22 June 2017
EMA/CHMP/630402/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Efavirenz/Emtricitabine/Tenofovir disoproxil Mylan

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

Procedure No. EMEA/H/C/004240/0000

Note

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

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List of abbreviations

AR	Assessment report
ASM	Active substance manufacturer
ASMF	Active Substance Master File
BSE	Bovine Spongiform Encephalopathy
B/R	Benefit/Risk balance
CHMP	The Committee for Medicinal Products for Human Use
CoA	Certificate of analysis
Cmax	Maximum Concentration observed
CTD	Common technical document
CRS	Chemical reference substance
DMF	Drug Master File = Active Substance Master File, ASMF
DNA	Deoxyribonucleic acid
DP	Drug product
DS	Drug substance
EC50	Half maximal effective concentration
FDC	Fixed dose combination
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good manufacturing practice
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
ICH	International conference on harmonisation
IC50	half maximal inhibitory concentration
INN	International Non-proprietary Name
IPC	In-process control
LoQ	List of Questions
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation holder
NfG	Note for guidance
NLT	Not less than
NMT	Not more than
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NOAEL	No-observed-adverse-effect-level
PBMCs	peripheral blood mononuclear cells
Ph. Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
ppm	parts per million
QOS	Quality Overall Summary
QP	Qualified Person
QWP	Quality Working Party
RH	Relative Humidity
RSD	Relative standard deviation
RMP	Risk management plan
RRT	Relative retention time
RT	Reverse transcriptase
Rt	Retention time
SD	Standard deviation
SLS	Sodium lauryl sulphate
SmPC	Summary of Product Characteristics
SPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
TTC	Threshold of toxicological concern
USP	United States Pharmacopeia

This is a general list of abbreviations. Not all abbreviations may be used.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mylan S.A.S submitted on 29 July 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Efavirenz/Emtricitabine/Tenofovir disoproxil Mylan, 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 25 June 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 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication

Efavirenz/Emtricitabine/Tenofovir disoproxil Mylan 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 Mylan prior to initiation of their first antiretroviral treatment regimen (see sections 4.4 and 5.1).

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 (see section 5.1). 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 tablets
- Marketing authorisation holder: Bristol-Myers Squibb and Gilead Sciences Limited
- Date of authorisation:13-12-2007
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/07/430/001 and EU/1/07/430/002

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 tablets
- Marketing authorisation holder: Bristol-Myers Squibb and Gilead Sciences Limited
- Date of authorisation:13-12-2007
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/07/430/001 and EU/1/07/430/002

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 tablets
- Marketing authorisation holder: Bristol-Myers Squibb and Gilead Sciences Limited
- Date of authorisation:13-12-2007
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/07/430/001 and EU/1/07/430/002

Bioavailability study number(s): EFEMTE-15-13

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 appointed by the CHMP was:

Rapporteur: Bruno Sepodes

- The application was received by the EMA on 29 July 2016.
- The procedure started on 18 August 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 17 and 28

November 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 18 November 2016.

- During the meeting on 15 December 2016, 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 17 March 2017.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 27 April 2017.
- During the PRAC meeting on 5 may 2017 the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 18 May 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 23 May 2017.
- During the meeting on 22 June 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 Mylan.

2. Scientific discussion

2.1. Introduction

Efavirenz/Emtricitabine/Tenofovir disoproxil Mylan 600mg/200mg/245mg mg Film Coated tablet has been submitted under Article 10(1) (generic of a reference medicinal product) of Directive 2001/83/EC as amended.

Efavirenz/Emtricitabine/Tenofovir disoproxil Mylan is a fixed-dose combination of efavirenz,emtricitabine and tenofovir disoproxil and the proposed indication is 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 Mylan 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.

Efavirenz is an NNRTI of HIV-1. Efavirenz non-competitively inhibits HIV-1 reverse transcriptase (RT) and does not significantly inhibit human immunodeficiency virus-2 (HIV-2) RT or cellular deoxyribonucleic acid (DNA) polymerases (α, β, γ, and δ). Emtricitabine is a nucleoside analogue of

cytidine. Tenofovir disoproxil maleate is converted in-vivo to Tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate. 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.

The proposed commercial formulation is an immediate-release film-coated 600mg+200mg+245mg tablet. The recommended dose is one tablet taken orally once daily on an empty stomach.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 600 mg of efavirenz, 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (as maleate) as active substance.

Other ingredients are: Tablet core: croscarmellose sodium, hydroxypropylcellulose, low-substituted hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, colloidal anhydrous silica, sodium metabisulfite, lactose monohydrate, iron oxide red (E172). Film-coating: iron oxide yellow (E172), iron oxide red (E172), macrogol, poly(vinyl alcohol), talc, titanium dioxide (E171).

The product is available in a HDPE bottle with PP child-resistant screw cap with aluminium liner wad and desiccant labelled 'DO NOT EAT' as described in section 6.5 of the SmPC.

2.2.2. Active substance

The ASMF procedure was followed for each of the three active substances; efavirenz, emtricitabine and tenofovir disoproxil.

Efavirenz

General information

The chemical name of efavirenz is (4S) -6-chloro-4-(cyclopropylethynyl)-1,4 -dihydro-4-(trifluoromethy 1)-2H-3,1-benzoxazin-2-one corresponding to the molecular formula $C_{14}H_9ClF_3NO_2$ and has a relative molecular mass 315.68 g/mol and has the following structure (Figure 1):

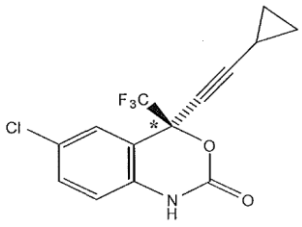

Figure 1. Structure of efavirenz

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

Efavirenz is a white to off-white powder, practically insoluble in water, practically insoluble over a pH range 1.2 – 8.0. Its pKa is 10.2. Efavirenz exhibits stereoisomerism due to the presence of one chiral centre. The isomer produced by the manufacturer corresponds to the S-isomer. Enantiomeric purity is controlled routinely by chiral specific optical rotation (R-isomer NMT 0.50%).

Efavirenz is known to exhibit polymorphism and exists in many polymorphic forms, i.e. Form-I, Form-I, Form-III, Form-IV, Form-V & Form-β. PXRD data confirms that the manufacturer produces Form-β consistently and that it remains stable upon storage. Polymorph identification test by PXRD is included in the active substance specification.

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.

Efavirenz is synthesized in three main steps using well defined starting materials with acceptable specification.

The critical process parameters have been presented and adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Powder processing steps (Micronization / Compaction / Milling / Sieving / Blending) are performed in order to produce the required particle size/bulk density.

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 packed in double polyethylene bags which are in turn packed in triple laminated aluminium packs, heat sealed, and placed in HDPE containers which comply with the Ph. Eur. and relevant EC regulations 2015/174.

Specification

The active substance specification includes tests for description, solubility, identification (IR, HPLC, XRD), water content (KF), specific optical rotation ($[\alpha]_D^{25}$ in methanol), sulfated ash (Ph. Eur.), heavy metals (Ph. Eur.), related substances (HPLC), Enantiomeric purity (HPLC), assay (HPLC), residual solvents (GC), amino alcohol impurity (LC-MS/MS), Microbiology analysis (Ph. Eur.) and particle size (Malvern).

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 for 3 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 three production scale and three pilot scale batches of active substance from the proposed manufacturer for 24 months and 60 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

Efavirenz stability batches were stored in simulated market packaging with the following configuration: first packed in LDPE bag as primary pack then kept in HMLDPE bag as secondary pack, and finally the triple laminated aluminum bag used as tertiary pack, similar to packing conditions of commercial packages.

The following parameters were tested: description, identification (IR, HPLC, XRD), water content (KF), specific optical rotation, related substances (HPLC), enantiomer content (HPLC) and assay (HPLC). The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications.

Forced degradation studies were carried out under: acid, base, oxidative, thermal (60ºC) and UV degradation conditions in solution state, and thermal (105ºC) and photolytic (white fluorescence light and UV at 365 nm) conditions in solid state. Significant degradation was observed in basic media (hydrolysis) and under UV irradiation. A slight increase in the enantiomer content was also detected in basic media. The forced degradation studies confirmed the stability-indicating nature of related substances and assay methods.

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.

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)-pyrimidinone corresponding to the molecular formula $C_8H_{10}FN_3O_3S$. It has a relative molecular mass of 247.24 g/mol and the following structure (Figure 2):

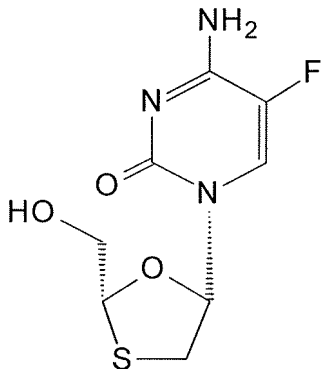

Figure 2. Structure of emtricitabine

The structure of the active substance was elucidated by a combination of ^{1}H- and ^{13}C-NMR spectroscopy, IR spectroscopy, UV spectroscopy, mass spectrometry, elemental analysis and XRD.

Emtricitabine appears as a white to off-white crystalline powder, non-hygroscopic, freely soluble in methanol and water and soluble in ethanol. Its pKa is 4.90 and the partition coefficient LogP is -0.43. It has 2 chiral centres at carbons 2 and 5 of the oxathiolane ring. There are four possible isomers due to these asymmetric carbons in the molecule and the isomer 2*R*,5*S* is commercially produced. Enantiomeric purity is controlled routinely by chiral HPLC and specific optical rotation.

Various polymorphs of emtricitabine exist (Form I, Form II, Form III and amorphous form). XRD data confirms that the manufacturer consistently produces the same form and that it remains stable upon storage. Polymorph identification test by XRD is included in the active substance specification.

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 synthesized in six main steps using well defined starting materials with acceptable specifications.

The critical process parameters were presented and justified. 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 packed in polyethylene bags (LDPE) inside HDPE drums which comply with the European Pharmacopeia and relevant EU regulations.

Specification

Emtricitabine specification includes tests and limits for description (visual), solubility (Eur. Ph.), identification (IR, HPLC, PXRD), melting range (Ph. Eur.), specific optical rotation (Ph. Eur.), loss on drying (Ph. Eur.), sulfated ash (Ph. Eur.), heavy metals (Ph. Eur.), content of emtricitabine enantiomer (chiral HPLC), related substances (HPLC), assay (HPLC), residual solvents (GC), content of triethylamine (GC), formaldehyde content (UPLC) and particle size (laser diffraction particle).

The set limits in the active substance specification are sufficiently justified and the acceptance criteria of the related substances are in accordance with ICH guidelines. The limits for residual solvents are in accordance with the ICH Q3C guideline except for triethylamine for which the acceptance criteria is adequately justified toxicologically.

The analytical methods used have been adequately discussed and non-compendial methods appropriately validated in accordance with 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 were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on six production scale batches (from both proposed manufacturers) and three pilot scale batches (from one of the manufacturers) of active substance stored in the intended commercial package for up to 60 months under long term conditions at 25 ºC / 60% RH, for up to 36 months under intermediate conditions at 30 ºC / 65% RH or for up to 24 months at alternative conditions 30 ºC / 75% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH, according to the ICH guidelines, was provided.

The following parameters were tested: description, identification (IR, HPLC), melting range, specific optical rotation, loss on drying, limit of emtricitabine enantiomer, related substances and assay. The analytical methods used were the same as for release and were stability indicating.

Results on forced degradation studies (stress studies and solid state stability studies) were also provided as part of the related substances method validation of. Exposure to acid hydrolysis, basic hydrolysis, oxidation, heat degradation and UV as well as white fluorescence light, UV at 365 nm and heat at 105 ºC in solid state was measured.

All tested parameters were within the specifications. The degradation of emtricitabine is significantly increased upon exposure to acid, base and heat. The major degradants formed were *S*-oxide and desamino. Emtricitabine solutions were found to be stable under UV exposure. No degradation was observed in solid state indicating that emtricitabine is stable upon exposure to white fluorescent light, UV light and heat at 105 ºC.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 60 months in the proposed packaging and the storage precaution "Store below 30 ºC".

Tenofovir disoproxil

General information

The chemical name of tenofovir disoproxil (as maleate) is *bis*({[propan-2-yloxy)carbonyl]oxy}methyl) ({[2*R*)-1-(6-amino-9*H*purin-9-yl)propan-2-yl]oxy}methyl)phosphonate(2*Z*)-but-2-enedioate, corresponding to the molecular formula $C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$. It has a relative molecular mass of 635.51 g/mol and the following structure (Figure 3):

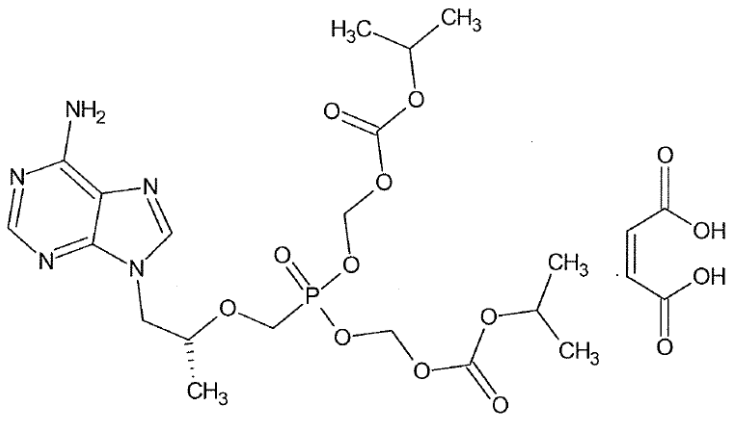

Figure 3. Structure of tenofovir disoproxil maleate

The structure of the active substance was elucidated by a combination of ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, UV spectroscopy, mass spectrometry, elemental analysis and XRD.

Tenofovir disoproxil maleate is a white to off-white, non-hygroscopic, crystalline powder, freely soluble in DMF and soluble in aqueous solutions (pH 1.2-8.0) and methanol. Its pKa is 3.5 and its partition coefficient is 0.67.

Tenofovir disoproxil maleate exhibits stereoisomerism due to the presence of one chiral centre at C-11 (the C-2 position of the propyl side-chain). Two isomers are possible due to this asymmetric carbon. The *R*-isomer is commercially produced. Enantiomeric purity is controlled routinely by chiral HPLC and specific optical rotation.

Tenofovir disoproxil maleate exhibits polymorphism and different forms are reported in the literature (form I and form II). The PXRD method distinguishes the polymorphic forms and PXRD data confirmed that a single polymorphic form is consistently produced and that it is stable upon storage. Three tenofovir disoproxil maleate batches were undergone compaction followed by milling. The milled tenofovir disoproxil maleate batches were analysed by PXRD. The XRD pattern comparison demonstrated that compaction followed by milling operations does not affect polymorphism.

Manufacture, characterisation and process controls

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

Tenofovir disoproxil maleate is synthesized in three main steps using commercially available well defined starting materials with acceptable specifications.–

The process has been shown able to consistently produce tenofovir disoproxil maleate that meets the required quality standards.

The critical process parameters have been presented and adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Powder processing steps (Micronization / Compaction / Milling / Sieving / Blending) are performed in order to produce the required particle size/bulk density.

The characterisation of the active substance and its impurities is in accordance with the relevant EU guidance. Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packed in double polyethylene bags which are in turn packed in triple laminated aluminium packs, heat sealed, and placed in HDPE containers which comply with the Ph. Eur. and relevant EC regulations 2015/174.

Specification

The active substance specification includes tests for description (visual), solubility (visual), identification (IR, HPLC), identification of maleic acid (HPLC), clarity of solution (visual), water content (KF), sulfated ash (in house), heavy metals (Ph. Eur.), *S*-isomer content (chiral HPLC), related substances (HPLC), assay (HPLC), residual solvents (GC), chloromethyl isopropyl carbonate (GC), 9-propenyl adenine (LC-MS), impurities (sum of diethyl(hydroxymethyl)phosphonate and tosyl phosphonate) (LC-MS), formaldehyde content (UPLC), total genotoxic impurities (LC-MS, UPLC) and particle size (laser diffraction).

All the proposed specification limits are considered justified and in line with the relevant ICH guidelines. 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 three consecutive production scale batches of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three production scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 12 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under intermediate conditions (30 ºC / 75% RH), according to the ICH guidelines were provided. Stability studies under accelerated conditions (40 ºC / 75% RH) were conducted.

The following parameters were tested*:* description, identification (IR, HPLC), water content (KF), *S*-isomer content (HPLC) and assay (HPLC). The analytical methods used were the same as for release and were stability indicating.

Results from forced degradation studies were also provided. Tenofovir disoproxil maleate was exposed to aqueous acid, aqueous base, oxidant, heat and UV. Solid samples were exposed to white fluorescent light (according to ICH Q1B), UV at 365 nm and heat at 60 ºC.

Significant degradation of tenofovir disoproxil maleate was observed in solution under alkaline, acid and oxidative conditions and when exposed to heat or UV light. No significant degradation was observed in solid state when samples were exposed to heat or white fluorescent light but slight degradation was observed on exposure to UV light.

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 12 months in the proposed container and the storage precaution "store below 25 ºC".

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Efavirenz, Emtricitabine and Tenofovir disoproxil 600 mg/200 mg/245 mg Film-coated tablets [20.65 mm x 10.90 mm] are described as a pink film-coated, capsule shaped, biconvex, beveled edge tablet debossed with "M" on one side of the tablet and "TME" on the other side.

Efavirenz, Emtricitabine and Tenofovir disoproxil 600mg/200mg/245mg Film-coated tablets are packed in round wide mouth white High Density Polyethylene (HDPE) bottle with white opaque polypropylene screw cap with aluminium induction sealing liner wad and desiccant. The HDPE bottle pack may either be placed in an outer cardboard carton or provided without a carton based on commercial requirement.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. The Opadry pink coating material is proprietary material supplied to an agreed specification and the individual components used in its manufacturing comply with the Ph. Eur. and EU regulation 231/2012. 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 formulation of Efavirenz/Emtricitabine/Tenofovir disoproxil Mylan 600mg/200mg/245mg Film-coated tablets is based on the literature search and characterization of reference product, i.e. Atripla 600 mg/200 mg/245 mg Film-coated tablets (Bristol-Myers Squib and Gilead Sciences Limited, Ireland).

Compatibility studies with the drug substances and excipients have been done and demonstrate that the drug substances (efavirenz, emtricitabine, and tenofovir disoproxil maleate) are compatible with all the excipients intended to use in the product development. Solubility studies of efavirenz, emtricitabine and tenofovir disoproxil maleate were carried out in different pH buffers.

The feasibility of the various approaches was evaluated for the formulation development of tablets (Efavirenz/Emtricitabine/Tenofovir disoproxil Mylan 600mg/200mg/245mg Film-coated tablets) as follows: optimization of excipients in emtricitabine portion in emtricitabine and tenofovir disoproxil maleate layer (optimization of diluents: cellulose, microcrystalline and lactose monohydrated; optimization of lubricant: magnesium stearate; optimization of glidant: silica, colloidal anhydrous); optimization of excipients in extra-granular portion in emtricitabine and tenofovir disoproxil maleate layer (optimization of disintegrant: low-substituted hydroxypropyl cellulose; optimization of lubricant: magnesium stearate; optimization of stabilizer: sodium metabisulfite); optimization of excipients in efavirenz layer (optimization of diluent: cellulose, microcrystalline and lactose monohydrate; optimization of binder: hydroxypropylcellulose; optimization of disintegrant: croscarmellose sodium; optimization of lubricant: magnesium stearate); optimization of film coating (Opadry II pink 85F540043).

The dissolution profile of Efavirenz/Emtricitabine/Tenofovir disoproxil Mylan 600mg/200mg/245mg Film-coated tablets (Batch No 2007328, BE batch) and Atripla 600mg/200mg/245mg Film-coated tablets (Batch No PVPVD, BE batch) was compared in different media in purified water with 2 % sodium lauryl sulphate (release media), 0.1N HCl with 2% SLS, pH 4.5 acetate buffer with 2% SLS and pH 6.8 phosphate buffer with 2% SLS covering the pH range of pH 1.2 - pH 6.8. The results indicate that the dissolution profiles of the test product (Biobatch) and reference product are similar (more than 85% dissolution after 15 minutes) for emtricitabine in the all media tested, are similar (more than 85% dissolution after 15 minutes) for tenofovir disoproxil maleate in purified water with 2 % SLS, pH 4.5 acetate buffer with 2% SLS and pH 6.8 phosphate buffer with 2% SLS and are similar (f2 > 50) for

efavirenz in pH 4.5 acetate buffer with 2.0% SLS. The values of f2 are found to be < 50 for efavirenz in purified water with 2 % SLS, 0.1N HCl with 2.0% SLS and pH 6.8 phosphate buffer with 2.0% SLS and for tenofovir disoproxil maleate in 0.1N HCl with 2.0% SLS. This may be due to differences in qualitative and quantitative composition in excipients and in the manufacturing process between test and reference product. However, as the test product was demonstrated to be bio-equivalent with the reference product, the differences observed between the dissolution profiles in certain media were not considered relevant.

To evaluate the effect of particle size of the drug substances on dissolution, studies were undertaken with tablets manufactured with lots of efavirenz, emtricitabine and tenofovir disoproxil of varying particle size. The tablets were evaluated for weight variation, thickness, hardness and dissolution profile. All the physical parameters and the dissolution profile were found to be satisfactory in the tablets prepared using efavirenz, emtricitabine and tenofovir disoproxil maleate drug substances with particle size distributions in the ranges proposed for commercial manufacture.—The final agreed formulation for efavirenz, emtricitabine and tenofovir disoproxil 600mg/200mg/245mg film-coated tablets consist of two layers. Dry granulation technique was selected for the tenofovir disoproxil maleate and emtricitabine layer due to their very poor flow characteristics. Wet granulation process was chosen for efavirenz layer based on its low solubility and very poor flow characteristics.

The possible variables during various stages involved in manufacturing process were identified and the effect of the critical variables on the performance of the formulation was evaluated.

Dissolution method development was conducted in parallel with formulation and process development of the current 600/200/245 mg tablet. The dissolution method used for the routine analysis of Efavirenz, Emtricitabine and Tenofovir disoproxil 600/200/245 mg Tablets, is as follows: 1000 ml of Purified water with 2.0 % Sodium lauryl sulphate, Apparatus II - Paddle, 100 rpm. The justification for the selection of the dissolution medium, use of surfactant and the concentration used, agitation speed and dissolution volume are provided; whereas emtricitabine and tenofovir disoproxil are BCS class 1 and 3 respectively, efavirenz is the least soluble of the three active substances (low solubility according to BCS), and required selection of these parameters to achieve full dissolution and sink conditions.

The suitability of dissolution method with respect to discrimination was investigated with respect to formulation and manufacturing process changes. The selected dissolution conditions are appropriate for the routine release testing of Efavirenz/Emtricitabine/Tenofovir disoproxil Mylan 600mg/200mg/245mg Film-coated tablets. Based on these experiments the discriminatory power of the dissolution method has been demonstrated. The proposed specification limit for dissolution for all three drug substances in the release and shelf-life specifications was accepted.

The primary packaging is round wide mouth white High Density Polyethylene (HDPE) bottle with white opaque polypropylene screw cap with aluminium induction sealing liner wad and 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 manufacturing process consists of four main steps:

1. Preparation of efavirenz blend

   (Sifting; Granulation; Drying; Dry screening: Sifting of extragranular materials, Blending),

2. Preparation of emtricitabine and tenofovir disoproxil maleate blend

   (Sifting; Pre-compaction blending: Blender, Compaction; Milling and Sifting; Mixing: Blender),

3. Manufacturing of Efavirenz, Emtricitabine and Tenofovir disoproxil Tablets using the blends manufactured in step 1 and step 2 (as a bi-layered tablets)

   (Sifting of extra granular materials; Final Blending: Blender; Compression)

4. Film-coating of compressed tablets followed by packaging

The intermediates of the manufacturing process have been clearly specified and the absence of holding times has been justified. Critical steps of the process have been identified as follows: preparation of efavirenz layer, preparation of emtricitabine portion, preparation of tenofovir disoproxil maleate portion, preparation of final blend for emtricitabine and tenofovir disoproxil maleate layer and compression and coating. Appropriate in-process controls are applied throughout the process and are adequately justified. The control strategy ensures that the manufacturing process consistently delivers a product that meets the defined criteria for all release specifications.

The manufacturing process has been validated by a number of studies of smaller pilot scale batches. 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 / pharmaceutical form. As the manufacturing process is considered to be standard process, the proposed larger production scale batch size has been accepted, as the applicant has presented an acceptable process validation protocol/scheme to be completed prior to commercialisation of the product.

In conclusion, it is considered that the manufacturing process is sufficiently robust to provide assurance that film-coated tablets of consistent quality, complying with the designated specification, are produced.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form description, identification (HPLC, TLC), identification of maleic acid (HPLC), identification of colorants, dissolution (HPLC), uniformity of dosage units (Ph. Eur.), assay (HPLC), related substances (HPLC), monoester impurity of tenofovir disoproxil maleate (HPLC), Water (KF),microbiological test (Ph. Eur.) and sodium metabisulfite (HPLC).

The proposed limits for related substances have been appropriately justified in line with the relevant ICH guidelines. 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 four batches of pilot production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of two pilot production scale batches of finished product stored under long term conditions for 24 months at 25 ºC / 60% RH, under intermediate stability conditions for 12 months (30

± 2°C /65 ± 5% RH) and for up to 3 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. Stability data of two additional pilot production scale batches of finished product stored under long term conditions for 9 months at 25 ºC / 60% RH and under intermediate stability conditions for 9 months (30 ± 2°C /65 ± 5% RH) according to the ICH guidelines were also provided.

The stability batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for description, assay, estimation of sodium metabisulfite, dissolution, related substances, Water and Microbial limits. The analytical procedures used are stability indicating.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results confirmed that the finished product is photostable.

Forced degradation studies confirmed the suitability of the HPLC assay and degradation product methods for use in the analysis of stability samples.

The finished product batches did not comply with the proposed finished product shelf life specification during initial accelerated stability studies performed on HDPE bottle pack. Therefore, the Applicant has performed intermediate stability studies. The data presented indicates that the product complies with the proposed finished product shelf life specification during intermediate and long term stability studies in HDPE bottle pack.

Therefore, based on this available stability data, a proposed shelf-life of 18 months for the product packed in HDPE bottle pack and the storage conditions of "Do not store above 25°C. Store in the original package in order to protect from light", as stated in the SmPC (section 6.3), are acceptable.

In-use stability studies for 30 days have been performed on various batches after 1 month, 6 months 24 months on long-term storage, and a further study will be performed after 36 months storage. Based on available in-use stability data, the proposed in-use shelf-life of "use within 30 days after first opening", as stated in the SmPC (section 6.3), is also acceptable.

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.

No other 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. 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.

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 agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Efavirenz/Emtricitabine/Tenofovir disoproxil Mylan manufactured by Mylan S.A.S. is considered unlikely to result in any significant increase in the combined sales volumes for all efavirenz/emtricitabine/tenofovir disoproxil 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

The pharmacodynamics, pharmacokinetics, and toxicological profile of efavirenz, emtricitabine, tenofovir disoproxil fumarate as well as efavirenz/emtricitabine/tenofovir disoproxil fumarate combination have been sufficiently well characterised by standard methodological approaches and the available studies indicate, from a non-clinical point of view, a positive risk/benefit profile for its intended clinical use.

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 Mylan 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 not considered necessary.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablet containing efavirenz/emtricitabine/tenofovir disoproxil. To support the marketing authorisation application the applicant conducted one bioequivalence study with an open label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period crossover design under fasting conditions. This study was the pivotal study for the assessment.

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 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

Not applicable.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study - EFEMTE-15-13.

Table 1. Tabular overview of clinical studies

Type of study	Study number	Objective of the study	Study design	Test products; dosage regimen; route of administration	No of subjects	Healthy subjects or patients	Duration of treatment
BE	EFEMTE-15-13	The objective of this study was to investigate the bioequivalence of Mylan's tenofovir disoproxil maleate, efavirenz and emtricitabine film coated tablets, 300 mg/600 mg/200 mg to BMS/Gilead's Atripla Film-	Open-label, balanced, randomised, single-dose, two treatment, two-sequence, two-period, crossover fasting oral bioequivalence study.	One tablet formulation, single dose, oral administration	Seventy-two (72) male and female (not of childbearing potential) volunteers were enrolled (68 males; 4 females). Sixty-three (63) subjects completed the study.	Healthy adult human subjects	Single dose

Type of study	Study number	Objective of the study	Study design	Test products; dosage regimen; route of administration	No of subjects	Healthy subjects or patients	Duration of treatment
		coated Tablets, 600 mg/200 mg/245 mg following a single, oral 300 mg/600 mg/200 mg (Mylan) or 600 mg/200 mg/245 mg (Atripla) dose administration under fasting conditions, and to monitor clinical status, adverse events and laboratory investigations and assess relative safety and tolerance.			Subjects 1-3, 5 7, 9- 14, 16, 18-24, 26-35, 38-43 are included in pharmacokinetic analysis of emtricitabine and tenofovir, as defined by the protocol. All subjects who completed the study are included in the pharmacokinetic analysis of efavirenz.		

2.4.2. Pharmacokinetics

Study EFEMTE-15-13, Study title: *An open label, balanced, randomized, single-dose, two-treatment, two sequence, two-period crossover fasting oral bioequivalence study of Efavirenz/Emtricitabine/ Tenofovir Maleate 600mg/ 200mg/ 300mg Tablets of Mylan Laboratories Limited, India (T) and Atripla (Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil 245 mg (as fumarate) film-coated tablets (R) of Bristol-Myers Squibb and Gilead Sciences Limited, IDA Business & Technology Park, Carrigtohill, County Cork, Ireland in healthy males and females (not of child-bearing potential).*

Methods

Study design

The Fixed Dose Combination Product in this application is essentially similar to the existing individual licensed product, Atripla (Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil 245 mg (as fumarate) film-coated tablets' of Bristol- Myers Squibb & Gilead Sciences Limited, IDA Business & Technology Park, Carrigtohill, County Cork, Ireland. The active ingredient and the route of administration are the same for both products.

Single bioequivalence study was conducted in fasting state in healthy volunteers; comparing the applicant's Efavirenz/ Emtricitabine/ Tenofovir disoproxil 600mg/ 200mg/ 245mg Tablets with Atripla

(Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil 245 mg, as fumarate) film-coated tablets' of Bristol- Myers Squibb & Gilead Sciences Limited, IDA Business & Technology Park, Carrigtohill, County Cork, Ireland. In the bioequivalence study, plasma levels of the Efavirenz, Tenofovir and Emtricitabine were measured and subjected to the confidence interval approach.

This was an open-label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover fasting oral bioequivalence study of Mylan's tenofovir disoproxil maleate, efavirenz and emtricitabine film-coated tablets, 300 mg/600 mg/200 mg and BMS/Gilead's Atripla Film-coated Tablets, 600 mg/200 mg/245 mg in seventy-two (72) healthy, male and females (not of child-bearing potential) volunteers under fasting conditions.

Since this was an open-label study, the randomization code was available to clinical staff for dosing, and to the statisticians and medical writers for report writing purposes. The randomization scheme was computer generated by Mylan Pharmaceuticals Inc., and the subjects were randomized prior to Period I dose administration.

This study was initiated with seventy-two (72) healthy adult subjects. Subjects checked into the clinical facility the evening prior to dosing. Check-in occurred at least 15 hours prior to dose administration for each study period. On study day 1, each subject received either a single oral dose (1 x 300 mg/600 mg/200 mg tablet) of Mylan's tenofovir disoproxil maleate, efavirenz and emtricitabine film-coated tablets, 300 mg/600 mg/200 mg, or a single oral dose (1 x 600 mg/200 mg/ 245 mg tablet) of BMS/Gilead's Atripla Film-coated Tablets, 600 mg/200 mg/245 mg. Dosing occurred following an overnight fast of at least 10 hours. Following a 21-day washout period, subjects returned to the clinical facility to be dosed with the alternative treatment per the randomization schedule.

During each study period, blood samples (1 x 10 mL) were collected in K2 EDTA tubes from each subject within 120 minutes prior to dose administration (0 hour) and post-dose at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6, 8, 10, 12, 24, 36, 48 and 72 hours. The subjects were allowed to leave the clinical facility after the 24 hour blood sample collection. They returned to the clinical facility for the scheduled blood sample collections at 36, 48, and 72 hours post-dose.

Samples were assayed for efavirenz in the Bioanalytical Department of Mylan Laboratories Ltd. The method developed for the analysis of efavirenz in human plasma was performed using solid phase extraction and high performance liquid chromatography with tandem mass spectrometric detection.

Samples were assayed for emtricitabine and tenofovir in the Bioanalytical Department of Mylan Laboratories Ltd.-The assay for tenofovir was linear over the range of 5.006 to 600.743 ng/mL. The method developed for the analysis of emtricitabine and tenofovir in human plasma was performed using solid phase extraction and high performance liquid chromatography with tandem mass spectrometric detection.

During the confinement study hours, when fluids were not restricted, subjects were allowed water ad lib. However, in general water consumption was controlled. No fluid, except that given with drug administration, was allowed from one hour prior to dose administration to one hour following dose administration.

Following an overnight fast of at least 10 hours, the study drug was administered with 240 mL of ambient temperature water. The subjects were instructed to swallow the tablet whole without breaking, sucking, chewing, crushing, or touching the tablet. Mouth and hand checks were performed to ensure drug ingestion. A fast was maintained for at least 4 hours after dosing. Water was allowed during fasting except when restricted as noted above.

At 4 and 10 hours after dose administration, standardized low-fat (i.e. ≤ 20% of calories from fat) meals and beverages were served to subjects. All meals were free from grapefruit, xanthine-, and caffeine-containing products. Meals were identical during both study periods, and the percentage of meal consumed by each subject was recorded for each meal provided over the course of the study.

During the first 4 hours after dose administration, subjects remained in an upright position and seated on hardback chairs, except for brief periods when subjects were permitted to leave their seats under close supervision (e.g., to use the restroom).

Assuming a true ratio between 90%-111% and an intra-subject variability of 27%, a minimum of sixty-six (66) subjects was calculated to be required to conclude bioequivalence with approximately 80% power. To account for subject withdrawal and dropouts due to adverse events, non-compliance or personal reasons, seventy-two (72) subjects were randomized and dosed. Subjects who failed to complete the study (drop-outs) were not replaced.

Test and reference products

Tenofovir Disoproxil Maleate, Efavirenz and Emtricitabine Film-coated Tablets, 300 mg/600 mg/200 mg manufactured by Mylan Laboratories Ltd. (Lot # 2007328 Exp. July 2016) has been compared to Atripla Film-coated Tablets (efavirenz, emtricitabine and tenofovir disoproxil [as fumarate]), 600 mg/200 mg/245 mg manufactured by Gilead Sciences Ireland UC for Bristol-Myers Squibb (BMS) and Gilead Sciences Limited (Lot #PVPVD Exp. 08-2018).

Population studied

Seventy-two (72) non-tobacco using, healthy males and females (not of child bearing potential) were dosed in the study. Only sixty-three (63) completed the clinical trial.

Inclusion Criteria

Subjects who met the following criteria were included in the study:

1. Age: 18 years of age or older.

2. Sex: Male and females not of childbearing potential.

a. Women were not considered of childbearing potential if one of the following was reported and documented on the medical history:

(1) postmenopausal with spontaneous amenorrhea for at least one (1) year,

(2) surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy had been performed)

b. During the course of the study, from study screen until study exit – including the washout period, all men and women were instructed that they must use a spermicide containing barrier method of contraception in addition to their current contraceptive method.

3. All subjects had a Body Mass Index (BMI) less than or equal to 30.0 kg/m2 but greater than or equal to 18.5 kg/m2.

4. Weight: Minimum of 50 kg.

5. All subjects were able to communicate effectively in English with study personnel.

6. All subjects gave written informed consent to participate in the study.

7. Only non-tobacco and/or non-nicotine product(s) users were included in this study (i.e. having no past history of smoking and tobacco consuming for at least one year prior to the study).

8. All subjects had a normal or non-clinically significant 12-lead ECG during screening.

9. All subjects were judged by the Principal Investigator or Medical Sub- Investigator physician as normal and healthy during a pre-study safety assessment

Data are presented for sixty-three (63) subjects for the efavirenz analysis. Subject 61 was discontinued post Period 1 dosing due to an adverse event (vomiting). Subjects 4 and 8 did not report to the clinic for Period 2 dosing. Subject 55 was discontinued prior to Period 2 dosing due to an adverse event (blood pressure increased). Subject 17 was discontinued post Period 2 dosing due to an adverse event (vomiting). Subjects 15 and 25 withdrew consent for personal reasons at Period 2 check-in. Subject 36 was discontinued due to a positive urine drug screen at Period 2 check-in. Subject 37 was discontinued due to a positive urine cotinine test at Period 2 check-in.

Per protocol, only the first thirty-six (36) subjects that completed the study were to be included in the analysis for emtricitabine and tenofovir. Therefore, subjects 1-3, 5-7, 9-14, 16, 18-24, 26-35, 38-43 are included in pharmacokinetic analysis of emtricitabine and tenofovir, as defined by the protocol.

Exclusion Criteria

Subjects who met any of the following criteria were excluded from the study:

1. History of hypersensitivity or idiosyncratic reaction to efavirenz, emtricitabine, tenofovir maleate and related drugs, or any of its formulation ingredients.

2. Have significant diseases or clinically significant abnormal findings during screening (medical history, physical examination, laboratory evaluations, ECG)

3. Any disease or condition which might compromise the hemopoeitic, gastrointestinal, renal, hepatic, cardiovascular, respiratory, central nervous system, diabetes, psychosis or any other body system.

4. History or presence of bronchial asthma.

5. Use of any hormone replacement therapy within 3 months prior to receiving the first dose of study medication.

6. A depot injection or implant of any drug within 3 months prior to receiving the first dose of study medication.

7. Use of any vitamins or herbal products within 7 days prior to the initial dose of the study medication.

8. Use of any medication, including over-the-counter products for 14 days prior to the initial dose of study medication.

9. Use of enzyme-modifying drugs within 28 days prior to receiving the first dose of study medication.

10. Must not have had a history of drug and or alcohol abuse within one year of the start of the study.

11. Subject who donated blood (1 unit = 450 ml) within 90 days prior to the first dose of the study drug.

12. History of allergic response to heparin.

13. Positive serologic findings for human immunodeficiency virus (HIV) antibodies, hepatitis B surface antigen (HBsAg), and/or hepatitis C virus (HCV) antibodies

14. History of difficulty in swallowing, or of any gastrointestinal disease which could affect drug absorption.

15. Intolerance to venipuncture

16. Any food allergy, intolerance, restriction or special diet that, in the opinion of the principal or sub-investigator physician, could have contraindicated the subject's participation in the study.

17. Consumption of grapefruit, grapefruit-like or grapefruit-containing products within 7 days of drug administration, during the study, or during the washout periods.

18. Ingestion of any alcoholic, caffeine or xanthine containing food or beverage within 48 hours prior to the administration of study medication and throughout the sample collection periods.

19. Use of any tobacco or nicotine-containing products throughout the duration of the study.

20. Institutionalized subjects.

21. Subjects who had received an investigational drug within 30 days prior to the planned initial dose of study medication.

The subjects remained confined at the clinical facility until after the 24-hour blood sample collection. At 36, 48 and 72 hours post-dose, the subjects returned to the clinical facility for scheduled blood sample collections.

Most of the protocol violations were related to blood sample collection time deviations. The blood sample collection time point deviations should not have any impact on the outcome of the study as the actual blood sample collection times were utilized for pharmacokinetic analysis if the collection times were outside the protocol-defined window.

Analytical methods

The Applicant provided a bioanalytical report of the bioequivalence study including representative number of chromatograms and other raw data. Main characteristics of the method used (selectivity, lower limit of quantitation, calibration curve performance, accuracy, precision, stability) were validated before study and the validation criteria are met.

Pharmacokinetic variables

Statistical analyses were performed on the pharmacokinetic parameters using the General Linear Models Procedure (PROC GLM) of SAS Software (SAS Institute, Cary, NC). The model tests for treatment effects in the parameter means at an alpha level of 0.05. The parameters TPEAK, KEL and HALFLIFE were analyzed statistically using the non-transformed data. The natural log transformed parameters LNAUCL, LNAUCINF, LNAUC72 and LNCPEAK were also be analyzed. Tests were performed to analyze for statistically significant differences in the pharmacokinetic parameters and to determine the test to reference ratios of the pharmacokinetic parameters using Least Squares Means. Ninety (90%) percent confidence intervals were constructed using the two one-sided tests procedure.

Bioequivalence Criteria:

The 90% confidence interval for the LSMeans ratio of CPEAK, AUCL, and AUCINF for the test and reference product should be between 80% and 125% for the natural log-transformed data for emtricitabine and tenofovir. The 90% confidence interval for the LSMeans ratio of CPEAK and pAUC72 for the test and reference product should be between 80% and 125% for the natural log-transformed data for efavirenz. The PK variables were adequate. Standard methods were used.

Statistical methods

The 90% confidence interval for the LSMeans ratio of CPEAK, AUCL, and AUCINF for the test and reference product should be between 80% and 125% for the natural log-transformed data for emtricitabine and tenofovir.

The 90% confidence interval for the LSMeans ratio of CPEAK and pAUC72 for the test and reference product should be between 80% and 125% for the natural log-transformed data for efavirenz.

Single-dose pharmacokinetic parameters for efavirenz, emtricitabine and tenofovir were calculated using non-compartmental techniques. Statistical analyses were performed on the pharmacokinetic parameters using the General Linear Models Procedure (PROC GLM) of SAS Software (SAS Institute, Cary, NC).

Results

Table 2. Efavirenz Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC0-72 mcg.h/ml	AUC0-∞ mcg.h/ml	Cmax mcg/ml	tmax h
Test	49.66 (13.480)	-	2.010 (0.497)	3.806 (1.927)
Reference	52.58 (14.929)	-	2.092 (0.560)	3.802 (1.444)
*Ratio (90% CI)	94.89 % (92.21% - 97.64%)		96.56 % (91.86% - 101.51%)	

AUC0-t Area under the plasma concentration curve from administration to last observed concentration at time t.

AUC0-72h can be reported instead of AUC0-t, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products

AUC0-∞ Area under the plasma concentration curve extrapolated to infinite time.

AUC0-∞ does not need to be reported when AUC0-72h is reported instead of AUC0-t

Cmax Maximum plasma concentration

tmax Time until Cmax is reached

*ln-transformed values

Table 3. Emtricitabine Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} mcg.h/ml	$AUC_{0-\infty}$ mcg.h/ml	C_{max} mcg/ml	t_{max} h
Test	9.113 (1.710)	9.471 (1.697)	1.730 (0.364)	1.986 (0.806)
Reference	8.452 (1.401)	8.825 (1.399)	1.672 (0.465)	1.667 (0.665)
***Ratio (90% CI)**	107.30 % (103.20% - 111.56%)		104.87 % (96.84% - 113.56%)	

AUC0-t Area under the plasma concentration curve from administration to last observed concentration at time t.

AUC0-72h can be reported instead of AUC0-t, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products

AUC0-∞ Area under the plasma concentration curve extrapolated to infinite time.

AUC0-∞ does not need to be reported when AUC0-72h is reported instead of AUC0-t

Cmax Maximum plasma concentration

tmax Time until Cmax is reached

*ln-transformed values

Table 4. Tenofovir Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h
Test	1826.787 (596.202)	2067.779 (610.975)	212.355 (55.802)	1.590 (0.740)
Reference	1773.544 (610.232)	1980.535 (601.476)	232.5 (76.813)	1.188 (0.487)
***Ratio (90% CI)**	103.79 % (97.43% - 110.57%)		92.59 % (85.57% - 100.19%)	

AUC0-t Area under the plasma concentration curve from administration to last observed concentration at time t.

AUC0-72h can be reported instead of AUC0-t, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products

AUC0-∞ Area under the plasma concentration curve extrapolated to infinite time.

AUC0-∞ does not need to be reported when AUC0-72h is reported instead of AUC0-t

Cmax Maximum plasma concentration

tmax Time until Cmax is reached

*ln-transformed values

No pre-dose levels were detected for any of the analytes. tmax was never observed in any subject in the first sample time. Cmax was inside the validated range. For Efavirenz, truncated AUC at 72h was considered which is acceptable due to the long half-life of the drug. For Emtricitabine, extrapolated AUC was not higher than 20% in any subject. For Tenofovir, extrapolated AUC was higher than 20% in 4 subjects (5 occasions).

In this Single dose bioequivalence study, the 90% confidence intervals of the geometric means for log transformed primary PK parameters were within the accepted range of 80.00-125.00%, thus the rate and extent of absorption of the applicant's Efavirenz/ Emtricitabine/ Tenofovir disoproxil 600mg/ 200mg/ 245mg Tablets are similar to the existing licensed product.

Safety data

Neither death nor serious adverse event occurred during the study. Total 6 adverse events occurred in study out of them 4 adverse events were moderate in nature and 2 adverse events were mild in nature:

For Test Product: Subject 8 had nausea in Period I. Subject 29 had pain in extremity in Period I.

For Reference Product: Subject 12 had nausea in Period I. Subject 30 had headache in washout period. Subject 31 had constipation in Period I. Subject 34 had pain in extremity in Period I.

The Applicant explained that the adverse events that occurred in the study are possibly related to the study products. These adverse events considered as the most common adverse events mentioned in the literatures.

All physical examinations and all laboratory parameters were considered as normal by the investigator. Blood pressures, heart rate and ECG results were judged as normal (except Subject 02, 14, 25, 28 and 34 for pre-study, Subject 02, 05, 14 and 29 for post-study for only ECG) by the investigator.

The Applicant summarised that overall tolerability of the products found to be favourable. It was agreed that the medicines were generally safe and well tolerated by the subjects in the study

Conclusions

Based on the presented bioequivalence study Efavirenz/Emtricitabine/Tenofovir disoproxil Mylan is considered bioequivalent with Atripla.

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 overview on clinical pharmacology, efficacy and safety provided was considered adequate. To support this application the MAA a bioequivalence study was submitted and a statement that study complies with GCP principles was provided.

All statistical analyses reveal that 90% confidence intervals are within the acceptable bioequivalent range of 80% and 125% for the natural log transformed parameters, LNAUCL, LNAUCINF and LNCPEAK for emtricitabine and tenofovir and for LNpAUC72 and LNCPEAK for efavirenz. This study demonstrates that Mylan's tenofovir disoproxil maleate, efavirenz and emtricitabine tablets, 300 mg/600 mg/200 mg are bioequivalent to BMS/Gilead's Atripla Film-coated Tablets, 600 mg/200 mg/245 mg following a single, oral dose of 300 mg/600 mg/200 mg (Mylan) or 600 mg/200 mg/245 mg (Atripla) administered under fasting conditions.

2.4.6. Conclusions on clinical aspects

A summary of the literature with regard to clinical data of Efavirenz/Emtricitabine/Tenofovir disoproxil Mylan 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 considered necessary.

2.5. Risk management plan

Safety concerns

Summary of safety concerns	
Important identified risks	• Psychiatric and nervous system symptoms (efavirenz) • Skin rash and skin reactions (efavirenz) • High grade hepatic enzyme elevation and severe hepatic events • Potential association with neural tube abnormalities (efavirenz) • Post-treatment hepatic flares in HIV/HBV co-infected patients (emtricitabine and tenofovir) • Interaction with didanosine (tenofovir) • Pancreatitis (tenofovir) • Renal toxicity (tenofovir) • Alteration in efavirenz blood levels and CYP2B6 genetic polymorphisms (efavirenz) • Bone fractures/loss of bone density (tenofovir)
Important potential risks	• Overdose (occurring through accidental concurrent use of Efavirenz/Emtricitabine/Tenofovir disoproxil with any of its active components. • Lack of efficacy • Malignant neoplasm • Urolithiasis/nephrolithiasis
Missing information	• Safety in children (<3 monhs old for EFV, including long-term safet for TDF) • Safety in elderly (tenofovir, efavirenz and emtricitabine) • Safety in pregnancy (tenofovir, efavirenz and emtricitabine) • Safety in patients with hepatic impairment (efavirenz) • Safety in patients with renal impairment (tenofovir)

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
The Antiretroviral Pregnancy Registry (category 3)	To collect information on the risk of birth defects in patients exposed to efavirenz/ emtricitabine/ tenofovir during pregnancy	Safety in pregnancy	Planned	To be decided

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risks: Psychiatric and nervous system disorders	Section 4.2 & 4.8 of the SPC contain adequate information on this safety concern.	None
Important identified risks: Skin rash and skin reactions	Section 4.2 & 4.8 of the SPC contain adequate information on this safety concern.	None
Important identified risks: High grade hepatic enzyme elevation and severe hepatic events	Section 4.3, 4.4 & 4.8 of the SPC contain adequate information on this safety concern.	None
Important identified risks: Potential association with neural tube abnormalities.	Section 4.6 of the SPC contains adequate information on this safety concern.	None
Important identified risks: Post-treatment hepatic flares in HIV/HBV co-infected patients.	Section 4.4 of the SPC contains adequate information on this safety concern.	None
Important identified risks: Interaction with didanosine	Section 4.4 & 4.5 of the SPC contain adequate information on this safety concern.	None
Important identified risks:	Section 4.4 & 4.5 & 4.8 of the SPC	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Pancreatitis	contain adequate information on this safety concern.	
Important identified risks: Renal toxicity	Section 4.2, 4.4, 4.5 & 4.8 of the SPC contain adequate information on this safety concern.	Educational materials
Important identified risks: Alteration in efavirenz blood levels and CYP2B6 genetic polymorphisms.	Section 5.2 of the SPC contains adequate information on this safety concern.	None
Important identified risks: Bone fractures/loss of bone density.	Section 4.4 of the SPC contain adequate information on this safety concern.	None
Important potential risks: Overdose	Section 4.4 of the SPC contains adequate information on this safety concern.	None
Important potential risks: Lack of efficacy	Sections 4.1, 4.4 and 4.5 of the SPC and section 3 of the PIL contain adequate information on this safety concern	None
Important potential risks: Malignant neoplasm	Section 5.3 of the SPC contains the currently available information on this safety concern.	None
Important potential risks: Urolithiasis/nephrolithiasis	Section 4.1 4.2 and 5.1 of The SPC and PIL do not contain any information of this safety concern.	None
Missing information: Safety in children (<3 monhs old for EFV, including long-term safet for TDF).	Section 4.2 and 4.8 of the SPC contain adequate information on this safety concern.	None
Missing information: Safety in elderly.	Section 4.2 and 4.8 of the SPC contain adequate information on this safety concern.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Missing information: Safety in pregnancy	Section 4.6 of the SPC contains adequate information on this safety concern.	None
Missing information: Safety in patients with hepatic impairment	Section 4.2, 4.3, 4.4 and 4.8 of the SPC contain adequate information on this safety concern.	None
Missing information: Safety in patients with renal impairment	Section 4.2, 4.4 and 4.8 of the SPC contain adequate information on this safety concern.	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 4.0 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 film-coated tablet. The reference product Atripla is indicated for 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. 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 randomized, single-dose, two-treatment, two sequence, two-period crossover under fasting conditions 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 Mylan met the protocol-defined criteria for bioequivalence when compared with the 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 [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 Efavirenz/Emtricitabine/Tenofovir disoproxil Mylan is favourable in the following indication:

"Efavirenz/Emtricitabine/Tenofovir disoproxil Mylan 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 Mylan prior to initiation of their first antiretroviral treatment regimen (see sections 4.4 and 5.1).

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 (see section 5.1). 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 Mylan 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 Mylan

• Efavirenz/Emtricitabine /tenofovir disoproxil Mylan is not recommended for patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min)

• That use of Efavirenz/Emtricitabine /tenofovir disoproxil Mylan should be avoided with concomitant or recent use of nephrotoxic medicinal products. If Efavirenz/Emtricitabine /tenofovir disoproxil Mylan 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 Mylan therapy

• The importance of regular monitoring of renal function during Efavirenz/Emtricitabine /tenofovir disoproxil Mylan 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 Mylan therapy should be interrupted. Interrupting treatment with Efavirenz/Emtricitabine /tenofovir disoproxil Mylan 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