14 December 2017
EMA/846772/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Efavirenz / Emtricitabine / Tenofovir disoproxil Krka

International non-proprietary name: efavirenz / emtricitabine / tenofovir disoproxil

Procedure No. EMEA/H/C/004274/0000

Note

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

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List of abbreviations

ART	Antiretroviral therapy
ASMF	Active substance master file
AUC $_{0-T}$	Cumulative area under the plasma concentration time curve calculated from 0 to TLQC using the linear trapezoidal method
AUC $_{0-\infty}$	Area under the plasma concentration time curve extrapolated to infinity, calculated as AUC0-T + $\hat{C}LQC/\lambda z$, where $\hat{C}LQC$ is the estimated concentration at time TLQC
AUC $_{0-T/\infty}$	Relative Percentage of AUC_T with respect of AUC_∞
BMD	Bone Mineral Density
C_{max}	Maximum observed plasma concentration
CHMP	Committee for Human Medicinal Products
CYP	Cytochrome
DAD	Diode array detection
DS	Disoproxil succinate
DSC	Differential Scanning Calorimetry
DF	Disoproxil fumarate
ERA	Environmental Risk Assessment
GC-HS	Gas Chromatography head space
HDPE	High Density Polyethylene
HIV	Human Immunodeficiency Virus
HBV	Hepatitis B Virus
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements
IR	Infrared
KF	Karl Fischer titration
LDPE	Low Density Polyethylene
Ph. Eur.	European Pharmacopoeia
RMP	Risk Management Plan
T_{max}	Time of maximum observed plasma concentration; if it occurs at more than one time point, Tmax was defined as the first time point with this value
T_{LQC}	Time of last observed quantifiable plasma concentration
T_{LIN}	Time point where log-linear elimination phase begins
λ_z	Apparent elimination rate constant, estimated by linear regression of the terminal linear portion of the log concentration *versus* time curve

$T_{half.}$	Terminal elimination half-life
TLSB	Triple laminated sunlight barrier
UHPLC	Ultra high performance liquid chromatography
UV	Ultraviolet
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 26 April 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Efavirenz/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 July 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, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 10b of Directive 2001/83/EC.

The applicant applied for the following indication:

Efavirenz/Emtricitabine/Tenofovir disoproxil Krka is a fixed-dose combination of efavirenz, emtricitabine and tenofovir disoproxil. It is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years and over with virologic suppression to HIV-1 RNA levels of < 50 copies/ml on their current combination antiretroviral therapy for more than three months. Patients must not have experienced virological failure on any prior antiretroviral therapy and must be known not to have harboured virus strains with mutations conferring significant resistance to any of the three components contained in Efavirenz/Emtricitabine/Tenofovir disoproxil Krka prior to initiation of their first antiretroviral treatment regimen.

The demonstration of the benefit of efavirenz/emtricitabine/tenofovir disoproxil is primarily based on 48-week data from a clinical study in which patients with stable virologic suppression on a combination antiretroviral therapy changed to efavirenz/emtricitabine/tenofovir disoproxil. No data are currently available from clinical studies with efavirenz/emtricitabine/tenofovir disoproxil in treatment-naïve or in heavily pretreated patients.

No data are available to support the combination of efavirenz/emtricitabine/tenofovir disoproxil and other antiretroviral agents.

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 Atripla instead of non-clinical and clinical unless justified otherwise.

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:Atripla 600 mg/ 200 mg/ 245 mg film-coated tablet
- Marketing authorisation holder: Bristol-Myers Squibb and Gilead Sciences Limited
- Date of authorisation: 13-12-2007
- Marketing authorisation granted by:
  - Union
- EU Marketing authorisation number: EU/1/07/430/001-002

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

- Product name, strength, pharmaceutical form:Atripla 600 mg/ 200 mg/ 245 mg film-coated tablet
- Marketing authorisation holder: Bristol-Myers Squibb and Gilead Sciences Limited
- Date of authorisation: 13-12-2007
- Marketing authorisation granted by:
  - Union
- EU Marketing authorisation number: EU/1/07/430/001-002

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:Atripla 600 mg/ 200 mg/ 245 mg film-coated tablet
- Marketing authorisation holder: Bristol-Myers Squibb and Gilead Sciences Limited
- Date of authorisation: 13-12-2007
- Marketing authorisation granted by:
  - Union
- EU Marketing authorisation number: EU/1/07/430/001-002
- Bioavailability study number(s): KRS-P7-060 (SponsorNo 16-520)

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.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: John Joseph Borg Co-Rapporteur: n/a

- The application was received by the EMA on 26 April 2017.
- The procedure started on 18 May 2017.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 4 August 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 17 August 2017
- During the meeting on 14 September 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 13 October 2017
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 20 November 2017.
- During the PRAC meeting on 30 November 2017, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 14 December 2017, 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 Efavirenz/Emtricitabine/Tenofovir disoproxil Krka.

2. Scientific discussion

2.1. Introduction

Efavirenz-Emtricitabine-Tenofovir disoproxil Krka 600-200-245 mg film-coated tablets were developed as a generic equivalent to the innovator´s product Atripla 600/200/245 mg film-coated tablets. The innovator´s product was authorized in EU on 13.12.2007 as a fixed dose combination for treatment of HIV-1 infected adults aged 18 years and over. The marketing authorization holder is Bristol-Myers Squibb and Gilead Science Ltd., UK.

Efavirenz/Emtricitabine/Tenofovir is a well-known, well-described antiviral combination for the treatment of HIV. The pharmacodynamics and pharmacokinetics are currently well described and a number of PK data in less frequently studied compartments and in special populations have been published recently.

Efavirenz binds directly to the HIV-1 reverse transcriptase resulting in allosteric inhibition of DNA- and RNA- dependent DNA polymerase.

Emtricitabine is a synthetic nucleoside analogue of cytidine and undergoes intracellular phosphorylation to form the active metabolite, emtricitabine 5´-triphosphate, which competes with deoxycytidine 5´-triphosphate and becomes incorporated into HIV-1 DNA, resulting in viral DNA chain termination and the inhibition of HIV-1 reverse transcriptase activity.

Tenofovir is a nucleotide analogue of adenosine monophosphate. Its active metabolite, tenofovir diphosphate, competes with natural deoxyadenosine triphosphate for the active binding site on the HIV-induced reverse transcriptase (HIV DNA polymerase). Incorporation of tenofovir

diphosphate into viral DNA results in chain termination, since tenofovir diphosphate lacks the hydroxyl group in the 3´-position, which acts as the point of attachment for the next deoxyribonucleoside triphosphate. Hence, reverse transcription, the key step in HIV proliferation, is inhibited.

The applicant applied for the following indication:

Efavirenz/Emtricitabine/Tenofovir disoproxil Krka is a fixed-dose combination of efavirenz, emtricitabine and tenofovir disoproxil. It is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years and over with virologic suppression to HIV-1 RNA levels of < 50 copies/ml on their current combination antiretroviral therapy for more than three months. Patients must not have experienced virological failure on any prior antiretroviral therapy and must be known not to have harboured virus strains with mutations conferring significant resistance to any of the three components contained in Efavirenz/Emtricitabine/Tenofovir disoproxil Krka prior to initiation of their first antiretroviral treatment regimen.

The demonstration of the benefit of efavirenz/emtricitabine/tenofovir disoproxil is primarily based on 48-week data from a clinical study in which patients with stable virologic suppression on a combination antiretroviral therapy changed to efavirenz/emtricitabine/tenofovir disoproxil. No data are currently available from clinical studies with efavirenz/emtricitabine/tenofovir disoproxil in treatment-naïve or in heavily pretreated patients.

No data are available to support the combination of efavirenz/emtricitabine/tenofovir disoproxil and other antiretroviral agents.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film coated tablets containing 600 mg/200 mg/245 mg of efavirenz/emtricitabine/tenofovir disoproxil as active substances.

Other ingredients are:

Tablet core: microcrystalline cellulose, hydroxypropylcellulose, sodium laurilsulfate, croscarmellose sodium, ferric oxide red (E172), magnesium stearate, and sodium stearyl fumarate

Film coating: poly(vinyl alcohol), macrogol 3350, titanum dioxide (E171), talc, ferric oxide red (E172), and ferric oxide yellow (E172)

The product is available in high density polyethylene (HDPE) bottle with a polypropylene closure with integrated a silica gel desiccant as described in section 6.5 of the SmPC.

2.2.2. Active substance

Information of the three active substances has been provided in three ASMFs. All three ASMFs have already been assessed in other centralised procedures (all concluded). Only updates to previously assessed (and approved) versions have been assessed in this centralised procedure, for each ASMF for each active substance.

Efavirenz

General information

The chemical name of efavirenz is (4S)-6-chloro-4-(2-cyclopropylethynyl)-4-(trifluoromethyl)-1H-3,1-benzoxazin-2-one corresponding to the molecular formula $C_{14}H_9ClF_3NO_2$. It has a relative molecular mass of 316.67 g/mol and the following structure:

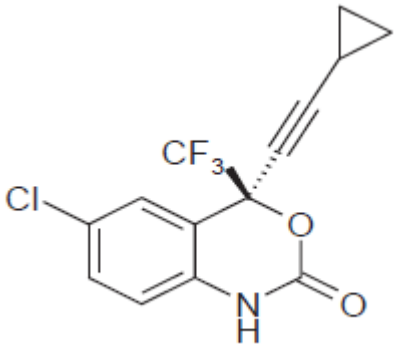

Figure 1: Efavirenz structure

The chemical structure of the active substance was elucidated by a combination of elemental analysis (C, H, N), mass spectroscopy, nuclear magnetic resonance spectroscopy (^{1}H NMR and ^{13}C NMR), infra-red spectroscopy, UV spectroscopy, identification by HPLC, XPRD and DSC.

The active substance is a white to off-white powder, non-hygroscopic and feely soluble in methanol and in dichloromethane and practically insoluble in water.

Efavirenz exhibits stereoisomerism due to the presence of 1 chiral centre and corresponds to the S-enantiomer. Enantiomeric purity is controlled routinely in the specifications by chiral HPLC.

Polymorphism has been observed for efavirenz. The polymorphic form consistently manufactured is Form I. Form I is confirmed by DSC and XRD.

Manufacture, characterisation and process controls

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

The active substance is manufactured by one manufacturer.

The active substance is synthesized in 4 main steps using well defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
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 were well discussed with regards to their origin and characterised.

The active substance is packaged in double LDPE bags (inner transparent, outer black) placed in a HDPE drum which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification set by the manufacturer of the finished product includes tests for appearance (visual), solubility (Ph. Eur.), identification (IR, HPLC), water content (KF), sulphated ash (Ph. Eur.), enantiomeric purity (HPLC), impurities (HPLC), assay (HPLC), residual solvents (GC-HS), microbiological quality (Ph. Eur.) , and particle size (laser diffraction).

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 on 18 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 40 production scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 60 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 following parameters were tested*:* description, identification, polymorphic form, specific optical rotation, water content, limit of efavirenz enantiomer, related substances, and assay. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications under long term and accelerated conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months store in a well closed container, protected from light at a temperature not exceeding 25º C. in the proposed container.

Emtricitabine

General information

The chemical name of emtricitabine is 4-Amino-5-fluoro-1-[(2R,5S)-2-(hydroxymethyl)- 1,3-oxathiolan-5- yl]-2(1H)-pyrimidinonecorresponding to the molecular formula $C_8H_{10}FN_3O_3S$. It has a relative molecular mass of 247.30 g/mol and the following structure:

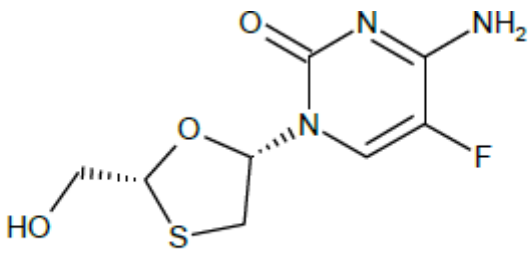

Figure 2: Emtricitabine structure

The chemical structure of emtricitabine was elucidated by a combination of elemental analysis (C,H,N &S), mass spectroscopy, nuclear magnetic resonance spectroscopy (^{1}H NMR & ^{13}C NMR), IR spectroscopy, UV spectroscopy, identification by HPLC, and X-Ray diffraction

The active substance is a white to almost white crystalline powder, it is not hygroscopic and it is freely soluble in methanol and water, practically insoluble in dichloromethane.

Emtricitabine exhibits stereoisomerism due to the presence of 2 chiral centres and corresponds to the cis enantiomer with 2R, 5S absolute configuration. Enantiomeric purity is controlled routinely by chiral HPLC in the specifications of the active substance.

Polymorphism has been observed for emtricitabine. A number of different forms, such as form I, II, III, hydrated forms and an amorphous form are known. The polymorphic form consistently manufactured is Form I. The polymorph Form I is confirmed by XRD.

Manufacture, characterisation and process controls

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

Emtricitabine is manufactured by one manufacturing site.

Emtricitabine is synthesized in 5 main steps using commercially available well defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
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 were well discussed with regards to their origin and characterised.

The active substance is packaged in transparent low density polyethylene bag with tag seal, followed by secondary transparent low density polyethylene bag with heat seal and finally kept in high density polyethylene container which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance (visual), solubility (Ph. Eur.), identification ((IR, specific optical rotation (Ph. Eur.)), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), enantiomer and emtricitabine diasteromers content (HPLC), related substances (HPLC), assay (HPLC), residual solvents (GC-HS), microbiological quality (Ph. Eur.), and particle size (laser diffraction).

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 impurities testing has been presented.

Batch analysis data on 24 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 15 production scale batches of active substance from the proposed manufacturer stored in the intended commercial packagefor up to 60 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 following parameters were tested*:* description, identification, loss on drying, related substances and assay. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications under long term and accelerated conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months in the proposed container. Store in a well closed container, do not store above 30°C.

Tenofovir disoproxil succinate

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 637.51 g/mol and the following structure:

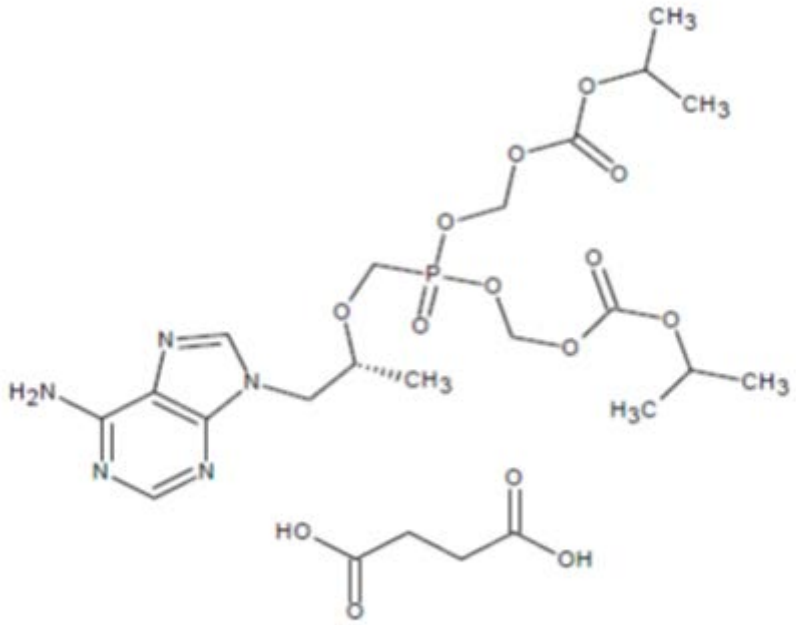

Figure 3: Tenofovir disoproxil succinate structure

The chemical structure of the active substance was elucidated by a combination of elemental analysis (C,H & N), mass spectroscopy, nuclear magnetic resonance spectroscopy (^{1}H NMR & ^{13}C NMR), infra-red spectroscopy, UV spectroscopy, identification by HPLC, and X-Ray diffraction.

The active substance is a no hygroscopic white to off white powder, freely soluble in dimethylformamide, soluble in methanol, and soluble in water at pH 1.2.

Tenofovir disoproxil succinate exhibits stereoisomerism due to the presence of 1 chiral centre. The R-isomer is consistently manufactured. Enantiomeric purity is controlled routinely in the specifications by chiral HPLC.

Polymorphism has been observed for the active substance. The same crystalline form is consistently produced. Confirmation X-Ray diffractograms of validation batches of the active substance were presented.

Manufacture, characterisation and process controls

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

Tenofovir disoproxil succinate is manufactured by one manufacturing site.

Tenofovir disoproxil succinate is synthesized in 3 main steps using commercially available well defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. 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 were well discussed with regards to their origin and characterised.

The active substance is packaged in transparent low density polyethylene bag tied with nylon strip seal. This bag is kept in another transparent low-density polyethylene (LDPE) bag again tied with nylon strip seal. This pack is kept in triple laminated sunlight barrier (TLSB) bag and is heat sealed. This is finally kept in high density polyethylene (HDPE) drum which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

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

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 on 3 commercial scale and 6 pilot scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 24 months under long term conditions (5±3 ºC) and for up to 6 months under accelerated conditions (25 ºC / 60% RH) according to the ICH guidelines were provided. Additional data from 3 revalidation batches and 3 scale up batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 6 months under long term conditions (5±3 ºC) and for up to 6 months under accelerated conditions (25 ºC / 60% RH) were also provided.

The following parameters were tested*:* description, identification, water content, S-isomer content, related substances, tenofovir disoproxil dimer impurity, chloromethyl isopropyl carbonate and assay. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications under long term and accelerated conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 30 months stored at 2°-8°C in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Efavirenz/emtricitabine/tenofovir 600 mg/200 mg/245 mg film-coated tablets are light orange pink, oval, biconvex, film-coated tablets with bevelled edges.

The aim of the development was to develop a product essentially similar to the reference medicinal product (Atripla 600mg/200mg/245mg film-coated tablets), with acceptable quality and a manufacturing process to consistently deliver the intended performance of the product and acceptable stability in the proposed packaging.

The present formulation was developed in the form of film-coated bilayer tablet, wherein emtricitabine and tenofovir disoproxil are present in one layer and efavirenz is present in a separate layer. Bilayer formulation solution was also used for the manufacturing of the reference medicinal 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.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The objective of the development of the formulation was to ensure adequate chemical stability of the finished product, develop a robust formulation and an efficient, simple and reproducible manufacturing process. For this reason, the aim was that the tablet formulation should possess the following physical properties to assure optimal technical feasibility and stability of the formulation: flowability, compatibility, lubricating ability and appearance.

During formulation development, composition was modified based on the knowledge from emtricitabine/tenofovir formulation development in order to improve product's chemical stability and at the same time achieve optimal technological processability. To evaluate the effect of this compositional change on emtricitabine/tenofovir layer dissolution properties, experiments were carried out. No difference in dissolution of emtricitabine was observed between the experiments. Efavirenz is known as low solubility BCS class II substance; formulation parameters of efavirenz layer and particle size were also tested to understand and define key formulation properties during development.

Bioequivalence study was performed showing bioequivalence between the reference medicinal product and the proposed generic medicinal product.

The discriminative power of the dissolution methods was checked. The discriminatory power of the dissolution method for efavirenz was also challenged with a variety of experiments that were prepared during development. These experiments included: differences in manufacturing process, differences in the characteristics of active pharmaceutical ingredient and differences in the finished product composition. The results of testing the discriminative power for emtricitabine/tenofovir confirmed that dissolution methods are proven as selective and capable to discriminate. Therefore, the discriminatory power of the dissolution methods was considered to be demonstrated.

Comparative dissolution profile was performed on pilot scale batches only. The applicant committed that, as the full scale production batches were not available at the time of submission, comparative dissolution profile testing will be undertaken on the first three full scale production scale batches, and the applicant will not market a batch until this comparative dissolution profile testing has been completed. The results will be provided at a competent authority's request or if the dissolution profiles are not similar together with proposed action to be taken

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

The primary packaging is high density polyethylene (HDPE) bottle with a child-resistant tamper evident polypropylene closure with integrated a silica gel desiccant. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site.

The manufacturing process consists of 8 main steps: sieving, mixing, granulating, blending, roller compaction, milling, tabletting and film-coating. The process is considered to be a standard manufacturing process. The flow chart of the manufacturing process of the finished product was provided and considered satisfactory.

Process validation data has been provided on three batches pilot scale batches. A process validation scheme has also been provided. The process validation data complies with the established specifications, for each stage of the manufacturing process. The applicant committed that the first three production scale batches of the finished product will be validated at each scale in accordance with the validation protocol presented.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), water (Ph. Eur.), uniformity of dosage units – content uniformity of efavirenz, emtricitabine and tenofovir disoproxil (Ph. Eur.), identification of efavirenz, emtricitabine and tenofovir disoproxil (HPLC, DAD), impurities (UHPLC), content of efavirenz, emtricitabine and tenofovir disoproxil (HPLC), dissolution of efavirenz, emtricitabine and tenofovir disoproxil (Ph. Eur.) and microbiological quality (Ph. Eur.).

The analytical methods used have been adequately described and 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 results are provided for three commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing

Stability of the product

Stability data from 2 production scale batches of finished product stored for up to 12 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of the finished product are identical to those proposed for marketing and were packed in in plastic containers with desiccant (different to the container proposed for marketing).

Samples were tested for appearance, water, related substances of efavirenz, related substances of emtricitabine, related substances of tenofovir disoproxil, content of efavirenz, content of emtricitabine, content of tenofovir disoproxil, dissolution of efavirenz, dissolution of emtricitabine, dissolution of tenofovir disoproxil, microbiological quality. The same analytical methods are used in the stability testing as for finished product release testing. The analytical procedures used are stability indicating. No significant changes have been observed under long term and accelerated conditions. The applicant committed that stability testing on the two batches presented will be continued until the end of the shelf-life period is reached. In case of out of specification results, authorities will be informed with proposed actions to be taken. The applicant also committed that additional first three larger production scale batches will be placed on long-term stability studies throughout the proposed shelf-life and at accelerated conditions for 6 months. In case of out of specification results authorities will he informed with proposed actions to be taken ,and that first three larger production scale batches put on stability testing in plastic containers with desiccant will be closed with the child resistant temper evident screw caps. Moreover, the applicant also committed that in accordance with GMP requirements, one production batch per year will be put on follow-up stability testing program on long term condition 25°C/60%RH. Stability testing will be performed until the end of shelf-life period is reached. In case of out of specification results authorities will be informed with proposed actions to be taken.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant changes were observed.

In-use stability testing (after the first opening of the container) was performed in 2 batches. In one batch, the testing started at the beginning of the shelf life for 2 months. For the second batch, samples were stored in original packaging before The in-use test simulates the intended use of product packed in multidose containers application of 1 tablet per day. The containers were opened, shaken and closed daily for 60 days.

Practically no change of testing parameters has been observed after in-use testing neither for both batches. As seen from stability profile during in-use testing of final product, where practically no increase in impurity profile and no change of other testing parameters have been observed, it was considered that no stability issue is expected also for in-use stability testing of final product that will be performed at the end of 24 months stability testing. Nevertheless, the CHMP recommended that 2 months in-use stability testing should be performed also on one batch towards the end of the 24 month shelf life according to the stability protocol for in-use stability testing. In case of out of specification results authorities will be informed with proposed actions to be taken.

Open-air stability testing was performed on one batch at 25±2°C/60±5%RH in open containers. The test simulates the intended use of product outside immediate packaging for hospital dispensing. An increase of some parameters was observed but the values still comply with the requirements. Other tested parameters remained unchanged.

Based on available stability data, the proposed shelf-life of 24 months, do not store above 30°C, and keep the container tightly closed in order to protect from moisture, and 2 months shelf life after first opening when stored in original packaging at the temperature not above 25°C as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

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 for this generic medicinal product. 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.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

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.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following point for investigation:

1. 2 months in-use stability testing should be performed also on one batch towards the end of the 24 month shelf life according to the stability protocol for in-use stability testing. In case of out of specification results authorities will be informed with proposed actions to be taken.

2.3. Non-clinical aspects

2.3.1. Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of efavirenz, emtricitabine and tenofovir DS are well known. As this combination is widely used and well-known, the applicant did not provide additional studies and further studies were not required by the CHMP. Overall, the non-clinical overview based on literature review was considered appropriate.

A summary of the literature with regard to non-clinical data of efavirenz, emtricitabine and tenofovir DS included justifications that the different salt of the active substance did not differ significantly in properties with regards to safety and efficacy from the reference product. This is in accordance with the relevant guideline and additional non-clinical studies were not considered necessary by the CHMP.

2.3.2. Ecotoxicity/environmental risk assessment

The applicant submitted a statement that this combination product of efavirenz, emtricitabine and tenofovir DS does not contain any genetically modified organisms. Since efavirenz, emtricitabine and tenofovir has already been present on the European market with the originator's product for several years with recognized efficacy and an acceptable level of safety, the introduction of the generic product onto the market is unlikely to result in any significant increase in the environmental exposure and would thus not be expected to have an adverse effect upon the environment. With this regard and on the basis of CHMP Guideline on the Environmental Risk

Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), a formal environmental risk assessment for efavirenz, emtricitabine and tenofovir DS was not considered necessary by the Applicant and this is acceptable to the CHMP.

2.3.3. Discussion on non-clinical aspects

The applicant did not submit any new non-clinical data on efavirenz, emtricitabine and tenofovir DS. The literature discussion of the available scientific information on efavirenz, emtricitabine and tenofovir DS was considered adequate and made reference to recent and relevant publications. The impurities and excipients were discussed and should have no impact on the safety profile of efavirenz, emtricitabine and tenofovir DS when used at therapeutic doses in line with the approved indications. The non-clinical sections of the SmPC were considered acceptable by the CHMP.

2.3.4. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Efavirenz/Emtricitabine/Tenofovir disoproxil Krka and justifications that the different salt of the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional non clinical studies were considered necessary.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablets containing Efavirenz/Emtricitabine/Tenofovir disoproxil succinate. To support the marketing authorisation application the applicant conducted one bioequivalence study with cross-over design under fasting 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) in its current version, is of particular relevance.

GCP

The Clinical trials were 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 one bioequivalence study.

2.4.2. Pharmacokinetics

Study KRS-P7-060 (Sponsor Project No 16-520): Single Dose Crossover Comparative Bioavailability Study of Efavirenz/Emtricitabine/Tenofovir Disoproxil 600 mg/200 mg/245 mg Film-Coated Tablets in Healthy Male Volunteers / Fasting 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 Efavirenz/Emtricitabine/Tenofovir 600mg/200mg/245mg film coated tablets (test manufactured by Krka Slovenia) and Atripla 600mg/200mg/245mg film coated tablets (MAH: Bristol-Myers Squibb and Gilead Sciences Intl. Ltd. Ireland) in 36 healthy, adult male human subjects under fasting 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 EU. The study was conducted between 16 January 2017 and 04 March 2017 and bioanalysis was performed between 27 February 2017 and 17 March 2017.

based on the randomisation schedule and following overnight fast of at least 10 hours subjects received single dose of the assigned formulation with approximately 240 mL of still bottled water at room temperature,. Subjects were allowed to leave the clinical site after the 24-hour post dose blood draw and were asked to return to the clinical site before each of the 3 remaining blood samples.

Blood samples were taken at the following time points: pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.33, 1.67, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 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. The two periods were separated by a wash-out phase of at least 35 days.

Test and reference products

Table 1. Test and reference product information

Product Characteristics	Test Product	Reference Product
Name	Efavirenz/Emtricitabine/ Tenofovir disoproxil 600 mg/200 mg/245 mg film-coated tablets (tenofovir disoproxil equivalent to 301 mg of tenofovir disoproxil succinate or 136 mg of tenofovir)	Atripla® 600 mg/200 mg/245 mg film-coated tablets (efavirenz/emtricitabine/ tenofovir disoproxil, with tenofovir disoproxil equivalent to 300 mg of tenofovir disoproxil fumarate or 136 mg of tenofovir)
Strength	600 mg/200 mg/245 mg	600 mg/200 mg/245 mg
Dosage form	Film-coated tablet	Film-coated tablet
Manufacturer	Krka d. d., Novo mesto, Slovenia, EU	Gilead Sciences Limited, Ireland, EU
Batch number	R42296	PVPYD Packaging Batch No.: PVPYD-P
Expiry date (Retest date)	February 2017 (re-test date)	August 2018 March 2017 (re-test date)

N/AV = Not available

Population studied

36 healthy adult male human subjects were enrolled as per the protocol whilst 35 subjects completed both study periods.

Main inclusion criteria:

Subjects were male, at least 18 years of age but not older than 55 years. The main inclusion criteria were:

- Non- or ex-smokers
- body mass index (BMI) within 18.5 kg/m^2 to 30.0 kg/m^2, inclusively
- 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), including negative Human Immunodeficiency Virus (HIV), Hepatitis B and Hepatitis C tests as well as negative screening of alcohol, cotinine and drugs of abuse.
- Mental status was scored using the Major Depression Inventory (MDI) questionnaire

Analytical methods

Analysis of emtricitabine and tenofovir was performed using test method BMR-1601.

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

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 1500*g* 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 16 January 2017 and the bioanalysis was performed between 27 February to 16 March 2017 (59 days of storage).

The long-term stability of Efavirenz, Emtricitabine and Tenofovir in human plasma was adequately covered.

1692 samples were expected according to the protocol however 1655 blood samples were received (37 missing samples). The missing samples are accounted for in the dossier.

Bioanalytical report

The bioanalytical report as well as the method SOPs were provided by the Applicant and considered adequate by the CHMP.

Pharmacokinetic variables

For efavirenz

Primary parameters: Cmax and AUC0-72,

For emtricitabine and tenofovir

Primary parameters: Cmax and AUC0-t,

Secondary parameters: AUC0-∞, Tmax, residual area, λZ and T1/2.

Bioequivalence criteria: The 90% confidence intervals of the relative mean AUC 0-t ,AUC0-T (AUC0-72 for efavirenz) and Cmax 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. For emtricitabine and tenofovir, the terminal phase estimation was based on maximizing the coefficient of determination.

For efavirenz, the main pharmacokinetic parameters of interest for this study were Cmax and AUC0-72. Tmax was calculated and provided for information purposes only.

For emtricitabine and tenofovir, the main pharmacokinetic parameters of interest for this study were Cmax and AUC0-T. Other parameters such as Tmax, $AUC_{0-\infty}$, residual area, λZ and T_{half} were provided for information purposes only.

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,

AUC0-T (AUC0-72 for efavirenz) and AUC0-∞ was based on ln-transformed data; the parameter Tmax was analyzed using a non-parametric approach.

ANOVA model:

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

Criteria for Bioequivalence:

Statistical inference of efavirenz was based on a bioequivalence approach using the following standards:

- The ratio of geometric LS means with corresponding 90% confidence interval calculated from the exponential of the difference between the Test and Reference product for the ln-transformed parameters C_{max} and AUC_{0-72} were all to be within the 80.00 to 125.00% bioequivalence range.

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

- The ratio of geometric LS means with corresponding 90% confidence interval calculated from the exponential of the difference between the Test and Reference product for the ln-transformed parameters C_{max} and AUC_{0-t} were all to be within the 80.00 to 125.00% bioequivalence range.

Safety:

Descriptive statistics was applied.

Results

Table 2. Pharmacokinetic parameters for Efavirenz 600mg n=35 (non-transformed values)

Pharmacokinetic parameter	Arithmetic Means (±SD)	
	Test Product	Reference Product
$AUC_{(0-72)}$ (ng·h/mL)	50754.3 (±10074.0)	51067.9 (±10658.8)
C_{max} (ng/mL)	2142.4 (±514.4)	2111.4 (±703.1)
T_{max} [1] (hours)	3.00 (1.00, 5.00)	4.50 (1.00, 24.00)

[1] Median (Min, Max)

Table 3. Pharmacokinetic parameters for Emtricitabine 200mg n=35 (non-transformed values)

Pharmacokinetic parameter	Arithmetic Means (±SD)	
	Test Product	Reference Product
$AUC_{(0-T)}$ (ng·h/mL)	10094.1 (±1686.7)	10236.5 (±1890.7)
$AUC_{(0-\infty)}$ (ng·h/mL)	10429.4 (±1791.5)	10564.1 (±2008.9)
C_{max} (ng/mL)	1821.7 (±381.0)	1957.7 (±508.1)
T_{max} [1] (hours)	1.33 (0.75, 2.50)	1.67 (0.75, 3.05)

[1] Median (Min, Max)

Table 4. Pharmacokinetic parameters for Tenofovir 245mg n=35 (non-transformed values)

Pharmacokinetic parameter	Arithmetic Means (±SD)	
	Test Product	Reference Product
$AUC_{(0-T)}$ (ng·h/mL)	1913.14 (±492.17)	1952.68 (±627.57)
$AUC_{(0-\infty)}$ (ng·h/mL)	2042.72 (±529.26)	2078.45 (±649.09)
C_{max} (ng/mL)	256.54 (±63.07)	257.01 (±72.15)
T_{max}[1] (hours)	1.00 (0.50, 2.50)	1.00 (0.50, 1.67)

[1] Median (Min, Max)

Table 5. Statistical analysis for Efavirenz 600mg n=35 (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals (%)	CV%[1]
$AUC_{(0-72)}$	99.89	96.30 - 103.62	8.9
C_{max}	103.62	95.76 - 112.12	19.7

[1] Estimated from the Residual Mean Squares

Table 6. Statistical analysis for Emtricitabine 200mg n=35 (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals (%)	CV%[1]
$AUC_{(0-T)}$	98.90	95.56 - 102.35	8.5
C_{max}	94.22	89.38 - 99.32	13.1

[1] Estimated from the Residual Mean Squares

Table 7. Statistical analysis for Tenofovir 245mg n=35 (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals (%)	CV%[1]
$AUC_{(0-T)}$	99.76	93.74 - 106.16	14.9
C_{max}	100.85	94.54 - 107.59	16.1

[1] Estimated from the Residual Mean Squares

Safety data

A total of 36 subjects entered the study, all of them (36 subjects) received the Reference (Atripla 600mg/200 mg/245 mg film-coated tablets) and 35 subjects (97%) received the Test (Efavirenz/Emtricitabine/Tenofovir disoproxil 600 mg/200 mg/245 mg film-coated tablets).

No serious adverse events (SAE) and no deaths were reported for any of the subjects enrolled in this study. No subject was withdrawn by the investigator for safety reasons.

A total of 58 AEs were reported by 18 (50%) of the 36 subjects who participated in this study.

Most of the AEs were considered related to drug administration (49/58; 85%). Eighteen different study drug related adverse events were noted in this study all known as undesirable effects of efavirenz/emtricitabine/tenofovir and therefore all judged as reasonably possibly related to study drug, i.e. dizziness, headache, somnolence, nausea, vomiting, dry mouth, stomach pain, pain in

legs, abnormal dreams, anxiety, feels weak, vertigo, feels stoned, hiccups, feeling of food stuck in the oesophagus, decreased concentration, fatigue and hot flash occurring with various frequency.

After 71 administrations of study medicines to 36 subjects (one subject received only Reference product), 49 cases of drug related post dose AE were reported. Most frequently reported AE was dizziness which occurred in 6 subjects after administration of Test and 5 subjects after administration of the Reference. Other AEs were reported with lesser frequency, appearing after administration of test as well as reference product.

The severity of 6 AEs was graded as “moderate” (vomiting – 2, headache-1, nausea-2, dizziness-1), whereas all other 43 AEs that were reported were graded as “mild”. All reported AEs were resolved or resolving by the end of the study.

All the abnormal clinical laboratory values were marginally higher or lower than their reference ranges and none were considered clinically significant by the investigator. Furthermore, there were no clinically significant abnormalities in the vital signs of the subjects in this study. All physical examinations performed during the study were considered normal or without any changes.

No new safety concerns were raised during the conduct of the study.

Conclusions

Based on the presented bioequivalence study the test formulation Efavirenz/Emtricitabine/Tenofovir 600mg/200mg/245mg film coated tablets of Krka d.d. Slovenia was considered bioequivalent with the reference Atripla 600mg/200mg/245mg film coated tablets manufactured by Gilead Sciences Intl. Ltd. Ireland MA holder: Bristol-Myers Squibb and Gilead Science Limited, Ireland EU.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application. Dissolution studies have been presented to support the dosage form.

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 $AUC0\text{-}_t$ and C_{max} were within 80-125% acceptance range for Emtricitabine and Tenofovir.

The 90% confidence intervals for the ratios of test and reference product (least-squares means) derived from the analysis of log transformed pharmacokinetic parameters $AUC0\text{-}_{72}$ and C_{max} were within 80-125% acceptance range for Efavirenz.

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 safety 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 Efavirenz/Emtricitabine/Tenofovir 600mg/200mg/245mg film coated tablets of Krka d.d. Slovenia is considered bioequivalent with the reference Atripla 600mg/200mg/245mg film coated tablets manufactured by Gilead Sciences Intl. Ltd. Ireland MA holder: Bristol-Myers Squibb and Gilead Science Limited, Ireland EU.

A summary of the literature with regard to clinical data of Efavirenz/Emtricitabine/Tenofovir disoproxil Krka and justifications that the different salt of the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional clinical studies were not considered necessary.

2.5. Risk management plan

Safety concerns

Important identified risks:	High-grade hepatic enzyme elevation and severe hepatic events
	Neural tube developmental abnormalities
	Psychiatric and nervous system symptoms
	Skin rashes and severe skin reactions
	Alteration in efavirenz blood levels and CYP2B6 genetic polymorphisms
	Post-treatment hepatic flares in HIV -1/HBV coinfected patients
	Renal toxicity
	Bone events due to proximal renal tubulopathy/loss of BMD
	Interaction with didanosine
	Pancreatitis
Important potential risks:	Lack of efficacy
	Overdose (occurring through accidental concurrent use of ATR with any of its active components)
	Urolithiasis/nephrolithiasis
	Malignant neoplasms
Missing information:	Safety in patients with hepatic impairment
	Safety in children(< 3 months old for efavirenz, including long-term safety forTdisoproxil)
	Safety in elderly patients
	Safety in pregnancy
	Safety in lactation
	Safety in patients with renal impairment

Pharmacovigilance plan

Routine pharmacovigilance activities are sufficient to identify and evaluate new information about actual or potential risks.
Follow-up questionnaires for spontaneous adverse event reports have been implemented correctly (Renal toxicity, Renal tubulopathy, Bone events due to proximal renal toxicity/loss of bone mineral density, Lack of Efficacy, Increased efavirenz blood levels and CYP2B6 genetic polymorphisms, High-grade hepatic enzyme elevation and severe hepatic events, Pregnancy and pregnancy outcome forms, Nephrolithiasis).

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
High-grade hepatic enzyme elevation and severe hepatic events	Content in SmPC: Section 4.3 in SmPC: • Statement that Efavirenz/Emtricitabine/Tenofovir disoproxil is contraindicated in patients with severe hepatic impairment. Section 4.4 in SmPC: • Warning that Efavirenz/Emtricitabine/Tenofovir disoproxil is contraindicated in patients with severe hepatic impairment and not recommended in patients with moderate hepatic impairment. • Warning that caution should be exercised when the drug is administered to patients with mild hepatic impairment and these patients should be cafeully monitored for efavirenz adverse reactions and laboratory tests should be performed at periodic intervals to evaluate their liver disease. • Statement that patients with pre-existing liver dysfunction should be monitored to standard practice and that if there is evidence of worsening liver disease or persistent elevations of serum transaminases to >5 times the ULN, intenuption or discontinuation of treatment must be considered. • Advice to monitor the liver enzymes of patients treated with other medicinal products associated with liver toxicity. • Warning that reports of hepatic failure have occurred in patients with no pre-existing hepatic disease or other identifiable risk factors and that liver enzyme monitoring is advised for all patients independent of pre-existing hepatic dysfunction or other risk factors. • Warning that patients with HIV and hepatitis B (HBV) or C virus (HCV) co-infection and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. Section 4.8 in SmPC: • Warning that hepatic failure sometimes characterized by a fulminant course has been reported post-marketing in patients with no pre-existing hepatic disease or other identifiable risk factors. • The following hepatobiliary disorders: ADRs are listed in the tabulated summary of adverse reactions for the efavirenz component: hepatitis acute, hepatic failure.	None proposed
Neural tube developmental	Content in SmPC:	None

abnormalities	Section 4.6 in SmPC: • Advisory statement that pregnancy should be avoided in women receiving Efavirenz/Emtricitabine/Tenofovir disoproxil . • Advisory statement that barrier contraception should always be used in combination with other methods of contraception and due to the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of Efavirenz/Emtricitabine/Tenofovir disoproxil is recommended. • Information on neural tube defects seen inchildren whose mothers were exposed to efavirenz ontaining regimens. • Statement that malformations have been observed in foetuses from efavirenz-treated monkeys. • Statement that a moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicates oo malformations or foetaJJneonatal toxicity associated with emtricitabine and tenofovir disoproxil. Prominent wording io Efavirenz/Emtricitabine/Tenofovir disoproxil PIL: • Warning that women should not get pregnant during treatment with Efavirenz/Emtricitabine/Tenofovir disoproxil and for 12 weeks thereafter. • Advice on contraceptive methods. • Advice to tell their doctor immediately if they are pregnant or intend to become pregnant. • Statement that birth defects have been seen in unborn animals and in the babies of women treated with efavirenz.	proposed
Psychiatric and nervous system symptoms	Content in SmPC: Warning in section 4.4: •Waming that psychlatric adverse reactions have been reported in patients treated with efavirenz and those patients with a history of psychiatric disorder appear to be at a greater risk of serious psychiatric adverse reactions. •Statement that patient should contact their doctor immediately if they experience symptoms such as severe depression, psychosis or suicidal ideation to assess if the symptoms may be related to efavirenz and to determine whether the risk of continued therapy outweighs the benefits. •Warning that nervous system symptoms including, but not limited to, dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming are frequently reported as undesirable effects in patients receiving efavirenz in clinical trials.	None proposed

	•Statement that dizziness was also seen in clinical studies with emtricitabine and tenofovir disoproxil and headache has been reported in clinical studies with erntricitabine. Section 4.5 in SmPC: •Recommendation that patients receiving Efavirenz/Emtricitabine/Tenofovir disoproxil concomitantly with ledipasvir/sofosbuvir should be monitored for adverse reactions associated with tenofovir disoproxil. Section 4.8 in SmPC: •Statement that patients with a history of psychiatric disorder appear to be at greater risk of serious psychiatric adverse reactions. •Statement advising on Efavirenz/Emtricitabine/Tenofovir disoproxil dosing to minimize nervous system disorders. •The following psychiatric disorder ADRs are listed in the tabulated summary of adverse reactions for the efavirenz component: depression, anxiety, abnormal dreams, insomnia, suicide attempt, suicidal ideation, psychosis mania, paranoia, hallucination, euphoric mood, affect lability, confusional state, aggression, completed suicide, delusion, neurosis. •The following nervous system disorder ADRs are listed in the tabulated summary of adverse reactions for the efavirenz component: cerebellar coordination and balance disturbances, somnolence, headache, disturbance in attention, dizziness, convulsions, amnesia, thinking abnormal, ataxia, coordination abnormal, agitation, tremor.	
Skin rashes and severe skin reactions (efavirenz)	Content in SmPC: Section 4.4 in SmPC: • Statements describing the appearance of typical rashes associated with efavirenz and their management. • Warning that severe rash has been reported in patients treated with efavirenz. • Warning that Efavirenz/Emtricitabine/Tenofovir disoproxil is not recommended for patients who have bad a life-threatening cutaneous reaction while taking an NNRTI (nucleoside reverse transcriptase inhibitors). Section 4.8 in SmPC: • Statements describing the appearance of typical rashes associated with efavirenz and their management. • The following skin and subcutaneous tissue disorders ADRs are listed in the tabulated summary of adverse reactions for the efavirenz component: rash, severe rash, pruritus, Stevens-Johnson syndrome, erythema	None proposed

	multiforme, photo allergic dermatitis.	
Alteration in efavirenz blood levels and CYP2B6 genetic polymorphisms	Content in SmPC: Section 4.2 in SmPC: • Statement that patients coinfected with HIV and HBV should be closely monitored for evidence of exacerbations of hepatitis following the discontinuation of Efavirenz/Emtricitabine/Tenofovir disoproxil . Section 4.4 of Efavirenz/Emtricitabine/Tenofovir disoproxil SmPC: • Warning that patients with chronic hepatitis B or C treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. • Warning about the risk of exacerbation of hepatitis in HIV-1/HBV co-infected patients following discontinuation of treatment, guidance that these patients should be closely monitored with both clinical and laboratory follow up for at least four months after stopping treatment, and guidance that, if appropriate, resumption of anti-HBV therapy may be warranted. • Recommendation that treatment is not discontinued in patients with advanced liver disease or cirrhosis since post-treatment exacerbation of hepatitis may lead to hepatic decompensation. Section 4.8 in SmPC: • Statement indicating that discontinuation of Efavirenz/Emtricitabine/Tenofovir disoproxil therapy may be associated with acute exacerbations of hepatitis.	None proposed
Post-treatment hepatic flares in HIV-1/HBV co-infected patients	Content in SmPC: Section 4.2 in SmPC: • Statement that patients co-infected with HIV and HBV should be closely monitored for evidence of exacerbations of hepatitis following the discontinuation of Efavirenz/Emtricitabine/Tenofovir disoproxil. Section 4.4 of Efavirenz/Emtricitabine/Tenofovir disoproxil SmPC: • Warning that patients with chronic hepatitis B or C treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. • Warning about the risk of exacerbation of hepatitis in HIV-1/HBV co-infected patients following discontinuation of treatment, guidance that these patients should be closely monitored with both clinical and laboratory follow up for at least four months after stopping treatment, and guidance that, if appropriate, resumption of anti-HBV therapy may be warranted. • Recommendation that treatment is not	None proposed

	discontinued in patients with advanced liver disease or cirrhosis since post-treatment exacerbation of hepatitis may lead to hepatic decompensation. Section 4.8 of Efavirenz/Emtricitabine/Tenofovir disoproxil SmPC: • Statement indicating that discontinuation of Efavirenz/Emtricitabine/Tenofovir disoproxil therapy may be associated with acute exacerbations of hepatitis.	
Renal toxicity	Content in SmPC: Section 4.2 in SmPC: • Statement indicating that Efavirenz/Emtricitabine/Tenofovir disoproxil is not recommended for patients with moderate or severe renal impairment (C r<SO rnUmin) as the appropriate dose adjustment of emtricitabine and tenofovir disoproxil cannot be achieved with the combination tablet. Section 4.4 in SmPC: • Warning that Efavirenz/Emtricitabine/Tenofovir disoproxil is not recommended for patients with moderate or severe renal impairment (CI-a <50 mL/min) as the appropriate dose adjustment of emtricitabine and tenofovir disoproxil cannot be achieved with the combination tablet. • Warning that the use of Efavirenz/Emtricitabine/Tenofovir disoproxil should be avoided with concurrent or recent use of a nephrotoxic medicinal product. If concomitant use is unavoidable, renal function must be monitored weekly. • Warning statement that cases of acute renal failure after initiation of high dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) have been reported in patients treated with tenofovir disoproxil fumarate and with risk factors for renal dysfunction. If l efavirenz/Emtricitabine/Tenofovir disoproxil is co-administered with an NSAID, renal function should be monitored adequately. • Recommendation that baseline creatinine clearance is calculated in patients prior to initiating therapy and for renal function to be monitored after two to four weeks, after three months of treatment and every three to six months thereafter in patients without renal risk factors. Patients with a history of renal dysfunction or in patients who are at risk of renal dysfunction require a more frequent monitoring of renal function. Warning statement that renal function should be re-evaluated within a week should serum phosphate decrease <1.5 mg/dL, or creatinine clearance decrease to <50 mL/mio in any patient receiving Efavirenz/Emtricitabine/Tenofovir disoproxil . If confirmed creatinine clearance < 50 mVmin or decreases in serum phosphate to< 1.0 mg/dl (0.32 nunovt), or if there is	Educational material: "Renal management and dose adjustment advice for healthcare professionals with adult patients receiving tenofovir disoproxil".

	a progressive decline in renal function when no other cause has been identified, treatment with Efavirenz/Emtricitabine/Tenofovir disoproxil must be interrupted Section 4.5 in Efavirenz/Emtricitabine/Tenofovir disoproxil SmPC: • An interaction statement that emtricitabine and tenofovir disoproxil are primarily eliminated by the kidneys and therefore co-administration of Efavirenz/Emtricitabine/Tenofovir disoproxil with medicinal products that reduce renal function or compete for active tubular secretion may increase serum concentrations of emtricitabine/tenofovir disoproxil and/or the co-administered products. • Recommendation that the use of Efavirenz/Emtricitabine/Tenofovir disoproxil should be avoided with concurrent or recent use of nephrotoxic medications. • Recommendation that patients receiving Efavirenz/Emtricitabine/Tenofovir disoproxil concomitantly with ledipasvir/sofosbuvir should be monitored for adverse reactions associated with tenofovir. Section 4.8 in SmPC: • Statement to indicate that rare events of renal impairment, renal failure and proximal renal tubulopathy including Fanconi syndrome sometimes leading to bone abnormalities have been reported. • Statement recommending that renal function is monitored for patients receiving Efavirenz/Emtricitabine/Tenofovir disoproxil as Efavirenz/Emtricitabine/Tenofovir disoproxil may cause renal damage. • The following ADRs are listed in the tabulated summary of adverse reactions: increased creatinine, proteinuria, renal failure (acute and chronic), acute tubular necrosis, proximal renal tubulopathy including Fanconi syndrome, nephritis, (including interstitial nephritis) and nephrogenic diabetes insipidus.	
Bone events due to proximal renal tubulopathy / loss of BMD	Content in SmPC: Section 4.4 in SmPC: • Statement that in HIV infected patients from a 144-week controlled clinical study that compared tenofovir disoproxil with stavudine in combination with lamivudine and efavirenz in antiretroviral-naive lpatients, small decreases in bone mineral density of the hip and spine were observed in both treatment groups. Decreases in bone mineral density of spine and changes in bone biomarkers from baseline were significantly greater in the TOP treatment group at 144 weeks. Decreases in bone mineral density of hip were significantly greater in this group until 96 weeks. However, there was no increased risk of fractures or evidence for clinically relevant	None proposed

	bone abnormalities over 144 weeks. • Warning that bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy and that if bone abnormalities are suspected then appropriate consultation should be obtained. Section 4.8 in SmPC: • Statement to indicate that rare events of renal impairment, renal failure and proximal renal tubulopathy including Fanconi syndrome sometimes leading to bone abnormalities have been reported • Osteomalacia (manifested as bone pain and infrequently contn'buting to fractures) is included as an ADR with tenofovir disoproxil in the tabulated summary of adverse reactions.	
Interaction with didanosine	Content in SmPC: Section 4.4 in SmPC: • Warning that that the coadministration of tenofovir disoproxil and didanosine is not recommended since exposure to didanosine is significantly increased following coadministration with tenofovir disoproxil that may increase the risk of didanosine-related adverse reactions. Section 4.5 in SmPC: • Warning that the coadministration of Efavirenz/Emtricitabine/Tenofovir disoproxil and didanosine is not recommended. Section 4.8 in SmPC: • Statement that coadministration of Efavirenz/Emtricitabine/Tenofovir disoproxil and didanosine is not recommended as it results in an increase in systemic exposure to didanosine that may increase the risk of didanosine-related ADRs.	None proposed
Pancreatitis	Content in SmPC: Section 4.4 and 4.5 in SmPC: • Warning statement regarding the risk of pancreatitis associated with the interaction between tenofovir disoproxil and didanosine. Section 4.8 of the Efavirenz/Emtricitabine/Tenofovir disoproxil SmPC: • Waming that rarely pancreatitis has been reported with coadministration of Efavirenz/Emtricitabine/Tenofovir disoproxil and didanosine. • Pancreatitis is included as an ADR with tenofovir disoproxil in the tabulated summary of adverse reactions.	None proposed
Lack of efficacy	Content in SmPC: Section 4.4 in SmPC: • Warning that current data indicate a trend that in patients on a PI-based antiretroviral regimen the switch to Efavirenz/Emtricitabine/Tenofovir disoproxil may lead to a reduction of the response to therapy and these patients should be carefully monitored for viral load.	None proposed
Overdose (occurring through	Content in SmPC:	None

accidental concurrent use of ATR with any of its active components)	Section 4.4 in SmPC: • Warning that Efavirenz/Emtricitabine/Tenofovir disoproxil should not be coadministered with other medicinal products containing any of the same active components.	proposed
Urolithiasis/nephrolithiasis	None currently proposed	None proposed
Malignant Neoplasms	None currently proposed	None proposed
Safety In patients with hepatic impairment	Content in SmPC: Sections 4.3, 4.4 and 4.8 in SmPC: Efavirenz/Emtricitabine/Tenofovir disoproxil is contraindicated in patients with severe hepatic impairment and not recommended in patients with moderate hepatic impairment. Since efavirenz is principally metabolised by the CYP system, caution should be exercised in administering Efavirenz/Emtricitabine/Tenofovir disoproxil to patients with mild hepatic impairment.	None proposed
Safety in children (including long-term safety)	Content in SmPC: Section 4.2 in SmPC: Statement indicating that the safety and efficacy of Efavirenz/Emtricitabine/Tenofovir disoproxil in children under the age of 18 years have not been established. Section 4.8 in SmPC: Statement that insufficient safety data are available for children under the age of 18 years and therefore the Efavirenz/Emtricitabine/Tenofovir disoproxil is not recommended in this population.	None proposed
Safety in elderly patients	Content in SmPC: Section 4.2 in Sm.PC: • Warning that Efavirenz/Emtricitabine/Tenofovir disoproxil should be administered with caution to elderly patients. Sections 4.4 and 4.8. in SmPC: • Statement indicating that Efavirenz/Emtricitabine/Tenofovir disoproxil has not been studied in elderly patients(> 65 years). • Statement that, as elderly patients are more likely to have decreased renal function, therefore caution should be exercised when treating elderly patients with Efavirenz/Emtricitabine/Tenofovir disoproxil.	None proposed
Safety in pregnancy	Content in SmPC: Section 4.6 in SmPC: There have been seven retrospective reports of findings consistent with neural tube defects, including meningomyelocele, all in mothers exposed to efavirenz-containing regimens (excluding any efavirenz-containing fixed-dose combination tablets) in the first trimester.	None proposed
Safety in lactation	Content in SmPC: Section 4.6 in SmPC: Statement that Efavirenz/Emtricitabine/Tenofovir disoproxil	None proposed

	should not be used during breast-feeding. Statement indicating that emtricitabine and tenofovir have been shown to be excreted in human milk but there is insufficient information on their effects in newborns/infants. Statement that efavirenz has been shown to be excreted in milk in rats at concentrations much higher than those in maternal plasma. Recommendation that in order to avoid transmission of HIV to the infant, HIV infected women, do not breast-feed.	
Safety in patients with renal impairment	Content in SmPC: Section 4.2 in SmPC: Efavirenz/Emtricitabine/Tenofovir disoproxil is not recommended for patients with moderate or severe renal impairment (creatinine clearance (CrCl) < 50 ml/min). Patients with moderate or severe renal impairment require dose interval adjustment of emtricitabine and tenofovir disoproxil that cannot be achieved with the combination tablet.	None proposed

Conclusion

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

2.6. 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.

Periodic Safety Update Reports submission requirements

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. Product information

2.7.1. 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 Efavirenz+Emtricitabine+Tenofovir Disoproxil succinate film-coated tablets. The reference product Atripla is indicated for treatment 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 randomised, laboratory blinded, two-way, two- period, two-sequence, single centre, balanced, single dose, crossover design. 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 Efavirenz+Emtricitabine+Tenofovir Disoproxil (as succinate) 600/200/245 mg film coated tablets met the protocol-defined criteria for bioequivalence when compared with Atripla. 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 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.

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 Efavirenz/Emtricitabine/Tenofovir disoproxil Krka is favourable in the following indication:

Efavirenz/Emtricitabine/Tenofovir disoproxil Krka is a fixed-dose combination of efavirenz, emtricitabine and tenofovir disoproxil. It is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years and over with virologic suppression to HIV-1 RNA levels of < 50 copies/ml on their current combination antiretroviral therapy for more than three months. Patients must not have experienced virological failure on any prior antiretroviral therapy and must be known not to have harboured virus strains with mutations conferring significant resistance to any of the three components contained in Efavirenz/Emtricitabine/Tenofovir disoproxil Krka prior to initiation of their first antiretroviral treatment regimen.
The demonstration of the benefit of efavirenz/emtricitabine/tenofovir disoproxil is primarily based on 48-week data from a clinical study in which patients with stable virologic suppression on a combination antiretroviral therapy changed to efavirenz/emtricitabine/tenofovir disoproxil. No data are currently available from clinical studies with efavirenz/emtricitabine/tenofovir disoproxil in treatment-naïve or in heavily pretreated patients.
No data are available to support the combination of efavirenz/emtricitabine/tenofovir disoproxil and other antiretroviral agents.

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 Efavirenz/Emtricitabine /tenofovir disoproxil Krka are provided with a physician educational pack containing the following:

- The Summary of Product Characteristics
- HIV renal educational brochure, including the creatinine clearance slide ruler

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 Efavirenz/Emtricitabine /tenofovir disoproxil Krka
- Efavirenz/Emtricitabine /tenofovir disoproxil Krka is not recommended for patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min)
- That use of Efavirenz/Emtricitabine /tenofovir disoproxil Krka should be avoided with concomitant or recent use of nephrotoxic medicinal products. If Efavirenz/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 Efavirenz/Emtricitabine /tenofovir disoproxil Krka therapy
- The importance of regular monitoring of renal function during Efavirenz/Emtricitabine /tenofovir disoproxil Krka therapy
- Recommended schedule for monitoring renal function considering the presence or absence of additional risk factors for renal impairment
- If serum phosphate is < 1.5 mg/dl or creatinine clearance decreases during therapy to < 50 ml/min then renal function must be re-evaluated within one week. If creatinine clearance is confirmed as < 50 ml/min or serum phosphate decreases to < 1.0 mg/dl then Efavirenz/Emtricitabine /tenofovir disoproxil Krka therapy should be interrupted. Interrupting treatment with Efavirenz/Emtricitabine /tenofovir disoproxil Krka should also be considered in case of progressive decline of renal function when no other cause has been identified.
- Instructions on the use of the creatinine clearance slide ruler

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

These conditions fully reflect the advice received from the PRAC.