproxil as the fumarate salt, while the proposed product contains tenofovir disoproxil as a phosphate salt.

Emtricitabine is a nucleoside analogue of cytidine. Tenofovir disoproxil phosphate is converted *in vivo* to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate. Both emtricitabine and tenofovir have activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2) and hepatitis B virus.

Emtricitabine and tenofovir are phosphorylated by cellular enzymes to form emtricitabine triphosphate and tenofovir diphosphate, respectively. *In vitro* studies have shown that both emtricitabine and tenofovir can be fully phosphorylated when combined in cells. Emtricitabine triphosphate and tenofovir diphosphate competitively inhibit HIV-1 reverse transcriptase, resulting in DNA chain termination.

Both emtricitabine triphosphate and tenofovir diphosphate are weak inhibitors of mammalian DNA polymerases and there was no evidence of toxicity to mitochondria *in vitro* and *in vivo*.

No new non-clinical studies were conducted, which is acceptable given that this is a generic application of originator product that has been in clinical use for over 10 years.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

A bioequivalence study was submitted to support this application comparing the test product, Emtricitabine/tenofovir disoproxil Glenmark 200 mg/245 mg Film-coated Tablets with the reference product, Truvada 200mg/245mg film- coated tablets (Gilead Sciences International Limited), in healthy, adult, male, human subjects under fed conditions. The applicant has stated that the bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP), including International Conference on Harmonisation (ICH) Guidelines, Directive 2001/20/EC of the European Parliament and the most recent version of the declaration of Helsinki.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

The RMS has been assured that acceptable standards of Good Manufacturing Practice 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.

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.

All involved Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 208 – 13 June 2017). After a subsequent national phase, the UK granted a Marketing Authorisation (PL 25258/0210) for this product on 04 July 2017.

II QUALITY ASPECTS

II.1 Introduction

This product is presented as film-coated tablets. Each tablet contains 200 mg of emtricitabine and 245 mg of tenofovir disoproxil equivalent to 291 mg of tenofovir disoproxil phosphate or 136 mg of tenofovir, as active ingredients. The excipients present are microcrystalline cellulose (E460), mannitol, croscarmellose sodium, silica, hydrophobic colloidal and stearic acid making up the tablet core, and the film-coat is composed of Opadry II blue Y-30-10701 (lactose monohydrate, hypromellose (E464), titanium dioxide (E171) triacetin and indigo carmine aluminium lake (E132)).

All excipients used comply with their respective European Pharmacopoeia monographs with the exception of Opadry II blue Y-30-10701 which complies with an in house specification.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. Confirmation has also been given that the stearic acid used in the tablets is of vegetable origin.

The finished product is packed in high density polyethylene (HDPE) bottle with a polypropylene child-resistant closure containing 30 or 90 (3 packs of 30) film-coated tablets. Desiccant sachets are included in each bottle. Not all pack sizes may be marketed.

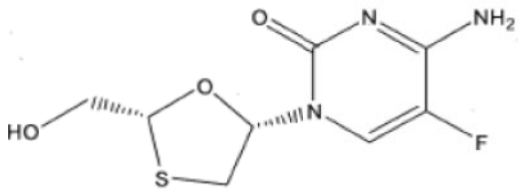
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substances

rINN: **Emtricitabine**

Chemical name: (2*R*-cis)-4-amino-5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan -5-yl]-2(1H) pyrimidinone or 5-fluoro-1-[(2*R*,5 *S*)-2-(hydroxymethyl)-1,3-oxathiolan -5-yl] cytosine

Structural formula:



Molecular formula: $C_8H_{10}FN_3O_3S$
Molecular mass: 247.3 g/mol
Appearance: White to off white powder.
Solubility: Emtricitabine is sparingly soluble in methanol.

Emtricitabine is the subject of an active substance master file (ASMF).

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. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analyses data are provided that comply with the proposed specification.

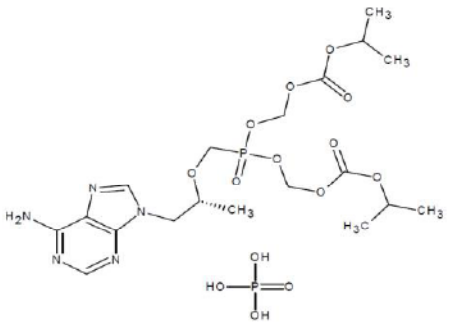
Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

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

INN: Tenofovir disoproxil phosphate

Chemical name: 9-[(R)-2-[[Bis[[(isopropoxycarbonyl)oxy[methoxy] phosphinyl]methoxy]propyl]adenine phosphate Structural formula:

Structure:



Molecular formula: $C_{19}H_{33}N_5O_{14}P_2$
Molecular mass: 617.4 g/mol
Appearance: White to off white powder.
Solubility: Tenofovir disoproxil phosphate is slightly soluble in methanol.

Tenofovir disoproxil phosphate is the subject of an active substance master file (ASMF).

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. Satisfactory certificates of analysis have been provided for all working standards. Batch analyses data are provided that comply with the proposed specification.

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 develop a generic equivalent of Truvada 200mg/245mg film-coated tablets (Gilead Sciences Int. Ltd, UK).

Comparative dissolution profiles have been presented for the proposed and reference products.

Manufacture of the product

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 at production scale and has shown satisfactory results.

Finished Product Specification

The finished product specification is satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability of the product

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results a shelf-life of 2 years with a storage condition 'Store below 25ºC' is set. This is satisfactory.

Bioequivalence/bioavailability

Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of emtricitabine and tenofovir disoproxil phosphate are well-known, no new non-clinical studies are required and none has been provided. An overview based on the literature review is, thus, appropriate.

The Applicant proposes a change in salt from the fumarate to the phosphate. The proposed combination product of tenofovir disoproxil as phosphate and emtricitabine contains 291 mg tenofovir disoproxil as phosphate salt (equivalent to 245 mg of tenofovir disoproxil or 136 mg of tenofovir) and 200 mg of emtricitabine. The Applicant provided no new *in vivo* non-clinical data in support of this change of salt. However clinical data was provided to support this change. It is acceptable that no non-clinical *in vivo* study was conducted, given the clinical studies with the applicant's product and the pharmaceutical comparative exercise that has been conducted.

The *in silico* toxicity of tenofovir disoproxil phosphate and tenofovir disoproxil fumarate using structural alert software was examined. Via this tool it was shown that toxicity prediction for both tenofovir disoproxil phosphate and tenofovir disoproxil fumarate was satisfactory.

Sections 4.6 and 5.3 of the summary product characteristics (SmPC) are provided.

The applicant has provided an in-depth discussion of the impurities of the drug substance and drug product specifications.

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
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Environmental Risk Assessment (ERA)
Since Emtricitabine/tenofovir disoproxil Glenmark 200 mg/245 mg Film-coated Tablets are intended for generic substitution, their use will not lead to an increased exposure to the environment. An environmental risk assessment is, therefore, not deemed necessary.

III.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

There are no objections to the approval of this application from a non-clinical point of view.

IV CLINICAL ASPECTS
IV.1 Introduction
The clinical pharmacology of emtricitabine and tenofovir disoproxil phosphate is well-known. With the exception of data from the bioequivalence study 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 emtricitabine and tenofovir disoproxil phosphate.

Based on the data provided, Emtricitabine/tenofovir disoproxil Glenmark 200 mg/245 mg Film-coated Tablets can be considered bioequivalent to Truvada 200 mg/245 mg film-coated tablets (Gilead Sciences International Limited.

IV.2 Pharmacokinetics
In support of this application, the Marketing Authorisation Holder has submitted results from the following bioequivalence study carried out under fed conditions.

Study

This was an open-label, a single dose, randomised, two-treatment, two-period, two-sequence, crossover bioequivalence study of the test product Emtricitabine/tenofovir disoproxil Glenmark 200 mg/245 mg Film-coated Tablets and the reference product Truvada 200 mg/245 mg film-

coated tablets (Gilead Sciences International Limited) in healthy, adult, male, human subjects under fed conditions.

A single dose of 200mg/ 245 mg of test and reference formulation was administered in each period. Blood samples were collected pre-dose and up to and including 72.00 hours post-dose. The washout period was 7 days.

Results

Geometric Least Square Mean, Ratios and 90% Confidence Interval for emtricitabine

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals
$AUC^2_{(0-t)}$	10.3.02%	100.05%-106.07%
C_{max}	101.04%	95.14%-107.31

Geometric Least Square Mean, Ratios and 90% Confidence Interval for tenofovir

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals
$AUC^2_{(0-t)}$	99.30%	94.17%-104.70%
C_{max}	96.05%	88.45%-104.30

The 90% confidence intervals for C_{max} and $AUC^2_{(0-t)}$ for emtricitabine and tenofovir were within the pre-defined acceptance criteria specified in "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**). Bioequivalence has been shown for the test formulation (Emtricitabine/tenofovir disoproxil Glenmark 200 mg/245 mg Film-coated Tablets) and the reference formulation (Truvada 200 mg/245 mg film-coated tablets (Gilead Sciences International Limited) in healthy adult subjects, under fed conditions.

IV.3 Pharmacodynamics

No new data have been submitted and none are required for applications of this type.

IV.4 Clinical efficacy

The efficacy of emtricitabine and tenofovir is well known. No new efficacy data have been submitted and none are required for applications of this type.

IV.5 Clinical safety

The safety of emtricitabine and tenofovir is well known No new safety data were submitted and none are required. The proposed product contains a phosphate salt of tenofovir, while the reference product is a fumarate. The additional phosphate intake may be relevant in patients on a phosphate restricted diet.

IV.6 Risk Management Plan (RMP)

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 Emtricitabine/tenofovir disoproxil Glenmark 200 mg/245 mg Film-coated Tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risk(s)		
Post-treatment hepatic flares in HIV-1/HBV co-infected patients	Information regarding this risk is provided in the following sections of the SmPC: • Section 4.4; Special warnings and precautions for use: • Section 4.8; Undesirable effects Information is provided in PIL for patients. Prescription only medicine.	None
Renal toxicity	Information regarding this risk is provided in the following sections of the SmPC: • Section 4.2; Posology and method of administration • 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 • Section 5.2; Pharmacokinetic properties Information is provided in PIL for patients. Prescription only medicine.	Educational material (renal educational brochure including creatinine clearance slide ruler for prescribers.
Bone events due to proximal renal tubulopathy/loss of BMD	Information regarding this risk is provided in the following sections of the SmPC: • Section 4.4; Special warnings and precautions for use • Section 4.8; Undesirable effects • Section 5.3; Preclinical safety data Information is provided in PIL for patients. Prescription only medicine.	None
Drug interaction with Didanosine	Information regarding this risk is provided in the following sections of the SmPC: • Section 4.4; Special warnings and precautions for use	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• Section 4.5: Interaction with other medicinal products and other forms of interaction • Section 4.8; Undesirable effects Information is provided in PIL for patients. Prescription only medicine.	
Pancreatitis	Information regarding this risk is provided in the following sections of the SmPC: • 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 Information is provided in PIL for patients. Prescription only medicine.	None
Development of resistance in patients with unrecognized or acute HIV-1 infection (PrEP indication)	Information regarding this risk is provided in the following sections of the SmPC: • Section 4.3; Contraindications • Section 4.4; Special warnings and precautions for use Information is provided in PIL for patients. Prescription only medicine.	PrEP educational brochure for prescribers (Annex 11b), Checklist for prescribers (Annex 11c) PrEP educational brochure for Individuals at risk (Annex 11d) and Patient reminder card (annex 11e)
HIV-1 acquisition, including infection resulting from non-adherence (PrEP indication)	Information regarding this risk is provided in the following sections of the SmPC: • Section 4.3; Contraindications • Section 4.4; Special warnings and precautions for use Information is provided in PIL for patients. Prescription only medicine.	PrEP educational brochure for prescribers (Annex 11b), Checklist for prescribers (Annex 11c) PrEP educational brochure for Individuals at risk (Annex 11d) and Patient reminder card (annex 11e)
Important Potential Risk(s)		
None	Not applicable	Not applicable
Missing Information		
Safety in children (including long-term safety)	Information regarding this risk is provided in the following sections of the SmPC: • Section 4.2; Posology and method of administration • Section 4.8; Undesirable effects • Section 5.1; Pharmacodynamic properties	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Information is provided in PIL for patients. Prescription only medicine.	
Safety in elderly patients	Information regarding this risk is provided in the following sections of the SmPC: • Section 4.2; Posology and method of administration • Section 4.4; Special warnings and precautions for use • Section 4.8; Undesirable effects • Section 5.2; Pharmacokinetic properties Information is provided in PIL for patients. Prescription only medicine.	None
Safety in pregnancy and lactation	Information regarding this risk is provided in the following sections of the SmPC: • Section 4.6; Fertility, Pregnancy and lactation Information is provided in PIL for patients. Prescription only medicine.	None
Safety in patients with renal impairment	Information regarding this risk is provided in the following sections of the SmPC: • Section 4.2; Posology and method of administration • 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 Information is provided in PIL for patients. Prescription only medicine.	None

Additional risk minimisation measures are proposed for the safety concern of renal toxicity, in the form of Educational material (renal educational brochure including creatinine clearance slide ruler for Prescribers) and also for the safety concerns relevant to the pre-exposure prophylaxis (PrEP) indication, in the form of an educational brochure for prescribers, an educational brochure for the individual at risk, a checklist for prescribers and a reminder card for patients.

IV.7 Discussion on the clinical aspects

The grant of a Marketing Authorisation is recommended.

V User consultation

The applicant has provided a bridging report. The proposed leaflet has been bridged to an approved leaflet for Emtricitabine/tenofovir disoproxil (as fumarate) (PT/H/1427/001/DC). This is satisfactory.

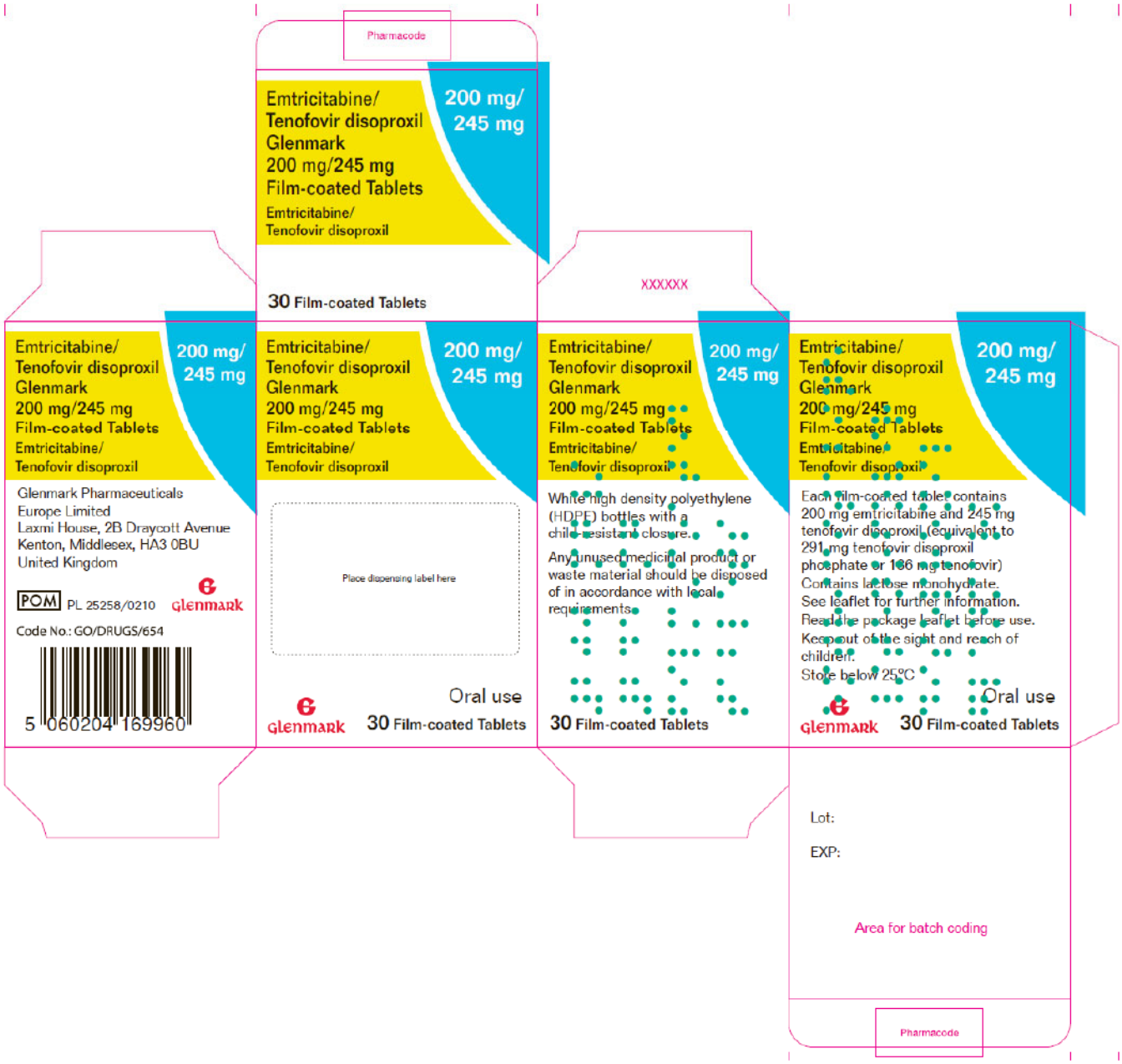
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT AND RECOMMENDATION

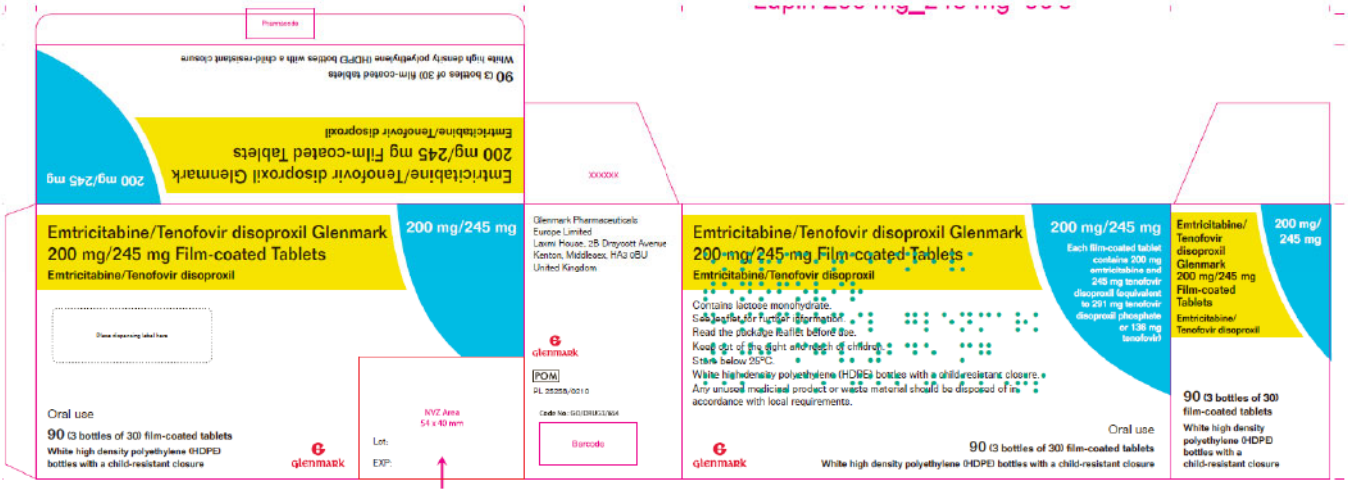
The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. Bioequivalence has been demonstrated between the applicant's product and the reference product. The benefit-risk assessment is, therefore, considered to be positive.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Emtricitabine/tenofovir disoproxil Glenmark 200 mg/245 mg Film-coated Tablets is presented below:




Emtricitabine/Tenofovir disoproxil Glenmark 200 mg/245 mg Film-coated Tablets
Emtricitabine/Tenofovir disoproxil
200 mg/245 mg
Oral use
90 (3 bottles of 30) film-coated tablets
White high density polyethylene (HDPE) bottles with a child-resistant closure
glenmark
NVZ Area 54 x 40 mm
Lot:
EXP:
Glenmark Pharmaceuticals Europe Limited
Laxmi House, 2B Draycott Avenue
Kenton, Middlesex, HA3 0BU
United Kingdom
POM
PL 25258/0210
Barcode
Each film-coated tablet contains 200 mg emtricitabine and 245 mg tenofovir disoproxil (equivalent to 291 mg tenofovir disoproxil phosphate or 136 mg tenofovir).
Contains lactose monohydrate.
See leaflet for further information.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Store below 25°C.
White high density polyethylene (HDPE) bottles with a child-resistant closure.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
Emtricitabine/ Tenofovir disoproxil Glenmark 200 mg/245 mg Film-coated Tablets
200 mg/ 245 mg
90 (3 bottles of 30) film-coated tablets
White high density polyethylene (HDPE) bottles with a child-resistant closure

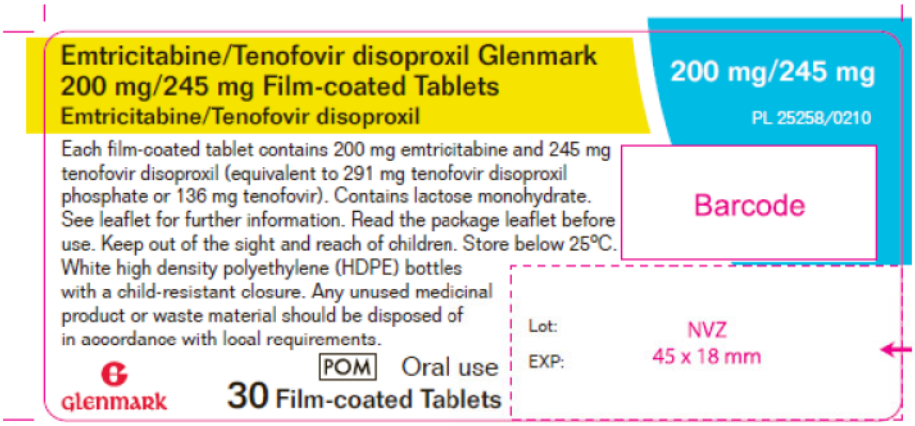

Emtricitabine/Tenofovir disoproxil Glenmark 200 mg/245 mg Film-coated Tablets
Emtricitabine/Tenofovir disoproxil
200 mg/245 mg
PL 25258/0210
Each film-coated tablet contains 200 mg emtricitabine and 245 mg tenofovir disoproxil (equivalent to 291 mg tenofovir disoproxil phosphate or 136 mg tenofovir). Contains lactose monohydrate. See leaflet for further information. Read the package leaflet before use. Keep out of the sight and reach of children. Store below 25°C. White high density polyethylene (HDPE) bottles with a child-resistant closure. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
Barcode
Lot:
EXP:
NVZ
45 x 18 mm
glenmark
POM
Oral use
30 Film-coated Tablets

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)

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)