▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

SCHEDULING STATUS
Prescription Only
POM

GILEAD SUPPLY FOR AFRICA

1. NAME OF THE MEDICINAL PRODUCT

Descovy 200 mg/10 mg film-coated tablets
Descovy 200 mg/25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg of emtricitabine and tenofovir alafenamide fumarate equivalent to 10 mg of tenofovir alafenamide.

Each tablet contains 200 mg of emtricitabine and tenofovir alafenamide fumarate equivalent to 25 mg of tenofovir alafenamide.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Grey, rectangular-shaped, film-coated tablet of dimensions 12.5 mm x 6.4 mm debossed with “GSI” on one side and “210” on the other side of the tablet.

Blue, rectangular-shaped, film-coated tablet of dimensions 12.5 mm x 6.4 mm debossed with “GSI” on one side and “225” on the other side of the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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) (see sections 4.2 and 5.1).

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of HIV infection.

Posology

Adults and adolescents aged 12 years and older, weighing at least 35 kg

Descovy should be administered as shown in Table 1.

Table 1: Dose of Descovy according to third agent in the HIV treatment regimen

Dose of Descovy	Third agent in HIV treatment regimen (see section 4.5)
Descovy 200/10 mg once daily	Atazanavir with ritonavir or cobicistat Darunavir with ritonavir or cobicistat[1] Lopinavir with ritonavir
Descovy 200/25 mg once daily	Dolutegravir, efavirenz, maraviroc, nevirapine, rilpivirine, raltegravir

1 Descovy 200/10 mg in combination with darunavir 800 mg and cobicistat 150 mg, administered as a fixed-dose combination tablet, was studied in treatment naive subjects, see section 5.1.

If the patient misses a dose of Descovy within 18 hours of the time it is usually taken, the patient should take Descovy as soon as possible and resume the normal dosing schedule. If a patient misses a dose of Descovy by more than 18 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.

If the patient vomits within 1 hour of taking Descovy another tablet should be taken.

Elderly

No dose adjustment of Descovy is required in elderly patients (see sections 5.1 and 5.2).

Renal impairment

No dose adjustment of Descovy is required in adults or adolescents (aged at least 12 years and of at least 35 kg body weight) with estimated creatinine clearance (CrCl) ≥ 30 mL/min.

Descovy should not be initiated in patients with estimated CrCl < 30 mL/min as there are no data available regarding the use of Descovy in this population (see sections 5.1 and 5.2).

Descovy should be discontinued in patients with estimated CrCl that declines below 30 mL/min during treatment (see sections 5.1 and 5.2).

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 sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of Descovy in children younger than 12 years of age, or weighing < 35 kg, have not yet been established. No data are available.

Method of administration

Descovy should be taken orally, once daily with or without food (see section 5.2). The film-coated tablet should not be chewed, crushed, or split.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Patients co-infected with HIV and hepatitis B or C virus

Patients with chronic hepatitis B or C treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

The safety and efficacy of Descovy in patients co-infected with HIV-1 and hepatitis C virus (HCV) have not been established. Tenofovir alafenamide is active against hepatitis B virus (HBV), but its clinical efficacy against this virus is under investigation and is not yet fully established.

Discontinuation of Descovy therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis. Patients co-infected with HIV and HBV who discontinue Descovy should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment.

Descovy should not be administered concomitantly with medicinal products containing tenofovir disoproxil (as fumarate), lamivudine or adefovir dipivoxil used for the treatment of HBV infection.

Liver disease

The safety and efficacy of Descovy in patients with significant underlying liver disorders have not been established (see sections 4.2 and 5.2).

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Mitochondrial dysfunction

Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or postnatally to nucleoside analogues. The main adverse reactions reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactataemia, hyperlipasaemia). These events are

often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative children, should have clinical and

laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Immune Reactivation Syndrome

In HIV infected patients treated with CART, including with emtricitabine, immune reactivation syndrome has been reported. In HIV infected patients with severe immune deficiency at the time of institution of CART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples include cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable, and these events can occur many months after initiation of treatment.

Patients with HIV-1 harbouring mutations

Descovy should be avoided in antiretroviral-experienced patients with HIV-1 harbouring the K65R mutation (see section 5.1).

Triple nucleoside therapy

There have been reports of a high rate of virological failure and of emergence of resistance at an early stage when tenofovir disoproxil fumarate was combined with lamivudine and abacavir as well as with lamivudine and didanosine as a once daily regimen. Therefore, the same problems may be seen if Descovy is administered with a third nucleoside analogue.

Opportunistic infections

Patients receiving Descovy or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and, therefore, should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV disease and/or long-term exposure to CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Nephrotoxicity

A potential risk of nephrotoxicity resulting from chronic exposure to low levels of tenofovir due to dosing with tenofovir alafenamide cannot be excluded (see section 5.3).

Co-administration of other medicinal products

The co-administration of Descovy is not recommended with certain anticonvulsants (e.g., carbamazepine, oxcarbazepine, phenobarbital and phenytoin), antimycobacterials (e.g., rifampicin, rifabutin, rifapentine), boceprevir, telaprevir, St. John's wort and HIV protease inhibitors (PIs) other than atazanavir, lopinavir and darunavir (see section 4.5).

Descovy should not be administered concomitantly with medicinal products containing tenofovir disoproxil (as fumarate), emtricitabine, lamivudine or adefovir dipivoxil.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Descovy should not be administered concomitantly with medicinal products containing tenofovir disoproxil (as fumarate), emtricitabine, lamivudine or adefovir dipivoxil.

Emtricitabine

In vitro and clinical pharmacokinetic drug-drug interaction studies have shown that the potential for CYP-mediated interactions involving emtricitabine with other medicinal products is low. Co-administration of emtricitabine with medicinal products that are eliminated by active tubular secretion may increase concentrations of emtricitabine, and/or the co-administered medicinal product. Medicinal products that decrease renal function may increase concentrations of emtricitabine.

Tenofovir alafenamide

Tenofovir alafenamide is transported by P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Medicinal products that strongly affect P-gp activity and BCRP may lead to changes in tenofovir alafenamide absorption. Medicinal products that induce P-gp activity (e.g., rifampicin, rifabutin, carbamazepine, phenobarbital) are expected to decrease the absorption of tenofovir alafenamide, resulting in decreased plasma concentration of tenofovir alafenamide, which may lead to loss of therapeutic effect of Descovy and development of resistance. Co-administration of Descovy with other medicinal products that inhibit P-gp (e.g., cobicistat, ritonavir, ciclosporin) are expected to increase the absorption and plasma concentration of tenofovir alafenamide. It is not known whether the co-administration of Descovy and xanthine oxidase inhibitors (e.g., febuxostat) would increase systemic exposure to tenofovir.

Tenofovir alafenamide is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 *in vitro*. It is not an inhibitor of CYP3A4 *in vivo*. Tenofovir alafenamide is a substrate of OATP1B1 and OATP1B3 *in vitro*. The distribution of tenofovir alafenamide in the body may be affected by the activity of OATP1B1 and OATP1B3.

Other interactions

Tenofovir alafenamide is not an inhibitor of human uridine diphosphate glucuronosyltransferase (UGT) 1A1 *in vitro*. It is not known whether tenofovir alafenamide is an inhibitor of other UGT enzymes. Emtricitabine did not inhibit the glucuronidation reaction of a non-specific UGT substrate *in vitro*.

Interactions between the components of Descovy and potential co-administered medicinal products are listed in Table 2 (increase is indicated as "↑", decrease as "↓", no change as "↔"). The interactions described are

based on studies conducted with Descovy, or the components of Descovy as individual agents and/or in combination, or are potential drug-drug interactions that may occur with Descovy.

Table 2: Interactions between the individual components of Descovy and other medicinal products

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}[1]**	**Recommendation concerning co-administration with Descovy**
ANTI-INFECTIVES		
Antifungals		
Ketoconazole Itraconazole	Interaction not studied with either of the components of Descovy. Co-administration of ketoconazole or itraconazole, which are potent P-gp inhibitors, is expected to increase plasma concentrations of tenofovir alafenamide.	The recommended dose of Descovy is 200/10 mg once daily.
Fluconazole Isavuconazole	Interaction not studied with either of the components of Descovy. Co-administration of fluconazole or isavuconazole may increase plasma concentrations of tenofovir alafenamide.	Dose Descovy according to the concomitant antiretroviral (see section 4.2).
Antimycobacterials		
Rifabutin Rifampicin Rifapentine	Interaction not studied with either of the components of Descovy. Co-administration of rifampicin, rifabutin, and rifapentine, all of which are P-gp inducers, may decrease tenofovir alafenamide plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	Co-administration of Descovy and rifabutin rifampicin, or rifapentine is not recommended.
Anti-hepatitis C virus medicinal products		
Boceprevir Telaprevir	Interaction not studied with either of the components of Descovy.	Co-administration with boceprevir or telaprevir has the potential to adversely affect the intracellular activation and clinical antiviral efficacy of tenofovir alafenamide, therefore co-administration of Descovy and boceprevir or telaprevir is not recommended.

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}[1]**	**Recommendation concerning co-administration with Descovy**
Ledipasvir (90 mg once daily)/ sofosbuvir (400 mg once daily), emtricitabine (200 mg once daily)/ tenofovir alafenamide (10 mg once daily)[2]	Ledipasvir: AUC: ↑ 79% C_{max}: ↑ 65% C_{min}: ↑ 93% Sofosbuvir: AUC: ↑ 47% C_{max}: ↑ 29% Sofosbuvir metabolite GS-331007: AUC: ↑ 48% C_{max}: ↔ C_{min}: ↑ 66% Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir alafenamide: AUC: ↔ C_{max}: ↔	No dose adjustment of ledipasvir or sofosbuvir is required. Dose Descovy according to the concomitant antiretroviral (see section 4.2).
Ledipasvir (90 mg once daily)/ sofosbuvir (400 mg once daily), emtricitabine (200 mg once daily)/ tenofovir alafenamide (25 mg once daily)[3]	Ledipasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Sofosbuvir: AUC: ↔ C_{max}: ↔ Sofosbuvir metabolite GS-331007: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir alafenamide: AUC: ↑ 32% C_{max}: ↔	No dose adjustment of ledipasvir or sofosbuvir is required. Dose Descovy according to the concomitant antiretroviral (see section 4.2).

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}[1]**	**Recommendation concerning co-administration with Descovy**
ANTIRETROVIRALS		
HIV protease inhibitors		
Atazanavir/cobicistat (300 mg/150 mg once daily)	Tenofovir alafenamide: AUC: ↑ 75% C_{max}: ↑ 80% Atazanavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔	The recommended dose of Descovy is 200/10 mg once daily.
Atazanavir/ritonavir (300/100 mg once daily), tenofovir alafenamide (10 mg)	Tenofovir alafenamide: AUC: ↑ 91% C_{max}: ↑ 77% Atazanavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔	The recommended dose of Descovy is 200/10 mg once daily.
Darunavir/cobicistat (800/150 mg once daily), tenofovir alafenamide (25 mg once daily)[4]	Tenofovir alafenamide: AUC: ↔ C_{max}: ↔ Tenofovir: AUC: ↑ 224% C_{max}: ↑ 216% C_{min}: ↑ 221% Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔	The recommended dose of Descovy is 200/10 mg once daily.
Darunavir/ritonavir (800/100 mg once daily), tenofovir alafenamide (10 mg once daily)	Tenofovir alafenamide: AUC: ↔ C_{max}: ↔ Tenofovir: AUC: ↑ 105% C_{max}: ↑ 142% Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔	The recommended dose of Descovy is 200/10 mg once daily.

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}[1]**	**Recommendation concerning co-administration with Descovy**
Lopinavir/ritonavir (800/200 mg once daily), tenofovir alafenamide (10 mg once daily)	Tenofovir alafenamide: AUC: ↑ 47% C_{max}: ↑ 119% Lopinavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔	The recommended dose of Descovy is 200/10 mg once daily.
Tipranavir/ritonavir	Interaction not studied with either of the components of Descovy. Tipranavir/ritonavir results in P-gp induction. Tenofovir alafenamide exposure is expected to decrease when tipranavir/ritonavir is used in combination with Descovy.	Co-administration with Descovy is not recommended.
Other protease inhibitors	Effect is unknown.	There are no data available to make dosing recommendations for co-administration with other protease inhibitors.
Other HIV antiretrovirals		
Dolutegravir (50 mg once daily), tenofovir alafenamide (10 mg once daily)[2]	Tenofovir alafenamide: AUC: ↔ C_{max}: ↔ Dolutegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔	The recommended dose of Descovy is 200/25 mg once daily.
Rilpivirine (25 mg once daily), tenofovir alafenamide (25 mg once daily)	Tenofovir alafenamide: AUC: ↔ C_{max}: ↔ Rilpivirine: AUC: ↔ C_{max}: ↔ C_{min}: ↔	The recommended dose of Descovy is 200/25 mg once daily.
Efavirenz (600 mg once daily), tenofovir alafenamide (40 mg once daily)[4]	Tenofovir alafenamide: AUC: ↓ 14% C_{max}: ↓ 22%	The recommended dose of Descovy is 200/25 mg once daily.

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}[1]**	**Recommendation concerning co-administration with Descovy**
Maraviroc Nevirapine Raltegravir	Interaction not studied with either of the components of Descovy. Tenofovir alafenamide exposure is not expected to be affected by maraviroc, nevirapine or raltegravir, nor is it expected to affect the metabolic and excretion pathways relevant to maraviroc, nevirapine or raltegravir.	The recommended dose of Descovy is 200/25 mg once daily.
ANTICONVULSANTS		
Oxcarbazepine Phenobarbital Phenytoin	Interaction not studied with either of the components of Descovy. Co-administration of oxcarbazepine, phenobarbital, or phenytoin, all of which are P-gp inducers, may decrease tenofovir alafenamide plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	Co-administration of Descovy and oxcarbazepine, phenobarbital or phenytoin is not recommended.
Carbamazepine (titrated from 100 mg to 300 mg twice a day), emtricitabine/tenofovir alafenamide (200 mg/25 mg once daily)[4,5]	Tenofovir alafenamide: AUC: ↓ 55% C_{max}: ↓ 57% Co-administration of carbamazepine, a P-gp inducer, decreases tenofovir alafenamide plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	Co-administration of Descovy and carbamazepine is not recommended.
ANTIDEPRESSANTS		
Sertraline (50 mg once daily), tenofovir alafenamide (10 mg once daily)[2]	Tenofovir alafenamide: AUC: ↔ C_{max}: ↔ Sertraline: AUC: ↑ 9% C_{max}: ↑ 14%	No dose adjustment of sertraline is required. Dose Descovy according to the concomitant antiretroviral (see section 4.2).
HERBAL PRODUCTS		
St. John's wort (*Hypericum perforatum*)	Interaction not studied with either of the components of Descovy. Co-administration of St. John's wort, a P-gp inducer, may decrease tenofovir alafenamide plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	Co-administration of Descovy with St. John's wort is not recommended.

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}[1]**	**Recommendation concerning co-administration with Descovy**
IMMUNOSUPPRESSANTS		
Ciclosporin	Interaction not studied with either of the components of Descovy. Co-administration of ciclosporin, a potent P-gp inhibitor, is expected to increase plasma concentrations of tenofovir alafenamide.	The recommended dose of Descovy is 200/10 mg once daily.
SEDATIVES/HYPNOTICS Orally		
administered midazolam (2.5 mg once daily), tenofovir alafenamide (25 mg once daily) Intravenously	Midazolam: AUC: ↔ C_{max}: ↔	No dose adjustment of midazolam is required. Dose Descovy according to the concomitant antiretroviral (see section 4.2).
administered midazolam (once daily), tenofovir alafenamide (25 mg once daily)	Midazolam: AUC: ↔ C_{max}: ↔	

1 When data are available from drug-drug interaction studies.
2 Study conducted with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fixed-dose combination tablet.
3 Study conducted with emtricitabine/rilpivirine/tenofovir alafenamide fixed-dose combination tablet.
4 Study conducted with Descovy.
5 Emtricitabine/tenofovir alafenamide was taken with food in this study.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies of Descovy or its components in pregnant women. There are no or limited data (less than 300 pregnancy outcomes) from the use of tenofovir alafenamide in pregnant women. However, a large amount of data on pregnant women (more than 1,000 exposed outcomes) indicate no malformative nor foetal/neonatal toxicity associated with emtricitabine.

Animal studies do not indicate direct or indirect harmful effects of emtricitabine with respect to fertility parameters, pregnancy, foetal development, parturition or postnatal development. Studies of tenofovir alafenamide in animals have shown no evidence of harmful effects on fertility parameters, pregnancy, or foetal development (see section 5.3).

Descovy should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Breast-feeding

It is not known whether tenofovir alafenamide is excreted in human milk. Emtricitabine is excreted in human milk. In animal studies it has been shown that tenofovir is excreted in milk.

There is insufficient information on the effects of emtricitabine and tenofovir in newborns/infants. Therefore, Descovy should not be used during breast-feeding.

In order to avoid transmission of HIV to the infant it is recommended that HIV infected women do not breast-feed their infants under any circumstances.

Fertility

There are no data on fertility from the use of Descovy in humans. In animal studies there were no effects of emtricitabine and tenofovir alafenamide on mating or fertility parameters (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients should be informed that dizziness has been reported during treatment with Descovy.

4.8 Undesirable effects

Summary of the safety profile

Assessment of adverse reactions is based on safety data from across all Phase 2 and 3 studies in which 2,832 HIV-1 infected patients received medicinal products containing emtricitabine and tenofovir alafenamide. In clinical studies of 866 treatment-naïve adult patients receiving emtricitabine and tenofovir alafenamide with elvitegravir and cobicistat as the fixed-dose combination tablet elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide (as fumarate) 10 mg (E/C/F/TAF), the most frequently reported adverse reactions were diarrhoea (7%), nausea (10%), and headache (6%).

Tabulated summary of adverse reactions

The adverse reactions in Table 3 are listed by system organ class and frequency. Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100).

Table 3: Tabulated list of adverse reactions[1]

Frequency	Adverse reaction
Blood and lymphatic system disorders	
Uncommon:	anaemia[2]
Psychiatric disorders	
Common:	abnormal dreams
Nervous system disorders	
Common:	headache, dizziness
Gastrointestinal disorders	
Very common:	nausea
Common:	diarrhoea, vomiting, abdominal pain, flatulence
Uncommon:	dyspepsia
Skin and subcutaneous tissue disorders	
Common:	rash
Uncommon:	angioedema[2,3], pruritus
Musculoskeletal and connective tissue disorders	
Uncommon:	arthralgia
General disorders and administration site conditions	
Common:	fatigue

[1] With the exception of angioedema and anaemia (see footnotes 2 and 3), all adverse reactions were identified from clinical studies of F/TAF containing products. The frequencies were derived from Phase 3 E/C/F/TAF clinical studies in 866 treatment-naïve adult patients through 48 weeks of treatment (GS-US-292-0104 and GS-US-292-0111).

[2] This adverse reaction was not observed in the clinical studies of F/TAF containing products but identified from clinical studies or post-marketing experience for emtricitabine when used with other antiretrovirals.

[3] This adverse reaction was identified through post-marketing surveillance for emtricitabine but was not observed in randomised

controlled clinical studies in adults or paediatric HIV clinical studies of emtricitabine. The frequency category of uncommon was estimated from a statistical calculation based on the total number of patients exposed to emtricitabine in these clinical studies (n = 1,563).

Description of selected adverse reactions

Immune Reactivation Syndrome

In HIV infected patients with severe immune deficiency at the time of initiation of CART, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) have also been reported; however, the reported time to onset is more variable, and these events can occur many months after initiation of treatment (see section 4.4).

Osteonecrosis

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to CART. The frequency of this is unknown (see section 4.4).

Changes in lipid laboratory tests

Increases from baseline were observed in both the tenofovir alafenamide fumarate and tenofovir disoproxil fumarate containing treatment groups for the fasting lipid parameters total cholesterol, direct low-density lipoprotein (LDL)- and high-density lipoprotein (HDL)-cholesterol, and triglycerides at Week 48. The median increase from baseline for those parameters was greater in the E/C/F/TAF group compared with the elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil (as fumarate) 245 mg (E/C/F/TDF) group at Week 48 ($p < 0.001$ for the difference between treatment groups for fasting total cholesterol, direct LDL- and HDL-cholesterol, and triglycerides). The median (Q1, Q3) change from baseline in total cholesterol to HDL-cholesterol ratio at Week 48 was 0.1 (-0.3, 0.5) in the E/C/F/TAF group and 0.0 (-0.5, 0.4) in the E/C/F/TDF group ($p < 0.001$ for the difference between treatment groups).

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

Paediatric population

The safety of emtricitabine and tenofovir alafenamide was evaluated through 48 weeks in an open-label clinical study (GS-US-292-0106) in which HIV-1 infected, treatment-naïve paediatric patients aged 12 to < 18 years received emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet. The safety profile of emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat in 50 adolescent patients was similar to that in adults (see section 5.1).

Other special populations

Patients with renal impairment

The safety of emtricitabine and tenofovir alafenamide was evaluated through 48 weeks in an open-label clinical study (GS-US-292-0112) in which 248 HIV-1 infected patients who were either treatment-naïve (n = 6) or virologically suppressed (n = 242) with mild to moderate renal impairment (estimated glomerular filtration rate by Cockcroft-Gault method [$eGFR_{CG}$]: 30-69 mL/min) received emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet. The safety

profile in patients with mild to moderate renal impairment was similar to that in patients with normal renal function (see section 5.1).

Patients co-infected with HIV and HBV

The safety of emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet was evaluated in approximately 70 HIV/HBV co-infected patients currently receiving treatment for HIV in an open-label clinical study (GS-US-292-1249). Based on this limited experience, the safety profile of Descovy in patients with HIV/HBV co-infection appears to be similar to that in patients with HIV-1 monoinfection (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

To report suspected adverse reactions, **contact Gilead Sciences, Inc. at safety_fc@gilead.com**.

4.9 Overdose

If overdose occurs the patient must be monitored for evidence of toxicity (see section 4.8). Treatment of overdose with Descovy consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient.

Emtricitabine can be removed by haemodialysis, which removes approximately 30% of the emtricitabine dose over a 3 hour dialysis period starting within 1.5 hours of emtricitabine dosing. Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54%. It is not known whether emtricitabine or tenofovir can be removed by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral for systemic use; antivirals for treatment of HIV infections, combinations. ATC code: J05AR17.

Mechanism of action

Emtricitabine is a nucleoside reverse transcriptase inhibitor (NRTI) and nucleoside analogue of 2'-deoxycytidine. Emtricitabine is phosphorylated by cellular enzymes to form emtricitabine triphosphate. Emtricitabine triphosphate inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase (RT), which results in DNA chain-termination. Emtricitabine has activity against HIV-1, HIV-2, and HBV.

Tenofovir alafenamide is a nucleotide reverse transcriptase inhibitor (NtRTI) and phosphonoamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). Tenofovir alafenamide is permeable into cells and due to increased plasma stability and intracellular activation through hydrolysis by cathepsin A, tenofovir alafenamide is more efficient than tenofovir disoproxil fumarate in concentrating tenofovir in peripheral blood mononuclear cells (PBMCs) or HIV target cells including lymphocytes and macrophages. Intracellular tenofovir is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate.

Tenofovir diphosphate inhibits HIV replication through incorporation into viral DNA by the HIV RT, which results in DNA chain-termination.

Tenofovir has activity against HIV-1, HIV-2, and HBV.

Antiviral activity *in vitro*

Emtricitabine and tenofovir alafenamide demonstrated synergistic antiviral activity in cell culture. No antagonism was observed with emtricitabine or tenofovir alafenamide when combined with other antiretroviral agents.

The antiviral activity of emtricitabine against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, the MAGI CCR5 cell line, and PBMCs. The 50% effective concentration (EC_{50}) values for emtricitabine were in the range of 0.0013 to 0.64 μM. Emtricitabine displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007 to 0.075 μM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.007 to 1.5 μM).

The antiviral activity of tenofovir alafenamide against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells and CD4+-T lymphocytes. The EC_{50} values for tenofovir alafenamide were in the range of 2.0 to 14.7 nM. Tenofovir alafenamide displayed antiviral activity in cell culture against all HIV-1 groups (M, N, and O), including subtypes A, B, C, D, E, F, and G (EC_{50} values ranged from 0.10 to 12.0 nM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.91 to 2.63 nM).

Resistance

In vitro

Reduced susceptibility to emtricitabine is associated with M184V/I mutations in HIV-1 RT.

HIV-1 isolates with reduced susceptibility to tenofovir alafenamide express a K65R mutation in HIV-1 RT; in addition, a K70E mutation in HIV-1 RT has been transiently observed.

In treatment-naïve patients

In a pooled analysis of antiretroviral-naïve patients receiving emtricitabine and tenofovir alafenamide (10 mg) given with elvitegravir and cobicistat as a fixed-dose combination tablet in GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102, genotyping was performed on plasma HIV-1 isolates from all patients with HIV-1 RNA > 400 copies/mL at confirmed virological failure, at Week 48, or at the time of early study drug discontinuation. Through Week 48, the development of one or more primary emtricitabine, tenofovir alafenamide, or elvitegravir resistance-associated mutations was observed in HIV-1 isolates from 7 of 14 patients with evaluable genotypic data from paired baseline and E/C/F/TAF treatment-failure isolates (7 of 978 patients [0.7%]) compared with 7 of 15 treatment-failure isolates from patients in the E/C/F/TDF group (7 of 925 patients [0.8%]). In the E/C/F/TAF group, the mutations that emerged were M184V/I (n = 7) and K65R (n = 1) in RT and T66T/A/I/V (n = 2), E92Q (n = 2), Q148Q/R (n = 1), and N155H (n = 1) in integrase. In the E/C/F/TDF group, the mutations that emerged were M184V/I (n = 7) and K65R (n = 2) in RT and E92E/Q (n = 3) and Q148R (n = 2) in integrase. All HIV-1 isolates from patients in both treatment groups who developed resistance mutations to elvitegravir in integrase also developed resistance mutations to emtricitabine in RT.

Cross-resistance in HIV-1 infected, treatment-naïve or virologically suppressed patients

Emtricitabine-resistant viruses with the M184V/I substitution were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir, and zidovudine.

The K65R and K70E mutations result in reduced susceptibility to abacavir, didanosine, lamivudine, emtricitabine, and tenofovir, but retain sensitivity to zidovudine.

Multinucleoside-resistant HIV-1 with a T69S double insertion mutation or with a Q151M mutation complex including K65R showed reduced susceptibility to tenofovir alafenamide.

Clinical data

There are no efficacy and safety studies conducted in treatment-naïve patients with Descovy.

Clinical efficacy of Descovy was established from studies conducted with emtricitabine and tenofovir alafenamide when given with elvitegravir and cobicistat as the fixed-dose combination tablet E/C/F/TAF.

HIV-1 infected, treatment-naïve patients

In studies GS-US-292-0104 and GS-US-292-0111, patients were randomised in a 1:1 ratio to receive either emtricitabine 200 mg and tenofovir alafenamide 10 mg (n = 866) once daily or emtricitabine 200 mg + tenofovir disoproxil (as fumarate) 245 mg (n = 867) once daily, both given with elvitegravir 150 mg + cobicistat 150 mg as a fixed-dose combination tablet. The mean age was 36 years (range: 18-76), 85% were male, 57% were White, 25% were Black, and 10% were Asian. Nineteen percent of patients were identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.5 $\log_{10}$ copies/mL (range: 1.3-7.0) and 23% had baseline viral loads > 100,000 copies/mL. The mean baseline CD4+ cell count was 427 cells/mm^3 (range: 0-1,360) and 13% had a CD4+ cell count < 200 cells/mm^3.

E/C/F/TAF met the non-inferiority criteria in achieving HIV-1 RNA < 50 copies/mL when compared to E/C/F/TDF. Pooled treatment outcomes at 48 weeks are shown in Table 4.

Table 4: Pooled virological outcomes of studies GS-US-292-0104 and GS-US-292-0111 at Week 48[a,b]

	E/C/F/TAF (n = 866)	E/C/F/TDF[e] (n = 867)
HIV-1 RNA < 50 copies/mL	92%	90%
Treatment difference	2.0% (95% CI: -0.7% to 4.7%)	
HIV-1 RNA ≥ 50 copies/mL[c]	4%	4%
No virologic data at Week 48 window	4%	6%
Discontinued study drug due to AE or death[d]	1%	2%
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[e]	2%	4%
Missing data during window but on study drug	1%	< 1%
Proportion (%) of patients with HIV-1 RNA < 50 copies/mL by subgroup		
Age		
< 50 years	716/777 (92%)	680/753 (90%)
≥ 50 years	84/89 (94%)	104/114 (91%)
Sex		
Male	674/733 (92%)	673/740 (91%)
Female	126/133 (95%)	111/127 (87%)
Race		
Black	197/223 (88%)	177/213 (83%)
Non-black	603/643 (94%)	607/654 (93%)
Baseline viral load		
≤ 100,000 copies/mL	629/670 (94%)	610/672 (91%)
> 100,000 copies/mL	171/196 (87%)	174/195 (89%)
Baseline CD4+ cell count		
< 200 cells/mm^3	96/112 (86%)	104/117 (89%)
≥ 200 cells/mm^3	703/753 (93%)	680/750 (91%)
HIV-1 RNA < 20 copies/mL	84.4%	84.0%
Treatment difference	0.4% (95% CI: -3.0% to 3.8%)	

E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide

E/C/F/TDF = elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate

a Week 48 window was between Day 294 and 377 (inclusive).

b In both studies, patients were stratified by baseline HIV-1 RNA (≤ 100,000 copies/mL, > 100,000 copies/mL to ≤ 400,000 copies/mL, or > 400,000 copies/mL), by CD4+ cell count (< 50 cells/μL, 50-199 cells/μL, or ≥ 200 cells/μL), and by region (US or ex-US).

c Included patients who had ≥ 50 copies/mL in the Week 48 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.

d Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

e Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy; e.g., withdrew consent, loss to follow-up, etc.

The mean increase from baseline in CD4+ cell count at Week 48 was 230 cells/mm^3 in patients receiving emtricitabine and tenofovir alafenamide and 211 cells/mm^3 in patients receiving emtricitabine and tenofovir disoproxil fumarate (p = 0.024).

Clinical efficacy of Descovy in treatment-naïve patients was also established from a study conducted with emtricitabine and tenofovir alafenamide (10 mg) when given with darunavir (800 mg) and cobicistat as a

fixed-dose combination tablet (D/C/F/TAF). In study GS-US-299-0102, patients were randomised in a 2:1 ratio to receive either fixed-dose combination D/C/F/TAF once daily (n = 103) or darunavir and cobicistat and emtricitabine/tenofovir disoproxil fumarate once daily (n = 50). The proportions of patients with plasma HIV-1 RNA < 50 copies/mL and < 20 copies/mL are shown in Table 5.

Table 5: Virological outcomes of study GS-US-299-0102 at Week 24 and 48[a]

	Week 24		**Week 48**	
	D/C/F/TAF (n = 103)	**Darunavir, cobicistat and emtricitabine/tenofovir disoproxil fumarate (n = 50)**	**D/C/F/TAF (n = 103)**	**Darunavir, cobicistat and emtricitabine/tenofovir disoproxil fumarate (n = 50)**
HIV-1 RNA < 50 copies/mL	75%	74%	77%	84%
Treatment difference	3.3% (95% CI: -11.4% to 18.1%)		-6.2% (95% CI: -19.9% to 7.4%)	
HIV-1 RNA ≥ 50 copies/mL[b]	20%	24%	16%	12%
No virologic data at Week 48 window	5%	2%	8%	4%
Discontinued study drug due to AE or death[c]	1%	0	1%	2%
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[d]	4%	2%	7%	2%
Missing data during window but on study drug	0	0	0	0
HIV-1 RNA < 20 copies/mL	55%	62%	63%	76%
Treatment difference	-3.5% (95% CI: -19.8% to 12.7%)		-10.7% (95% CI: -26.3% to 4.8%)	

D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide

a Week 48 window was between Day 294 and 377 (inclusive).

b Included patients who had ≥ 50 copies/mL in the Week 48 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.

c Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

d Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy; e.g., withdrew consent, loss to follow-up, etc.

HIV-1 infected virologically suppressed patients

In study GS-US-311-1089, the efficacy and safety of switching from emtricitabine/tenofovir disoproxil fumarate to Descovy while maintaining the third antiretroviral agent were evaluated in a randomised, double-blind study of virologically suppressed HIV-1 infected adults (n = 663). Patients must have been stably suppressed (HIV-1 RNA < 50 copies/mL) on their baseline regimen for at least 6 months and had HIV-1 with no resistance mutations to emtricitabine or tenofovir alafenamide prior to study entry. Patients were

randomised in a 1:1 ratio to either switch to Descovy (n = 333), or stay on their baseline emtricitabine/tenofovir disoproxil fumarate containing regimen (n = 330). Patients were stratified by the class of the third agent in their prior treatment regimen. At baseline, 46% of patients were receiving emtricitabine/tenofovir disoproxil fumarate in combination with a boosted PI and 54% of patients were receiving emtricitabine/tenofovir disoproxil fumarate in combination with an unboosted third agent.

Treatment outcomes of study GS-US-311-1089 through 48 weeks are presented in Table 6.

Table 6: Virological outcomes of study GS-US-311-1089 at Week 48[a]

	Emtricitabine+tenofovir alafenamide containing regimen (n = 333)	**Baseline regimen (n = 330)**
HIV-1 RNA < 50 copies/mL	**94%**	**93%**
Treatment difference	1.3% (95% CI: -2.5% to 5.1%)	
HIV-1 RNA ≥ 50 copies/mL[b]	< 1%	2%
No virologic data at Week 48 window	5%	5%
Discontinued study drug due to AE or death[c]	2%	1%
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[d]	3%	5%
Missing data during window but on study drug	< 1%	0
Proportion (%) of patients with HIV-1 RNA < 50 copies/mL by prior treatment regimen		
Boosted PIs	142/155 (91.6%)	140/151 (92.7%)
Other third agents	172/178 (96.6%)	167/179 (93.3%)

PI = protease inhibitor

a Week 48 window was between Day 294 and 377 (inclusive).

b Included patients who had ≥ 50 copies/mL in the Week 48 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.

c Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

d Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy; e.g., withdrew consent, loss to follow-up, etc.

HIV-1 infected patients with mild to moderate renal impairment

In study GS-US-292-0112, the efficacy and safety of emtricitabine and tenofovir alafenamide were evaluated in an open-label clinical study in which 242 HIV-1 infected patients with mild to moderate renal impairment ($eGFR_{CG}$: 30-69 mL/min) were switched to emtricitabine and tenofovir alafenamide (10 mg) given with elvitegravir and cobicistat as a fixed-dose combination tablet. Patients were virologically suppressed (HIV-1 RNA < 50 copies/mL) for at least 6 months before switching.

The mean age was 58 years (range: 24-82), with 63 patients (26%) who were ≥ 65 years of age. Seventy-nine percent were male, 63% were White, 18% were Black, and 14% were Asian. Thirteen percent of patients were identified as Hispanic/Latino. At baseline, median eGFR was 56 mL/min, and 33% of patients had an eGFR from 30 to 49 mL/min. The mean baseline CD4+ cell count was 664 cells/mm^3 (range: 126-1,813). At Week 48, 92% (222/242 patients) maintained HIV-1 RNA < 50 copies/mL after switching to emtricitabine and

tenofovir alafenamide given with elvitegravir and cobicistat as a fixed-dose combination tablet. Three patients had virological failure at Week 48.

Changes in measures of bone mineral density

In studies in treatment-naïve patients, emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat or darunavir and cobicistat as a fixed-dose combination tablet was associated with smaller reductions in bone mineral density (BMD; as measured by hip and lumbar spine dual energy X ray absorptiometry [DXA] analysis) compared to E/C/F/TDF or darunavir, cobicistat, emtricitabine and tenofovir disoproxil fumarate after 48 weeks of treatment. Small improvements in BMD were noted at 48 weeks after switching to emtricitabine and tenofovir alafenamide containing regimen from a TDF containing regimen compared to maintaining the TDF containing regimen.

Changes in measures of renal function

In studies in treatment-naïve patients, emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat or darunavir and cobicistat as a fixed-dose combination tablet was associated with lower impact of renal safety parameters (as measured by $eGFR_{CG}$, urine protein to creatinine ratio, and urine albumin to creatinine ratio) compared to E/C/F/TDF or darunavir and cobicistat and emtricitabine/tenofovir disoproxil fumarate after 48 weeks of treatment (see also section 4.4).

Paediatric population

In study GS-US-292-0106, the efficacy, safety, and pharmacokinetics of emtricitabine and tenofovir alafenamide were evaluated in an open-label study in which 50 HIV-1 infected, treatment-naïve adolescents received emtricitabine and tenofovir alafenamide (10 mg) given with elvitegravir and cobicistat as a fixed-dose combination tablet. Patients had a mean age of 15 years (range: 12-17), and 56% were female, 12% were Asian, and 88% were Black. At baseline, median plasma HIV-1 RNA was 4.7 $\log_{10}$ copies/mL, median CD4+ cell count was 456 cells/mm^3 (range: 95-1,110), and median CD4+% was 23% (range: 7-45%). Overall, 22% had baseline plasma HIV-1 RNA > 100,000 copies/mL. At 48 weeks, 92% (46/50) achieved HIV-1 RNA < 50 copies/mL, similar to response rates in studies of treatment-naïve HIV-1 infected adults. The mean increase from baseline in CD4+ cell count at Week 48 was 224 cells/mm^3. No emergent resistance to E/C/F/TAF was detected through Week 48.

The European Medicines Agency has deferred the obligation to submit the results of studies with Descovy in one or more subsets of the paediatric population in the treatment of HIV-1 infection (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Emtricitabine is rapidly and extensively absorbed following oral administration with peak plasma concentrations occurring at 1 to 2 hours post-dose. Following multiple dose oral administration of emtricitabine to 20 HIV-1 infected subjects, the (mean ± SD) steady state plasma emtricitabine peak concentrations (C_{max}) were 1.8 ± 0.7 μg/mL and the area-under the plasma concentration-time curve over a 24-hour dosing interval (AUC) was 10.0 ± 3.1 μg•h/mL. The mean steady state plasma trough concentration at 24 hours post-dose was equal to or greater than the mean *in vitro* IC90 value for anti-HIV-1 activity.

Emtricitabine systemic exposure was unaffected when emtricitabine was administered with food.

Following administration of food in healthy subjects, peak plasma concentrations were observed approximately 1 hour post-dose for tenofovir alafenamide administered as F/TAF (25 mg) or E/C/F/TAF (10 mg). The mean C_{max} and AUC_{last}, (mean ± SD) under fed conditions following a single 25 mg dose of tenofovir alafenamide administered in Descovy were 0.21 ± 0.13 μg/mL and 0.25 ± 0.11 μg•h/mL, respectively. The mean C_{max} and AUC_{last} following a single 10 mg dose of tenofovir alafenamide administered in E/C/F/TAF were 0.21 ± 0.10 μg/mL and 0.25 ± 0.08 μg•h/mL, respectively.

Relative to fasting conditions, the administration of tenofovir alafenamide with a high fat meal (~800 kcal, 50% fat) resulted in a decrease in tenofovir alafenamide C_{max} (15-37%) and an increase in AUC_{last} (17-77%).

Distribution

In vitro binding of emtricitabine to human plasma proteins was < 4% and independent of concentration over the range of 0.02-200 μg/mL. At peak plasma concentration, the mean plasma to blood drug concentration ratio was ~1.0 and the mean semen to plasma drug concentration ratio was ~4.0.

In vitro binding of tenofovir to human plasma proteins is < 0.7% and is independent of concentration over the range of 0.01-25 μg/mL. *Ex vivo* binding of tenofovir alafenamide to human plasma proteins in samples collected during clinical studies was approximately 80%.

Biotransformation

In vitro studies indicate that emtricitabine is not an inhibitor of human CYP enzymes. Following administration of [^{14}C]-emtricitabine, complete recovery of the emtricitabine dose was achieved in urine (~86%) and faeces (~14%). Thirteen percent of the dose was recovered in the urine as three putative metabolites. The biotransformation of emtricitabine includes oxidation of the thiol moiety to form the 3'-sulfoxide diastereomers (~9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (~4% of dose). No other metabolites were identifiable.

Metabolism is a major elimination pathway for tenofovir alafenamide in humans, accounting for > 80% of an oral dose. *In vitro* studies have shown that tenofovir alafenamide is metabolised to tenofovir (major metabolite) by cathepsin A in PBMCs (including lymphocytes and other HIV target cells) and macrophages; and by carboxylesterase-1 in hepatocytes. *In vivo*, tenofovir alafenamide is hydrolysed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite tenofovir diphosphate. In human clinical studies, a 10 mg oral dose of tenofovir alafenamide (given with emtricitabine and elvitegravir and cobicistat) resulted in tenofovir diphosphate concentrations > 4-fold higher in PBMCs and > 90% lower concentrations of tenofovir in plasma as compared to a 245 mg oral dose of tenofovir disoproxil (as fumarate) (given with emtricitabine and elvitegravir and cobicistat).

In vitro, tenofovir alafenamide is not metabolised by CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Tenofovir alafenamide is minimally metabolised by CYP3A4. Upon co-administration with the moderate CYP3A inducer probe efavirenz, tenofovir alafenamide exposure was not significantly affected. Following administration of tenofovir alafenamide, plasma [^{14}C]-radioactivity showed a time-dependent profile with tenofovir alafenamide as the most abundant species in the initial few hours and uric acid in the remaining period.

Elimination

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

Renal excretion of intact tenofovir alafenamide is a minor pathway with < 1% of the dose eliminated in urine. Tenofovir alafenamide is mainly 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.

Age, gender, and ethnicity

No clinically relevant pharmacokinetic differences due to age, gender or ethnicity have been identified for emtricitabine, or tenofovir alafenamide.

Paediatric population

Exposures of emtricitabine and tenofovir alafenamide (given with elvitegravir and cobicistat) achieved in 24 paediatric patients aged 12 to < 18 years who received emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat in study GS-US-292-0106 were similar to exposures achieved in treatment-naïve adults (Table 7).

Table 7: Pharmacokinetics of emtricitabine and tenofovir alafenamide in antiretroviral-naïve adolescents and adults

	Adolescents			**Adults**		
	FTC[a]	TAF[b]	TFV[b]	FTC[a]	TAF[c]	TFV[c]
AUC_{tau} (ng•h/mL)	14,424.4 (23.9)	242.8 (57.8)	275.8 (18.4)	11,714.1 (16.6)	206.4 (71.8)	292.6 (27.4)
C_{max} (ng/mL)	2,265.0 (22.5)	121.7 (46.2)	14.6 (20.0)	2,056.3 (20.2)	162.2 (51.1)	15.2 (26.1)
C_{tau} (ng/mL)	102.4 (38.9)[b]	N/A	10.0 (19.6)	95.2 (46.7)	N/A	10.6 (28.5)

E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate
FTC = emtricitabine; TAF = tenofovir alafenamide fumarate; TFV = tenofovir
N/A = not applicable
Data are presented as mean (%CV).
a n = 24 adolescents (GS-US-292-0106); n = 19 adults (GS-US-292-0102)
b n = 23 adolescents, (GS-US-292-0106, population PK analysis)
c n = 539 (TAF) or 841 (TFV) adults (GS-US-292-0111 and GS-US-292-0104, population PK analysis)

Renal impairment

No clinically relevant differences in tenofovir alafenamide, or tenofovir pharmacokinetics were observed between healthy subjects and patients with severe renal impairment (estimated CrCl > 15 but < 30 mL/min) in studies of tenofovir alafenamide. There are no pharmacokinetic data on tenofovir alafenamide in patients with estimated CrCl < 15 mL/min. Mean systemic emtricitabine exposure was higher in patients with severe renal impairment (CrCl < 30 mL/min) (33.7 μg•h/ml) than in subjects with normal renal function (11.8 μg•h/mL).

Hepatic impairment

The pharmacokinetics of emtricitabine have not been studied in subjects with hepatic impairment; however, emtricitabine is not significantly metabolised by liver enzymes, so the impact of liver impairment should be limited. Clinically relevant changes in tenofovir pharmacokinetics in patients with hepatic impairment were not observed in patients with mild to moderate hepatic impairment, and no tenofovir alafenamide dose adjustment is required in patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of tenofovir alafenamide has not been studied.

Hepatitis B and/or hepatitis C virus co-infection

The pharmacokinetics of emtricitabine and tenofovir alafenamide have not been fully evaluated in patients co-infected with HBV and/or HCV.

5.3 Preclinical safety data

Non-clinical data on emtricitabine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. Emtricitabine has demonstrated low carcinogenic potential in mice and rats.

Non-clinical studies of tenofovir alafenamide in rats and dogs revealed bone and kidney as the primary target organs of toxicity. Bone toxicity was observed as reduced BMD in rats and dogs at tenofovir exposures at least four times greater than those expected after administration of Descovy. A minimal infiltration of histiocytes was present in the eye in dogs at tenofovir alafenamide and tenofovir exposures of approximately 4 and 17 times greater, respectively, than those expected after administration of Descovy.

Tenofovir alafenamide was not mutagenic or clastogenic in conventional genotoxicity assays.

Because there is a lower tenofovir exposure in rats and mice after the administration of tenofovir alafenamide compared to tenofovir disoproxil fumarate, carcinogenicity studies and a rat peri-postnatal study were conducted only with tenofovir disoproxil fumarate. No special hazard for humans was revealed in conventional studies of carcinogenic potential and toxicity to reproduction and development. Reproductive toxicity studies in rats and rabbits showed no effects on mating, fertility, pregnancy or fetal parameters. However, tenofovir disoproxil fumarate reduced the viability index and weight of pups in a peri-postnatal toxicity study at maternally toxic doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core Descovy 200 mg/10 mg and 200 mg/25 mg

Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate

Film-coating Descovy 200 mg/10 mg

Polyvinyl alcohol
Titanium dioxide
Macrogol 3350
Talc
Iron oxide black (E172)

Film-coating Descovy 200 mg/25 mg

Polyvinyl alcohol
Titanium dioxide
Macrogol 3350
Talc
Indigo carmine aluminium lake (E132)

6.4 Special precautions for storage

Store below 30 °C (86 °F).

- Keep container tightly closed.
- Dispense only in original container.
- Do not use if seal over bottle opening is broken or missing.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with a polypropylene continuous-thread, child-resistant cap, lined with an induction activated aluminium foil liner containing 30 film-coated tablets. Each bottle contains silica gel desiccant and polyester coil.

The following pack sizes are available: outer cartons containing 1 bottle of 30 film-coated tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Manufactured and distributed by:
Gilead Sciences, Inc.
Foster City, CA 94404

Registration Numbers: