Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Emtricitabine/Tenofovir alafenamide (as fumarate)

Proprietary Product Name: Descovy

Sponsor: Gilead Sciences Pty Ltd

December 2016

TGA Health Safety Regulation

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- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Common abbreviations

Abbreviation	Meaning
3TC	Lamivudine
ABC	Abacavir
ADME	Absorption, distribution, metabolism, and elimination
ADR	Adverse drug reaction
AE	Adverse event
aGFR	Actual glomerular filtration rate
AIDS	Acquired immunodeficiency syndrome
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ART	Antiretroviral therapy
ARV	Antiretroviral
ATR	Efavirenz/emtricitabine/tenofovir disoproxil fumarate (coformulated; Atripla)
ATV/co	Cobicistat-boosted atazanavir
ATV/r	Ritonavir-boosted atazanavir
BHIVA	British HIV association
BLQ	Below the limit of quantitation
BMD	Bone mineral density
BMI	Body mass index
Cat A	Cathepsin A
CD4	Cluster determinant 4
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COBI, C	Cobicistat (Tybost)

Abbreviation	Meaning
CSR	Clinical study report
C-telopeptide	Type I collagen C-telopeptide
CYP	Cytochrome P450 enzyme
Cys C	Cystatin C
ddI	Didanosine
DHHS	Department of Health and Human Services
DNA	Deoxyribonucleic acid
dNTP	2' deoxynucleoside triphosphate
DRV, D	Darunavir
DTG	Dolutegravir
DXA	Dual-energy x-ray absorptiometry
EASC	European aids clinical society
EC50	Concentration of a compound inhibiting virus replication by 50%
EOP2	End of Phase II
E/C/F/TAF	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated; Genvoya)
EFV	Efavirenz
eGFR	Estimated glomerular filtration rate
eGFRCG	Estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
ESRD	End-stage renal disease
EU	European union
EVG, E	Elvitegravir (Vitekta)
FAS	Full analysis set
FDA	Food and Drug Administration
FDC	Fixed-dose combination

Abbreviation	Meaning
FTC, F	Emtricitabine (Emtriva)
FTC-DP	Emtricitabine diphosphate
GCP	Good clinical practice
Gilead	Gilead sciences
GLSM	Geometric least-squares mean
GS-7340	Tenofovir alafenamide fumarate
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV, HIV-1, HIV-2	Human immunodeficiency virus, type 1, type 2
IC95	Concentration that results in xx% inhibition
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IN	Integrase
IND	Investigational new drug
INSTI	Integrase strand-transfer inhibitor
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
LDL	Low-density lipoprotein
LOCF	Last observation carried forward
LSM	Least-squares mean
M = F	Missing = failure
mtDNA	Mitochondrial DNA
N or n	Number of subjects in a population (N) or subset (n)
NCEP	National cholesterol education program
NNRTI	Nonnucleoside reverse transcriptase inhibitor

Abbreviation	Meaning
NRTI	Nucleoside reverse transcriptase inhibitor
NtRTI	Nucleotide reverse transcriptase inhibitor
OATP	Organic anion transporting polypeptide
P1NP	Procollagen type 1 N-terminal propeptide
PBMC	Peripheral blood mononuclear cell
PD	Pharmacodynamic(s)
P-gp	P-glycoprotein
PI	Protease inhibitor
PIP	Paediatric investigational plan
PK	Pharmacokinetic(s)
PP	Per protocol
PRT	Proximal renal tubulopathy
PSP	Pediatric study plan
PTH	Parathyroid hormone
PVF	Pure virologic failure
Q1, Q3	First quartile, third quartile
-R	Resistant
RBP	Retinol binding protein
RNA	Ribonucleic acid
rNTP	Ribonucleoside triphosphate
RPV	Rilpivirine
RT	Reverse transcriptase
RTV	Ritonavir
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation

Abbreviation	Meaning
SI	Selectivity index (ratio of CC50 to IC50)
SOC	System organ class
STB	Elvitegravir/cobicistat/emtricitabine/ tenofovir disoproxil fumarate (coformulated; Stribild)
STR	Single-tablet regimen
TAF	Tenofovir alafenamide
TAM	Thymidine analog mutation
TBLH	Total body less head
TDF	Tenofovir disoproxil fumarate (Viread)
TFV	Tenofovir
TFV-DP	Tenofovir diphosphate
TFV-MP	Tenofovir monophosphate
TVD	Emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada)
UACR	Urine albumin to creatinine ratio
UGT	Uridine diphosphate glucuronosyltransferase
ULN	Upper limit of normal
UPCR	Urine protein to creatinine ratio
US	United states
vs	Versus

I. Introduction to product submission

Submission details

Type of submission:	New fixed-dose combination of two established drug substances
Decision:	Approved
Date of decision:	28 June 2016
Date of entry onto ARTG	1 July 2016
Active ingredient(s):	Emtricitabine/Tenofovir alafenamide (as fumarate)
Product name(s):	Descovy
Sponsor's name and address:	Gilead Sciences Pty Ltd St Kilda Road, Melbourne VIC 3004
Dose form(s):	Fixed Combination, film-coated tablets
Strength(s):	200/10 mg and 200/25 mg
Container(s):	High-density polyethylene (HDPE) bottle with a polypropylene (PP) child-resistant cap with desiccant sachet
Pack size(s):	30 tablets
Approved therapeutic use:	*Descovy is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and adolescents aged 12 years and older with body weight at least 35 kg. The patients must not have a history of treatment failure or known mutations associated with resistance to the individual components of Descovy (see Pharmacology). Descovy is not for use in Pre-Exposure Prophylaxis (PrEP). This approval is based on the evaluation of the information and data provided with the original letter of application and with any subsequent correspondence and submissions relating to the application.*
Route(s) of administration:	Oral (PO)
Dosage:	In adults and adolescent patients aged 12 years and older and weighing ≥ 35 kg Descovy is taken orally once daily with or without food. The recommended dose of Descovy is 200/25 mg. If Descovy is used in combination with an HIV-1 protease inhibitor that is administered with either ritonavir or cobicistat, the recommended dose of Descovy is 200/10 mg (see Table 16). See also Drug Interactions and Other Forms of Interactions. For specific dosing recommendations for coadministered antiretroviral agents, refer to their respective Product Information.
ARTG number (s):	246092 and 246093

Product background

This AusPAR describes the application by the sponsor Gilead Sciences Pty Ltd to register a fixed dose combination (FDC) tablet from two active ingredients emtricitabine (FTC or F) and tenofovir alafenamide fumarate (TAF fumarate) previously approved by the TGA, as Descovy for the following indication:

> *Descovy is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and paediatric patients 12 years of age and older without any known mutations associated with resistance to the individual components of Descovy.*

The two strengths of Descovy (FTC/TAF) FDC are proposed for use with (200/10 mg) or without (200/25 mg) boosting with cobicistat (COBI) or ritonavir (RTV).

TAF fumarate is related to a previously approved tenofovir pro-drug, tenofovir disoproxil fumarate (TDF as Viread 300 mg AUST R 90370) see structure below under *Quality findings*). TDF and FTC are currently approved components of the fixed dose combination Truvada (TDF/FTC 300/200 mg; ARTG 107072).

TDF is the first oral prodrug of tenofovir (TFV). TAF is a prodrug of tenofovir which is metabolised intracellularly by Cathepsin A (CatA) to tenofovir diphosphate, the form that has anti-viral activity. After absorption, both TAF and TDF are converted to TFV which is metabolised intracellularly to the active metabolite, tenofovir diphosphate (TFV-DP). TFV-DP is a competitive inhibitor of human immunodeficiency virus 1 (HIV-1) (and hepatitis B virus (HBV)) reverse transcriptase (RT) enzyme thereby effectively blocking the replication and spread of the HIV virus.

FTC/TDF is the most commonly used nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) backbone, in combination with other antiretroviral agents, in the treatment of HIV infection.

The reason the sponsor is applying for a FTC/TAF FDC is that TDF has higher and more prolonged plasma circulating levels of tenofovir.

TAF fumarate was only recently approved as an active component of another FDC tablet submission (Genvoya[1]).

The proposed dosage for Descovy (FTC/TAF) is as follows:

> *In adults and paediatric patients 12 years of age and weighing ≥ 35 kg Descovy is taken orally once daily with or without food.*
>
> *The recommended dose of Descovy is 200/25 mg.*
>
> *If Descovy is used in combination with an HIV-1 protease inhibitor that is administered with either ritonavir or cobicistat, the recommended dose of Descovy is 200/10 mg (see Drug Interactions and Other Forms of Interactions).*
>
> *See also Drug Interactions and Other Forms of Interactions. For specific dosing recommendations for coadministered antiretroviral agents, refer to their respective Product Information.*
>
> *No data are available on which to make a dose recommendation for pediatric patients younger than 12 years or weighing less than 35 kg.*
>
> *Elderly: No dose adjustment is required for elderly patients. In clinical trials of 80 of the 97 patients enrolled aged 65 years and over received FTC+TAF given with EVG+COBI as a fixed-dose combination tablet. No differences in safety or efficacy*

[1] Gilead Science: Genvoya elvitegravir (E)/cobicistat (C)/emtricitabine (F)/TAF fumarate 150/150/200/10 mg tablet (AUST R 233398)

have been observed between elderly patients and those between 12 and less than 65 years of age.

Renal impairment: No dose adjustment of Descovy is required in adult patients with estimated creatinine clearance greater than or equal to 30 mL per minute.

Descovy should not be initiated in patients with estimated creatinine clearance below 30 mL per minute as there are no data available regarding the use of Descovy in this population.

No data are available to make dose recommendations in pediatric patients with renal impairment.

Hepatic Impairment: No dose adjustment of Descovy is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Descovy has not been studied in patients with severe hepatic impairment (Child-Pugh Class C); therefore, Descovy is not recommended for use in patients with severe hepatic impairment (see Pharmacological Properties: Pharmacokinetics in Special Populations).

Regulatory status

In Australia, emtricitabine (Emtriva) was first registered on the Australian Register of Therapeutic Goods (ARTG) as a single daily oral dose of 200 mg on 7 January 2005. In March 2012, Emtriva was designated as an orphan drug for the treatment of HIV-1 infection in paediatric patients aged 12 to 17 years inclusive

Emtricitabine has been registered for for combination use (Eviplera; Atripla; Truvada; Stribild; Genvoya).

Tenofovir alafenamide received first registration on the ARTG on 15 January 2016 as a component of the FDC elvitegravir/ cobicistat/emtricitabine/tenofovir alafenamide (as fumarate) marketed as Genvoya.

Genvoya is currently registered in Australia for the following indications:

Genvoya is indicated as a single tablet regimen for the treatment of HIV-1 infection in adults and adolescents aged 12 years of age and older with body weight at least 35 kg who are either treatment±naïve; or virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen (see CLINICAL TRIALS). Patients must not have a history of treatment failure or known mutations associated with resistance to the antiretroviral components of Genvoya. Genvoya is a fixed dose combination of one integrase inhibitor, one pharmacokinetic enhancer and two nucleotide HIV-1 reverse transcriptase inhibitors.

Emtriva is currently registered in Australia for the following indications:

Emtriva is indicated for the treatment of HIV in combination with other antiretroviral agents in adults and paediatric patients 12 years of age and older, weighing more than 33 kg. Evidence to support this claim is based on surrogate markers (plasma HIV RNA and CD4 count) in antiretroviral naïve individuals and in antiretroviral experienced individuals with virological suppression (See Clinical Trials).

Truvada (tenofovir disoproxil fumarate/emtricitabine 300/200 mg) was registered on the ARTG in September 2005 and is currently registered for the following indication:

Treatment of HIV-1 infection

Truvada is indicated for the treatment of HIV infected adults over the age of 18 years, in combination with other antiretroviral agents.

Pre-Exposure Prophylaxis

Truvada is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk. This indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1 infection and in heterosexual serodiscordant couples (see Clinical Studies).

Atripla (tenofovir disoproxil fumarate 300 mg, emtricitabine 200 mg, efavirenz 600 mg) was registered on the 03 August 2009.

Eviplera (tenofovir disoproxil fumarate 300 mg, emtricitabine 200 mg, rilpivirine 25 mg) was registered on the 30 January 2012.

Stribild (tenofovir disoproxil fumarate 300 mg, emtricitabine 200 mg, elvitegravir 150 mg, cobicistat 150 mg) was registered on the 22 February 2013.At the time the TGA considered this application a similar application had been approved in the USA, European Union (EU) and Canada (see Table 1).

Table 1: International regulatory status

Country	Application	Approval Date	Approved Indication
USA	Descovy (200/25 mg)	04 April 2016	Descovy is indicated, in combination with other antiretroviral agents, for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older.
EU	Descovy 200/10 mg and 200/25 mg	21 April 2016	Descovy is indicated in combination with other antiretroviral agents for the treatment of adults and adolescents (aged 12 years and older with body weight at least 35 kg) infected with human immunodeficiency virus type 1 (HIV-1).
Canada	Descovy 200/10 mg and 200/25 mg	29 April 2016	Descovy is indicated in combination with other antiretrovirals (such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors) for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients 12 years of age and older (and weighing ≥35 kg).
USA	Descovy 200/10 mg	Withdrawn	Descovy (200/10 mg) application has been withdrawn, but not for safety reasons.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

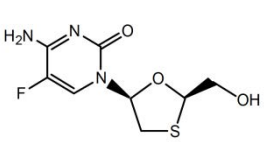
II. Quality findings

Introduction

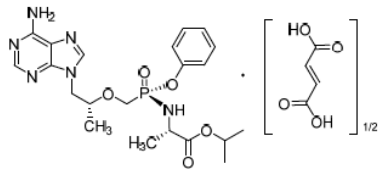
Two dose strengths are proposed for registration with one tablet containing 200 mg emtricitabine (FTC or F), and 10 mg tenofovir alafenamide fumarate (TAF or GS-7340); and the other dose strength containing 200 mg emtricitabine and 25 mg tenofovir alafenamide fumarate. The proposed trade name for the new FDC tablets is Descovy although the company has been asked to revise the trade names to include the product strengths ('*tradename* 200/10'), in accordance with the TGA's 'Best practice guideline on prescription medicine labelling'[2].

Structures of the two active ingredients are shown below, together with the related, previously approved drug substance tenofovir disoproxil fumarate (TDF).

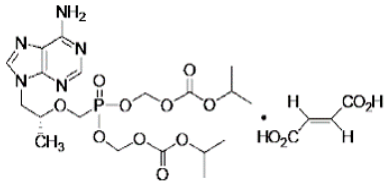
Figure 1: Chemical structures



Emtricitabine ('F' or 'FTC')



Tenofovir alafenamide fumarate ('TAF fumarate')



Tenofovir disoproxil fumarate ('TDF')

The proposed FDC tablet is very similar to the TGA approved Stribild tablets which is formulated with E/C/F/TDF 150/150/200/300 mg, and the recently approved Genvoya tablet formulated with E/C/F/TAF 150/150/200/10 mg. Tenofovir disoproxil fumarate (TDF) was developed as a first generation oral prodrug of tenofovir (TFV).

TAF is claimed to have a unique metabolism that provides enhanced lymphatic delivery of TFV, resulting in higher intracellular levels of the active phosphorylated metabolite TFV-DP and lower circulating levels of TFV when compared to TDF. Thus, the clinical dose of TAF is much lower than the clinical dose of TDF. These features have the potential to translate into less risk of nephrotoxicity and less decrease in bone mineral density, which are noted risks with TDF administration. Cobicistat (C) acts as a 'booster' for Tenofovir alafenamide (TAF) and co-administration with cobicistat has been shown to increase the

[2] https://www.tga.gov.au/publication/best-practice-guideline-prescription-medicine-labelling

peak plasma concentration (C_{max}) and area under the plasma concentration versus time curve (AUC) of TAF by more than 2 times.

With TAF as an improved pro-drug of tenofovir, Gilead has co-formulated TAF with the nucleoside reverse transcriptase inhibitor, emtricitabine, into a fixed dose combination tablet.

With regard to the active drug substances, the sponsor has previously obtained TGA approval for the respective monotherapy treatments (emtricitabine only) and FDC treatments, the details of which are listed below (Table 2). The applicant has cross-referenced to the approved Emtriva, Viread and Stribild FDC Tablet submissions, as well as the submission for Genvoya FDC Tablet which was recently approved.

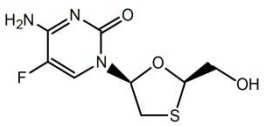
Table 2: Related submissions

Trade Name	Active	Dose Strength	Dosage Form	Pack Type	AUST R
Stribild	Elvitegravir Cobicistat Emtricitabine Tenofovir disoproxil fumarate	150 mg 150 mg 200 mg 300 mg	Tablet	Bottle	194081
Viread	Tenofovir disoproxil fumarate	300 mg	Tablet	Bottle	90370
Emtriva	Emtricitabine	200 mg	Capsule	Bottle	96426
				Blister pack	96427
Genvoya	Elvitegravir Cobicistat Emtricitabine Tenofovir alafenamide fumarate	150 mg 150 mg 200 mg 10 mg	Tablet	Bottle	233398

Drug substance (active ingredient)

The chemical structure of emtricitabine is shown below (Figure 1).

Figure 1: Chemical structure of emtricitabine

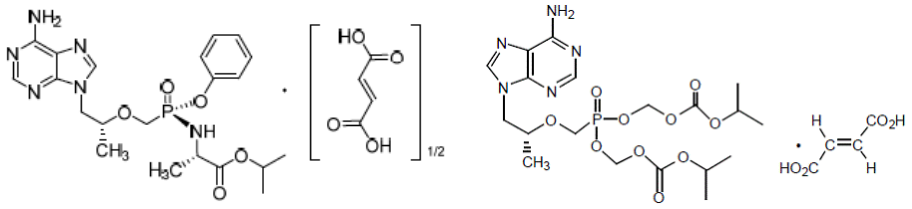


Details of the drug substance were previously evaluated by the TGA as part of the submissions, to register Emtriva emtricitabine 200 mg capsules, and the fixed dose combination tablet Stribild elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate tablets. The sponsor has provided an assurance stating that all details relating to the drug substance, emtricitabine, are identical to those previously evaluated for the above-mentioned applications and any subsequent amendments.

The drug substance specifications applied to the drug substance are considered adequate to ensure the quality and consistency of manufacture of the finished product.

The chemical structure of Tenofovir alafenamide fumarate is shown below (Figure 2).

Figure 2: Tenofovir alafenamide or disoproxil fumarate



A: NCE Tenofovir alafenamide fumarate ('TAF' fumarate) B: tenofovir disoproxil fumarate ('TDF', approved)

Tenofovir alafenamide fumarate (TAF fumarate) is the next-generation oral prodrug of tenofovir, developed as an alternative to the registered pro-drug 'tenofovir disoproxil fumarate, TDF'. Both TAF and TDF are converted to tenofovir, although the required clinical dose of TAF fumarate is much lower than the clinical dose of TDF (10 mg versus 300 mg), apparently due to 'enhanced lymphatic delivery' of TAF fumarate.

'Tenofovir alafenamide fumarate' is defined as the 'hemi-fumarate' salt depicted above and is consistently isolated as an unsolvated anhydrous polymorph (Form I). The sponsor also investigated use of the mono-fumarate salt but chose the above hemi-fumarate due to its greater stability.

TAF fumarate is a non-hygroscopic white to off-white or tan powder that is '*soluble to slightly soluble'* in aqueous media over a wide pH range, with the solubility decreasing with an increase in pH. Tenofovir alafenamide fumarate has five chiral centres, and is chirally pure (>98%). It is considered to be a BCS Class III substance (high solubility, low permeability).[3] The drug substance is micronised and particle size is adequately controlled.

Details of the drug substance were previously evaluated by the TGA as part of the submissions, to register Genvoya elvitegravir (E)/cobicistat (C)/emtricitabine (F)/TAF fumarate 150/150/200/10 mg Tablet. All details relating to the drug substance, TAF fumarate, are identical to those previously evaluated by the TGA.

The drug substance specifications applied to the drug substance are considered adequate to ensure the quality and consistency of manufacture of the finished product.

The drug substance is relatively photostable but is susceptible to hydrolysis, particularly in acidic solutions. However it shows good solid state stability and adequate stability data have been provided to support a retest period for the drug substance of 24 months stored under refrigerated conditions (5ºC ± 3ºC).

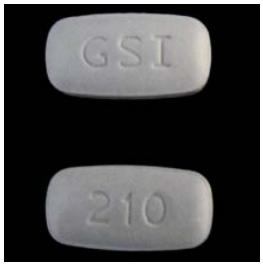
Drug product

The proposed products are immediate-release fixed combination tablets containing emtricitabine ('F') 200 mg, and tenofovir alafenamide ('TAF') 10 mg or 25 mg [equivalent to 11.2 mg or 28.0 mg of 'tenofovir alafenamide fumarate' ('TAF fumarate'), respectively]. The combination tablets are referred to as 'F/TAF' in the submission and below.

[3] The Biopharmaceutics Classification System is a system to differentiate the drugs on the basis of their solubility and permeability. The solubility classification is based on a United States Pharmacopoeia (USP) aperture.

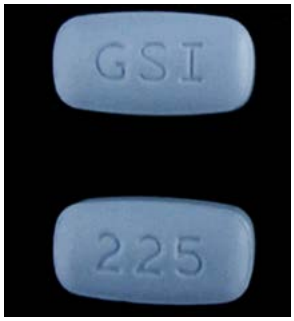
The F/TAF 200/10 mg tablets are gray, rectangular-shaped, film-coated tablets with *'GSI'* debossed on one side and *'210'* on the other side. The tablet dimensions are approximately 12.5 mm long and 6.4 mm wide. A photo of the dosage form is provided below.

Figure 4: F/TAF 200/10 mg tablets



The F/TAF 200/25 mg tablets are blue, rectangular-shaped, film-coated tablets with *'GSI'* debossed on one side and *'225'* on the other side. The tablet dimensions are approximately 12.5 mm long and 6.4 mm wide. A photo of the dosage form is provided below.

Figure 5: F/TAF 200/25 mg tablets



The FDC tablet dose strengths are not direct scales of one another.

The tablets are packaged in 60 mL white HDPE bottles containing 30 tablets and either a canister or sachet containing 3 grams of silica gel desiccant and a polyester coil. Each bottle is capped with a white continuous thread, child-resistant polypropylene screw cap fitted with an induction sealed, aluminium faced liner.

All excipients, (microcrystalline cellulose, croscarmellose sodium, magnesium stearate) are conventional ingredients used in numerous registered oral dosage forms.

The drug product is formulated using conventional dry processes. Emtricitabine and TAF fumarate are granulated with intra-granular excipients followed by milling and lubricating with magnesium stearate to yield the final powder blend for compression. Compressed tablets cores are film-coated with their respective proprietary coating mixtures and are packaged.

Dissolution performance of the proposed tablets during development and for quality control purposes was monitored by an adequately justified test method. Little or no change in dissolution was observed on storage.

An in-house, validated gradient-elution Ultra Performance Liquid chromatography (UPLC) test method is employed to test for assay of each drug substance and for specified degradants associated with each. Two wavelengths of detection are employed.

Release and expiry limits are applied for individual unspecified degradants associated with each drug substance is within the applicable International Conference on Harmonisation qualification threshold.

Degradation pathways for each drug substance have been adequately investigated and limits are applied for specified impurities for each drug substance. These limits have been

qualified by toxicological studies, which have been assessed as acceptable by the TGA nonclinical section.

The limits applied to emtricitabine-related degradation products and TAF-related degradation products are equivalent to or tighter than those proposed for the degradation products in the approved Genvoya tablets.

Batches of each tablet strength typically have very low levels of total impurities associated with each drug substance at release. On long-term storage (12 months, 30°C/65%RH) there were no significant increases in degradants associated with emtricitabine with moderate increases in TAF-related degradants. All results were well within specified limits.

The proposed finished product specifications have been adequately justified and comply with TGA requirements. They are considered adequate to ensure the quality of the finished product at release and throughout the shelf-life.

The tablets show good stability and a shelf life of 24 months when stored below 30ºC, is considered justified.

Formulation Development

The entirety of the F/TAF tablet development was performed using a solid oral tablet dosage form, manufactured using a dry granulation process equivalent to the intended commercial process. No major changes other than those associated with process scale-up, film-coating colour and tablet debossing were made to the tablet manufacturing process after the completion of the Phase I clinical trials.

The F/TAF tablet formulation evolved throughout clinical development. F/TAF core tablet formulations containing F/TAF 200/25 mg and F/TAF 200/40 mg were initially developed with a total tablet core weight of 450 mg and evaluated for their drug-drug interaction potential with efavirenz and cobicistat-boosted darunavir [Study GS-US-301-0101]. Based upon the clinical demonstration of the ability of cobicistat to boost TAF exposure, the 40 mg dose of TAF was discontinued in favour of a lower 10 mg TAF dose. Tablet formulation compositions were then adjusted to develop the lower fixed-dose combination 200/10 mg strength and to increase the relative drug load, resulting in a total weight of 350 mg for both the F/TAF 200/10 mg and 200/25 mg core tablets. A higher relative drug load was shown to improve the solid-state chemical stability of TAF.

It is noted that the tablet formulations used in the two pivotal bioavailability studies reviewed in this submission (GS-US-31-1472 and GS-US-31-1473) are equivalent to the two tablet formulations proposed for commercialisation.

During the development phase, two critical material attributes of the new drug substance, TAF fumarate were investigated; (1) Sensitivity to moisture; and (2) Particle size.

1. TAF fumarate was known for its susceptibility to hydrolysis in aqueous solutions as well as hydrolytic degradation after exposure to humidity and heat. Adequately justified strategies were incorporated into the selection of excipients, the manufacturing process, and the primary packaging configuration to limit the sources of moisture and their exposure to TAF fumarate.
2. Content uniformity and particle size concerns for TAF fumarate were adequately investigated and acceptable uniformity of the F/TAF 200/10 mg final powder blend and uniformity and dissolution of the corresponding tablets was demonstrated for a TAF fumarate D(v,0.9) particle size up to and exceeding 350 µm. The in-process control testing of the TAF fumarate drug substance (D(v,0.9) NMT 350 µm) ensures appropriate control of the content uniformity of TAF in the manufactured tablets.

Biopharmaceutics

Source of information

The draft Product Information (PI) document submitted.

Rate and extent of absorption

Following oral administration of the proposed drug product in HIV-1 infected patients, peak plasma concentrations were observed approximately 3 hours post-dose for emtricitabine (FTC), and 1 hour post-dose for tenofovir alafenamide (TAF).

Metabolism and distribution

Emtricitabine: In vitro binding of emtricitabine to human plasma proteins is <4% and is independent of concentration over the range of 0.02 to 200 µg/mL. The metabolites of emtricitabine include 3'-sulfoxide diastereomers and their glucuronic acid conjugate.

Tenofovir alafenamide: Metabolism is a major elimination pathway for tenofovir alafenamide in humans, accounting for > 80% of an oral dose. In vitro, TAF is not metabolised by cytochrome P450 isozymes CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. TAF is minimally metabolised by CYP3A4.
In vitro binding of tenofovir to human plasma proteins is less than 0.7% and is independent of concentration over the range of 0.01 to 25 µg/mL. Ex vivo binding of tenofovir alafenamide to human plasma proteins in samples collected during clinical studies was approximately 80%.

Notably, results from a Phase I study for Genvoya (GS-US-292-0101) showed that exposure to tenofovir alafenamide when administered as a component of a combination tablet containing cobicistat was approximately 2.2 to 2.6-fold that when administered alone. The greater exposure to tenofovir alafenamide when administered as a component of the combination tablet is presumed to result from the inhibition of tenofovir alafenamide intestinal secretory transport by cobicistat.

Mode, route and rate of elimination

Emtricitabine: Following administration of radiolabelled emtricitabine approximately 86% is recovered in the urine and 13% is recovered as metabolites. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of Emtriva, the plasma emtricitabine half-life is approximately 10 hours.

Tenofovir alafenamide: Tenofovir alafenamide is eliminated following metabolism to tenofovir. Tenofovir alafenamide and tenofovir have a median plasma half-life of 0.51 and 32.37 hours, respectively. Tenofovir is eliminated from the body by the kidneys by both glomerular filtration and active tubular secretion. Renal excretion of intact tenofovir alafenamide is a minor pathway with less than 1% of the dose eliminated in urine. The pharmacologically active metabolite, tenofovir diphosphate, has a half-life of 150 to 180 hours within PBMCs.

Active entity

The pharmacological activity is caused by the active entities emtricitabine and tenofovir.

Effects of food

Relative to fasting conditions, the administration of Descovy with a high fat meal (800 kilo calories (kcal), 50% fat) resulted in a decrease of FTC C_{max} and AUC_{last} of 27% and 9%, respectively; and a decrease in TAF C_{max} (15-37%) and an increase in AUC_{last} (17-77%). These changes are not considered clinically meaningful and Descovy can be administered without regard to food.

Summary of bioavailability and bioequivalence studies

Absolute bioavailability

The sponsor provided a justification for not providing any biopharmaceutic and/or absolute bioavailability data and this is considered acceptable, in part because of the similarity of the proposed product to the previously-approved Genvoya Tablet.

Comparative bioavailability

Two pivotal bioequivalence studies (GS-US-311-1472 and GS-US-311-1473) have been presented to demonstrate bioequivalent exposure of FTC and TAF between 200/10 mg and 200/25 mg respectively when administered simultaneously with elvitegravir 150 mg (EVG) and cobicistat 150 mg (COBI) under fed conditions and compared against the Genvoya E/C/F/TAF 150/150/200/10 mg fixed-dose combination (FDC) Tablet.

Study No. GS-US-311-1473 (Descovy 200/25 mg tablet)

This study compared the bioavailability of emtricitabine and tenofovir alafenamide, following the administration of:

- Test: a single-tablet of the proposed Emtricitabine and Tenofovir Alafenamide (200/25 mg) and
- Reference: a single-tablet of Genvoya Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (150/150/200/10 mg) Fixed-Dose Combination Tablets.

The study was a single-centre, randomised, open-label, single-dose, 2-period, crossover study in 116 healthy adult subjects.

The geometric least square mean (GLSM) ratios and corresponding 90% confidential intervals (CIs) of AUC_{last}, AUC_{inf}, and C_{max} for emtricitabine and TAF were contained within the 80-125% criteria specified for bioequivalence. Hence the emtricitabine and TAF components of the proposed Descovy emtricitabine /TAF 200/25 mg fixed-dose combination tablet are bioequivalent to the Genvoya E/C/F/TAF 150/150/200/10 mg fixed-dose combination tablet.

Study No. GS-US-311-1472 (Descovy 200/ 10 mg tablet)

This study compared the bioavailability of emtricitabine and tenofovir alafenamide, following the administration of:

- Test: a single-tablet of the proposed Emtricitabine and Tenofovir Alafenamide (200/10 mg), administered simultaneously with a emtricitabine (EVG) 150 tablet, and a cobicistat 150 mg tablet , and
- Reference: a single-tablet of Genvoya Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (150/150/200/10 mg) Fixed-Dose Combination Tablets (identical to that used in Study No. GS-US-311-1473, above).

The study was a single-centre, randomised, open-label, single-dose, 2-period, crossover study in 98 healthy adult subjects.

The geometric least square mean (GLSM) ratios and corresponding 90% CIs of AUC_{last}, AUC_{inf}, and C_{max} for emtricitabine and TAF were contained within the 80-125% criteria specified for bioequivalence. Hence the emtricitabine and TAF components of the proposed Descovy emtricitabine /TAF 200/10 mg fixed-dose combination tablet, administered simultaneously with EVG 150 mg and COBI 150 mg, are bioequivalent to the Genvoya E/C/F/TAF 150/150/200/10 mg fixed-dose combination tablet.

The PI statements reflecting these conclusions (Pharmacokinetics section) are considered adequately supported from a pharmaceutical chemistry perspective.

Quality summary and conclusions

All pharmaceutical chemistry issues raised during the initial evaluation of this application have now been satisfactorily resolved apart from:

- The company has been asked to revise the trade names to include the product strengths ('tradename 200/10'), in accordance with the TGA's 'Best practice guideline on prescription medicine labelling' and to incorporate these in revised PI and labels.
- Six extended Good Manufacturing Practice (GMP) clearances for overseas manufacturing sites are required.

It is anticipated that the sponsor will take steps to resolve the above issues prior to the Delegate's decision.

Pending resolution of the above issues, the proposed 'Descovy' emtricitabine and tenofovir alafenamide fumarate (200/25 mg and 200/10 mg) fixed dose combination tablets are recommended for registration with respect to pharmaceutical chemistry aspects.

III. Nonclinical findings

Introduction

The proposed maximum daily dose of Descovy is FTC/TAF 200/25 mg. However, the daily dose and dosage regimen for TAF has only been evaluated for 10 mg (Genvoya).

The sponsor claimed that 2 clinical studies demonstrated bioequivalence of TAF between Descovy and Genvoya.

The nonclinical studies for Genvoya, which were assessed for the registration of Descovy, were in accordance with regulatory guidelines for registration of a new chemical entity (TAF), and all pivotal safety studies were Good Laboratory Practice (GLP) compliant. The ICH M3 (R2) questions and answers guideline[4] states that toxicity studies are generally not warranted for drug combinations for HIV, and adequate scientific justification was provided for their absence. The FDA and European Medicines Agency (EMA) waived requirements for carcinogenicity and peri-postnatal studies due to lack of TAF exposure in rats and TgRasH2 mice, and lower TFV exposure after TAF administration.

Pharmacology

Studies submitted for the registration of Emtriva for FTC evaluation

Emtricitabine had marginal to no effect on any organ system investigated ex vivo (up to 100 μM) or in vivo (up to 1000 mg/kg PO, 100 mg/kg IP, and 38.5 mg/kg IV). Up to 100 μM FTC in the ex vivo studies was about 13 times higher than the FTC C_{max} (7.4 μM) at the proposed clinical dose. No plasma kinetic data were derived in the in vivo studies. Radioligand binding studies showed that FTC (10 μM) had no significant affinity for a wide range of receptors in several organs/tissues in vitro.

Emtricitabine was rapidly and extensively absorbed after oral (PO) administration for all species, including humans. Oral bioavailability was high in all species. Systemic clearance was lower in humans (0.2-0.5 L/kg/h) compared to mice (1.3-2.3 L/kg/h), rats (1.5-1.8 L/kg/h) and monkeys (0.7-1.5 L/kg/h), resulting in a prolonged elimination half-life.

[4]May 2012 EMA/CHMP/ICH/507008/2011

Volumes of distribution were similar across species, and indicated a wide tissue distribution throughout the body. The highest levels of drug-related radioactivity were found in the gastrointestinal and elimination organs, consistent with its passage through these tissues, and greatly exceeded plasma concentrations. Emtricitabine readily crossed the placental barrier to the developing fetus (40-50% of maternal plasma levels in mice and rabbits), suggesting direct in utero exposure in embryofetal development studies in these species.

Studies submitted for the registration of Genvoya for TAF evaluation

Absorption

Studies submitted for the registration of Genvoya found that TAF showed a dose dependent increase in forward permeability and a decrease in efflux ratio indicating saturable efflux transport, with the addition of CsA diminishing the efflux ration and increasing forward permeability.

The various in vivo absorption, single- or repeat-dose studies submitted for Genvoya demonstrated that TAF generates sufficient exposure in the animal models chosen and is rapidly converted to TVF after administration, with some accumulation of TFV-DP in the liver.

Distribution

In vitro analysis found TAF moderately bound in plasma, was well tolerated in mice and was rapidly distributed into tissues with most reaching maximum concentration by 1 h post-dose. Radioactivity was mainly retained in the liver, which is consistent with high hepatic extraction, and kidneys, with low levels of radioactivity observed in the brain and testis indicating minimal crossing into the blood: brain and blood: testis barrier.

Metabolism

Radiolabelled TAF underwent rapid biotransformation in mice via oxidation, hydrolysis, dealkylation, glucuronidation, and acetylation pathways, with hydrolysis of isopropylalanine and phenoxy groups being the major pathway. In mice, the major route of radioactive elimination was via faeces and renal elimination. Metabolism in dogs was indicated to be via oxidation, hydrolysis, dealkylation, and glucuronidation, with a major route elimination of radioactivity in bile duct-intact dogs via faeces. The major enzymes involved in intracellular conversion of TAF to TFV in PBMCs and primary human hepatocytes are Cathepsin A (CatA) and carboxylic ester hydrolase (CES1), respectively.

Excretion

Elimination of a large percentage of radioactivity was via bile in bile duct-cannulated dogs, indicating a major route of elimination is through biliary excretion and via faeces.

Pharmacokinetic drug interactions

FTC (Emtriva)

FTC is primarily eliminated in urine as unchanged drug with very little metabolism, especially very minor Phase I oxidative metabolism, which suggests that it has a low potential for pharmacokinetic drug interactions at the level of hepatic or other organ metabolism in humans. Since FTC is predominantly eliminated by the renal route, interaction with drugs that are also mainly eliminated by the kidney is a possibility. Studies submitted showed high stability of FTC in the presence of CYP450, Uridine Diphosphate Glucuronyltransferase (UDPGT) and Flavin-Containing Monooxygenase (FMO) systems, and suggest that any minor hepatic and extra-hepatic metabolism is unlikely to have a significant impact on its in vivo clearance in humans. Studies suggest

that FTC appears unlikely to alter the activity of CYP450 isoenzymes at clinically relevant concentrations, suggesting no significant potential for drug-drug interactions.

TAF

The stability of TAF in intestinal subcellular fractions was not markedly affected following incubation with HIV-1 protease inhibitors or CYP inhibitors, indicating that FTC is unlikely to interact with high specificity of the enzymes catalysing the phosphorylation of nucleoside analogues. TAF's lack of or weak potency for CYP inhibition indicates it will be unlikely to:

1. Significantly affect hepatic CYP3A activity;
2. Affect the metabolism of Elvitegravir (EVG) or cobicistat (COBI);
3. Activate either proline-x-proline (PXP) or aryl hydrocarbon (AhR) receptors;
4. Contribute to renal tubular cell loading of TFV, since it is not a substrate for renal transporters (organic anion transporters 1 and 3 (OAT1 and OAT3).
5. Be a pharmaceutical agent to mediate transporter drug interactions.

However, TAF is a substrate for intestinal efflux transporters (P-glycoprotein (P-gp); Breast Cancer Resistance Protein (BCRP)) and hepatic uptake transporters (OATP1B1; OATP1B3), its exposure may be affected by inhibitors and/or inducers of the intestinal efflux transporters and inhibitors or genetic polymorphisms of OATPs.

Pharmacology

No nonclinical efficacy studies with the proposed combination were submitted.

Toxicity

FTC (Emtriva)

A comprehensive package of toxicology studies was submitted in support of FTC registration, documenting acute toxicity in rodents, chronic toxicity in rodents and monkeys (up to 3-12 months), carcinogenicity studies in rodents (up to 2 years), genotoxicity in vitro and in vivo, reproductive toxicity in rodents and rabbits, and immunotoxicity in rats. Emtricitabine was generally well-tolerated in the toxicity studies.

Relative exposure in repeat-dose toxicity studies

Relative exposures (animal: human) in the repeat-dose studies are shown below in Table 3.

Table 3: Emtricitabine (table sourced from Emtriva Submission)

Species	Duration	Dose mg/kg / day	$AUC_{0\text{-}24\ h}$ µg.h/mL		Exposure ratio	
			♂	♀	♂	♀
Mouse	1 month (Day	120	103	73.9	11	8
		600	499	304	52	32

Species	Duration	Dose mg/kg / day	$AUC_{0\text{-}24\ h}$ µg.h/mL		Exposure ratio	
	32)	3000	1936	1516	201	157
	6 month (Week 26)	167	82.3	93.1	9	10
		500	248	284	26	29
		1500	732	899	76	93
	6 month (Day 175)	120	170	115	18	12
		600	586	491	61	51
		3000	2026	1549	210	161
	2 year (Week 26)	80	27.5	23.7	3	2
		250	90.9	91.7	9	10
		750	287	323	30	33
Rat	3 month (Day 90)	120	65.6	69.3	7	7
		600	329	362	34	38
		3000	1276	1646	132	171
	2 year (Week 26)	60	42.9	52.5	4	5
		200	137	171	14	18
		600	327	404	34	42
Monkey (as 2 equal divided doses)	1 month ♠ (Day 27)	80	63.2	67.2	7	7
		400	392	328	41	34
		2000	1460	1464	151	152
	3 month ♠ (Day 87)	40	26.2	29.0	3	3
		200	130	109	13	11
		1000	806	548	84	57
	12	50	18.1	33.3	2	3

Species	Duration	Dose mg/kg / day	$AUC_{0\text{-}24\ h}$ µg.h/mL		Exposure ratio	
	month ◊	200	97.2	97.8	10	10
	(Week 52)	500	274	238	28	25

Sampling time indicated in parenthesis. Exposure ratio = animal/human ratio of AUC. ♠Systemic exposure was determined over a single 6 hour sampling period ($AUC_{0\text{-}6\ h}$) therefore AUC values were doubled to account for the two equal doses given over the 24 hour period; ◊Estimated steady state $AUC_{0\text{-}24\ h}$ values presented due to short sampling time (6 h).

Exposure ($AUC_{0\text{-}24\ h}$) to FTC at the proposed clinical dose (200 mg PO, once daily) was estimated to be 9.65 µg.h/mL from 20 HIV-infected patients (Clinical Studies FTC-101 and FTC-303). No correction for protein binding was necessary, given the very low, similar extent of plasma protein binding (< 10%) in all species, including humans. The systemic FTC exposure at the highest doses employed in the chronic toxicity and carcinogenicity studies was associated with large multiples (25 to 210 times) of the anticipated clinical AUC. High dose selection was adequate based on pharmacokinetic endpoints (≥ 25-fold human AUC) for all studies.

TAF

A series of GLP compliant oral repeat-dose toxicity studies in mice (2, 13 weeks), rats (1, 4, 26 weeks), dogs (4, 39 weeks) and monkeys (4 weeks) were submitted. The studies were in accordance with ICH Guidelines[5] on repeat dose toxicity, where the repeat-dose toxicity studies have been conducted in at least two mammalian species (one non-rodent). The studies have been well designed and attained high relative systemic exposures (Table 4).

It should be noted that the highest clinical dose for TAF (25 mg) has not been investigated in humans.

Relative exposure in repeat-dose toxicity studies

Relative exposures (animal: human) in the repeat-dose studies are shown below in Table 4.

Table 4: Tenofovir alafenamide fumarate (Table sourced from Genvoya; Submission)

Species	Study duration drug	Sex	Study dose mg/kg/day	TFV $AUC_{ss\ 0\text{-}24h}$ ng·h/mL	TAF $AUC_{ss\ 0\text{-}24h}$ ng·h/mL	TFV/TAF exposure ratio#*
Mouse (CD-1)	13 weeks (TAF)	Combined	10	213	NC	0.72/NC
			30	1507	NC	5.14/NC

[5] ICH M3 (R2) Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals.

Species	Study duration drug	Sex	Study dose mg/kg/day	TFV $AUC_{ss\ 0-24h}$ ng·h/mL	TAF $AUC_{ss\ 0-24h}$ ng·h/mL	TFV/TAF exposure ratio#*
			100	7397	NC	25.24/NC
	2 years (TDF) [carcinogenicity]	Males	600	44,300	NA	151.19/NA
		Females		50,900	NA	173.72/NA
Rat (SD)	6 months (TAF)	Males	5	740	NA	2.52
			25	3530	NA	12.05
			100	15,930	NA	54.37
		Females	5	600	NA	2.05
			25	4000	NA	13.65
			100	15,140	NA	51.67
	2 years (TDF) [carcinogenicity]	Males	10/300	16,690	NA	56.96/NA
			30	2700	NA	9.22/NA
			100	6600	NA	22.53/NA
		Females	10/300	15,720	NA	53.65/NA
			30	3060	NA	10.44/NA
			100	7460	NA	25.46/NA
Dog (Beagle)	9 months (TAF)	Males	2	1300	90	4.44/0.44
			6	3890	1290	6.25/6.26
			18/12	14,900	2160	13.28/10.48
		Females	2	1070	60	3.65/0.29
			6	5010	780	17.10/3.79
			18/12	12,570	1750	42.90/8.50
Monkey Rhesus	4 weeks (TAF)	Combined	3	350	NC	1.19/NA
			30	5870	1030	20.03/5.0

Species	Study duration drug	Sex	Study dose mg/kg/day	TFV $AUC_{ss\ 0-24h}$ ng·h/mL	TAF $AUC_{ss\ 0-24h}$ ng·h/mL	TFV/TAF exposure ratio#*
Human healthy volunteers	steady state (TAF)	–	[10 mg]	293*	206*	–

* Mean steady-state AUC_{SS} in pivotal studies for TFV (GS-US-292-0104 and GS-US-292-0111);
** = animal: human plasma $AUC_{ss\ 0-24h}$; NC = Not calculated, NA = Not applicable.

Exposure ratios have been calculated based on TFV animal: human plasma $AUC_{0-24\ h}$. Human reference values are from Clinical Study GS-US-292-0104 and GS-US-292-0111. Relative exposure in mice was observed from very low at the lowest concentration of TAF used to very high at the highest TAF dose used. A 6 month rat study found that the relative exposure for TAF ranged from very low to extremely high, while the carcinogenicity study using TDF and compared to TFV steady state values in humans found that the relative exposure ranged from moderate to extremely high in the doses used for both sexes. The 9 month study in dogs observed exposure ratios ranging from subclinical to moderate. The exposures observed in the repeat-dose toxicity studies have greatly exceeded the human exposure levels observed in the clinical studies of TAF within the FDC.

There have been no safety, single and/or repeat dose toxicity studies submitted using the FDC. The absence of nonclinical safety studies with the FDC is in accordance with the relevant EU guideline[6].

Reproductive toxicity

No toxicological interactions are expected with the FDC and further studies are not required in accordance with the ICH M3 (R2) guideline[5]. Previously submitted studies for the registration of FTC and TAF demonstrated no significant effects on embryo-fetal development in rats or rabbits.

FTC (Emtriva)

A comprehensive reproductive toxicology assessment of FTC was conducted in mice and rabbits, with an additional male fertility study conducted in rats. All studies were conducted according to GLP, utilising adequate animal numbers and appropriate high doses (based on pharmacokinetic endpoints; refer below). Mice and rats were appropriate models for human reproductive toxicity testing. Placental transfer was demonstrated in both mice and rabbits and semen penetration was reported in healthy volunteers. No milk excretion studies were performed.

Estimated FTC exposure at the highest doses employed in the reproductive toxicity studies was associated with large multiples (52-132 times) of the anticipated clinical AUC (Table 5).

Emtricitabine had no effect on fertility or reproductive performance in female or male mice given PO doses up to 1000 mg/kg/day (52 and 77 times the anticipated clinical AUC) or male rats given PO doses up to 3000 mg/kg/day (132 times the anticipated clinical AUC). No effects on embryofetal development were observed in mice or rabbits, given PO emtricitabine doses up to 1000 mg/kg/day (52 and 130 times the anticipated clinical

[6] Committee for Medicinal Products for Human Use (CHMP) Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products (EMEA/CHMP/SWP/258498/2005, January 2008)

AUC). No effects on pre or post-natal development were also observed in mice at PO emtricitabine doses up to 1000 mg/kg/day (52 times the anticipated clinical AUC).

Relative exposure

Relative exposures (animal: human) in the reproductive toxicity studies are shown below in Table 5.

Table 5: Emtricitabine (Table sourced from Emtriva submission)

Species	Study/Treatment Duration	Dose mg/kg/day	Estimated $AUC_{0\text{-}24\ h}$ µg.h/mL	Estimated Exposure ratio
Mouse*	Fertility, Embryofetal Pre- & post-natal development (4 studies)	250	211♂ 141♀	22♂ 15♀
		500	416♂ 253♀	43♂ 26♀
		1000	739♂ 506♀	77♂ 52♀
Rat#	Male Fertility	150	82	8
		750	411	43
		3000	1276	132
Rabbit	Embryofetal development	100	87.3	9
		300	315	33
		1000	1258	130

Extrapolations made by the evaluator from toxicokinetic data obtained on Day 32 from the 1 month study in male and non-pregnant female mice (TOX599)* and on Day 90 from the 3 month study in male rats (TOX097)#.

TAF

A fertility and early embryonic development study in rats with TAF found no statistically significant treatment-related changes in organ weights for the epididymis, prostate, seminal vesicles or pituitary. Females were observed with no treatment-related differences in any reproductive parameters measured, or macroscopic findings at necropsy. There were no statistically significant differences in reproductive organ weights or treatment-related effects on any of the caesarean section parameters. Embryofetal development studies in rats and rabbits found no treatment-related evidence of embryolethality or teratogenicity. The perinatal/postnatal reproduction study in rats administered TDF found:

- No significant treatment-related behavioural evaluations of F1 generation pups.
- Mating performance of both F1 generation sexes was unaffected by treatment of F0 generation dams.
- Administration of TAF to the F0 generation dams resulted in no treatment-related effects in F1 generation female rats. Analysis of caesarean-sectioning and litter parameters found that litter averages for corpora lutea, implantations, litter sizes, live fetuses, early and late resorptions, fetal body weights, per cent resorbed conceptuses, and per cent live male fetuses were comparable to control.
- All placentae appeared normal.

Relative exposure

Relative exposures (animal: human) in the studies are shown below in Table 6 and 7.

Table 6: Tenofovir (TFV) after administration of TAF in embryofetal development studies (Table sourced from Genvoya)

Species	Study	Test Article	Test dose mg/kg/ day	TFV AUC_{0-t} ng·h/mL	TAF AUC_{0-t} ng·h/ mL	TFV/TAF exposure ratio#*
Rat (SD)	TX-120-2001	TAF	5	414	NC	1.41/NA
			100	20,588	NC	70.27/NA
			200	35,682	NC	121.78/NA
	TX-120-2002	TAF	25	2803	NC	9.57/NA
			100	17,392	242	59.36/1.17
			250	55,728	1382	190.20/6.71
Rabbit (NZW)	TX-120-2004	TAF	5	1560	NC	5.32/NA
			25	6014	NC	20.53/NA
			20	11,769	NC	40.17/NA
			100	23,525	NC	80.29/NA
	TX-120-2005	TAF	10	2018	NC	6.89/NA
			30	5005	1135	17.08/5.51
			100	27,251	11,043	93.00/53.61
Human healthy volunteers	steady state *	–	[10 mg]	293.00	206.0	–

* Mean steady-state AUC_{SS} in pivotal studies for TAF (GS-US-292-0104 and GS-US-292-0111);
*# = animal: human plasma AUC_{0-24h}; NC = Not calculated; NA = Not applicable.

Table 7: TFV/TAF exposure ratios at the NOAELs in reproductive toxicity studies

Target Organ Effect	Study	Species	Study duration	TAF NOAEL mg/kg /day	AUC_{ss} ng.h/mL NOAEL	Margin Relative to Human AUC_{ss}
					TFV/TAF	TFV[a]/TAF[b]
Fertility [c]	TX-120-	Rat	≤10 weeks	160	NA	NA

Target Organ Effect	Study	Species	Study duration	TAF NOAEL mg/kg /day	AUC_{ss} ng.h/mL NOAEL	Margin Relative to Human AUC_{ss}
	2012					
Embryo-fetal develop-ment [c]	TX-120-2002	Rat	12 days (GD6–GD17)	<100	17,392/ 242	59.36/1.17
	TX-120-2005	Rabbit	14 days (GD7–GD20)	100	27,251/ 11,043	93.01/53.61
Perinatal postnatal [c]	R990202	Rat	27 days (GD7–LD20)	150	11,716/ NA	39.99/NA

NA = not applicable; NC = insufficient data to calculate
a Predicted safety margin for TFV human exposure is based on pooled PK data from E/C/F/TAF Phase III pivotal studies GS-US-292-104 and GS-US-292-111 where the mean TFV AUCss = 293 ng.h/mL;
b Predicted safety margin for TAF human exposure is based on pooled PK data from E/C/F/TAF Phase III pivotal studies GS-US-292-104 and GS-US-292-111 where the mean TAF AUCss = 206 ng.h/mL;
c NOAEL for reproductive endpoints provided; AUC data is for maternal exposure; the peri/postnatal study was conducted with TDF not TAF

Pregnancy classification

The pregnancy category for FTC is B1[7] and for TAF is B3[8]. The sponsor has proposed Pregnancy Category B3 for Descovy, which is appropriate.

Nonclinical summary and conclusions

- The daily FTC dose of 200 mg in Descovy is the same as the approved once daily combination products, Truvada, Atripla, Stribild and Genvoya. TAF is an oral prodrug of tenofovir with an improved renal and bone toxicity profile to the previously registered tenofovir disoproxil fumarate (TDF). TAF has been registered at a daily dose of 10 mg for use in combination with emtricitabine (FTC), elvitegravir (EVG), and cobicistat (COBI) in Genvoya. The lower TAF dose of 10 mg TAF in Descovy is recommended in combination with a protease inhibitor (such as atazanavir, darunavir and lopinavir) boosted with either ritonavir or cobicistat, that substantially increase TAF exposure by inhibition of intestinal P-glycoprotein.

[7]Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have not shown evidence of an increased occurrence of fetal damage.
[8]Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

- The one new nonclinical secondary pharmacology study regarding TAF metabolites found that M28 showed very weak inhibition of HIV-1 replication with ≤ 2630 times lower inhibitory potency compared to TAF. In comparison, M18 showed higher antiviral activity, however values were ≤ 130 times lower in potency compared to TAF. The TAF metabolites had no observed cellular toxicity up to the highest tested drug concentration of 57 μM.
- No toxicity studies with FTC in combination with TAF were submitted, and adequate scientific justification was provided for their absence. The ICH M3 (R2) – questions and answers guideline[4] states '*It is accepted that combination toxicity studies on … HIV products are generally not warranted unless there is a specific cause for concern under clinically relevant conditions.*' Although the TAF high-dose of 25 mg/day in the FTC/TAF combination is higher than the TAF dose of 10 mg/day in Genvoya, the sponsor claimed that 2 pivotal clinical studies demonstrated bioequivalence of TAF and FTC between the 2 combinations.
- There are no nonclinical objections to the registration of Descovy, provided that the clinical evaluator is satisfied that bioequivalence has been demonstrated between TAF 10 mg (with ritonavir or cobicistat) and 25 mg (without booster) and emtricitabine in Descovy and Genvoya.
- Amendments to the draft Product Information were recommended but these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Standard of care for the treatment of HIV-1 infection uses combination antiretroviral therapy (ART) to suppress viral replication to below detectable limits, increase CD4 cell counts, and stop disease progression. For ART-naive HIV-1 infected patients, current treatment guidelines suggest that initial therapy consist of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTI) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI), or an integrase strand-transfer inhibitor (INSTI).

The success of potent and well-tolerated antiretroviral therapy (ART) means that morbidity and mortality in the HIV-infected population is increasingly driven by non-AIDS–associated co-morbidities. Clinical attention has become more focused on the optimisation of tolerability, long-term safety, and adherence to potent ART regimens. There remains a significant medical need for new, effective therapies that take into consideration the non-HIV co-morbidities, demographics of the aging HIV-infected population, antiretroviral (ARV) resistance, and regimen simplification. Chronic kidney disease is important, since observational studies have demonstrated a relationship between kidney disease and progression to AIDS and death. Moreover, HIV-associated nephropathy present in up to 30% of patients is a common cause of end-stage renal disease (ESRD) requiring dialysis and potential transplantation. ART with proven efficacy and safety in the both elderly and young patients is important; however there are limited data and treatment options are available in both populations. The elderly have increased risks for co-morbidities, including those related to renal function and bone mineralisation.

There are specific and complex challenges for the treatment of adolescents, especially related to adherence, and who also represent the population that will require ART for the longest time.

Given the duration for which a newly diagnosed person with HIV-1 may take an ART regimen throughout his or her lifetime, the F/TAF (Descovy) tablet, when administered with other antiretroviral agents, may provide the potential for the longevity of treatment that optimises tolerability, long-term safety and durable efficacy. For HIV-infected patients, Descovy may have advantages over the existing marketed product of Truvada; specifically less proteinuria, less need for renal monitoring and less impact on bone mineralisation relative to F/TDF treatment. The relatively low dose of TAF (10 mg versus TDF 300 mg) that is used in the boosted F/TAF also allows for co-formulation and co-administration with multiple other third ARV agents. This will allow HIV-infected, virologically suppressed patients to convert from a TDF-based regimen with possible renal and bone safety advantages.

Comment: The rationale for developing HIV-1 therapies that have long-term effectiveness while minimising non-HIV related morbidities is an essential goal.

Guidance

During pre-submission, the TGA noted that there were no clinical Phase III studies being submitted to support the clinical safety and efficacy of the proposed FDC. This was accepted by the sponsor who observed that the Phase III study results may be available at the second round question/follow-up stage of the submission process. The relevant study may be GS-US-311-1089 which is a Phase III study. The justification for not including Phase III data with this submission is based on the bioequivalence between the Genvoya clinical trial data and the bioavailability studies of Descovy which form the basis of this submission. The TGA noted that a lack of Phase III studies would be an evaluation issue, and a strong justification would be required at pre-submission.

The evaluator notes here that there remains the critically important issue of both a lack of direct clinical Phase III data in the target population and clinical trial data on the use of F/TAF with other antiretroviral agents that are boosted with Ritonavir, for example lopinavir, darunavir and atazanavir and those not boosted with either cobicistat or ritonavir. Preliminary bioequivalence data are available and presented in this assessment but there are no clinical data, except for the Genvoya clinical trial data. Study GS-US-120-0118 has been submitted as a Phase I bioequivalence drug-drug interaction study that will be discussed. This will be highlighted throughout the assessment and represents a major omission by the sponsor

TGA has adopted the following EU guidelines relevant to this submission:

- Guideline on the Clinical Development of Medicinal Products for the Treatment of HIV Infection EMEA/CPMP/EWP/633/02 Revision 2, which came into effect in June 2009 and as adopted by TGA in July 2009
- Points to Consider on Switching Between Superiority and Non inferiority CPMP/EWP/482/99, which came into effect in July 2000 and was adopted by TGA in June 2000
- Guideline on Reporting the Results of Population Pharmacokinetic Analyses. CHMP/EWP/185990/06 which came into effect in January 2008 and was adopted by TGA in February 2009

Contents of the clinical dossier

Scope of the clinical dossier

The submission is divided into two components

1. The two bioequivalence studies describing the bioequivalence of F/TAF as stand-alone FDC when compared with the Genvoya FDC, which contains F/TAF and for which there are substantial Phase III efficacy and safety data. The bioequivalence data are for the FDC F/TAF 200 mg/10 mg and F/TAF 200 mg/25 mg as studies GS-US-311-1472 and GS-US-311-1473. The additional study, not included in the Genvoya dossier, is the GS-US-311-1089, which is a preliminary PK report of TFV-DP in PBMCs in a cohort of patients who are enrolled in a pivotal Phase III clinical efficacy and safety study of Descovy versus Truvada and various third agents, both boosted and unboosted. This study has not been reported in full as it appears not to have been completed and analysed at the time of this submission.
2. The sponsor has included, in this submission, the total dossier for their Genvoya application in order to support their supposition that, as there is bioequivalence between F/TAF as an FDC and F/TAF as a component of Genvoya, the Phase III clinical trial data for Genvoya should be considered in the assessment of this Descovy application. In total, the sponsor has submitted 27 study dossiers of clinical trial data, in addition to clinical discussion papers. Many of these studies overlap in terms of their objectives and therefore cannot be clearly categorised as efficacy, safety or pharmacokinetics/pharmacodynamics. The assessor has focussed on the most relevant and pivotal studies for review as many of the studies submitted have identical designs, methodologies and analytical frameworks and geographic locations.

The following clinical data from the Genvoya application were submitted:

- 15 Phase I and Phase II studies of clinical pharmacology, including 10 that provided pharmacokinetic data and 5 that provided pharmacodynamic data. For further detailed analysis of these studies please refer to assessment for Genvoya (Genvoya AusPAR (https://www.tga.gov.au/auspar/auspar-tenofovir-alafenamide-fumarate-elvitegravir-cobicistat-emtricitabine)).
- 2 pivotal efficacy/safety studies GS-US-292-0104 and GS-US-292-0111. Both studies are randomised; double-blind trials conducted in HIV-1 infected adults and provide a direct comparison of E/C/F/TAF (Genvoya) with E/C/F/TDF (Stribild), the currently approved and marketed FDC.
- Additional studies include GS-US-292-0109; a Phase III, open-label study to evaluate the potential renal and/or bone mineralisation benefits of switching from a TDF-based regimen to the Genvoya in virologically-suppressed HIV-1 positive subjects; GS-US-292-0112; an open-label study of Genvoya in patients with mild to moderate renal impairment and GS-US-292-0106; an open-label study of Genvoya in HIV-infected treatment naive adolescents.
- Data on the bioequivalence of Descovy with a range of third antiretroviral agents are submitted in GS-US-120-0118.

Paediatric data

The submission included paediatric data as related to clinical studies on Genvoya, not specifically on Descovy. The Genvoya data are provided on HIV infected treatment naive adolescents 12 years old or greater (GS-US-292-0106). There are no bioequivalence or clinical data for Descovy in adolescents. This is especially relevant in relation to the recommended use of Descovy 200 mg/10 mg administered in combination with anti-

retroviral therapies boosted by Ritonavir and those in the 200 mg/25 mg dosage not boosted with either cobicistat or ritonavir.

Good clinical practice

The clinical studies reviewed in this evaluation were in compliance with CPMP/ICH/135/95 Note for Guidance on Good Clinical Practice. All of the studies were conducted under a United States Investigational New Drug Application (IND) and in accordance with recognised international scientific and ethical standards, including but not limited to the International Conference on Harmonisation guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the US Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312), and the European Community Directive 2001/20/EC.

The protocol, consent form, study subject information sheets, and advertisement were submitted by each investigator to a duly constituted Institutional Review Board for review and approval before study initiation. All patients provided written informed consent after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 8 below shows the studies relating to each pharmacokinetic topic.

Table 8: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	Primary Drug
PK in healthy adults	General PK Single dose	GS-US-292-0108	E/C/F/TAF
	Multi-dose	GS-US-292-0103	E/C/F/TAF
		GS-US-292-0101	TAF
	Bioequivalence† - Single dose	GS-US-311-1472 and GS-US-311-1473 GS-US-311-1089	F/TAF
	Food effect	GS-US-292-0110	E/C/F/TAF
PK in	Target HIV infected	GS-US-292-	TAF

PK topic	Subtopic	Study ID	Primary Drug
special populations	Multi-dose	0112	
	Hepatic impairment	GS-US-120-0114	TAF
	Renal impairment	GS-US-120-0108	E/C/F/TAF
	Adolescents (12-18 years of age)	GS-US-292-0106	E/C/F/TAF
	Elderly		
	Japanese Healthy subjects	GS-US-292-0108	E/C/F/TAF
PK interactions of Genvoya	Sertraline	GS-US-292-1316	E/C/F/TAF
	Sofosbuvir	GS-US-342-1167	E/C/F/TAF
	Efavirenz and Darunavir	GS-US-311-0101	TAF+COBI
	Rilpivirine	GS-US-120-0117	TAF
	ATV+RTV/DRV+RTV/LPR/r	GS-US-120-0118	TAF
	Methadone and Buprenorphine/Naloxone	GS-US-216-0125	EVG/COBI

† Bioequivalence of different formulations.
§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration. *Studies where the primary drug is E/C/F/TAF were submitted as part of the Genvoya assessment dossier.*

Evaluator's conclusions on pharmacokinetics

TAF is a prodrug of tenofovir which is metabolised intracellularly by CatA to tenofovir diphosphate, the form that has anti-viral activity. The reason the sponsor is applying to replace TDF with TAF is that TDF has higher and more prolonged plasma circulating levels of tenofovir which is associated with an increased risk of renal and bone toxicity. The PK studies submitted by the sponsor indicate that TAF at a dose of 10 mg in the STR (boosted by COBI or RTV) or 25 mg (unboosted) have a circulating level of tenofovir that is 90% less than the current dose of TDF 300 mg, which is the approved dose component of

Truvada. The sponsor has submitted an extensive number of studies to support this application which indicate that the pharmacokinetics of TAF are not affected by race, mild to moderate hepatic failure, renal failure or age (for teenagers more than 12 years of age). Specifically, the clinical trial with Japanese subjects GS-US-292-0108 demonstrated no PK effect of Japanese origins. PK studies conducted as a part of the pivotal efficacy/safety clinical trial, GS-US-292-0104 and GS-US-0111 show that the AUC_{tau} of E/C/F/TAF was 91% lower than tenofovir exposure compared with E/C/F/TDF and the PBMC AUC_{tau} was 4.1 times higher with administration of E/C/F/TAF compared with E/C/F/TDF.

The Study GS-US-311-1386 indicated that under fed conditions the overall TAF exposure increased by 75%, when compared with fasted conditions. While this increase may not be relevant in relation to the safety margin for dosing, it may be relevant for the role of boosting the 10 mg dose when substituted for the 25 mg dose. As it appears the 10 mg dose when increased by 75% following ingestion with food may be equal to the exposure when administered as with a booster. The difference is not made clear by the sponsor and requires some clarification. The observation that one subject had a spontaneous abortion after stopping the TAF dose, and this was related to the study drug was not addressed by the sponsor. This observation may require further clarification, especially in relation to the issue of increased exposure following ingestion with food. The study looking at boosters with TAF shows that DRV+Rtv does not increase TAF exposure while the other combination does increase TAF exposure. The study with boosters should be repeated in fasted state rather than fed state as it is not possible to determine the role of booster vs fed state.

In Study GS-US-311-1089 the results of F/TAF with the boosted third agents indicate the intracellular concentration of TFV-DP is around 2 to 3 times the concentration seen with FTC/TDF, rather than the four fold difference noted by the sponsor in the Genvoya studies. It is also noted that the concentration seems to be independent of the level of boosting agent used as the PBMC concentration is marginally lower with 200 mg of RTV (LPV/r) compared with boosting with RTV 100 mg (ATV+RTV and DRV+RTV). As the 95% CIs are so wide for many of the results, it would be useful to also have the median values. It appears the exposure of TAF does not have a proportional relationship with the intracellular TFV-DP concentration and may be interpreted as not totally dependent of boosting with RTV at the dose of 10 mg and that taking the 10 mg dose with food may have the same PBMC intracellular effect.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 9 shows the studies relating to each pharmacodynamic topic

Table 9: Submitted pharmacodynamic studies, primarily from Genvoya dossier; Not specifically for Descovy as taking with third agents, other than EVG/COBI

PD Topic	Subtopic	Study ID	Primary Drug
Primary Pharmacology	Effect on antiviral activity	GS-US-120-1101	TAF
	Effect on Antiviral activity of escalating doses	GS-US-120-0104	TAF
Secondary Pharmacology	Effect on QTcF	GS-US-120-0107	TAF
Population PD and PK-PD analyses	Healthy subjects	GS-US-292-0103 GS-US-292-0108 GS-US-292-0110	
	Target population ‡§	GS-US-292-0102 GS-US-292-0106 GS-US-292-0104 GS-US-292-0109 GS-US-292-0111 GS-US_292-0112	

* Indicates the primary aim of the study.
§ Subjects who would be eligible to receive the drug if approved for the proposed indication.
‡ And adolescents if applicable.

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacodynamics

The pharmacodynamic data presented in this section has been assessed from the Genvoya dossier as there are no specific pharmacodynamic studies related to Descovy. Study GS-US-311-1089 has data on the concentration of TFV-DP in PBMCs in the presence Descovy and a range of third agents, both boosted with RTV and unboosted. These pharmacokinetic data provide some indirect evidence that the pharmacodynamics of Descovy will be similar to those of Truvada, but this is not specifically addressed in the submission. It is possible that when the GS-US-311-1089 study is analysed there will be specific pharmacodynamic data to draw conclusions on Descovy.

Dosage selection for the pivotal studies

The pivotal studies submitted by the sponsor are two Phase I bioequivalence studies in healthy subjects. The studies have been presented in detail in Attachment 2 Extract from the CER.

Efficacy

No clinical efficacy studies using the FDC FTC/TAF have been submitted to directly support this application. The sponsor has provided two pivotal bioequivalence Studies GS-US-311-1472 and GS-US-311-1473. These Phase I studies in healthy adults do not address any issues of clinical efficacy. By demonstrating bioequivalence the sponsor is then using the Genvoya data on clinical efficacy to support the inference that Descovy as a standalone FDC will have the same clinical efficacy as Genvoya when combined with COBI and EVG (as in Genvoya) or with other boosted or unboosted anti-retroviral combinations.

The six clinical studies (GS-US-292-0102 (Phase II); GS-US-292-0104 (Phase III; naive); GS-US-292-0111 (Phase III; naive); GS-US-292-0109 (Phase III; virologically suppressed; switch study)

GS-US-292-0106 (single arm; adolescents); GS-US-292-0112 (renal impairment) submitted to support the application were conducted with the Genvoya FDC and not with the Descovy FDC. While this may indirectly support the clinical efficacy of Descovy, the studies do not address the issues of Descovy administered in any form other than as an FDC in combination with COBI and EVG. The clinical efficacy of this combination was assessed in the Genvoya submission (Genvoya AusPAR[9]).

This dossier contains exactly the same efficacy studies that were submitted for the Genvoya application. No other clinical efficacy Phase III studies are included in the dossier. Study GS-US-311-1089 is a Phase III clinical efficacy and safety study which would possibly provide data to support the application. A preliminary pharmacokinetic sub-study of this clinical trial is assessed in detail in this report, but it is limited to the concentration of TFV-DP in PBMCs.

Safety

Studies providing safety data

No specific studies were submitted to address safety issues in the target population. The pivotal bioequivalence Studies GS-US-311-1472 and GS-US-311-1473 were conducted in healthy adults and the food affect study was also conducted in healthy adults. These were the only studies where safety was directly observed, as a secondary outcome, in a population administered Descovy. GS-US-120-0118 is the other study where safety was observed was an open label study in healthy adults administered Descovy and a range of other anti-retroviral drugs, both boosted and non-boosted to measure pharmacokinetics. The studies on clinical safety have been assessed in detail in the Genvoya evaluation[10].There were 6 pivotal safety efficacy studies assessed in the Genvoya dossier and these are the same studies submitted in this dossier. These studies include the FDC E/C/F/TAF as Genvoya and compare the safety and efficacy to Stribild, previous approved by TGA. There are no Phase III clinical studies in the target population of HIV-1 infected patients, either adults or adolescents, in this dossier that consider the safety of the FDC Descovy.

Data are provided on safety parameters for TAF and FTC as separate components but not in the form which is the subject of this application.

[9] at https://www.tga.gov.au/auspar/auspar-tenofovir-alafenamide-fumarate-elvitegravir-cobicistat-emtricitabine

[10] see https://www.tga.gov.au/auspar/auspar-tenofovir-alafenamide-fumarate-elvitegravir-cobicistat-emtricitabine

Postmarketing data

There is no post-marketing experience with Descovy.

Evaluator's conclusions on safety

The safety data for this submission contains no data for the specific FDC of Descovy that is directly the subject of the application by the sponsor. There are data on the combination of the components of Descovy (FTC and TAF) as they are combined with EVG and COBI in Genvoya, but there are no safety data for the subject of the application which is to use Descovy in combination with a boosted or unboosted range of second anti-retroviral agents such as ATV, DRV, and LPV. The limited safety data presented as secondary outcomes in the Phase I studies of fed and fasting conditions in healthy adults and in the pharmacokinetic studies with other anti-retroviral agents in healthy adult subjects do not meet the criteria of having appropriately designed Phase III clinical study in the target population. The sponsor will need to submit a Phase III study before clinical safety can be assessed for Descovy. The limited safety data presented as secondary outcomes in the GS-US-120-0118 study give some assurance that with a single dose of FTC and TAF as separate agents with selected secondary agents, there are limited safety concerns, except with the ATV+RTV combination where there appears to be suggestion that the FTC+TAF may exacerbate the bilirubin increase usually attributed to the ATV. This cannot be confirmed in this short-term Phase I study, considering the limited exposure to both FTC-TAF and to ATV+RTV and given this study was conducted in healthy subjects. The case of a spontaneous abortion in the GS-US-311-1386 appears to have been a coincidental finding, but given the investigator attributed the cause of the spontaneous abortion to the FTC+TAF study drug it needs to be considered as a safety issue. No information is provided by the sponsor to elucidate this issue, even though it was classified as a study drug related SAE.

First round benefit-risk assessment

First round assessment of benefits

The benefits of Descovy in the proposed usage are:

- The benefit of Descovy is the same as the benefit of Truvada which is an FDC comprising a nucleotide and a nucleoside reverse transcriptase inhibitor. However, the actual benefits of Descovy cannot be assessed until a Phase III clinical trial has been conducted and the results assessed.
- Descovy will be available in two dose formulations to be administered with and without booster. The described advantage of Descovy as a once daily tablet that can be taken with or without food is a potential advantage.
- The apparent benefit of the TAF component of Descovy, when administered to HIV-1 infected patients may be to reduce the risk of renal impairment and reduction in bone mineral density. However, this benefit has only been shown with the Genvoya FDC, not when used with other anti-retroviral drugs. The apparent benefits of Descovy have been shown with the TAF 10 mg dose when booster with Cobicistat 150 mg. No data have been submitted on the clinical benefit of TAF 25 mg when administered with FTC and other non-boosted anti-retroviral agents.

First round assessment of risks

The risks of Descovy in the proposed usage are:

- It is not possible to determine the risks of Descovy in the absence of a Phase III clinical trial in the target population. It appears a Study GS-US-311-1089 may provide some data to clarify this issue when it is analysed and the results presented by the sponsor.

First round assessment of benefit-risk balance

The benefit-risk balance of Descovy, given the proposed usage, is favourable, when administered as the FDC, Genvoya. There are not sufficient data to determine the benefit-risk balance in the proposed usage, except where Descovy will be used in combination with EVG and COBI either separately or as the FDC Genvoya. This combination is under consideration by the TGA.

First round recommendation regarding authorisation

The first round recommendation is that Descovy should not be approved for its proposed usage. The recommendation is that Descovy can be approved for HIV-1 infection when administered in the FTC/TAF 200 mg/10 mg formulation in combination with Cobicistat and Elvitegravir, including adolescents 12 to 18 years of age. As there are no Phase III data on the clinical efficacy and safety of Descovy in adults and adolescents (12 to 18 years of age) when administered with other anti-retrovirals or boosted with ritonavir, this indication should not be approved until Phase III clinical trial data are available in the target population.

Clinical questions

Pharmacokinetics

The administration of FTC/TAF 200 mg/10 mg with DRV + RTV indicated there was no change in the exposure to TAF in healthy adults. The rationale for administration of the 10 mg dose formula of TAF is that its serum exposure will be increased when administered with a booster such as COBI or RTV and the mechanism for this increased serum exposure is that the booster will increase exposure and therefore increase the intracellular TFV level. However, the booster increased the TAF level by 91% with ATV + RTV and 47% with LPV/rtv, but not at all with the DRV + RTV or the Dolutegravir alone. This can see in the table below.

Table 10: TAF Study GS-US-120-0118 Statistical Comparisons of TAF PK Parameter Estimates Between Test and Reference Treatments (PK Analysis Sets)

TAF PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (90% CI), %
Cohort 1: FTC+TAF 10 mg +ATV+RTV (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{inf} (ng•h/mL)	164.8 (18.1)	91.6 (39.9)	188.92 (155.37, 229.71)
AUC_{last} (ng•h/mL)	162.6 (18.8)	89.5 (40.8)	191.06 (155.08, 235.40)
Cmax (ng/mL)	146.5 (46.9)	76.8 (29.4)	176.72 (128.19, 243.63)
Cohort 2: FTC+TAF 10 mg +DRV+RTV (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{inf} (ng•h/mL)	80.5 (30.4)	80.0 (41.8)	104.34 (84.14, 129.39)

TAF PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (90% CI), %
AUC_{last} (ng•h/mL)	78.6 (30.9)	77.4 (43.6)	106.27 (83.59, 135.10)
Cmax (ng/mL)	102.3 (46.5)	73.4 (49.4)	141.80 (96.11, 209.22)
Cohort 3: FTC+TAF 10 mg +LPV/r (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{inf} (ng•h/mL)	122.5 (42.7)	82.7 (34.0)	144.75 (114.15, 183.55)
AUC_{last} (ng•h/mL)	120.8 (43.9)	80.0 (34.1)	146.73 (116.60, 184.65)
Cmax (ng/mL)	157.5 (39.4)	68.7 (28.7)	218.97 (171.88, 278.97)
Cohort 4: FTC+TAF 10 mg +DTG (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{inf} (ng•h/mL)	105.1 (31.7)	100.9 (51.2)	116.62 (93.49, 145.48)
AUC_{last} (ng•h/mL)	103.0 (30.6)	98.5 (53.3)	119.02 (95.83, 147.82)
Cmax (ng/mL)	83.4 (30.6)	79.9 (60.6)	123.64 (87.79, 174.13)

Therefore, there appears to be a completely inconsistent pattern of boosting with Ritonavir. The PK studies have been conducted in healthy adults, not in the target population who may have factors associated with bowel absorption of TAF in the presence of ritonavir. Can the sponsor explain the inconsistencies of boosting by ritonavir and why all studies have been conducted in fed populations when it is noted that TAF exposure increases by around 80% in the fed state as compared with the fasted state. Furthermore, there are no PK studies in the adolescent population for which the sponsor is seeking approval, especially given the possibility of dose adjustment requirements in young adolescent populations.

Regarding Study GS-US-311-1089 the results of F/TAF with the boosted third agents indicate the intracellular concentration of TFV-DP is around 2 to 3 times the concentration seen with FTC/TDF, rather than the four fold difference noted by the sponsor in the Genvoya studies. It is also noted that the concentration seems to be independent of the level of boosting agent used as the PBMC concentration is marginally lower with 200 mg of RTV (LPV/r) compared with boosting with RTV 100 mg (ATV+RTV and DRV+RTV). As the 95% CIs are so wide for many of the results, it would be useful to also have the median values. It appears the exposure of TAF does not have a proportional relationship with the intracellular TFV-DP concentration and may be interpreted as not totally dependent of boosting with RTV at the dose of 10 mg and that taking the 10 mg dose with food may have the same PBMC intracellular effect.

Pharmacodynamics

The Study GS-US-311-1386 conducted in healthy adult subjects investigated the effect of fed and fasted conditions on the exposure to TAF and FTC. This study, which is detailed in Attachment 2, demonstrated that the exposure of TAF 25 mg in a fed condition was increased by 75%. This is about the same level of increased exposure that was observed with boosted TAF. It is therefore unclear as to why the dose of TAF of 10 mg is recommended for unboosted when it would seem biologically plausible that a 10 mg dose with a meal would result in similar exposure to TAF as would be gained by administration

of a 25 mg dose. This discrepancy should be explained by the sponsor. The sponsor is requested to explain why all studies have been conducted in fed populations, rather than assessing the effect of food on the pharmacodynamics as it appears the increased exposure of TAF in the fed state, as compared with the fasted state as this may be an important factor in determining the intracellular concentration of TAF.

Efficacy

The efficacy of Descovy has not been shown in this submission, other than as a component of Genvoya. The efficacy of Descovy should be reported in the results of a Phase III clinical trial. It is necessary for the sponsor to provide evidence of efficacy of Descovy in combination with anti-retrovirals, other than EVG and boosted with other than COBI.

Safety

- The safety of Descovy is implied in this submission but requires controlled Phase III clinical trial scrutiny to document safety in the target population.
- The association between TAF 25 mg and spontaneous abortion should be clarified.
- The association between administration of Descovy, in combination with ATV+RTV and increase bilirubin, beyond the expected level, should be clarified.

Second round evaluation of clinical data submitted in response to questions

For details of the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Descovy in the proposed usage are:

- Non-inferior to Truvada when administered with a broad range of third agents.
- Statistically significant safety advantages over Truvada in terms of improvement in bone mineral density. There was a decrease in bone turnover after switching from FTC/TDF to F/TAF. Decreases from baseline were observed in serum levels of the bone formation biomarker P1NP and also in PTH, a hormone involved in bone formation and resorption, in the F/TAF+3rd Agent group compared with minimal changes in both parameters in the FTC/TDF+3rd Agent group at Week 48 ($p < 0.001$ for the differences between groups). In addition, decreases from baseline were observed in serum levels of the bone resorption biomarker CTx, which were greater in the F/TAF+3rd Agent group compared with the FTC/TDF+3rd Agent at Week 48 ($p < 0.001$).

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Descovy in the proposed usage are:

- There is a lack of specific clinical evidence for efficacy and safety in an adolescent population. However, data presented by the sponsor related to Genvoya and evidence from Study GS-US-311-1089, indicates that efficacy and safety of Descovy should be similar to that of Truvada and probably also have the same BMD and renal advantages of Descovy, when used with third agents. Study GS-US-292-0106 involved administering Genvoya to ART naïve adolescents and demonstrated similar efficacy (91.3%) to Descovy administered with third agents to HIV-1 infected adults and also to ART naïve adults. The similarity of both efficacy and safety in these populations provides a level of confidence that Descovy, when administered with third agents to adolescents, will have a similar level of efficacy and safety. While this level of confidence is reasonable, it is supported by inference, not by direct clinical trial evidence.
- There were increases from baseline in fasting values of total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, and triglycerides in the F/TAF+3rd Agent group, while these parameters had little change in the FTC/TDF+3rd Agent group at both Week 24 and Week 48 ($p < 0.001$ for the differences between groups for total cholesterol, LDL cholesterol, and HDL cholesterol; $p = 0.016$ at Week 24 and $p = 0.002$ at Week 48 for triglycerides). However, because TDF is known to reduce blood lipids, the apparent 'increases' in blood lipids observed with Descovy in GS-US-311-1089, compared with Truvada may be due to blood lipids returning to their pre-Truvada levels.

Second round assessment of benefit-risk balance

The benefit-risk balance of Descovy, given the proposed usage, is favourable.

Second round recommendation regarding authorisation

The evaluator recommends authorisation of Descovy.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP (Version: 0.1, dated 1 April 2015) with an Australian Specific Annex (ASA) as Annex 13 (undated) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 11.

Table 11: Summary of ongoing summary of safety concerns

	Safety concern
Important identified risks	Post-treatment hepatic flares in HIV/HBV co-infected patients
Important potential risk	None
Missing information	Long-term safety information in adults and adolescents
	Safety in children aged 4 weeks to < 18 years
	Safety in pregnancy
	Safety in lactation
	Safety in severe hepatic impairment (CPT Class C)
	Safety in patients with HBV and HCV co-infection

CPT=Child-Pugh-Turcotte; HBV=Hepatitis B virus; HPC=Hepatitis C virus; HIV=human immunodeficiency virus

Pharmacovigilance plan

The ASA proposes only routine pharmacovigilance activities to monitor all the specified safety concerns and missing information. However, the ASA states that routine activities include ongoing and planned clinical studies, including a Phase II/III switch study and the Antiretroviral Pregnancy Registry.

Risk minimisation activities

The ASA proposes routine risk minimisation activities for all the specified safety concerns and missing information are sufficient, except for the missing information: '*Long-term safety information in adults and adolescents*' for which no risk minimisation is proposed.

Reconciliation of issues outlined in the RMP report

Table 12 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised and an evaluation of the sponsor's responses.

Table 12: Reconciliation of issues outlined in the RMP Evaluation Report

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
The sponsor should apply appropriate document control (such as version and date) to the ASA.	The sponsor states*: 'Gilead has amended the ASA with version and date'.*	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
Safety considerations may be raised by the nonclinical and clinical evaluators. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	The sponsor states: '*Gilead confirms that no safety considerations were raised by the nonclinical and clinical evaluators'.*	This is acceptable, although it would be expected that safety data from Study GS-US-311-1089 will be included in the EU-RMP when this document is next updated.
The sponsor should systematically identify and justify any differences between the summaries of the safety concerns and missing information for the similar products, Descovy and Genvoya. Any subsequent changes to the summary of the safety concerns and missing information for Descovy as specified in the ASA must be entirely captured in a revised ASA to be provided to the TGA for review. In addition consideration must be given to proposing appropriate pharmacovigilance and risk minimisation activities for any new ongoing safety concerns, to be reflected accordingly in the revised ASA.	The sponsor has prepared a summary of the differences between the safety concerns and missing information for these similar products and concluded that no changes to the summary of the safety concerns or missing information are required, apart from the addition of safety in patients with severe renal impairment as missing information.	This is acceptable.
The sponsor should provide an assurance that the draft protocol for the planned clinical study of E/C/F/TAF in ARV treatment-experienced, HIV-1 infected patients from 6 to < 18 years of age (GS-US-292-0113) will be attached to the ASA once it becomes available.	The sponsor states *Study GS-US-292-0113 was planned to study E/C/F/TAF in ARV treatment-experienced, HIV-1 infected patients from 6 to < 18 years of age. Virologically suppressed, HIV-infected children 6 to < 12 years of age are now being enrolled into Cohort 2 of the ongoing, pediatric Study GS-US-292-0106 rather than Study GS-*	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	US-292-0113. Study GS-US-292-0113 has been renumbered as Study GS-US-292-1515 for administrative reasons. As younger children 6 to < 12 years of age are now being enrolled in Cohort 2 of Study GS-US-292-0106, Study GS-US-292-1515 is enrolling virologically suppressed, HIV-infected adolescents 12 to < 18 years of age only. The protocols for Studies GS-US-292-0106 and GS-US-292-1515 have been provided to the TGA in response to the Genvoya tablets application.	
Table 6: 'Summary Table of Pharmacovigilance Activities and Risk Minimization Measures' of the ASA is not consistent with Table 4-1: 'Required Additional Pharmacovigilance Activities (Category 3)' and Table 4-2: 'Stated Additional Pharmacovigilance Activities (Category 4)' of the EU-RMP, in that all the additional pharmacovigilance activities for the specified safety concerns and missing information have been erroneously classified as routine pharmacovigilance. These errors should be corrected in a revised ASA to be consistent with the EU-RMP.	The sponsor states: '*Gilead has revised the classification of pharmacovigilance activities accordingly'.*	This is acceptable.

Summary of recommendations

It is considered that the sponsor's response to the TGA has adequately addressed all of the issues identified in the RMP evaluation report.

Outstanding issues

Issues in relation to the RMP

There are no outstanding issues in relation to the RMP for this submission.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Key changes to the updated RMP

In their response to the TGA the sponsor provided an updated ASA (Version: 0.2, dated January 2016) Key changes from the versions evaluated at Round 1 are summarised below (Table 13).

Table 13: Key changes to the ASA

Document	Key change
ASA	Amend the missing information: 'Safety in children aged 4 weeks to < 18 years' to 'Safety in children aged 4 weeks to < 12 years' in order to align with the proposed indication statement. In regard to additional pharmacovigilance activities for the missing information: 'Safety in children aged 4 weeks to < 12 years', virologically suppressed, HIV-infected children 6 to < 12 years of age are now being enrolled into Cohort 2 of the ongoing, paediatric Study GS-US-292-0106 rather than planned Study GS-US-292-0113. Add 'Safety in patients with severe renal impairment' as missing information.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

> *The European Risk Management Plan (Version: 0.1, dated 1 April 2015), as qualified by the Australian Specific Annex (Version: 0.2, dated January 2016), must be implemented.*

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There are no outstanding issues in relation to the quality part for this submission. GMP clearance at all sites needs confirmation prior to finalisation. Pharmaceutical Subcommittee (PSC) advice was not sought.

Nonclinical

There are no nonclinical objections to the registration of Descovy. The TGA nonclinical reports prepared for Descovy and Genvoya both apply to this submission. Pregnancy class is B3. Recommendations for PI have been detailed.

Clinical

The clinical development program for Genvoya (EVG/COBI/FTC/TAF 150/150/200/10) is also the proposed evidence of clinical efficacy of Descovy.

Genvoya has been approved (ARTG 233398) for the following indication:

> *Genvoya is indicated as a single tablet regimen for the treatment of HIV-1 infection in adults and adolescents aged 12 years of age and older with body weight at least 35 kg who are either treatment-naïve; or virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen (see CLINICAL TRIALS). Patients must not have a history of treatment failure or known mutations associated with resistance to the antiretroviral components of Genvoya.*

The Genvoya clinical dossier included two pivotal Phase III efficacy trials in treatment naïve patients (GS-US-292-0104 and GS-US-292-0111) comparing Genvoya (EVG/COBI/FTC/TAF 150/150/200/10) versus Stribild (EVG/COBI/FTC/TDF 150/150/200/300), one Phase III TDF-based regimen/Genvoya switching study in treatment experienced patients (GS-US-292-0109), one Phase II Genvoya efficacy study (GS-US-292-0102, including patients rolled over from DRV/COBI containing regimen in another Study GS-US-299-0102), one Genvoya renal impairment study (GS-US-292-0112), one Genvoya study in treatment-naïve HIV-infected 12 to <18 years old adolescents (GS-US-292-0106) and one FTC/TAF drug interaction study (GS-US-120-0118).

The PK information, to be included in the Descovy PI, is also based on data already assessed in the Genvoya dossier including in vitro data, dose selection (GS-US-120-0104) and comparability of TAF 10 mg boosted versus 25 mg unboosted (studies GS-US-292-0103, GS-US-292-0101 and GS-US-311-0101), among others.

The Genvoya clinical evaluation report, Delegate's Request for Advisory Committee on Prescription Medicines (ACPM) advice and the ACPM minutes for Genvoya were provided to the ACPM and should be read in conjunction with this Delegate's Overview. Only the Studies GS-US-292-0106 (adolescents study) and GS-US-120-0118 (drug interactions) from the Genvoya dossier are also briefly discussed in this Delegate's Overview.

From regulatory standpoint, Descovy is not a generic of Truvada. Hence its assessment as a standalone product, based principally on the Genvoya clinical dossier, has limitations of inference for example, Genvoya studies do not address the issue of Descovy (200/10) administered with any ART other than with EVG/COBI or use of Descovy (200/25) unboosted with third anti-retroviral agents. In other words, the Genvoya dossier can only go so far as to establish the efficacy of FTC/TDF (200/10) in combination with EVG/COB (150/150) either as fixed dose or in free combination.

Pharmacokinetics

The PI data particular to this submission consists of two Bioequivalence (BE) studies of Descovy versus Genvoya. The FTC/TAF 200/10 and 200/25 formulations for which BE to EVG/COBI/FTC/TAF was demonstrated, are identical to the proposed commercial FTC/TAF tablets.

The 2 bioequivalence (BE) studies of Descovy (Study GS-US-311-1472 and Study GS-US-311-1473) were carried out as the bridging evidence linking Descovy (FTC/FTC) to Genvoya (EVG/COBI/FTC/TAF) implying that Descovy (FTC/TAF) has same clinical efficacy as Genvoya when combined with COBI and EVG in a free combination or when combined with various other anti-retroviral agents with or without boosting with cobicistat or ritonavir. The latter extrapolation is more problematic.

Both studies were single dose, 2-way crossover studies in healthy volunteers under fed conditions:

Study GS-US-311-1472 satisfactorily demonstrated the BE of FTC and TAF for FTC/TAF (200/10) plus EVG/COBI (150/150) versus EVG/COBI/FTC/TAF (150/150/200/10) (Table 14).

Table 14: Study GS-US-311-1472 results

Study GS-US-311-1472	Ratio of means (%)	90%CI
TAF		
C_{max}	96.86	89.36, 104.99
AUC_{inf}	98.34	94.81, 101.00
FTC		
C_{max}	99.57	96.78, 102.44
AUC_{inf}	100.67	98.24, 103.16

This study supports the use of TAF 10 mg dose when boosting (with COBI).

Study GS-US-311-1473 satisfactorily demonstrated the BE of FTC and TAF for unboosted FTC/TAF (200/25) versus EVG/COBI/FTC/TAF (150/150/200/10) (Table 15).

Table 16: Study GS-US-311-1473 results

Study GS-US-311-1473	Ratio of means (%)	90%CI
TAF		
C_{max}	103.63	95.46, 112.49
AUC_{inf}	98.54	94.61, 102.62
FTC		
C_{max}	97.26	94.57, 100.03
AUC_{inf}	90.20	89.06, 91.35

This study supports the use of TAF 25 mg dose without boosting (with COBI).

Study GS-US-311-1386 examined the PK of FTC/TAF (200/25) under fasting and fed conditions and (together with a Genvoya Study GS-US-292-0110) provides evidence of a moderate food effect.

This was a single dose, 2-way crossover study in healthy volunteers in which administration of a single dose of FTC/TAF (200/25) indicated (fed/fasting) approximately 75% higher TAF AUC under fed conditions (Table 17).

Table 17: Study GS-US-311-1386 results

Study GS-US-311-1386	Ratio of means (%)	90%CI
TAF		

Study GS-US-311-1386	Ratio of means (%)	90%CI
C_{max}	84.53	74.92, 95.27
AUC_{inf}	175.38	163.93, 187.63
FTC		
C_{max}	73.50	69.26, 78.00
AUC_{inf}	91.11	88.84, 93.44

No direct clinical data on the food effect with boosted 25/10 formulation (except as part of EVG/COBI/FTC/TAF) or boosting with RTV are available.

The sponsor's response and the evaluator's comment are noted and the Delegate agrees that food effect may not be used as a recommendation for dose-related administration of in the context of Descovy use in combination with other ART.

- **Study GS-US-120-0118** was a drug interaction study evaluated in the Genvoya dossier.

Descovy (FTC/TAF) is proposed for administration with a booster (using FTC/TAF 200/10) or without booster (using FTC/TAF 25 mg). The recommendation to use with COBI as a booster is supported by Genvoya data. The Study GS-US-120-0118 addresses the issue of use of FTC/TDF (200/10) with RTV as a booster.

In this steady-state study in (N=40) healthy volunteers, FTC/TAF (200/10) was given with or without various RTV-boosted HIV protease inhibitor (PI) containing regimens of atazanavir (ATV/r), darunavir (DRV/r) and (lopinavir) LPV/r, or unboosted integrase strand-transfer inhibitor dolutegravir (DTG).

The results (ratio of means with/without boosting) indicated higher systemic exposure of TFV, more consistently than TAF, on co-administration with the 3 boosted PIs. There was no effect on co-administration with DTG (Table 18D).

Table 18A: FTC/TAF (200/10) plus ATV/r (300/100)

TAF	Ratio (%)	90%CI (%)	TVF	Ratio (%)	90%CI (%)
AUC_{last}	191.06	155.08, 235.40	AUC_{last}	247.77	216.82, 283.14
C_{max}	176.72	128.19, 243.63	C_{max}	212.35	185.83, 242.65

Table 18B: FTC/TAF (200/10) plus DRV/r (800/100)

TAF	Ratio (%)	90%CI (%)	TVF	Ratio (%)	90%CI (%)
AUC_{last}	106.27	83.59, 135.10	AUC_{last}	242.74	207.17, 284.41

TAF	Ratio (%)	90%CI (%)	TVF	Ratio (%)	90%CI (%)
C_{max}	141.80	96.11, 209.22	C_{max}	241.54	198.10, 294.51

Table 18C: FTC/TAF (200/10) plus LPV/r (200/50)

TAF	Ratio (%)	90%CI (%)	TVF	Ratio (%)	90%CI (%)
AUC_{last}	146.73	116.60, 184.65	AUC_{last}	322.01	298.02, 347.93
C_{max}	218.97	172.88, 278.97	C_{max}	374.52	319.28, 439.30

Table 18D: FTC/TAF (200/10) plus DTG (50 mg)

TAF	Ratio (%)	90%CI (%)	TVF	Ratio (%)	90%CI (%)
AUC_{last}	119.02	95.83, 147.82	AUC_{last}	104.25	98.74, 110.08
C_{max}	123.64	87.79, 174.13	C_{max}	109.91	96.39, 125.32

The co-administration also did not affect the pharmacokinetics of the three PIs or DTG. The pharmacokinetics of FTC were not reported but are not expected to be affected.

Overall, the study supports the use of FTC/TAF (200/100) with RTV containing ART regimens. Please also see the Descovy CER and Genvoya documents in relation to other established and expected drug interactions including clinically important drug interactions with P-gp inducers (such as rifampicin) which may reduce, or inhibitors (for example, ketoconazole) which may increase bioavailability of TAF to clinically important extent.

Clinical efficacy

As noted earlier, the clinical dossier for Genvoya is also the proposed supporting evidence of clinical efficacy of Descovy. The only clinical study particular to Descovy included in the dossier was Study GS-US-311-1089 which is discussed below. In addition, the adolescent study from Genvoya dossier is noted below:

Study GS-US-311-1089 is an ongoing Phase III study for which the interim results have become available for review within this submission. This is a randomised, double-blind trial to assess switching from FTC/TDF (200/300) to FTC/TAF (200/25 or 200/10) versus maintaining FTC/TDF in HIV-1 patients who were virologically suppressed (HIV-1 RNA <50 copies/mL for ≥ 6 months prior to enrolment) and were currently on stable (for at least previous 6 months) ART regimens containing FTC/TDF. The purpose of the study was to establish the non-inferiority of FTC/TAF with a broad range of 3rd agents compared to continuing FTC/TDF with a similar broad range of 3rd agents.

At the time of this report, a total of 668 patients were randomised to two groups (334 each in group) i.e. FTC/TAF+3rd agent group and FTC/TDF+3rd agent group. At Week 48, the efficacy results supported the conclusion that switching to FTC/TAF+3rd agent was non-inferior to maintaining FTC/TDF+3rd agent as shown below (Table 19).

Table 19: Virologic Outcomes at Week 48 using Snapshot Algorithm and HIV-1 RNA <50 copies/mL (Full Analysis Set)

	F/TAF+ 3rd Agent (N = 333)	FTC/TDF+ 3rd Agent (N = 330)	F/TAF vs. FTC/TDF	
			P-value[a]	Difference in Proportions (95.002% CI)[b]
Virologic Success at Week 48				
HIV-1 RNA < 50 copies/mL	314 (94.3%)	307 (93.0%)	0.50	1.3% (−2.5% to 5.1%)
Virologic Failure at Week 48	1 (0.3%)	5 (1.5%)		
HIV-1 RNA ≥ 50 copies/mL	0	5 (1.5%)	—	—
Discontinued Study Drug Due to Lack of Efficacy	0	0	—	—
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL[c]	1 (0.3%)	0	—	—
Added New ARV	0	0	—	—
No Virologic Data in Week 48 Window	18 (5.4%)	18 (5.5%)	—	—
Discontinued Study Drug Due to AE/Death	7 (2.1%)	3 (0.9%)	—	—
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[c]	10 (3.0%)	15 (4.5%)	—	—
Missing Data During Window but on Study Drug	1 (0.3%)	0	—	—

a P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by third agent (ritonavir-boosted protease inhibitors vs. others).
b Difference in percentages of virologic success between treatment groups and its 95.002% CI were calculated based on the MH proportions adjusted by the third agent stratum.
c Discontinuation due to other reasons included subjects who prematurely discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study termination by sponsor.
Week 48 window is between Day 294 and 377 (inclusive).

Although not predefined, the virologic success rates were also similar between treatment groups for individual 3rd agents: (Table 20).

Table 20: Virologic Success rate (HIV-1 RNA < 50 copies/mL) at Week 48 using Snapshot Algorithm by 3rd agent (Full Analysis Set)

	n	F/TAF+3rd Agent (N = 333)	n	FTC/TDF+3rd Agent (N = 330)
DRV/r	84	90.5%	82	91.5%
ATV/r	53	90.6%	50	94.0%
LPV/r	18	100%	18	100%
NVP	74	97.3%	66	98.5%
RAL	66	95.5%	73	89.0%
DTG	26	96.2%	23	91.3%
EFV	8	100%	6	83.3%
RPV	3	100%	6	83.3%
MVC	1	100%	6	100%

The resistance analysis was comprised of 3 patients who experienced confirmed virologic rebound in first 48 weeks of study. This included 2 patients from FTC/TAF+3r agent group and one patient from FTC/TDF+3rd agent group.

In FTC/TAF+3rd agent group, 1 patient developed an NRTI resistance mutation to FTC (M184V) and one patient had pre-existing NNRTI resistance mutations detected.

In the FTC/TDF+3rd agent group, one patient had a pre-existing primary PI resistance mutation (Q58E) detected without phenotypic resistance to the 3rd agent (DRV/r).

The PK component of the study included measurement of intracellular levels of TFV-DP. The results at 48 weeks are indicative of higher intracellular concentration of TFV-DP with TCF/TAF (200/10 with boosted regimes and 200/25 with unboosted regimes) versus FTC/TDF (200/300) (Table 21).

Table 21: Median Intracellular TFV-DP levels between Test and Reference Treatments by Co-administered Third Agent (PBMC PK Analysis Set)

Intracellular PBMC TFV-DP concentration (pg/10^6 cells)	F/TAF (Test)		FTC/TDF (Reference)	
	n	Median	n	Median
Overall unboosted	156	154.500	148	32.650
+DTG	24	104.000	19	34.900
+EFV	8	50.900	6	31.200
+MVC	1	268.000	5	28.200
+NVP	65	157.000	56	32.650
+RAL	55	159.00	57	31.700
+RPV	3	271.000	5	21.800
Overall boosted	148	92.450	117	23.000
+ATV+RTV	50	133.000	34	23.050
+DRV+RTV	82	71.850	69	21.000
+LPV/r	16	86.650	14	37.650

Source: 311-1089 CSR Table 55.1, Table 56.1.1, 56.1.2, 56.1.3, 56.1.4

The study is study continuing to 96 weeks with respect to the clinical outcomes.

Study GS-US-292-0106 was a Phase II/III, single arm study of treatment with Genvoya (N=50) in HIV-1 infected, antiretroviral treatment-naive adolescents (12 to <18 years of age, body weight >35 kg) over 48 weeks with the objective of assessing pharmacokinetics, safety, tolerability and antiviral activity of EVG/COBI/FTC/TA. Some salient findings were as follows:

TAF plasma exposure in adolescents was consistent with the range of exposure associated with antiviral activity in adults, despite being lower than that in adults. TFV exposure in adolescents was similar to that in adults. FTC exposure in adolescents was consistent with adult data.

At Week 48, HIV-1 RNA <50 copies/mL virologic response rate (92%) was similar to response rates reported in trials of treatment naïve HIV-1 infected adults. The tolerability and the adverse effects profile was similar to that reported in adults.

While noting that there were no data on the use of Descovy with ART agents other than EVG/COBI, either administered alone or boosted with RTV, the clinical evaluator has observed that 'it is, however, reasonable to extrapolate the PK data from the GS-US-311-1089 study to adolescents, given there is no major differences between PK data from the Genvoya clinical study in adolescents (GS-US-292-0106) and the 1089 study'. The Delegate agrees with this assessment.

Clinical safety

A total of 2497 HIV-1 infected patients received FTC/TAF containing regimen as EVG/COBI/FTC/TAF (n=2394 with median exposure of 48 weeks) or DRV/COBI/FTC/TAF (n=103 with a median exposure of 68 weeks) in Phase II and III clinical trials of Genvoya. The occurrence of ocular icterus in 10 subjects (100) in FTC/TAF+ATV/r versus none in the control arm in Study GS-US-120-0118 is noted.

Detailed safety results for Study GS-US-311-1089 have been provided and reviewed in the Descovy clinical evaluation report and are indicative of an adverse effects profile of Descovy is similar to Truvada when administered with a range of 3rd ART. A clinically meaningful advantage with respect to bone and renal safety was reported in FTC/TAF+3rd agent arm compared with FTC/TDF+3rd agent arm.

Risk management plan

A Risk Management Plan (EU-RMP (Version 0.1, dated 1 April 2015) with an Australian Specific Annex (ASA) as Annex 13) is applicable to this submission. There are no outstanding issues in relation to the RMP.

ACSOM advice was not sought.

Risk-benefit analysis

Delegate's summary and comments

1. This is a Type B submission for registration of a new Fixed Dose Combination product Descovy (Emtricitabine/Tenofovir alafenamide fumarate) in two oral tablet strengths (200/10 mg and 200/25 mg) for the treatment of HIV-1 infection in patients above 12 years of age. It may be used in combination with boosted (using Cobicistat (COBI) or Ritonavir (RTV) as pharmacokinetic enhancer) or unboosted antiretroviral therapy.
2. Emtricitabine (FTC) and the earlier Tenofovir disoproxil fumarate (TDF) are established NRTI class of anti-HIV agents in current clinical practice. The newer form Tenofovir alafenamide fumarate (TAF) has also received approval in Australia as a component in the Fixed Dose Combination Genvoya (Elvitegravir/ COBI/FTC/TAF 150/150/200/10 mg) in the treatment of HIV-1 infection in patients 12 years of age and above.
3. Descovy (FTC/TAF 200/10 mg and 200/25 mg), which is the subject of this submission, has received approval in the USA (treatment of HIV-1 infection in patients 12 years of age and above) and has received positive opinion from the Committee for Medicinal Products for Human Use (CHMP) in the EU (expected use in the treatment of HIV-1 infection in patients 12 years and above with body weight at least 35 kg).
4. This submission for Descovy (FTC/TAF) relies principally on the previously evaluated dossier for Genvoya (EVG/COBI/FTC/TAF) in regard to all aspects such as Chemistry (quality), Toxicology (nonclinical), Pharmacodynamics and Pharmacokinetics including drug interactions and, Clinical Efficacy/Safety.
5. Absolute Bioavailability of TAF is expected to be around 40% based on animal data. The chemical structures of TAF and TDF are shown under Quality findings above.

TAF is subject to food effect and to boosting with strong P-gp inhibitors such as ketoconazole whereby the bioavailability may approach above 75%.

A Descovy specific food study (GS-US-311-1386) in this dossier and a previously evaluated drug-drug interactions study (GS-US-120-0118) provided further useful information about pharmacokinetic behaviour expected of TAF.

Known drug interactions based on Genvoya dossier also apply to Descovy such as clinically significant reduction in bioavailability with strong P-gp inducers such as rifampicin.

The data also support co-administration of TAF with the tested HIV protease inhibitors (DRV, ATV, LPV and RTV) but not the HCV protease inhibitors that are inhibitors of cathepsin A (for example, telaprevir and boceprevir).

TAF (10-25 mg) provides advantage over TDF (300 mg) by its ability to achieve very high intracellular levels of the active TFV-DP in target cells with much lower clinical doses. This has a clinically useful expectation of improved bone and renal effects profile.

Two Bioequivalence (BE) studies of Descovy were specific to this submission and successfully demonstrated the bioequivalence of Descovy (200/10 boosted with EVG/COBI 150/150 in study GS-US-311-1472) and Descovy (200/25 unboosted in study GS-US-311-1473) to the FTC and TAF components in Genvoya (EVG/COBI/FTC/TAF 150/150/200/10) using the conventional criterion of 90%CI for the ratio of means to be within 80-125% equivalence margin for both AUC and C_{max}. Thus these BE studies established a link for the clinical efficacy of Genvoya (including both the treatment new patients, that is treatment initiation and treatment-switching in virally suppressed patients who are currently stable on ART) to be extrapolated to Descovy for its use with EVG/COBI, but not its use with other antiretroviral agents or boosting with RTV.

However, results of a Phase III clinical efficacy/safety study (GS-US-311-1089) were made available for review in this submission. This was a randomised, double blind, controlled trial in which virally suppressed stable patients were switched from FTC/TDF (200/300) to FTC/TAF (200/10 or 200/25) component within their current ART regimen.

The results showed that viral suppression continued to be successfully maintained. At Week 48, the overall proportion of patients with HIV-1 RNA <50 copies/mL in FTC/TAF+3rd agent group was 314/333 (94.3%) compared to 93.0% (307/330) in FTC/TDF+3rd agent group. The treatment difference was 1.3% (95%CI from -2.5% to +5.1%) indicating non-inferiority. The response rates were also similar between the two groups for individual 3rd agents, although the numbers were too small for some agents.

HIV-1 RNA <50 copies/mL response rates by individual 3rd ART agents in patients with available plasma TAF levels (in FTC/TAF+3rd agent group) were as follows indicative effective maintenance of response in both groups (Table 22).

Table 22: HIV-1 RNA <50 copies/mL response rates by individual 3rd ART agents in patients with available plasma TAF levels (in FTC/TAF+3rd agent group)

			F/TAF+3rd Agent with Available PK Data		FTC/TDF+3rd Agent (N = 330)	
Third Agent	n	Mean (%CV) TAF AUC_{tau} (ng*h/mL)	n	Percent of Virologic Success at Week 48 (HIV-1 RNA < 50 copies/mL)	n	Percent of Virologic Success at Week 48 (HIV-1 RNA < 50 copies/mL)
ATV/r	44	149.6 (50.8)	53	90.6	50	94.0
DRV/r	72	73.5 (41.0)	84	90.5	82	91.5
DTG	25	155.6 (18.5)	26	96.2	23	91.3
EFV	6	141.6 (18.7)	8	100	6	83.3
LPV/r	15	89.8 (25.0)	18	100	18	100
MVC	1	191.3 (NA)	1	100	6	100
NVP	67	167.4 (32.1)	74	97.3	66	98.5
RAL	61	170.8 (37.2)	66	95.5	73	89.0
RPV	1	273.1 (NA)	3	100	6	83.3

NA = not applicable

The results of measurement of intracellular TFV-DP levels in PBMCs in a subgroup in this study was consistent with the expected high PBMC intracellular levels with FTC/TAF (200/10 with boosted ART regimes and 200/25 with unboosted ART regimes) compared with the administration of FTC/TDF.

The resistance analysis comprised 3 patients who experienced confirmed virologic rebound in first 48 weeks of study:

- In FTC/TAF+3rd agent group, these included 1 patient who developed an NRTI resistance mutation to FTC (M184V) and one patient who had pre-existing NNRTI resistance mutations detected.
- In FTC/TDF+3rd agent group, one patient had a pre-existing primary PI resistance mutation (Q58E) detected without phenotypic resistance to the 3rd agent (DRV/r).

The GS-US-311-1089 is continuing to 96 weeks. The study report should be submitted to TGA for evaluation when available.

Overall, clinical adverse effect profile with TAF is similar to that with TDF. The clinical efficacy/safety study GS-US-311-1089 in this dossier provided additional safety data including a demonstration of safer bone and renal profile with TAF. A Risk Management Plan applies to this submission.

The issue of differential TAF boosting with RTV versus boosting with COBI was addressed in the sponsor's response to TGA questions using data from different studies and was indicative (for example, ATV/r versus ARV/COBI) but not conclusive (overall limited data) of similar magnitude of boosting using RTV or COBI as shown below (Table 23).

Table 23: TAF boosting with RTV versus boosting with COBI

Concomitant Drug	TAF AUC_{last} (ng•h/mL) GLSMs by Treatment		GLSM Ratio (90% CI) Test/Reference (%)	Study
	Test: TAF + Concomitant Drug	Reference: TAF		
DRV + COBI*	221.95	227.30	97.64 (80.38, 118.62)	GS-US-311-0101
DRV+RTV	74.76	70.35	106.27 (83.59, 135.10)	GS-US-120-0118
ATV + COBI	182.21	104.08	175.06 (154.81, 197.96)	GS-US-311-1388
ATV+RTV	160.28	83.89	191.06 (155.08, 235.40)	GS-US-120-0118
LPV/r	111.07	75.70	146.73 (116.60, 184.65)	GS-US-120-0118

GLSM = geometric least square mean
* F/TAF 25 mg was used in this study, all other studies used F/TAF 10 mg.

Additional arguments explaining the differential absorption of TAF with RTV and COBI include mixed inductive/inhibitory effect on P-gp in the presence of full ART combination therapy, that is, influence of the 3rd agent.

However, with the availability of efficacy results in the treatment-switching study GS-US-311-1089, the differential boosting with COBI or RTV is considered clinically acceptable.

Descovy is proposed for use in HIV-1 patients 12 years of age and above. There are no direct PK/bioequivalence data or clinical data for Descovy in adolescents.

The proposed use in adolescents is inferred from the study GS-US-292-0106 which was part of the Genvoya dossier and led to the approval of Genvoya for use in this age group. Extrapolation to Descovy is considered clinically appropriate.

Delegate's conclusion and recommendation

The quality, nonclinical and RMP evaluators support approval of Descovy (FTC/TAF 200/10, 200/25) for the proposed use. The issues raised by the clinical evaluator have been satisfactorily addressed in the second round evaluation and the evaluator recommends approval. This was, in the main, a result of availability of 48 weeks data in the Descovy switching Study GS-US-311-1089.

Overall, the totality of evidence from Genvoya and Descovy dossiers supports approval for the proposed use from age 12 years and above, except where the proposed broad wording of indication may imply use beyond supplied data, that is previously failed patients.

The following therapeutic indication, along the lines approved for Genvoya, with additional note, is recommended:

> *Descovy is indicated, in combination with other antiretroviral agents, for the treatment of HIV-1 infection in adults and adolescents aged 12 years of age and older with body weight at least 35 kg. The patients must not have a history of treatment failure or known mutations associated with resistance to the individual components of Descovy.*
>
> *Descovy is not for use in Pre-Exposure Prophylaxis (PrEP).*

The recommended dosing is as proposed by the sponsor.

Summary of issues

- Adequacy of Genvoya clinical dossier as evidence of clinical efficacy/safety of Descovy in combination with ART agents other than EVG and boosting with agent other than COBI.
- Use Descovy 200/10 mg boosted versus 200/20 unboosted.
- Effect of food and concomitant drugs on bioavailability of TAF.
- Use in adolescents 12 years and above based on Genvoya study and approval for Genvoya.
- Proposed indication implies use in failed patients.

Proposed action

The Delegate had no reason to say, at this time, that the application for Descovy should not be approved for registration.

Request for ACPM advice

The ACPM is requested to provide advice on the following specific issues:

1. Does the committee consider the totality of evidence, including principal reliance on Genvoya dossier but with significant additional data specific to the current submission, sufficient to support the use Descovy, including use in adolescents aged 12 years and above?
2. Does the committee support the exclusion of 'patients with history or treatment failure' in the therapeutic indication or prefer a broader indication as proposed by the sponsor?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision including recommendations for the Australian PI.

Response from Sponsor

Summary

Descovy represents a new once-daily nucleos(t)ide reverse transcriptase inhibitor (N(t)RTI) backbone option for HIV-infected patients without any known mutations associated with resistance to the individual components of Descovy, including patients with mild to moderate renal impairment, and pediatric patients 12 years of age and older. Descovy is intended to be co-prescribed with a third agent from either the integrase strand-transfer inhibitor (INSTI), protease inhibitor (PI) or nonnucleoside reverse transcriptase inhibitor (NNRTI) classes.

In ART-naive or virologically suppressed patients, a fixed dose combination (FDC) that is a complete regimen (that is, single-tablet regimen) is generally preferred; however, the availability of a stand-alone nucleoside reverse transcriptase inhibitor (NRTI) backbone is important as it allows flexibility for clinicians to combine Descovy with other third antiretroviral (ARV) agents to address individual patient's specific efficacy or safety/tolerability concerns.

Truvada (FTC/TDF 200/300, AUST R 107072) has become the most-widely prescribed backbone in Australia in a wide range of patient populations, including treatment experienced patients. The FTC/TDF combination is contained in four of the five 'Recommended' antiretroviral therapy (ART) starting regimens cited in the current ASHM

guidelines[11]. It has been recognised, however, that some patients have TDF-associated renal and/or bone toxicities that may preclude its long-term use. Gilead proposes to address the unmet medical need for a highly efficacious N(t)RTI backbone that has an improved renal and bone safety profile compared with TDF-containing backbones, while maintaining the advantages of TDF over other NRTIs. Tenofovir alafenamide (TAF) is a new prodrug of tenofovir (TFV) and its active moiety is intracellular tenofovir diphosphate (TFV-DP). Compared to TDF, TAF achieves higher intracellular TFV-DP and lower plasma TFV exposures. By reducing plasma concentration of TFV by over 90% (versus TDF) at the clinical doses, TAF reduces the concentration-dependent renal and bone toxicity.

Descovy is similar to the TGA-approved Truvada, and is likely to replace it in practice following the availability of Descovy. The key difference between Descovy and Truvada is the different prodrug of TFV, that is, TAF versus TDF. Descovy has an improved renal and bone safety profile compared with Truvada, while maintaining the advantages of TDF over other NRTIs.

Gilead agrees with the Delegates recommendation that the application for Descovy should be approved for registration. Further, Gilead considers that the established efficacy and safety profile for Descovy tablets supports an indication for use in combination with other antiretroviral agents for the treatment of HIV-1 infection as follows:

> *Descovy is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and paediatric patients 12 years of age and older with body weight at least 35 kg without any known mutations associated with resistance to the individual components of Descovy.*
>
> *Descovy is not for use in Pre-Exposure Prophylaxis (PrEP).*

The indication statement as proposed by the Delegate that excludes 'patients with history of treatment failure' unnecessarily restricts the use of Descovy by excluding patients who may otherwise benefit from the potent efficacy and improved safety profile of Descovy.

Discussion of Delegate's comments

The Delegates' comments are presented in bold print, and are followed by Gilead's response.

ACPM advice being sought by the TGA Delegate

1. Does the Committee consider the totality of evidence, including principal reliance on Genvoya dossier but with significant additional data specific to the current submission, sufficient to support the use Descovy, including use in adolescents aged 12 years and above?

The registration strategy for Descovy is based on 2 pivotal bioequivalence studies that pharmacokinetically bridge the exposure of the parent drugs, FTC and TAF, between each of the Descovy tablet strengths (200/25 mg and 200/10 mg) to the FDC tablet, Genvoya (E/C/F/TAF), which has been shown to be efficacious, safe, and well tolerated in a broad spectrum of HIV-infected patients including renally impaired patients and adolescents aged 12 years and above. This was supported further with results from the Phase III randomised, controlled Study GS-US-311-1089 (Study 1089), which evaluated Descovy in virologically suppressed patients on regimens containing Truvada in combination with different third ARV agents.

[11] ASHM 2015 Australian Commentary on the US Department of Health and Human Services (DHHS) Guidelines for the use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. 20 August. Accessed Jan 2016. http://arv.ashm.org.au/.

In accordance with the TGA adopted industry guideline on the investigation of bioequivalence[12], Gilead considers that no further studies are required for the purposes of registration. This approach also ensures Descovy is made available to patients without unnecessary delay.

Gilead agrees with the Delegates' conclusion that the totality of evidence from the Genvoya and Descovy dossiers supports the approval of Descovy for the proposed use from age 12 years and above with body weight at least 35 kg.

2. Does the Committee support the exclusion of 'patients with history of treatment failure' in the therapeutic indication or prefer a broader indication as proposed by the sponsor?

Gilead believes that the indication statement as proposed by the Delegate that excludes 'patients with history of treatment failure' unnecessarily restricts the use of Descovy by excluding patients who may otherwise benefit from the potent efficacy and improved safety profile of Descovy.

Descovy will be used as a backbone for ART in combination with various 3rd agents. This is different from single tablet regimens, such as Genvoya, in which the 3rd agent is fixed to EVG+COBI. The flexibility to use Descovy with various 3rd agents (other than EVG+COBI) is an important benefit to patients who need a more individualised antiretroviral regimen, such as those who fail the available single tablet regimens (for example, Atripla [EFV/FTC/TDF, ATR]) as first line treatment.

Importantly, when patients experience treatment failure, one cannot assume that the treatment failure is due to virologic reasons (for example, emergent resistance), as it is more often due to other reasons (such as poor adherence, transient blips or low level viremia, adverse events, co-morbidities, difficulty in accessing drugs, etc). In these patients, clinicians often continue or restart the same regimen, and patients achieve virologic suppression, while resistance mutations rarely develop. In addition, as long as there is no documented or suspected mutation(s) that confer HIV-1 resistance to a given antiretroviral agent(s), there is no reason to think that such agent(s) will not be active. For example, when patients experience treatment failure while receiving ATR due to emergent K103N mutation, some clinicians will choose to construct a second line regimen using Descovy plus boosted PI, as long as there were no emergent resistances to FTC or TAF. Furthermore, Gilead considers that restricting the use of an antiretroviral agent(s) that is likely active against the HIV-1 in patients with history of treatment failure can severely limit the clinicians' ability to construct an effective regimen for them.

Gilead considers that previous treatment failure specifically due to emergent resistance to either or both components of Descovy is the only scenario where Descovy should not be used. The indication as proposed by Gilead addresses this scenario while preserving maximal treatment options for other patients.

Descovy is similar to the TGA-approved Truvada, and is likely to replace it in practice following the availability of Descovy. Truvada was approved by the TGA in 2005 based on a bioequivalence (BE) strategy similar to Descovy tablets, and is currently indicated *for the treatment of HIV infected adults over the age of 18 years, in combination with other antiretroviral agents.* Truvada has become the most-widely prescribed backbone in Australia in a wide range of patient populations, including treatment experienced patients. The FTC/TDF combination is contained in four of the five 'Recommended' anti-retroviral (ART) starting regimens cited in the current ASHM guidelines.

As such, Gilead considers that the established efficacy and safety profile for Descovy tablets supports an indication for use in combination with other antiretroviral agents for the treatment of HIV-1 infection as follows:

[12] CPMP/EWP/QWP/1401/98 Rev. 1/Corr** Guideline on the investigation of bioequivalence.

Descovy is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and paediatric patients 12 years of age and older with body weight at least 35 kg without any known mutations associated with resistance to the individual components of Descovy.

Descovy is not for use in Pre-Exposure Prophylaxis (PrEP).

3. The Committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision including recommendations for the Australian PI.

Gilead has noted the review of the PI and has amended the PI accordingly.

The Descovy PI was developed to be consistent with the approved Australian Truvada PI, whilst taking into account the improved safety profile of TAF compared to TDF.

Summary of issues raised by the TGA Delegate

The Delegates' comments are presented in bold print, and are followed by Gilead's response.

Adequacy of Genvoya clinical dossier as evidence of clinical efficacy/safety of Descovy in combination with ART agents other than EVG and boosting with agent other than COBI

As discussed above in the response to Point 1, the registration strategy for Descovy is based on 2 pivotal bioequivalence studies that pharmacokinetically bridge the exposure of FTC and TAF, between each of the Descovy tablet strengths (200/25 mg and 200/10 mg) to the Genvoya FDC tablet, which has been shown to be efficacious, safe, and well tolerated in a broad spectrum of HIV-infected patients including renally impaired patients and adolescents aged 12 years and above.

Gilead agrees with the Delegates' conclusion that the totality of evidence from the Genvoya and Descovy dossiers supports the approval of Descovy for the proposed use from age 12 years and above with body weight at least 35 kg.

Acceptability of the BE strategy as outlined above has been validated by the recent approval of Descovy tablets by the US FDA, European Medicines Agency and Health Canada. An update of the overseas regulatory status is provided.

Use Descovy 200/10 mg boosted vs 200/25 unboosted

The recommendation for Descovy administration is 200/10 mg for boosted regimens (with COBI or RTV), and 200/25 mg for unboosted regimens. The recommended dose of Descovy per the third ARV agent is based on ensuring that patients have a TAF systemic exposure that is within the range of the reference exposure achieved with TAF 10 mg when administered as Genvoya, for which an extensive efficacy and safety database exists. The different TAF dose (10 or 25 mg) is based on whether or not the coadministered third agent has any clinically relevant effect on TAF (for example, via inhibition of intestinal P-gp). Given the wide range of safe and efficacious TAF exposure established in the single-agent proof-of-concept study (Study GS-US-120-0104), in the Phase II study of D/C/F/TAF (Study GS-US-299-0102), and Phase II and Phase III studies of Genvoya, where uniformly high rates of virologic success were observed across all quartiles of TAF exposures (AUC_{tau} from 47 to 1869 ng•h/mL) in ART-naive patients with no trends in exposure response relationship, the variability in TAF-equivalent dose by the third agent is considered acceptable.

The dosing recommendations for Descovy (Table 23) are further supported by intracellular TFV-DP data from patients receiving Descovy 200/25 mg with an unboosted third agent (DTG, EFV, MVC, NVP, RAL or RPV) or Descovy 200/10 mg with a RTV-boosted

PI in Study GS-US-311-1089, which tracked closely with TAF-equivalent dose (Table 1) and were several fold higher than the intracellular TFV-DP concentrations following FTC/TDF administration.

Table 23: Dose recommendations for F/TAF with potential concomitant antiretroviral drugs

ARV Drug	Recommended F/TAF Dose (mg)	TAF-Equivalent Dose[a] (mg)
EFV	200/25	12[b]
RPV		24
DTG[c]		17[b]/30
RAL		-[d]
NVP		-[d]
ATV+COBI	200/10	-[e]
ATV+RTV		19
DRV+COBI		11
DRV+RTV		11
LPV/r		15

a TAF-Equivalent Dose calculated based on percentage change in TAF AUC with/without coadministered drug (assuming that both drugs are administered concurrently). Expected exposure in fed state unless otherwise noted.
b Expected exposure in fasted state.
c Because DTG may be administered without regard to food, expected exposures are provided for both the fed and fasted states.
d No DDI study performed. Dosing recommendation based on the nonclinical profiles of TAF and the specified ARV.
e No DDI study performed. Dosing recommendation extrapolated based on nonclinical information and the DDI study between TAF and ATV+RTV.

Effect of food and concomitant drugs on bioavailability of TAF

Food has minimum effect on TAF when Genvoya is administered, but increases TAF absorption when Descovy is administered without a booster. TAF exposure (AUC_{last}) increased by approximately 77% when Descovy (200/25 mg) was administered following a high fat meal compared with fasted conditions. However, the totality of TAF plasma PK data from DDI studies, and the wide range of safe and efficacious TAF exposures established in the proof-of-concept study and Phase II and Phase III Genvoya studies suggest that the difference of TAF exposure when administered with or without food is not considered clinically meaningful. As such, Gilead considers that Descovy can be administered without regard to food. This approach also has practical implication, since as an NRTI-backbone to be used in combination with third agents, Descovy will be administered under the food condition dictated by the co-administered third agent (that is, with or without food, or without regard to food). The Descovy 200/10 mg tablet is recommended to be used with boosted PIs, which are to be taken with food. The Descovy 200/25 mg tablet is expected to be used in combination with unboosted third agents. Most of those third agents are to be taken without regard to food (dolutegravir [DTG], raltegravir [RAL], nevirapine [NVP], and maraviroc [MVC]), with specific food restrictions that apply only for rilpivirine (RPV) (taken with a meal) and EFV (taken on an empty stomach). As such, the flexibility to use Descovy without regard to food makes it convenient for patients and clinicians to pair it with any third agent regardless of the food requirement.

A similar approach has been taken in making recommendations on the use of concomitant non ARV drugs. Generally, given the wide range of TAF exposures seen in clinical studies, concomitant non ARV drugs that lead to higher TAF exposures when coadministered with Descovy were considered more acceptable (for example, for itraconazole 'no dose adjustment is required') than those that lead to lower TAF exposures (for example, for rifampicin 'Coadministration of rifabutin, rifampicin, or rifapentine is not recommended.'). Table 12 within the proposed PI provides details of the 'Established and Other Potentially Significant Drug Interactions'.

Use in adolescents 12 years and above based on Genvoya study and approval for Genvoya

Clinical data, including pharmacokinetic data are available in the adolescent population for Genvoya Study GS-US-292-0106 (Study 0106). The exposures of the individual components and TFV in adolescents upon administration of Genvoya are comparable to those in adults. The submission for Descovy is based on 2 pivotal bioequivalence studies) that provide a pharmacokinetic (PK) bridge between the 2 Descovy tablet strengths (200/25 mg and 200/10 mg) and Genvoya. Both studies have demonstrated bioequivalent exposure of Descovy when compared to Genvoya within the guidance specified bioequivalence limit of 80 to 125% for the ratio of exposure parameters, therefore in line with current guidance, additional special population studies are not required for Descovy. Genvoya (AUST R 233398) was approved by the TGA on 12 January 2016 for use in adults and adolescents aged 12 years of age and older with body weight at least 35 kg.

Gilead agrees with the Delegates' conclusion that extrapolation of results from Study 0106 to Descovy is considered clinically appropriate.

Proposed indication implies use in failed patients

As discussed above in response to Point 2, exclusion of '*patients with history of treatment failure*' in the therapeutic indication, as proposed by the Delegate unreasonably restricts the use of Descovy tablets in instances where efficacy can still be expected. In fact, Gilead expects that Descovy will be used in patients with history of treatment failure. For example, in patients who have failed 1 or 2 single tablet regimens (for example, Atripla or Eviplera) due to emergent resistance to the third agent but not to the backbone, Descovy can be the backbone of choice if clinicians wish to construct a regimen containing a boosted protease inhibitor. Gilead considers that the established efficacy and safety profile for Descovy supports an indication for use in combination with other antiretroviral agents for the treatment of HIV-1 infection as follows:

> *Descovy is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and paediatric patients 12 years of age and older with body weight at least 35 kg without any known mutations associated with resistance to the individual components of Descovy.*
>
> *Descovy is not for use in Pre-Exposure Prophylaxis (PrEP).*

Conclusion

TAF represents an important advance in the development of ART and constitutes part of a dual N[t]RTI backbone, Descovy, which is designed to simplify and promote patient adherence and achieve maximum antiviral activity while minimising toxic effects. The benefits provided by Descovy, in particular the lessened impact of therapy on parameters associated with renal and bone toxicities, meet an important unmet need for the optimisation of long-term treatment in an aging cohort of HIV infected individuals who now have a life-expectancy close to that observed in the general population, and are therefore exposed to ARV drugs for long periods of time.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Descovy tablet containing 200 mg emtricitabine/

10 mg tenofovir alafenamide fumarate and 200 mg emtricitabine/ 25 mg tenofovir alafenamide fumarate to have an overall positive benefit–risk profile for the amended indication**;**

> *Descovy is indicated, in combination with other antiretroviral agents, for the treatment of HIV-1 infection in adults and adolescents aged 12 years of age and older with body weight at least 35 kg. The patients must not have a history of treatment failure or known mutations associated with resistance to tenofovir.*
>
> *Descovy is not for use in Pre-Exposure Prophylaxis (PrEP).*

In making this recommendation the ACPM:

- Advised that bioequivalence and efficacy data from the Genvoya data set, supported by pharmacokinetic data and efficacy data from the switch study are sufficient to support use of Descovy. In addition the bridging PK data, and the extrapolation of Genvoya data support use in adolescents
- Noted that in the Genvoya data set, tenofovir alafenamide (TAF) produced equivalent viral suppression to well established tenofovir disoproxil fumarate.
- Was of the view that the effect of food on the bioavailability of TAF was clinically acceptable. The ACPM noted that the effect of food/fasting upon any third/fourth drug was likely to be of more concern.
- Advised that it would be more appropriate if the indication specified that patients must not have a history of treatment failure or known mutations associated with resistance to tenofovir rather than components of Descovy.
- Agreed that the indication should specify that Descovy should not be used for PrEP as there are no data to support the use of this formulation.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- A statement in the Dosage and Administration section reflecting choice of dose according to use of third/subsequent additional agents and inclusion of Table 1 '*Dose of Descovy according to third agent in the HIV treatment regimen*' under Posology and method of administration from the European Summary of Product Characteristics.
- Amend the following statement in the PI regarding risk of HIV transmission: '*Patients should be advised that antiretroviral therapies, including Descovy, have not been proven to prevent the risk of transmission of HIV*' and replace with the following from the European Summary of Product Characteristics: '*While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded*.'
- Up-date the Drug interactions section of the PI with the missing information on dolutegravir, rilpivirine, efavirenz and anti-hepatitis C medications similar to Table 2 'Interactions Between The Individual Components Of Descovy And Other Medicinal Products' under Interaction with other medicinal products and other forms of interaction: Other Interactions as per the European Summary of Product Characteristics.

- Under Renal Impairment add a statement advising estimated creatinine clearance, urine glucose, and urine protein should be measured prior to starting Descovy, and should be monitored routinely during treatment. In addition, serum phosphate should be routinely measured in patients with chronic kidney disease.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. Does the committee consider the totality of evidence, including principal reliance on Genvoya dossier but with significant additional data specific to the current submission, sufficient to support the use Descovy, including use in adolescents aged 12 years and above?

The ACPM advised that bioequivalence and efficacy data from the Genvoya data set, supported by pharmacokinetic data and efficacy data from the switch study are sufficient to support use of Descovy. In addition the bridging PK data and the extrapolation of Genvoya data support use in adolescents.

2. Does the committee support the exclusion of 'patients with history or treatment failure' in the therapeutic indication or prefer a broader indication as proposed by the sponsor?

The ACPM advised studies were performed in treatment naive populations or drug-agent switching in already virologically suppressed populations on stable anti-retroviral (ARV) treatment. As resistance mutations may be archived, a history of ARV treatment failure to tenofovir should be specifically listed as an exclusion along with resistance mutations.

The Committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision including recommendations for the Australian PI.

- See Proposed Product Information/Consumer Medication Information amendments.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Descovy 200 mg/25 mg (200 mg emtricitabine/25 mg tenofovir alafenamide) and 200 mg/10 mg (200 mg emtricitabine/10 mg tenofovir alafenamide) tablets, indicated for:

> *Descovy is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and adolescents aged 12 years and older with body weight at least 35 kg. The patients must not have a history of treatment failure or known mutations associated with resistance to the individual components of Descovy (see Pharmacology).*
>
> *Descovy is not for use in Pre-Exposure Prophylaxis (PrEP).*

Specific conditions of registration applying to these goods

The Descovy fixed dose combination tablets of (emtricitabine/ tenofovir alafenamide fumarate) Risk Management Plan (RMP), the European Risk Management Plan (Version: 0.1, dated 1 April 2015), as qualified by the Australian Specific Annex (Version: 0.2, dated January 2016), included with submission PM-2015-01283-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Descovy approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au