13 October 2016
EMA/CHMP/522913/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Emtricitabine/Tenofovir disoproxil Krka

International non-proprietary name: emtricitabine / tenofovir disoproxil

Procedure No. EMEA/H/C/004215/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AIDS - acquired immunodeficiency syndrome

AS - active substance

ASMF – Active Substance Master File

AUC - area under curve

AUC_{0-T} Cumulative area under the plasma concentration time curve calculated from

$AUC_{0-\infty}$ Area under the plasma concentration time curve extrapolated to infinity, calculated as AUCT + CLOQ/λz, where CLOQ is the estimated concentration at time TLQC

AUC_0-T_{∞} - Relative percentage of AUC_T with respective to AUC_{∞}

BMD - bone mineral density

CFU - colony-forming units

Cmax Maximum observed plasma concentration

Cmin - minimum observed plasma concentration

DNA - deoxyribonucleic acid

DSC – Differential Scanning Calorimetry

EEA - European Economic Area

EU - European Union

GC – Gas Chromatography

GTIs - genotoxic impurities

^{1}H- & ^{13}C-NMR - Proton/ Carbon Nuclear Magnetic Resonance

HAART - highly active antiretroviral therapy

HDPE- high density polyethylene

HIV - human immunodeficiency virus

HPLC High Pressure Liquid Chromatography

ICH – International Conference on Harmonization

IPC – in-process control

IR – Infrared

KF – Karl Fischer method

LDPE - low density polyethylene

λZ - Apparent elimination rate constant, estimated by linear regression of the terminal linear portion of the log concentration versus time curve

NMT – no more than

OPA/Alu/PE+DES/Alu - Oriented Polyamide/Aluminium/Polyethylene+desiccant/ Aluminium

Ph. Eur. – European Pharmacopoeia

ppm – parts per million

RH – relative humidity

RRT – relative retention time

TAMC - total aerobic microbial count

TD - tenofovir disoproxil

T_{half} - term elimination half-life, calculated as ln(2)/λZ

TLC – thin layer chromatography

TLIN - time to point where log-linear elimination phase begins

TLQC -Time of last observed quantifiable plasma concentration

T_{max} - Time of maximum overserved plasma concentration; if it occurs at more than one time point, Tmax is defined as the first time point with this value

3TC – lamivudine

TSE - Transmissible Spongiform Encephalopathies

TTC – threshold of toxicological concern

TYMC - total combined yeasts/moulds count

UV – ultra violet

XRD – X-ray diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant KRKA, d.d., Novo mesto submitted on 7 December 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for Emtricitabine/Tenofovir disoproxil Krka, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 April 2015.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Emtricitabine/Tenofovir disoproxil Krka is indicated in antiretroviral combination therapy for the treatment of HIV-1 infected adults

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Truvada instead of non-clinical and clinical unless justified otherwise.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Truvada, 200mg/245mg, film-coated tablet
- Marketing authorisation holder: Gilead Sciences International Limited

- Date of authorisation: 24-02-2005
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/04/305/001-002

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Truvada, 200mg/245mg, film-coated tablet
- Marketing authorisation holder: Gilead Sciences International Limited
- Date of authorisation: 24-02-2005
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/04/305/001-002

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Truvada, 200mg/245mg, film-coated tablet
- Marketing authorisation holder: Gilead Sciences International Limited
- Date of authorisation: 24-02-2005
- Marketing authorisation granted by:
  - Community
  - Community) Marketing authorisation number(s): EU/1/04/305/001-002
- Bioavailability study number(s): KRS-P5-566 (Sponsor No 15-465)

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: John Joseph Borg

- The application was received by the EMA on 7 December 2015.
- The procedure started on 31 December 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 21 March 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 29 March 2016.
- During the meeting on 28 April 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 29 April 2016 .
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 July 2016.

- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 22 August 2016.
- During the PRAC meeting on 02 September 2016 the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP. The PRAC assessment Overview and Advice was sent to the applicant on 02 Sep 2016.
- During the CHMP meeting on 15 September 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 20 September 2016.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 28 September 2016.
- The Rapporteur circulated the updated Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 7 October 2016.
- During the meeting on 13 October 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing authorisation to Emtricitabine/Tenofovir disoproxil Krka.

2. Scientific discussion

2.1. Introduction

HIV infection remains a major public health concern in EU/EEA (European Union/European Economic Area) countries, characterised by a significant number of new infections. In contrast, the overall number of AIDS cases has continued to decline in correlation with the use of effective antiretroviral treatment, although in some eastern EU countries, the number of AIDS cases continues to rise. In 2012, 29 306 diagnosed cases of HIV infection were reported in 29 EU/EEA countries, a rate of 5.7 per 100 000 population. This number is likely to be an underestimation due to the delay in reporting HIV diagnoses in a number of countries. The highest proportion was reported among MSM (men who have sex with men) (40%); heterosexual contact accounted for 34% (including 12% in cases from countries with generalised HIV epidemics); and injecting drug use for 6%. The overall rate ranged from 6 cases per 100 000 population in 2008 to 5.7 per 100 000 in 2012. When adjusted for reporting delay, the rate was 6.2 cases per 100 000 in 2012, indicating a relatively stable rate over the period.

The most significant advance in the medical management of HIV-1 infection has been the treatment of patients with antiviral drugs, which can suppress HIV-1 replication to undetectable levels. The discovery of HIV-1 as the causative agent of AIDS together with an ever increasing understanding of the virus replication cycle have been instrumental in this effort by providing researchers with the knowledge and tools required to prosecute drug discovery efforts focused on targeted inhibition with specific pharmacological agents.

Since the first HIV-1 specific antiviral drugs were given as monotherapy in the early 1990s, the standard of HIV-1 care evolved to include the administration of a cocktail or combination of antiretroviral agents. The advent of combination therapy, also known as highly active antiretroviral therapy or HAART, for the treatment of HIV-1 infection was seminal in reducing the morbidity and mortality associated with HIV-1 infection and AIDS.

Combination antiretroviral therapy dramatically suppresses viral replication and reduces the plasma HIV-1 viral load to below the limits of detection of the most sensitive clinical assays (0,50 RNA copies/ mL) resulting in a significant reconstitution of the immune system as measured by an increase in circulating CD4+ T-lymphocytes. Importantly, combination therapy using three antiretroviral agents directed against at least two distinct molecular targets is the underlying basis for forestalling the evolution drug resistance.

With proper adherence, HAART can suppress viral replication for decades, dramatically increasing the life expectancy of the HIV-infected individual. However, HAART alone cannot eliminate HIV-1 infection. HIV-1 is a chronic infection for which there is currently no cure—the prospect of maintaining therapy for the lifetime of a patient presents major challenges. The potential for persistent viral replication in compartments and reservoirs may continue to drive pathogenic disease processes. The effect of therapy can be impaired by nonadherence, poor drug tolerability, and drug interactions among antiretroviral agents and other medications that decrease optimal drug levels. Each of these can lead to virologic failure and the evolution of drug resistance.

Combination of three antiretrovirals, typically two nucleoside/nucleotide reverse transcriptase inhibitors (NsRTI/NtRTI or NRTI) plus either a (boosted) HIV-protease inhibitor (PI), a nonnucleoside reverse transcriptase inhibitor (NNRTI) or an integrase inhibitor (INI), referred to as highly active antiretroviral therapy (HAART), is also recommended by international guidelines.

Physicians experienced in the management of HIV infection commonly refer to the two-drug NRTI combination as the "backbone" and the third agent as the "base" of the regimen. Co-formulation of tenofovir disoproxil and emtricitabine provides the nucleotide backbone for once-daily dosing, as a component of HAART, and improve patient adherence, thereby decreasing the risk of acquired drug resistance. Emtricitabine and tenofovir disoproxil have been investigated in numerous placebo controlled and comparative clinical studies and have been proven effective and safe drugs for the treatment of patients with the proposed indication in combination with other antiretroviral drugs.

2.2. Quality aspects

2.2.1. Introduction

Emtricitabine / Tenofovir disoproxil Krka is presented as film coated tablets containing a fixed-dose combination of 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (equivalent to 300.7 mg of tenofovir disoproxil succinate or 136 mg of tenofovir) as the active substances.

Other ingredients of the tablet core are pregelatinised starch, microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, sodium stearyl fumarate and stearic acid. The film coating is composed of Hypromellose 5 cP, titanium dioxide (E171), macrogol and indigo carmine aluminum lake (E132).

The product is available in OPA/Alu/PE+DES/Alu blisters or in high density polyethylene (HDPE) bottles with polypropylene closure with integrated a silica gel desiccant, as described in section 6.5 of the SmPC.

2.2.2. Active substance

Emtricitabine

General information

The chemical name of emtricitabine is 4-amino-5-fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan- -5-yl]-2(1*H*)- pyrimidinone corresponding to the molecular formula $C_8H_{10}FN_3O_3S$. It has a relative molecular mass of 247.3 g/mol and the following structure:

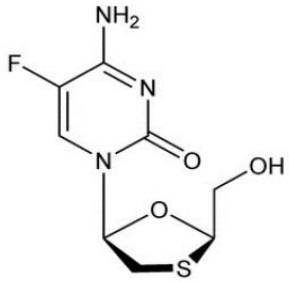

Figure 1. Structure of emtricitabine.

The structure of the active substance was elucidated by a combination of elemental analysis (C,H, N & S), mass spectrometry, ^{1}H- & ^{13}C-NMR spectroscopy, IR spectroscopy, UV spectroscopy, HPLC, and x-ray powder diffraction.
The active substance appears as a white to almost white non-hygroscopic crystalline powder, freely soluble in methanol and water. The solubility in aqueous solution is pH dependent being more soluble at acidic pH. Its pKa was found to be 2.27.

Emtricitabine has two chiral centres. The *cis* enantiomer having the 2*R*, 5*S* absolute configuration is produced. Enantiomeric purity and emtricitabine diastereomers content is controlled routinely by chiral HPLC.

Emtricitabine exhibits polymorphism with a number of different forms and an amorphous form known. The polymorphic form manufactured by the proposed manufacturer is consistently manufactured. The polymorphic form has been confirmed by XRD on three batches of emtricitabine.

Manufacture, characterisation and process controls

Detailed information on the manufacturing process of the active substance (AS) has been provided in the restricted part of the ASMF and it was considered satisfactory.

Emtricitabine is synthesized in five main chemical steps. The starting materials are well-defined with acceptable specifications. The first two steps of the synthesis leading to the intermediate are performed by one manufacturer and the last three steps by a different manufacturer.

The critical steps and process parameters have been adequately described and their control is acceptable. Adequate in-process controls are applied during the synthesis. The batch size range has been defined. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities including genotoxic impurities were well discussed with regards to their origin and characterised. The absence of genotoxic impurities has been demonstrated through carryover studies and where needed, by batch data.

Emtricitabine is packed in transparent low density polyethylene bag (LDPE) with tag seal, followed by a secondary transparent LDPE bag with heat seal all inside an HDPE container. The polythene bags used as primary packaging material are food grade and comply with the requirements of Ph. Eur. and European

Directive 10/2011 as amended. Specification, test procedures, and a certificate of analysis for the LDPE containers have been provided.

Specification

The active substance specification includes appropriate tests and limits for appearance (visual), solubility (Ph. Eur.), identity (IR, specific optical rotation), loss on drying (Ph. Eur.), sulfated ash (Ph. Eur.), enantiomer and emtricitabine diastereomers content (chiral HPLC), related substances (HPLC), assay (HPLC), residual solvents (GC), microbiological quality (Ph. Eur.) and particle size (laser diffraction).

The potential impurities and possible genotoxic impurities are controlled in the AS by validated test methods. Based on batch results which showed that impurities were either below detection limit or not detected, it has been demonstrated that the impurities are generally adequately controlled during manufacturing of the active substance.
The specification does not include a test for heavy metals and this has been justified in line with ICH Q3D Guideline, on the basis of batch analysis from commercial scale batches. Polymorphism is included in the specification (by DSC method) and is controlled by the ASMF holder and re-testing by the finished product manufacturer in not considered necessary.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from thirteen production scale batches of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on 15 batches, most of them manufactured at commercial scale, from the proposed manufacturers stored in the intended commercial packaging for up to 48 months under long term conditions (25 °C ± 2 °C / 60 %RH ± 5% RH) and for 6 months under accelerated conditions
(40 °C ± 2 °C /75 %RH ± 5% RH) according to the ICH guidelines were provided. Samples were tested for description, identification, loss on drying, related substances and assay. The analytical methods used were the same as for release and are stability indicating. No significant changes to any of the measured parameters were observed under either storage condition and all results remained within specification.

Photostability testing following ICH guideline Q1B was performed on one commercial scale batch. No significant change was observed in assay, related substances, enantiomer or diastereomers content. The results showed that the AS is not sensitive to light.

Forced degradation studies have been performed with the aim of showing that the HPLC method for assay and related substances is stability indicating by studying samples exposed to base, acid, oxidation and high temperature conditions. The active substance was found to be stable under thermal conditions whereas it is susceptible to acid, base and oxidative degradation. The main degradation pathways under acidic, basic and oxidative conditions were shown.

The stability results justify the proposed retest period of 60 months without specific storage conditions, stored in the proposed packaging is acceptable.

Tenofovir disoproxil

General information

The chemical name of tenofovir disoproxil succinate is 9-[(*R*)-2- [[bis(isopropoxycarbonyl)oxy]methoxy] phosphinyl] methoxy]propyl]adenine succinate corresponding to the molecular formula $C_{23}H_{36}N_5O_{14}P$. It has a relative molecular mass of 637.5 g/mol and the structure shown in figure 2:

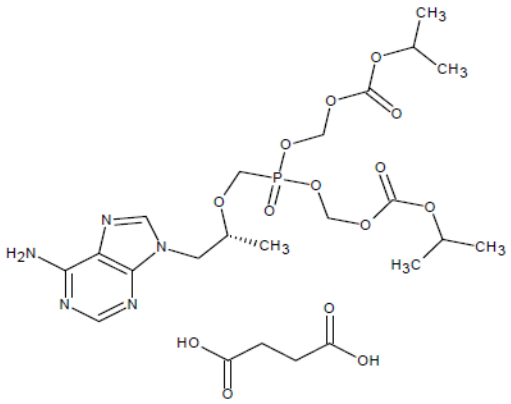

Figure 2. Structure of tenofovir disoproxil succinate.

The structure of the active substance (AS) was elucidated by a combination of elemental analysis (C,H, N & S), mass spectrometry, ^{1}H- and ^{13}C-NMR spectroscopy, IR spectroscopy, UV Spectroscopy, HPLC, and X-ray powder diffraction.

The active substance is a white to off-white, not hygroscopic crystalline powder. It is slightly soluble in water and sparingly soluble to soluble in aqueous media across the physiological pH range. Its pKa has been found to be 4.87 and its partition coefficient was found to be 0.94.

Tenofovir disoproxil succinate is known to exhibit polymorphism. A number of different forms are known. Batch data from three validation batches have been presented with X-ray diffractogrammes and theta values confirm consistent manufacture of the desired polymorphic form.

There is one chiral centre at C-2 position of the propyl side-chain which is controlled in the specification of the same and in the specification of the active substance.

Manufacture, characterisation and process controls

Detailed information on the manufacturing process of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Tenofovir disoproxil succinate is synthesized in three main steps using well-defined starting materials with acceptable specifications. The proposed have been properly justified. The single chiral centre is controlled in (*R*)-propylene carbonate and carries through unaltered to the active substance.

The critical steps and parameters have been adequately described and their control is acceptable. Adequate in-process controls are applied during the synthesis. The batch size has been defined.

Potential and actual impurities were well discussed with regards to their origin and characterised. A thorough assessment of potential genotoxic impurities (GTI) was carried out. The absence of carry-over of the

potential GTI compounds or their control below TTC limits has been demonstrated in commercial scale batches of the AS and the controls put in place are considered adequate.

The specifications and control methods for intermediate products, starting materials and reagents have been presented. The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances.

The active substance is packaged in double transparent low density polyethylene (LDPE) bags each on tied with nylon strip seal. The double LDPE bag is kept in heat sealed Triple Laminated Sunlight Barrier (TLSB) bag inside a high density polyethylene (HDPE) drum. The materials comply with the EC directive 2002/72/EC and EC 10/2011 as amended. Specification, test procedures, and a certificate of analysis for the LDPE containers have been provided as well.

Specification

The active substance specification includes tests for appearance, solubility (Ph. Eur.), identity (IR, HPLC), water content (KF), sulfated ash (Ph. Eur.), S-isomer content (chiral HPLC), related substances (HPLC), assay (HPLC), residual solvents (GC), microbiological purity (Ph. Eur.) and particle size (laser diffraction).

All unknown and specified related substances are limited according to the ICH Q3A guideline with the exception of the mono ester impurity, the isopropyl impurity and the potential genotoxic impurity. The proposed limit for the potentially genotoxic impurity has been sufficiently justified on the basis of bacterial reverse mutation (AMES) test and batch analysis of the reference product. For the limit of the isopropyl impurity and the mono ester impurity, reference is made to the WHO International Pharmacopoeia monograph in which they are listed which can be considered as valid and can be used for qualification purposes. The residual solvents limits are based on ICH Q3C.

The consistency of the crystalline form has been established and batch data from 9 commercial batches of tenofovir disoproxil succinate have been presented. In addition, this crystalline form has been shown to be stable for at least 24 months under long term storage conditions and the existing identification test by IR is specific for the correct polymorphic form. Therefore, the inclusion of another complementary test for polymorphism is not deemed necessary.

Batch data at the initial time point and after storage under long term conditions for 36 months shows that the micro-organisms are within the acceptance limits and the specified micro-organisms *Salmonella*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* have been found to be absent in the commercial scale batches. As tenofovir disoproxil succinate is a non-sterile active substance intended for oral administration, based on the ICH Q6A, Decision tree#6, inclusion of microbial limit test in the AS specification is not considered necessary.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from six production scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from six production scale batches of active substance from the proposed manufacturers stored in the intended commercial package for up to 24 months under long-term conditions (5 ± 3 °C) and for up to 6 months under accelerated conditions (25 ± 2 °C/60 ± 5% RH) according to the ICH guidelines were provided. Samples were tested for appearance, identification, water content, tenofovir, (*S*)-isomer content, related substances and assay. The analytical methods used were the same as for release and are stability indicating. No significant changes to any of the measured parameters were observed under either storage condition and all remained within specification.

Photostability testing following the ICH guideline Q1B was performed on one commercial scale batch. No significant change was observed in assay, related substances and (*S*)-isomer content. The results showed that the AS is not sensitive to light.

Stress testing (high temperature, acidic, basic and oxidising aqueous media) was performed on one batch. No significant change in assay, related substances and (*S*)-isomer content was observed at high temperature. Under the other tested conditions (*S*)-isomer content did not increase but assay decreased and different related substances were formed, depending on the conditions, and increased more prominently under acidic or oxidizing conditions.

The stability results indicate that the active substance is stable during the studied period of 24 months at 5±3 °C in the proposed container and in line with extrapolation applied in accordance to CPMP/QWP/122/02, rev 1 corr., and the commitment to continue the stability studies for the revalidation batches, a retest period of 30 months with the proposed storage conditions "Store at 2-8 °C", when stored in the proposed packaging materials, is acceptable.

2.2.3. Finished medicinal product

Pharmaceutical development

The finished product is a fixed dose combination of emtricitabine and tenofovir disoproxil succinate, presented as blue, oval biconvex film coated immediate release tablets, intended for oral administration.

The aim of the pharmaceutical development was to develop a generic product equivalent to the reference product Truvada which is an immediate release tablet for oral administration.

Emtricitabine, according to BCS, is a class I substance (highly soluble and highly permeable). It is optically active and corresponds to the *cis* enantiomer with 2*R*, 5*S* absolute configuration. Tenofovir disoproxil succinate is a BCS class III (highly soluble, low permeability) substance and thus particle size is not considered a critical parameter. Tenofovir disoproxil succinate is optically active and corresponds to *R*-isomer. It has been demonstrated for both active substances that the other stereoisomers do not form during the tablet manufacturing process or on exposure to stressed conditions, and thus there is no need to control them in the finished product.

A different salt of tenofovir disoproxil is used compared to the reference product (succinate rather than fumarate). The potential impact of this difference on pharmaceutical aspects (e.g. stability and compatibility

with excipients) and clinical performance (e.g. *in vivo* PK) has been discussed in detail. The choice of the succinate salt is considered justified.

Moreover it has been shown that both the selected polymorphic forms exhibit adequate chemical and physical stability as confirmed during the pharmaceutical development by results of batches of tablets after storage for 5 months in primary packaging under accelerated storage conditions (40 °C/75% RH).

The excipients used in the formulation are well known in the manufacture of solid dosage forms and are very similar to those used in the reference product. With the exception of indigo carmine aluminium lake, they are all described in the Ph. Eur. The results of compatibility studies of each AS with the excipients in binary mixtures have been provided. The impurity levels for binary mixtures of tenofovir disoproxil succinate (Krka AS) with the various excipients were also compared to binary mixtures of the same excipients with tenofovir disoproxil fumarate (reference product AS). No incompatibilities were identified and the two tenofovir disoproxil salts gave similar results.

Film-coating was chosen to protect the tablet core containing the active ingredients against the influence from environment and to achieve better compliance for patients.

Two different manufacturing processes were investigated and the most suitable was selected considering the physicochemical properties of the ASs; the suitable type of lubricant was determined and the effect of lactose was investigated.

The dissolution profile of the most promising trial formulation was compared with that of Truvada film-coated tablets. The release rate of both active ingredients was comparable with the reference product. A number of trials were carried out to improve the ease of processing of the product and the best prototype formulation was chosen.

Additional experiments were carried out in order to evaluate the effect of film coating on final product stability and in order to select the film coating. The formulation was optimised with regard to the type and amount of excipients. The effect of particle size of both ASs on dissolution was also investigated during the development of the product and suitable specifications have been set for each AS.

The impact of the tenofovir disoproxil salt on the formulation properties was also evaluated. The dissolution profiles of pilot scale batches with qualitatively and quantitatively similar composition but with different tenofovir disoproxil salt (fumarate vs succinate) were compared and found to be similar. The tablets were also compared in a pilot bioequivalence study and found to afford similar exposures. Finally the bioequivalence of the proposed formulation against the reference product was demonstrated in the bioequivalence study 15-465. The comparability of dissolution profiles of the test and reference batches used in this study was shown in three different pH media.

The dissolution of emtricitabine and tenofovir disoproxil is rapid in 0.1M hydrochloric acid, acetate buffer solution pH 4.5 and phosphate buffer solution pH 6.8. More than 85% of the ASs dissolved within 15 minutes, which means the dissolution profiles of the test product can be considered similar in the stated media without calculating the f2 similarity factors. The dissolution method for QC has been shown to be discriminatory in relation to minor changes in the composition of the tablets, their hardness and certain relevant process parameters.

The process parameters that could potentially affect the drug release were discussed and are controlled by suitable limits to ensure consistent product performance. The proposed holding times are supported by data.

The primary packaging of Emtricitabine/Tenofovir Disoproxil Krka 200/245 mg film coated tablets is OPA/Alu/PE+DES/Alu blisters with integrated desiccant or in high density polyethylene (HDPE) bottles with polypropylene closure with an integrated silica gel desiccant. The proposed packaging materials are used extensively in the pharmaceutical industry for solid oral dosage forms and provide good protection from moisture and light. A container closure system with a desiccant was selected in order to reduce exposure of active ingredients to moisture and improve chemical stability of the formulation. The suitability of the desiccant was evaluated during development and the most advantageous quantity and type for each container configuration was chosen. The provided stability results indicate that the proposed packaging materials are suitable for the storage of the finished product. The primary packaging material complies with relevant EU regulations.

Manufacture of the product

The manufacturing process is considered to be a standard process which comprises the following main steps: a) preparation of blend for roller compaction, b) roller compaction, c) preparation of compression mixture, d) tabletting, e) coating of tablets and f) packaging. The critical steps have been identified. Critical process parameters have been identified for those manufacturing steps and adequate IPCs are in place. Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The manufacturing process will be validated on three production batches prior to commercialisation which is acceptable since the process is a standard one. An acceptable validation protocol has been presented.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance, uniformity of dosage units (Ph. Eur.), content uniformity for emtricitabine and tenofovir disoproxil (Ph. Eur.), water content (Ph. Eur.), identification (emtricitabine & tenofovir: HPLC and TLC), related substances (emtricitabine & tenofovir: HPLC), assay (emtricitabine & tenofovir: HPLC), ethanol (GC), dissolution (emtricitabine & tenofovir: Ph. Eur.) and microbiological quality (Ph. Eur.).

The analytical methods used have been adequately described and non-compendial methods have been appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis data three pilot scale batches were presented. All batches are representative of the commercial formula and process. All batches meet the commercial specification limits.

Stability of the product

Stability data from three pilot and one smaller scale batch of finished product stored for up to 12 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The stability batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, average tablet weight, water content, dissolution, assay, related substances and microbial purity. The methods used were the same as for release testing and are stability indicating. There was no significant change in any of characteristic of Emtricitabine/ Tenofovir Disoproxil Krka 200/245 mg film coated tablets as tested at any time point. No trends were observed.

Photo-stability testing according to ICH Q 1B (Option 2) was performed on one pilot batch. All tested parameters remained unchanged apart from the blue colour of tablets exposed directly to light which became a bit lighter as compared with tablets outside the immediate packaging and protected from light.

In-use stability testing (after the first opening of the container) of final product packed in multidose (HDPE) containers with desiccant was performed in accordance with the Note for Guidance on In-Use Stability Testing of Human Medicinal Products (CPMP/QWP/2934/99). Testing was performed on a pilot batch at 25±2 °C / 60±5% RH, simulating the intended use of the product. The presented in-use stability data supports the proposed 1 month in-use shelf-life (SmPC section 6.3). Further data to support the 1 month in-use shelf life will be generated using a second pilot scale batch towards the end of its proposed shelf life as per the stability commitment provided.

Based on the overall data presented support the proposed shelf life and storage conditions as mentioned below and in the SmPC sections 6.3 and 6.4 is acceptable.

Blister: 2 years, "Do not store above 30°C" and "Store in the original blister in order to protect from moisture and light",

HDPE bottle: 1 year, "Do not store above 30°C" and "Keep the bottle tightly closed in order to protect from moisture and light".

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. Bioequivalence with the reference product has been demonstrated. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP considered that no further non-clinical studies are required.

Pharmacology

Emtricitabine is a nucleoside analogue of cytidine. Tenofovir disoproxil 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 together 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.

Antiviral activity in vitro: Synergistic antiviral activity was observed with the combination of emtricitabine and tenofovir in vitro. Additive to synergistic effects were observed in combination studies with protease inhibitors, and with nucleoside and non-nucleoside analogue inhibitors of HIV reverse transcriptase.

Resistance: Resistance has been seen in vitro and in some HIV-1 infected patients due to the development of the M184V/I mutation with emtricitabine or the K65R mutation with tenofovir. Emtricitabine-resistant viruses with the M184V/I mutation were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir and zidovudine. The K65R mutation can also be selected by abacavir or didanosine and results in reduced susceptibility to these agents plus lamivudine, emtricitabine and tenofovir. Tenofovir disoproxil should be avoided in patients with HIV- 1 harbouring the K65R mutation. In addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in low-level reduced susceptibility to abacavir, emtricitabine, lamivudine and tenofovir.

Patients with HIV-1 expressing three or more thymidine analogue associated mutations (TAMs) that included either the M41L or L210W reverse transcriptase mutation showed reduced susceptibility to tenofovir disoproxil.

In vivo resistance (antiretroviral-naïve patients): In an open-label randomised clinical study (GS-01- 934) in antiretroviral-naïve patients, genotyping was performed on plasma HIV-1 isolates from all patients with confirmed HIV RNA > 400 copies/ml at weeks 48, 96 or 144 or at the time of early study drug discontinuation. As of week 144:

- The M184V/I mutation developed in 2/19 (10.5%) isolates analysed from patients in the emtricitabine/tenofovir disoproxil /efavirenz group and in 10/29 (34.5%) isolates analysed from the lamivudine/zidovudine/efavirenz group (p-value < 0.05, Fisher's Exact test comparing the emtricitabine+tenofovir disoproxil group to the lamivudine/zidovudine group among all subjects).

- No virus analysed contained the K65R or K70E mutation.

- Genotypic resistance to efavirenz, predominantly the K103N mutation, developed in virus from 13/19 (68%) patients in the emtricitabine/tenofovir disoproxil /efavirenz group and in virus from 21/29 (72%) patients in the comparative group.

Pharmacokinetics

Reference is made to the SmPC of the Reference product.

Absorption

The bioequivalence of one emtricitabine/tenofovir disoproxil film-coated tablet with one emtricitabine 200 mg hard capsule and one tenofovir disoproxil 245 mg film-coated tablet was established following single dose administration to fasting healthy subjects. Following oral administration of emtricitabine/tenofovir disoproxil to healthy subjects, emtricitabine and tenofovir disoproxil are rapidly absorbed and tenofovir disoproxil is converted to tenofovir. Maximum emtricitabine and tenofovir disoproxil concentrations are observed in serum within 0.5 to 3.0 h of dosing in the fasted state. Administration of emtricitabine/tenofovir disoproxil with food resulted in a delay of approximately three quarters of an hour in reaching maximum tenofovir concentrations and increases in tenofovir AUC and Cmax of approximately 35% and 15%, respectively, when administered with a high fat or light meal, compared to administration in the fasted state. In order to optimise the absorption of tenofovir, it is recommended that Emtricitabine/tenofovir Krka should be taken with food.

Distribution

Following intravenous administration the volume of distribution of emtricitabine and tenofovir was approximately 1.4 l/kg and 800 ml/kg, respectively. After oral administration of emtricitabine or tenofovir disoproxil, emtricitabine and tenofovir are widely distributed throughout the body. In vitro binding of emtricitabine to human plasma proteins was < 4% and independent of concentration over the range of 0.02 to 200 µg/ml. 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

There is limited metabolism of emtricitabine. The biotransformation of emtricitabine includes oxidation of the thiol moiety to form the 3'-sulphoxide diastereomers (approximately 9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (approximately 4% of dose). In vitro studies have determined that

neither tenofovir disoproxil nor tenofovir are substrates for the CYP450 enzymes. Neither emtricitabine nor tenofovir inhibited in vitro drug metabolism mediated by any of the major human CYP450 isoforms involved in drug biotransformation. Also, emtricitabine did not inhibit uridine-5'-diphosphoglucuronyl transferase, the enzyme responsible for glucuronidation.

Elimination

Emtricitabine is primarily excreted by the kidneys with complete recovery of the dose achieved in urine (approximately 86%) and faeces (approximately 14%). Thirteen percent of the emtricitabine dose was recovered in urine as three metabolites. The systemic clearance of emtricitabine averaged 307 ml/min. Following oral administration, the elimination half-life of emtricitabine is approximately 10 hours.

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. The apparent clearance of tenofovir averaged approximately 307 ml/min. Renal clearance has been estimated to be 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 elimination half-life of tenofovir is approximately 12 to 18 hours.

Toxicology

The Applicant's product is a generic of branded product Truvada. Reference is therefore made to the SmPC of the Reference product.

Tenofovir disoproxil fumarate: Non-clinical safety pharmacology studies on tenofovir disoproxil fumarate reveal no special hazard for humans. Repeated dose toxicity studies in rats, dogs and monkeys at exposure levels greater than or equal to clinical exposure levels and with possible relevance to clinical use include renal and bone toxicity and a decrease in serum phosphate concentration. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (BMD) (rats and dogs). The bone toxicity in young adult rats and dogs occurred at exposures $\geqslant$ 5-fold the exposure in paediatric or adult patients; bone toxicity occurred in juvenile infected monkeys at very high exposures following subcutaneous dosing ($\geqslant$ 40-fold the exposure in patients). Findings in the rat and monkey studies indicated that there was a substance-related decrease in intestinal absorption of phosphate with potential secondary reduction in BMD.

Genotoxicity studies revealed positive results in the in vitro mouse lymphoma assay, equivocal results in one of the strains used in the Ames test, and weakly positive results in an UDS test in primary rat hepatocytes. However, it was negative in an in vivo mouse bone marrow micronucleus assay.

Oral carcinogenicity studies in rats and mice only revealed a low incidence of duodenal tumours at an extremely high dose in mice. These tumours are unlikely to be of relevance to humans.

Reproductive toxicity studies in rats and rabbits showed no effects on mating, fertility, pregnancy or foetal parameters. However, tenofovir disoproxil fumarate reduced the viability index and weight of pups in peri-postnatal toxicity studies at maternally toxic doses.

Combination of emtricitabine and tenofovir disoproxil fumarate: Genotoxicity and repeated dose toxicity studies of one month or less with the combination of these two components found no exacerbation of toxicological effects compared to studies with the separate components.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Emtricitabine/tenofovir disoproxil manufactured by KRKA, d.d., Novo mesto is considered unlikely to result in any significant increase in the combined sales volumes for all emtricitabine and tenofovir containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Discussion on non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided. The pharmacology, pharmacokinetics and toxicology data as well known for tenofovir disoproxil and thus new non-clinical data are not required. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed.

2.3.4. Conclusion on the non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided. The pharmacology, pharmacokinetics and toxicology data as well known for tenofovir disoproxil and thus new non-clinical data are not required. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablets containing emtricitabine / tenofovir disoproxil succinate. To support the marketing authorisation application the applicant conducted one bioequivalence study with two-way, two- period, two-sequence cross-over design under fed conditions. This study was the pivotal study for the assessment.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) <as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09) are of particular relevance.

GCP

The Clinical trial was performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

This is a generic application for only one strength; hence a biowaiver is not applicable.

Clinical studies

To support the application, the applicant has submitted KRS-P5-566 bioequivalence study.

Table 1. Tabular overview of clinical studies

Type of study	Study Identifier	Objectives of the study	Study design	Test products Dosage regimens Route of administration	Number of subjects	Study duration
BE	KRS-P5-566	Evaluate and compare bioavailability and assess bioequivalence of two different formulations of emtricitabine/tenofovir after a single oral dose administration under fed conditions. Determine the safety and tolerability of the Test product compared to the Reference formulation in healthy volunteers.	Cross-over, comparative Fed state	Emtricitabine/Tenofovir 200 mg/245/mg Truvada 200 mg/245 mg (emtricitabine/tenofovir disoproxil) Oral	28	Single dose

2.4.2. Pharmacokinetics

Study KRS-P5-566: Single Dose Crossover Comparative Bioavailability Study of Emtricitabine/Tenofovir 200 mg/245 mg Film-Coated Tablets in Healthy Male Volunteers/Fed State

Methods

Study design

This was a randomised, laboratory blinded, two-way, two- period, two-sequence, single centre, balanced, single dose, crossover comparative oral bioavailability study to establish comparative bioequivalence of Emtricitabine/Tenofovir disoproxil 200mg/245 mg film coated tablets (test manufactured by Krka Slovenia) and Truvada 200mg/245 mg film coated tablets (MAH: Gilead Sciences Intl. Ltd. Ireland) in 28 healthy, adult male human subjects under fed conditions. The objective of the study was to compare the rate and extent of absorption of both products and to monitor the adverse events to ensure the safety of the subjects.

The study centre was outside the EU . The study was conducted between 28 August 2015 and 22 September 2015 and bioanalysis was performed between 18 September 2015 and 08 October 2015.

Based on the randomised schedule and following an overnight fast of at least 10 hours subjects received a high-fat, high-calorie breakfast 30 minutes prior to drug administration.

The meal was comprised of approximately 240 mL of whole milk, 2 large eggs, 4 ounces of hash brown potatoes (2 potato patties), 1 English muffin with approximately 4.5 g of butter and 2 strips of bacon. This meal was composed of 14.5% of protein (136 calories), 30.3% of carbohydrate (284 calories) and 55.2% of fat (518 calories) for a total of 938 calories.

Thirty minutes after the start of the breakfast, a single dose of the assigned formulation was administered with approximately 240 ml of water at ambient temperature, starting at 08:30, to one subject per minute. Water was allowed ad libitum until 1 hour pre-dose and beginning 1 hour after drug administration.

Subjects fasted for at least 5 hours following drug administration, after which a standardized lunch was served. A supper and a light snack were also served at appropriate times thereafter, but not before 10 hours after dosing.

Subjects were confined to the clinical facility from at least 10 hours prior to dosing of the investigational product until after the 24-hour blood sample collection in each study period. The two periods were separated by a wash-out phase of at least 14 days.

Blood samples were taken at the following time points: pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 6.00, 8.00, 10.00, 12.00, 24.00, 36.00, 48.00 and 72.00 hours after dosing. Blood sampling time adjustments are presented in the dossier.

Test and reference products

Emtricitabine/Tenofovir disoproxil Krka 200mg/245 mg manufactured by KRKA, d.d., Novo mesto ; exp. Date November 2015) has been compared to Truvada (emtricitabine/tenofovir disoproxil) 200 mg/245 mg manufactured by Gilead Sciences Limited, exp. Date March 2018).

Table 2. Test and Reference Product information

Product Characteristics	Test product	Reference Product
Name	Emtricitabine/Tenofovir disoproxil 200 mg/245/mg Film coated tablets	Truvada 200 mg/245 mg (emtricitabine/tenofovir disoproxil) Film-coated tablets
Strength	200 mg/245/mg (emtricitabine/tenofovir)	200 mg/245 mg (emtricitabine/tenofovir disoproxil)
Dosage form	Flim-coated tablets	Flim-coated tablets
Manufacturer	Krka, d.d.d, Novo mesto Slovenia EU	Gilead Sciences Limited, Ireland
Expiry date	November 2015 (Retest date)	March 2018

Population studied

28 healthy adult male human subjects were enrolled as per the protocol whilst 26 subjects completed both study periods.

Main inclusion criteria:

- Subjects were male, age ≥18 and ≤ 55
- non- or ex-smokers
- body mass index (BMI) ≥18.50 kg/m2 and <30.00 kg/m2
- no clinically significant abnormality found in the 12-lead ECG performed at study entry

- healthy according to medical history, complete physical examination (including vital signs) and laboratory tests (general biochemistry, haematology and urinalysis)

Time deviations that were equal to or greater than 2 minutes were adjusted in the pharmacokinetic analysis to reflect actual sampling times. The other time deviations were considered to have a negligible impact on the assessment of bioequivalence and were not accounted for in the calculation of the pharmacokinetic parameters.

For the sample for which the exact collection time was not known or inconclusive, the scheduled time was used in the statistical analysis without any adjustment.

The protocol deviations reported for the subjects included in the analysis were judged to have no significant impact on the bioequivalence assessment or subject's safety.

Analytical methods

Analysis of emtricitabine and tenofovir was performed using test method KRS-P5-566.

This HPLC/MS/MS method involved the extraction of emtricitabine, tenofovir and the respective internal standards.

Storage period of study samples

Blood samples were collected in K2 EDTA Vacutainers. As soon as possible following blood collection, samples were centrifuged at a temperature of 4°C nominal and at approximately 1500g for 10 minutes. The plasma obtained was separated into duplicate polypropylene culture tubes, when feasible. The tubes were labelled with a code number that did not reveal formulation identity. The samples were frozen in an upright position and retained in the clinic's freezers at a temperature of -20°C nominal until sent on dry ice to the bioanalytical facility for assay. The time from blood sample collection to plasma aliquot storage should have been within 90 minutes.

Dosing started on the 29 August 2015 and the bioanalysis was performed between 21 September to 6 October 2015 (38 days of storage).

The long-term stability of Emtricitabine andTenofovir was adequately covered.

1204 samples were expected according to the protocol however 1163 blood samples were received (41 missing samples). The missing samples are accounted for in the dossier.

Bioanalytical report

The bioanalytical report was submitted KRS-P5-566 (dated 29 October 2015) with 20% of the subject chromatograms presented as well as the method SOPs.

Pharmacokinetic variables

Primary parameters: C_{max}, T_{max}, AUC_{0-T}, $AUC_{0-\infty}$, residual area, λZ and $T_{1/2}$.

Bioequivalence criteria: The 90% confidence intervals of the relative mean AUC 0-t and C_{max} of the test and reference product should be at least 80.00% and not more than 125.00% for log-transformed data.

Statistical methods

The main absorption and disposition parameters were calculated using a non-compartmental approach with a log-linear terminal phase assumption. The trapezoidal rule was used to estimate area under the curve. The terminal phase estimation was based on maximizing the coefficient of determination. The pharmacokinetic parameters of this trial were C_{max}, T_{max}, AUC_{0-T}, $AUC_{0-\infty}$, Residual Area, λZ and T_{half}.

The statistical analysis was based on a parametric ANOVA model of the pharmacokinetic parameters; the two-sided 90% confidence interval of the ratio of geometric means for the Cmax and AUC0-T was based on ln-transformed data; T_{max} was based on a non-parametric approach.

ANOVA model:

Fixed factors: sequence, period, treatment, subject (nested within sequence)

Criteria for Bioequivalence:

Statistical inference of emtricitabine and tenofovir was based on a bioequivalence approach using the following standards:

- The ratio of geometric LSmeans with corresponding 90% confidence interval calculated from the exponential of the difference between the Test and Reference product for the ln-transformed parameters Cmax and AUC0-T were all to be within the 80.00 to 125.00% bioequivalence range.

Safety: Descriptive statistics was applied.

Results

Table 3. Pharmacokinetic parameters for Emtricitabine 200mg n=26 (non-transformed values)

Pharmacokinetic parameter	Arithmetic Means (+/- SD)	
	Test product	**Reference product**
AUC(0-T) (ng·h/mL)	10605.0 (±1632.7)	10635.8 (±1723.7)
AUC(0-∞) (ng·h/mL)	10732.2 (±1654.2)	10788.7 (±1704.5)
Cmax (ng/mL)	1882.0 (±420.4)	1970.0 (±445.6)
Tmax 1 (hours)	2.00 (0.75, 4.00)	2.00 (1.00, 4.00)

1 Median (Min, Max)

Table 4. Pharmacokinetic parameters for Tenofovir 245mg n=26 (non-transformed values)

Pharmacokinetic parameter	Arithmetic Means (+/- SD)	
	Test product	Reference product
AUC(0-T) (ng·h/mL)	2579.66 (±581.14)	2621.23 (±545.83)
AUC(0-∞) (ng·h/mL)	2720.68 (±634.55)	2775.59 (±611.60)
Cmax (ng/mL)	259.75 (±64.72)	280.62 (±72.74)
Tmax 1 (hours)	2.25 (0.75, 4.00)	2.00 (1.00, 4.00)

1 Median (Min, Max)

Table 5. Statistical analysis for Emtricitabine 200mg n=26 (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%
AUC (0-T)	99.77	97.70 - 101.89	4.4
Cmax	95.58	90.16 - 101.33	12.4

1Estimated from the Residual Mean Squares

Table 6. Statistical analysis for Tenofovir 245mg n=26 (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%
AUC (0-T)	98.13	94.93 - 101.43	7.0
Cmax	92.64	86.44 - 99.29	14.7

1Estimated from the Residual Mean Squares

Safety data

A total of 28 subjects were included in this study and, after randomization, 27 subjects (96%) received the Test (Emtricitabine/Tenofovir disoproxil) and 27 subjects (96%) received the Reference (Truvada).

No deaths or serious adverse events (SAEs) occurred in the study. Also, no subject was withdrawn for safety reasons.

A total of 20 adverse events were reported by 10 (36%) of the 28 subjects who participated in this study. Of these events, 10 occurred after administration of each the Test and the Reference.

The AE reported with the highest incidence was headache, experienced by 2 subjects (7%) dosed with the Test and 4 subjects (15%) dosed with the Reference. Nausea was experienced by 2 subjects (7%) dosed with the Test and 1 subject (4%) dosed with the Reference. Dizziness was experienced by 1 subject (4%) per group. Upper abdominal pain, diarrhoea, dyspepsia, and vomiting were each experienced by 1 subject (4%) dosed with only the Test; while somnolence, fatigue, and procedural dizziness were experienced each by 1 subject (4%) dosed only with the Reference.

The incidence of AEs was similar for subjects administered the Test (19%) and the Reference (22%). Drug-related AEs were reported by 5 subjects (19%) administered the Test and 6 subjects (22%) administered the Reference.

All of the AEs were considered mild (16/20; 80%) or moderate (4/20; 20%) in this study. No severe AEs were reported in this study.

Generally, the subjects showed laboratory values within normal range in all treatment groups and all physical examination (including vital signs) were judged normal or not clinically significant.

Conclusions

Based on the presented bioequivalence study Emtricitabine/Tenofovir disoproxil Krka is considered bioequivalent with Truvada.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

The 90% confidence intervals for the ratios of test and reference product (least-squares means) derived from the analysis of log transformed pharmacokinetic parameters AUC0-t and Cmax were within 80-125% acceptance range for both Emtricitabine and Tenofovir. This is in line with the requirements of the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01/Corr **.

The two treatments were well tolerated by the subjects (in both periods) enrolled in the study. The adverse events mentioned above are all included in the SmPC and there are no new concerns arising from this study. The two products had similar safety profiles.

2.4.6. Conclusions on clinical aspects

Based on the presented bioequivalence study the test formulation Emtricitabine/Tenofovir disoproxil 200mg/245mg film coated tablets of Krka d.d. Slovenia is considered bioequivalent with the reference Truvada 200mg/245mg film coated tablets manufactured by Gilead Sciences Intl. Ltd. Ireland MA holder: Gilead Sciences UK.

2.5. Risk management plan

Safety concerns

	Summary of safety concerns
Important identified risks	Post-treatment hepatic flares in HIV-1/HBV co-infected patients

	Renal toxicity
	Bone events due to proximal renal tubulopathy/loss of bone mineral density
	Interaction with didanosine
	Pancreatitis
Important potential risks	Not applicable.
Missing information	Safety in children (including long-term safety)
	Safety in elderly patients
	Safety in pregnancy
	Safety in lactation
	Safety in patients with renal impairment

Pharmacovigilance plan

Most of safety concerns are addressed through routine pharmacovigilance. Renal toxicity, Bone events due to proximal renal tubulopathy/loss of bone mineral density and Safety in pregnancy are addressed through routine pharmacovigilance including targeted follow-up questionnaires as well.

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Post-treatment hepatic flares in HIV-1/HBV co-infected patients	Sections 4.4, 4.5 and 4.8 of the SmPC warn about the risk of exacerbation of hepatitis in HIV-1/HBV coinfected patients (including drug interactions) following discontinuation of the product. In sections 5.1 and 5.2 it is stated that there is limited clinical experience and pharmacokinetics in this sub-population.	None proposed
Renal toxicity	Section 4.2 of the SmPC states that product should be used in patients with renal impairment if the benefits of treatment are estimated to overweight the potential risks. Close	Educational material: "RENAL MANAGEMENT AND DOSE ADJUSTMENT ADVICE FOR HEALTHCARE PROFESSIONALS WITH ADULT PATIENTS RECEIVING TENOFOVIR

	monitoring of renal function may be required. Sections 4.2 recommend dosing in mild and moderate renal impairment. Sections 4.2 and 4.4 warn that the product is not recommended for severe renal impairment and patients who require hemodialysis. Section 4.4 recommends that baseline creatinine clearance is calculated prior to initiating therapy and according to proposed schedule. It is recommended to re-evaluate renal function whether serum phosphate decreases < 1.5 mg/dL or creatinine clearance < 50 mL/min. Sections 4.4 and 4.5 warn about higher risk of renal impairment associated with interactions with several drugs such as NSAID, ritonavir, cobistat boosted protease inhibitor, nephrotoxic medications. A close monitoring of renal function is proposed. Renal ADRs are listed in section 4.8. Proximal renal tubulopathy is generally resolved or improved after discontinuation. Incomplete recovery of renal function despite drug withdrawal may be expected in patients at risk of renal impairment. Sections 5.2 and 5.3 present pharmacokinetics and preclinical safety in renal impairment.	DISOPROXIL”.

Bone events due to proximal renal tubulopathy/loss of bone mineral density	Sections 4.2, 4.4 and 4.8 of the SmPC warn about loss of bone mineral density due to proximal renal tubulopathy and describe bone events associated with it. Section 5.3 present preclinical safety data on renal and bone toxicity.	None proposed
Interaction with didanosine	Sections 4.4 and 4.5 of the SmPC warn about interaction between tenofovir and didanosine. In section 4.8 it is stated that this interaction may lead to lactic acidosis and pancreatitis. Section 5.1 gives information on retained sensitivity to didanosine due to mutation.	None proposed
Pancreatitis	Sections 4.4, 4.5 and 4.8 of the SmPC warn about the risk of pancreatitis associated with interaction between tenofovir and didanosine. Pancreatitis is listed as ADR in section 4.8.	None proposed
Safety in children (including long-term safety)	Sections 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC note that safety and efficacy has not been studied in children < 18 years old and therefore the product is not recommended in this population.	None proposed
Safety in elderly patients	Sections 4.2, 4.4, and 5.2 of the SmPC note that safety and efficacy has not been studied in elderly > 65 years old and therefore the product should be used with caution in this population.	None proposed
Safety in pregnancy	Sections 4.4, 4.6 and 5.3 provide information on use of the product in pregnancy. It may be considered, if	None proposed

	necessary.	
Safety in lactation	Section 4.6 provides information on secretion of tenofovir in human milk. It should not be used during breastfeeding.	None proposed
Safety in patients with renal impairment	Sections 4.2, 4.4 and 5.2 warn about limited data on use of the product in mild and moderate renal impairment (different dosage regimen). It is not recommended for severe renal impairment in those on hemodialysis. Renal ADRs are listed in section 4.8.	None proposed

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.6. PSUR submission

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8. Product information

In line with the reference product, the SmPCs/PLs state that as method of administration the tablets may be disintegrated and mixed with water or food prior to administration in patients with difficulties swallowing tablets whole. The applicant has provided data as requested by the CHMP in support of the alternative method of administration. The data show that the disintegration time between test and reference product are comparable. Although the BE was demonstrated with tablets taken whole, the data support the applicability of specific administration recommendation in originator SmPC to the generic Emtricitabine/Tenofovir disoproxil Krka.

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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.

3. Benefit-risk balance

This application concerns a generic version of generic version of emtricitabine / tenofovir disoproxil film-coated tablets. The reference product Truvada is indicated for treatment and prevention of HIV infection. No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with a two-way, two- period, two-sequence cross-over design under fed conditions. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of emtricitabine/tenofovir disoproxil (succinate) met the protocol-defined criteria for bioequivalence when compared with Truvada. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Emtricitabine/Tenofovir disoproxil Krka is favourable in the following indication:

Emtricitabine/Tenofovir disoproxil Krka is indicated in antiretroviral combination therapy for the treatment of HIV-1 infected adults (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

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 European Medicines Agency;
- 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.

Additional risk minimisation measures

The Marketing Authorisation Holder (MAH) shall ensure that all physicians who are expected to prescribe/use Emtricitabine/Tenofovir disoproxil Krka in adult 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

The HIV renal educational brochure should contain the following key messages:

- That there is an increased risk of renal disease in HIV infected patients associated with tenofovir disoproxil fumarate-containing products such as Emtricitabine/ Tenofovir disoproxil Krka
- That Emtricitabine/ Tenofovir disoproxil Krka should only be used in patients with impaired renal function if the potential benefits are considered to outweigh the potential risks
- That use of Emtricitabine/ Tenofovir disoproxil Krka should be avoided with concomitant or recent use of nephrotoxic medicinal products. If Emtricitabine/ Tenofovir disoproxil Krka 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 Emtricitabine/ Tenofovir disoproxil Krka therapy
- The importance of regular monitoring of renal function during Emtricitabine/ Tenofovir disoproxil Krka therapy
- Recommended schedule for monitoring renal function considering the presence or absence of additional risk factors for renal impairment
- Instructions on the use of the creatinine clearance slide ruler