▼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.

POM

GILEAD SUPPLY FOR AFRICA

1. NAME OF THE MEDICINAL PRODUCT

Biktarvy™ 50 mg/200 mg/25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains bictegravir sodium equivalent to 50 mg of bictegravir, 200 mg of emtricitabine, and tenofovir alafenamide fumarate equivalent to 25 mg of tenofovir alafenamide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Purplish-brown, capsule-shaped, film-coated tablet debossed with "GSI" on one side and "9883" on the other side of the tablet. Each tablet is approximately 15 mm × 8 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Biktarvy is indicated for the treatment of adults infected with human immunodeficiency virus-1 (HIV-1) without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir (see section 5.1).

4.2 Posology and method of administration

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

Posology

One tablet to be taken once daily.

Missed doses
If the patient misses a dose of Biktarvy within 18 hours of the time it is usually taken, the patient should take Biktarvy as soon as possible and resume the normal dosing schedule. If a patient misses a dose of Biktarvy 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 Biktarvy another tablet should be taken. If a patient vomits more than 1 hour after taking Biktarvy they do not need to take another dose of Biktarvy until the next regularly scheduled dose.

Elderly

There are limited data on the use of Biktarvy in patients aged 65 years and over. No dose adjustment of Biktarvy is required in elderly patients (see sections 5.1 and 5.2).

Renal impairment
No dose adjustment of Biktarvy is required in patients with estimated creatinine clearance (CrCl) ≥ 30 mL/min.

Initiation of Biktarvy is not recommended in patients with estimated CrCl below 30 mL/min, as there are insufficient data available regarding the use of Biktarvy in this population (see section 5.2).

Hepatic impairment
No dose adjustment of Biktarvy is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Biktarvy has not been studied in patients with severe hepatic impairment (Child-Pugh Class C), therefore Biktarvy 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 Biktarvy in children under the age of 18 years have not yet been established. No data are available.

Method of administration

Oral use
Biktarvy can be taken with or without food (see section 5.2).
The film-coated tablets 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.

Co-administration with rifampicin and St John's Wort (*Hypericum perforatum*) (see section 4.5).

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.

There are limited safety and efficacy data for Biktarvy in patients co-infected with HIV-1 and hepatitis C virus (HCV).

Biktarvy contains tenofovir alafenamide, which is active against hepatitis B virus (HBV).

Discontinuation of Biktarvy 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 Biktarvy should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment.

Liver disease

The safety and efficacy of Biktarvy in patients with significant underlying liver disorders have not been established.

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 following exposure *in utero*

Nucleos(t)ide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or postnatally to nucleoside analogues; these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactatemia, hyperlipasemia). These events have often been transitory. Late onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed *in utero* to nucleos(t)ide analogues, who present with severe clinical findings of unknown etiology, particularly neurologic findings. 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 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.

Opportunistic infections

Patients should be advised that Biktarvy or any other antiretroviral therapy does not cure HIV infection and that they may still develop opportunistic infections and other complications of HIV infection. Therefore patients 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

Biktarvy should not be co-administered simultaneously with magnesium/aluminium-containing antacids or iron supplements under fasted conditions. Biktarvy should be administered at least 2 hours before, or with food 2 hours after antacids containing magnesium and/or aluminium. Biktarvy should be administered at least 2 hours before iron supplements, or taken together with food (see section 4.5).

Some medicinal products are not recommended for co-administration with Biktarvy: atazanavir, boceprevir, carbamazepine, ciclosporin (IV or oral use), oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifapentine, or sucralfate.

Biktarvy should not be co-administered with other antiretroviral medicinal products.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Biktarvy should not be administered concomitantly with medicinal products containing tenofovir alafenamide, tenofovir disoproxil, lamivudine or adefovir dipivoxil used for the treatment of HBV infection.

Bictegravir

Bictegravir is a substrate of CYP3A and UGT1A1. Co-administration of bictegravir and medicinal products that potently induce both CYP3A and UGT1A1, such as rifampicin or St. John's wort, may significantly decrease plasma concentrations of bictegravir, which may result in a loss of therapeutic effect of Biktarvy and development of resistance, therefore co-administration is contraindicated (see section 4.3). Co-administration of bictegravir with medicinal products that potently inhibit both CYP3A and UGT1A1, such as atazanavir, may significantly increase plasma concentrations of bictegravir, therefore co-administration is not recommended.

Bictegravir is both a P-gp and a BCRP substrate. The clinical relevance of this feature is not established. Therefore, caution is recommended when bictegravir is combined with medicinal products known to inhibit P-gp and/or BCRP (e.g. macrolides, ciclosporin, verapamil, dronedarone, glecaprevir/pibrentasvir) (see also table below).

Bictegravir inhibits organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter 1 (MATE1) *in vitro*. Co-administration of Biktarvy with the OCT2 and MATE1 substrate metformin did not result in a clinically significant increase in metformin exposure. Biktarvy may be co-administered with substrates of OCT2 and MATE1.

Bictegravir is not an inhibitor or inducer of CYP *in vivo*.

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). Co-administration of Biktarvy with medicinal products that strongly affect P-gp and BCRP activity may lead to changes in tenofovir alafenamide absorption. Medicinal products that induce P-gp activity (e.g. 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 Biktarvy and development of resistance. Co-administration of Biktarvy with other medicinal products that inhibit P-gp and BCRP may increase the absorption and plasma concentration of tenofovir alafenamide.

Tenofovir alafenamide is not an inhibitor or inducer of CYP3A *in vivo*.

Other interactions

Interactions between Biktarvy or its individual component(s) and co-administered medicinal products are listed in Table 1 below (increase is indicated as "↑", decrease as "↓" and no change as "↔"; all No Effect Boundaries are 70%-143%).

Table 1: Interactions between Biktarvy or its individual component(s) and other medicinal products

Medicinal product by therapeutic areas/Possible Mechanism of Interaction	Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with Biktarvy
HERBAL PRODUCTS		
St. John's wort (*Hypericum perforatum*) (Induction of CYP3A, UGT1A1, and P-gp)	Interaction not studied with any of the components of Biktarvy. Co-administration may decrease bictegravir and tenofovir alafenamide plasma concentrations.	Co-administration with St John's wort is contraindicated, due to the effect of St John's wort on the bictegravir component of Biktarvy.
ANTI-INFECTIVES		
Antimycobacterials		
Rifampicin (600 mg once daily), Bictegravir[1] (Induction of CYP3A, UGT1A1, and P-gp)	Bictegravir: AUC: ↓ 75% C_{max}: ↓ 28% Interaction not studied with tenofovir alafenamide. Co-administration of rifampicin may decrease tenofovir alafenamide plasma concentrations.	Co-administration is contraindicated due to the effect of rifampicin on the bictegravir component of Biktarvy.
Rifabutin (300 mg once daily), Bictegravir[1] (Induction of CYP3A and P-gp)	Bictegravir: AUC: ↓ 38% C_{min}: ↓ 56% C_{max}: ↓ 20% Interaction not studied with tenofovir alafenamide. Co-administration of rifabutin may decrease tenofovir alafenamide plasma concentrations.	Co-administration is not recommended due to the expected decrease of tenofovir alafenamide.
Rifapentine (Induction of CYP3A and P-gp)	Interaction not studied with any of the components of Biktarvy. Co-administration of rifapentine may decrease bictegravir and tenofovir alafenamide plasma concentrations.	Co-administration is not recommended.
HIV-1 Antiviral Agents		
Atazanavir (300 mg once daily), Cobicistat (150 mg once daily), Bictegravir[1] (Inhibition of CYP3A, UGT1A1, and P-gp/BCRP)	Bictegravir: AUC: ↑ 306% C_{max}: ↔	Co-administration is not recommended.
Atazanavir (400 mg once daily), Bictegravir[1] (Inhibition of CYP3A and UGT1A1)	Bictegravir: AUC: ↑ 315% C_{max}: ↔	
Hepatitis C Virus Antiviral Agents		
Boceprevir	Interaction not studied with any of the components of Biktarvy. Co-administration with boceprevir has the potential to adversely affect the intracellular activation and clinical antiviral efficacy of tenofovir alafenamide based on *in vitro* data.	Co-administration is not recommended.

Medicinal product by therapeutic areas/Possible Mechanism of Interaction	Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with Biktarvy
Ledipasvir/Sofosbuvir (90 mg/400 mg once daily), Bictegravir/Emtricitabine/ Tenofovir alafenamide[2]	Bictegravir: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Emtricitabine: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Tenofovir alafenamide: AUC: ↔ C_{max}: ↔ Ledipasvir: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Sofosbuvir: AUC: ↔ C_{max}: ↔ Sofosbuvir metabolite GS-331007: AUC: ↔ C_{min}: ↔ C_{max}: ↔	No dose adjustment is required upon co-administration.

Medicinal product by therapeutic areas/Possible Mechanism of Interaction	Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with Biktarvy
Sofosbuvir/Velpatasvir/ Voxilaprevir (400/100/100+100 mg[3] once daily), Bictegravir/Emtricitabine/ Tenofovir alafenamide (Inhibition of P-gp/BCRP)	Bictegravir: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Emtricitabine: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Tenofovir alafenamide: AUC: ↑ 57% C_{max}: ↑ 28% Sofosbuvir: AUC: ↔ C_{max}: ↔ Sofosbuvir metabolite GS-331007: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Velpatasvir: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Voxilaprevir: AUC: ↔ C_{min}: ↔ C_{max}: ↔	No dose adjustment is required upon co-administration.
Antifungals		
Voriconazole (300 mg twice daily), Bictegravir[1] (Inhibition of CYP3A)	Bictegravir: AUC: ↑ 61% C_{max}: ↔	No dose adjustment is required upon co-administration.
Itraconazole Posaconazole (Inhibition of P-gp/BCRP)	Interaction not studied with any of the components of Biktarvy. Co-administration of itraconazole or posaconazole may increase bictegravir plasma concentrations.	
Macrolides		
Azithromycin Clarithromycin (Inhibition of P-gp)	Not studied. Interaction not studied. Co-administration of azithromycin or clarithromycin may increase bictegravir plasma concentrations.	Caution is recommended due to the potential effect of these agents on the bictegravir component of Biktarvy.

Medicinal product by therapeutic areas/Possible Mechanism of Interaction	Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with Biktarvy
ANTICONVULSANTS		
Carbamazepine (titrated from 100 mg to 300 mg twice a day), Emtricitabine/Tenofovir alafenamide[4] (Induction of CYP3A, UGT1A1, and P-gp)	Tenofovir alafenamide: AUC: ↓ 54% C_{max}: ↓ 57% Interaction not studied with bictegravir. Co-administration of carbamazepine may decrease bictegravir plasma concentrations.	Co-administration is not recommended.
Oxcarbazepine Phenobarbital Phenytoin (Induction of CYP3A, UGT1A1, and P-gp)	Interaction not studied with any of the components of Biktarvy. Co-administration of oxcarbazepine, phenobarbital, or phenytoin may decrease bictegravir and tenofovir alafenamide plasma concentrations.	Co-administration is not recommended.
ANTACIDS, SUPPLEMENTS AND BUFFERED MEDICINES		
Magnesium/aluminium-containing antacid suspension (20 mL single dose[5]), Bictegravir (Chelation with polyvalent cations)	Bictegravir (antacid suspension 2 hours prior, fasted): AUC: ↓ 52% C_{max}: ↓ 58% Bictegravir (antacid suspension after 2 hours, fasted): AUC: ↔ C_{max}: ↔ Bictegravir (simultaneous administration, fasted): AUC: ↓ 79% C_{max}: ↓ 80% Bictegravir (simultaneous administration with food): AUC: ↓ 47% C_{max}: ↓ 49%	Biktarvy should not be taken simultaneously with supplements containing magnesium and/or aluminium due to the expected substantial decrease of bictegravir exposure (see section 4.4). Biktarvy should be administered at least 2 hours before, or with food 2 hours after antacids containing magnesium and/or aluminium.
Ferrous fumarate (324 mg single dose), Bictegravir (Chelation with polyvalent cations)	Bictegravir (simultaneous administration, fasted): AUC: ↓ 63% C_{max}: ↓ 71% Bictegravir (simultaneous administration with food): AUC: ↔ C_{max}: ↓ 25%	Biktarvy should be administered at least 2 hours before iron supplements, or taken together with food.

Medicinal product by therapeutic areas/Possible Mechanism of Interaction	Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with Biktarvy
Calcium carbonate (1200 mg single dose), Bictegravir (Chelation with polyvalent cations)	Bictegravir (simultaneous administration, fasted): AUC: ↓ 33% C_{max}: ↓ 42% Bictegravir (simultaneous administration with food): AUC: ↔ C_{max}: ↔	Biktarvy and calcium-containing supplements can be taken together, without regard to food.
Sucralfate (Chelation with polyvalent cations)	Interaction not studied with any of the components of Biktarvy. Co-administration may decrease bictegravir plasma concentrations.	Co-administration not recommended.
ANTIDEPRESSANTS		
Sertraline (50 mg single dose), Tenofovir alafenamide[6]	Tenofovir alafenamide: AUC: ↔ C_{max}: ↔ Sertraline: AUC: ↔ C_{max}: ↔ No interaction is expected with bictegravir and emtricitabine	No dose adjustment is required upon co-administration.
IMMUNOSUPPRESSANTS		
Ciclosporin (IV or oral use) (P-gp inhibition)	Interaction not studied with any of the components of Biktarvy. Co-administration of ciclosporin (IV or oral use) is expected to increase plasma concentrations of both bictegravir and tenofovir alafenamide.	Co-administration of ciclosporin (IV or oral use) is not recommended. If the combination is needed, clinical and biological monitoring, notably renal function, is recommended.
OPIOIDS		
Methadone	Not studied. (Inhibition of CYP1A2, 2B6, 2D6 by a bictegravir metabolite cannot be excluded).	Caution is recommended.
ORAL ANTI-DIABETICS		
Metformin (500 mg twice daily), Bictegravir/Emtricitabine/ Tenofovir alafenamide (Inhibition of OCT2/MATE1)	Metformin: AUC: ↑ 39% C_{min}: ↑ 36% C_{max}: ↔	No dose adjustment is required upon co-administration in patients with normal renal function. In patients with moderate renal impairment, close monitoring should be considered when starting coadministration of bictegravir with metformin, due to the increased risk for lactic acidosis in these patients. A dose adjustment of metformin should be considered if required.

Medicinal product by therapeutic areas/Possible Mechanism of Interaction	Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with Biktarvy
ORAL CONTRACEPTIVES		
Norgestimate (0.180/0.215/0.250 mg once daily)/ Ethinylestradiol (0.025 mg once daily), Bictegravir[1]	Norelgestromin: AUC: ↔ C_{min}: ↔ C_{max}: ↔	No dose adjustment is required upon co-administration.
Norgestimate (0.180/0.215/0.250 mg once daily), Ethinylestradiol (0.025 mg once daily), Emtricitabine/Tenofovir alafenamide[4]	Norgestrel: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Ethinylestradiol: AUC: ↔ C_{min}: ↔ C_{max}: ↔	
SEDATIVES/HYPNOTICS		
Midazolam (2 mg, oral syrup, single dose), Bictegravir/Emtricitabine/ Tenofovir alafenamide	Midazolam: AUC: ↔ C_{max}: ↔	No dose adjustment is required upon co-administration.

1 This study was conducted using bictegravir 75 mg single dose
2 This study was conducted using bictegravir/emtricitabine/tenofovir alafenamide 75/200/25 mg once daily
3 Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients
4 This study was conducted using emtricitabine/tenofovir alafenamide 200/25 mg once daily
5 Maximum strength antacid contained 80 mg aluminium hydroxide, 80 mg magnesium hydroxide, and 8 mg simethicone per mL
6 This study was conducted using elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide 150/150/200/10 mg once daily

Based on drug interaction studies conducted with Biktarvy or the components of Biktarvy, no clinically significant drug interactions are expected with: amlodipine, atorvastatin, buprenorphine, drospirenone, famciclovir, famotidine, fluticasone, naloxone, norbuprenorphin, omeprazole or rosuvastatin.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited data (less than 300 pregnancy outcomes) from the use of bictegravir or tenofovir alafenamide in pregnant women. 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 bictegravir and tenofovir alafenamide, administered separately, in animals have shown no evidence of harmful effects on fertility parameters, pregnancy, or foetal development (see section 5.3).

Biktarvy should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding

It is not known whether bictegravir or tenofovir alafenamide is excreted in human milk. Emtricitabine is excreted in human milk. In animal studies, bictegravir was detected in the plasma of nursing rat pups likely due to the presence of bictegravir in milk, without effects on nursing pups. In animal studies it has been shown that tenofovir is excreted in milk.

There is insufficient information on the effects of all the components of Biktarvy in newborns/infants, therefore Biktarvy 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

No human data on the effect of Biktarvy on fertility are available. Animal studies indicate no effects of bictegravir, emtricitabine or tenofovir alafenamide on mating or fertility (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 the components of Biktarvy (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The assessment of adverse reactions is based on safety data from across all Phase 2 and 3 studies with Biktarvy. In clinical studies of treatment-naive patients receiving Biktarvy through 48 weeks, the most frequently reported adverse reactions were headache (5%), diarrhoea (5%) and nausea (4%).

Tabulated summary of adverse reactions

The adverse reactions in Table 2 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 2: Tabulated list of adverse reactions[1]

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

[1] With the exception of angioedema and anaemia (see footnote 2), all adverse reactions were identified from clinical studies of emtricitabine+tenofovir alafenamide containing products. The frequencies were derived from Phase 3 Biktarvy clinical studies in treatment-naïve patients through 48 weeks (GS-US-380-1489 and GS-US-380-1490)
[2] This adverse reaction was not observed in the clinical studies of emtricitabine+tenofovir alafenamide 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=1563).

Description of selected adverse reactions

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

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 serum creatinine
Bictegravir has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine, however these changes are not considered to be clinically relevant since they do not reflect a change in glomerular filtration rate. Increases in serum creatinine occurred by Week 4 of treatment and remained stable through Week 48. In Studies GS-US-380-1489 and GS-US-380-1490, median (Q1, Q3) serum creatinine increased by 0.10 (0.03, 0.17) mg/dL, 0.11 (0.03, 0.18) mg/dL, and 0.11 (0.04, 0.19) mg/dL from baseline to Week 48 in the Biktarvy, abacavir/dolutegravir/lamivudine, and dolutegravir+emtricitabine/tenofovir alafenamide groups, respectively. There were no discontinuations due to renal adverse events through Week 48 in Biktarvy clinical studies.

Changes in bilirubin

In Studies GS-US-380-1489 and GS-US-380-1490, total bilirubin increases were observed in 12% of treatment-naïve patients administered Biktarvy through Week 48. Increases were primarily Grade 1 (9%) and Grade 2 (3%) (1.0 to 2.5 x Upper Limit of Normal [ULN]), and were not associated with hepatic adverse reactions or other liver related laboratory abnormalities. There were no discontinuations due to hepatic adverse events through Week 48 in Biktarvy clinical studies.

Other special populations

Patients co-infected with hepatitis B
In 16 HIV/HBV co-infected adults administered Biktarvy (8 HIV/HBV treatment-naïve adults in Study GS-US-380-1490; 8 HIV/HBV suppressed adults in Study GS-US-380-1878), the safety profile of Biktarvy was similar to that in patients with HIV-1 monoinfection (see section 5.1).

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. Healthcare professionals are asked to report any suspected adverse reactions **to 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 Biktarvy consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient.

There is no specific antidote for overdose with Biktarvy. As bictegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis. Emtricitabine can be removed by hemodialysis, 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 hemodialysis 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: J05AR20

Mechanism of action and pharmacodynamic effects

Bictegravir is an integrase strand transfer inhibitor (INSTI) that binds to the integrase active site and blocks the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. Bictegravir has activity against HIV-1 and HIV-2.

Emtricitabine is a nucleoside reverse transcriptase inhibitor (NRTI) and 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 phosphonamidate 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 loading tenofovir into peripheral blood mononuclear cells (PBMCs) (including lymphocytes and other HIV target cells) 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*

The antiviral activity of bictegravir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells, and CD4+ T-lymphocytes The 50% effective concentration (EC_{50}) values for bictegravir were in the range of < 0.05 to 6.6 nM. The protein-adjusted EC_{95} of bictegravir was 361 nM (0.162 micrograms/mL) for wild type HIV-1 virus. Bictegravir displayed antiviral activity in cell culture against HIV-1 group (M, N, O), including subtypes A, B, C, D, E, F, and G (EC_{50} values ranged from < 0.05 and 1.71 nM), and activity against HIV-2 (EC_{50} = 1.1 nM).

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 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 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, O), including subtypes A, B, C, D, E, F, and G (EC_{50} values ranged from 0.10 to 12.0 nM) and activity against HIV-2 (EC_{50} values ranged from 0.91 to 2.63 nM).

Resistance

In vitro
HIV-1 isolates with reduced susceptibility to bictegravir have been selected in cell culture. In one selection, amino acid substitutions M50I and R263K emerged and phenotypic susceptibility to bictegravir was reduced 1.3-, 2.2-, and 2.9-fold for M50I, R263K, and M50I+R263K, respectively. In a second selection, amino acid substitutions T66I and S153F emerged and phenotypic susceptibility to bictegravir was shifted 0.4-, 1.9-, and 0.5-fold for T66I, S153F, and T66I+S153F, respectively.

HIV-1 isolates with reduced susceptibility to emtricitabine have been selected in cell culture and had M184V/I mutations in HIV-1 RT.

HIV-1 isolates with reduced susceptibility to tenofovir alafenamide have been selected in cell culture and had the K65R mutation in HIV-1 RT; in addition, a K70E mutation in HIV-1 RT has been transiently observed. HIV-1 isolates with the K65R mutation have low level reduced susceptibility to abacavir, emtricitabine, tenofovir, and lamivudine. *In vitro* drug resistance selection studies with tenofovir alafenamide have shown no development of high-level resistance after extended culture.

In treatment-naïve (Studies GS-US-380-1489 and GS-US-380-1490) and virologically-suppressed patients (Studies GS-US-380-1844 and GS-US-380-1878), no patient receiving Biktarvy had HIV-1 with treatment emergent genotypic or phenotypic resistance to bictegravir, emtricitabine, or tenofovir alafenamide in the resistance analysis population (n=13 with HIV-1 RNA ≥ 200 copies/mL at the time of confirmed virologic failure, Week 48, or early study drug discontinuation). At the time of study entry, six treatment-naïve patients and one virologically-suppressed patient receiving Biktarvy had pre-existing INSTI resistance-associated mutations (6 subjects with T97A and one treatment-naïve subject with Q148H + G140S); all had HIV-1 RNA < 50 copies/mL at Week 48.

Cross-resistance
The susceptibility of bictegravir was tested against 64 INSTI-resistant clinical isolates (20 with single substitutions and 44 with 2 or more substitutions). Of these, all single and double mutant isolates lacking Q148H/K/R and 10 of 24 isolates with Q148H/K/R with additional INSTI resistance associated substitutions had ≤ 2.5-fold reduced susceptibility to bictegravir; > 2.5-fold reduced susceptibility to bictegravir was found for 14 of the 24 isolates that contained G140A/C/S and Q148H/R/K substitutions in integrase. Of those, 9 of the 14 isolates had additional mutations at L74M, T97A, or E138A/K. In addition, site-directed mutants with G118R and T97A+G118R had 3.4- and 2.8-fold reduced susceptibility to bictegravir, respectively. The relevance of these in vitro cross-resistance data remains to be established in clinical practice.

Bictegravir demonstrated equivalent antiviral activity against 5 NNRTI-resistant, 3 NRTI-resistant, and 4 PI-resistant HIV-1 mutant clones compared with the wild-type strain.

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

The efficacy and safety of Biktarvy in HIV-1 infected, treatment-naïve adults are based on 48-week data from two randomized, double-blind, active-controlled studies, GS-US-380-1489 (n=629) and GS-US-380-1490 (n=645).

The efficacy and safety of Biktarvy in virologically-suppressed HIV-1 infected adults are based on 48-week data from a randomized, double-blind, active-controlled study, GS-US-380-1844 (n=563); and a randomized, open label, active-controlled study, GS-US-380-1878 (n=577).

HIV-1 infected, treatment-naïve patients
In Study GS-US-380-1489, patients were randomized in a 1:1 ratio to receive either B/F/TAF (n=314) or abacavir/dolutegravir/lamivudine (600/50/300 mg) (n=315) once daily. In Study GS-US-380-1490, patients were randomized in a 1:1 ratio to receive either B/F/TAF (n=320) or dolutegravir + emtricitabine/tenofovir alafenamide (50+200/25 mg) (n=325) once daily.

In Studies GS-US-380-1489 and GS-US-380-1490, the mean age was 35 years (range 18-77), 89% were male, 58% were White, 33% were Black, and 3% were Asian. 24% percent of patients identified as Hispanic/Latino. The prevalence of different subtypes was comparable across all three treatment groups, with subtype B predominant in both groups; 11% were non-B subtypes. The mean baseline plasma HIV-1 RNA was 4.4 $\log_{10}$ copies/mL (range 1.3-6.6). The mean baseline CD4+ cell count was 460 cells/mm^3 (range 0-1636) and 11% had CD4+ cell counts less than 200 cells/mm^3. Eighteen percent of patients had baseline viral loads greater than 100,000 copies/mL. In both studies, patients were stratified by baseline HIV-1 RNA (less than or equal to 100,000 copies/mL, greater than 100,000 copies/mL to less than or equal to 400,000 copies/mL, or greater than 400,000 copies/mL), by

CD4 count (less than 50 cells/μL, 50-199 cells/μL, or greater than or equal to 200 cells/μL), and by region (US or ex-US).

Treatment outcomes of Studies GS-US-380-1489 and GS-US-380-1490 through Week 48 are presented in Table 3.

Table 3: Pooled Virologic Outcomes of Studies GS-US-380-1489 and GS-US-380-1490 at Week 48 in Treatment-Naïve Patients[a]

	B/F/TAF (n=634)[b]	ABC/DTG/3TC (n=315)[c]	DTG + F/TAF (n=325)[d]
HIV-1 RNA < 50 copies/mL	91%	93%	93%
Treatment Difference (95% CI) B/F/TAF vs. Comparator	-	-2.1% (-5.9% to 1.6%)	-1.9% (-5.6% to 1.8%)
HIV-1 RNA ≥ 50 copies/mL[e]	3%	3%	1%
No Virologic Data at Week 48 Window	6%	4%	6%
Discontinued Study Drug Due to AE or Death[f]	<1%	1%	1%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[g]	4%	3%	4%
Missing Data During Window but on Study Drug	2%	<1%	1%
Proportion (%) of Patients with HIV-1 RNA < 50 copies/mL by Subgroup[h]			
By Baseline Viral Load			
≤ 100,000 copies/mL	92%	94%	93%
> 100,000 copies/mL	87%	90%	94%
By Baseline CD4+ Cell Count			
< 200 cells/mm^3	90%	81%	100%
≥ 200 cells/mm^3	91%	94%	92%
HIV-1 RNA < 20 copies/mL	85%	87%	87%

ABC=abacavir DTG=dolutegravir 3TC=lamivudine F/TAF=emtricitabine/tenofovir alafenamide

a Week 48 window was between Day 295 and 378 (inclusive).

b Pooled from Study GS-US-380-1489 (n=314) and Study GS-US-380-1490 (n=320).

c Study GS-US-380-1489

d Study GS-US-380-1490

e Includes 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.

f 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.

g 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.

h Patients who had ≥ 50 copies/mL in the Week 48 window included patients who discontinued early due to lack or loss of efficacy (n=0), and patients who discontinued for reasons other than an AE, death or lack or loss of efficacy (B/F/TAF n=12; ABC/DTG/3TC n=2; DTG+F/TAF n=3), and at the time of discontinuation had a viral value of ≥ 50 copies/mL.

B/F/TAF was non-inferior in achieving HIV-1 RNA < 50 copies/mL at Week 48 when compared to abacavir/dolutegravir/lamivudine and dolutegravir+emtricitabine/tenofovir alafenamide, respectively. Treatment outcomes were similar across subgroups by age, sex, race, baseline viral load, baseline CD4+ cell count, and region.

In Studies GS-US-380-1489 and GS-US-380-1490, the mean increase from baseline in CD4+ count at Week 48 was 207, 229, and 201 cells/mm^3 in the pooled B/F/TAF, abacavir/dolutegravir/lamivudine, and dolutegravir+emtricitabine/tenofovir alafenamide groups, respectively.

HIV-1 infected, virologically suppressed patients
In Study GS-US-380-1844, the efficacy and safety of switching from a regimen of dolutegravir+abacavir/lamivudine or abacavir/dolutegravir/lamivudine to B/F/TAF were evaluated in a randomized, double-blind study of virologically-suppressed (HIV-1 RNA < 50 copies/mL) HIV-1 infected adults (n=563). Patients must have been stably suppressed (HIV-1 RNA < 50 copies/mL) on their baseline regimen for at least 3 months prior to study entry. Patients were randomized in a 1:1 ratio to either switch to B/F/TAF at baseline (n=282), or stay on their baseline antiretroviral regimen (n=281). Patients had a mean age of 45 years (range 20-71), 89% were male, 73% were White, and 22% were Black. 17% of patients identified as Hispanic/Latino. The prevalence of different HIV-1 subtypes was comparable between treatment groups, with subtype B predominant in both groups; 5% were non-B subtypes. The mean baseline CD4+ cell count was 723 cells/mm^3 (range 124-2444).

In Study GS-US-380-1878, the efficacy and safety of switching from either abacavir/lamivudine or emtricitabine/tenofovir disoproxil fumarate (200/300 mg) plus atazanavir or darunavir (boosted by either cobicistat or ritonavir) to B/F/TAF were evaluated in a randomized, open-label study of virologically-suppressed HIV-1 infected adults (n=577). Patients must have been stably suppressed on their baseline regimen for at least 6 months and must not have been previously treated with any INSTI. Patients were randomized in a 1:1 ratio to either switch to B/F/TAF (n=290), or stay on their baseline antiretroviral regimen (n=287). Patients had a mean age of 46 years (range 20-79), 83% were male, 66% were White, and 26% were Black. 19% of patients identified as Hispanic/Latino. The mean baseline CD4+ cell count was 663 cells/mm^3 (range 62-2582). The prevalence of different subtypes was comparable across treatment groups, with subtype B predominant in both groups; 11% were non-B subtypes. Patients were stratified by prior treatment regimen. At screening, 15% of patients were receiving abacavir/lamivudine plus atazanavir or darunavir (boosted by either cobicistat or ritonavir) and 85% of patients were receiving emtricitabine/tenofovir disoproxil fumarate plus atazanavir or darunavir (boosted by either cobicistat or ritonavir).

Treatment outcomes of Studies GS-US-380-1844 and GS-US-380-1878 through Week 48 are presented in Table 4.

Table 4: Virologic Outcomes of Studies GS-US-380-1844 and GS-US-380-1878 at Week 48[a]

	Study GS-US-380-1844		**Study GS-US-380-1878**	
	B/F/TAF(n=282)	**ABC/DTG/3TC (n=281)**	**B/F/TAF (n=290)**	**Baseline ATV- or DRV-based regimen (n=287)**
HIV-1 RNA < 50 copies/mL	94%	95%	92%	89%
Treatment Difference (95% CI)	-1.4% (-5.5% to 2.6%)		3.2% (-1.6% to 8.2%)	
HIV-1 RNA ≥ 50 copies/mL[b]	1%	<1%	2%	2%
Treatment Difference (95% CI)	0.7% (-1.0% to 2.8%)		0.0% (-2.5% to 2.5%)	
No Virologic Data at Week 48 Window	5%	5%	6%	9%
Discontinued Study Drug Due to AE or Death and Last Available HIV-1 RNA < 50 copies/mL	2%	1%	1%	1%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[c]	2%	3%	3%	7%
Missing Data During Window but on Study Drug	2%	1%	2%	2%

ABC= abacavir ATV=atazanavir DRV=darunavir DTG=dolutegravir 3TC=lamivudine
a Week 48 window was between Day 295 and 378 (inclusive).
b Includes 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 lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.
c 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.

B/F/TAF was non-inferior to the control regimen in both studies. Treatment outcomes between treatment groups were similar across subgroups by age, sex, race, and region.

In GS-US-380-1844, the mean change from baseline in CD4+ count at Week 48 was -31 cells/mm^3 in patients who switched to B/F/TAF and 4 cells/mm^3 in patients who stayed on abacavir/dolutegravir/lamivudine. In GS-US-380-1878, the mean change from baseline in CD4+ count at Week 48 was 25 cells/mm^3 in patients who switched to B/F/TAF and 0 cells/mm^3 in patients who stayed on their baseline regimen.

Patients co-infected with HIV and HBV
The number of patients co-infected with HIV and HBV treated with B/F/TAF is limited. In Study GS-US-380-1490, 7 of 8 patients with HIV/HBV co-infection at baseline who were randomized to receive B/F/TAF were HBV suppressed (HBV DNA < 29 IU/mL) and had HIV-1 RNA < 50 copies/mL at Week 48. One patient had missing HBV DNA data at Week 48.

In Study GS-US-380-1878, at Week 48, 100% (8/8) of the patients co-infected with HIV/HBV at baseline in the B/F/TAF arm maintained HBV DNA < 29 IU/mL (missing = excluded analysis) and HIV RNA < 50 copies/mL.

Paediatric population

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

5.2 Pharmacokinetic properties

Absorption

Bictegravir is absorbed following oral administration with peak plasma concentrations occurring at 2.0-4.0 hours after administration of B/F/TAF. Relative to fasting conditions, the administration of B/F/TAF with either a moderate fat (~600 kcal, 27% fat) or high fat meal (~800 kcal, 50% fat) resulted in an increase in bictegravir AUC (24%). This modest change is not considered clinically meaningful and B/F/TAF can be administered with or without food.

Following oral administration of B/F/TAF with or without food in HIV-1 infected adults, the multiple dose mean (CV%) pharmacokinetic parameters of bictegravir were C_{max} = 6.15 mcg/mL (22.9%), AUC_{tau} = 102 mcg•h/mL (26.9%), and C_{trough} = 2.61 mcg/mL (35.2%).

Emtricitabine is rapidly and extensively absorbed following oral administration with peak plasma concentrations occurring at 1.5-2.0 hours after administration of B/F/TAF. The mean absolute bioavailability of emtricitabine from 200 mg hard capsules was 93%. Emtricitabine systemic exposure was unaffected when emtricitabine was administered with food and B/F/TAF can be administered with or without food.

Following oral administration of B/F/TAF with or without food in HIV-1 infected adults, the multiple dose mean (CV%) pharmacokinetic parameters of emtricitabine were C_{max} = 2.13 mcg/mL (34.7%), AUC_{tau} = 12.3 mcg•h/mL (29.2%), and C_{trough} = 0.096 mcg/mL (37.4%).

Tenofovir alafenamide is rapidly absorbed following oral administration with peak plasma concentrations occurring at 0.5-2.0 hours after administration of B/F/TAF. Relative to fasting conditions, the administration of tenofovir alafenamide with a moderate fat meal (~600 kcal, 27% fat) and a high fat meal (~800 kcal, 50% fat) resulted in an increase in AUC_{last} by 48% and 63%, respectively. These modest changes are not considered clinically meaningful and B/F/TAF can be administered with or without food.

Following oral administration of B/F/TAF with or without food in HIV-1 infected adults, the multiple dose mean (CV%) pharmacokinetic parameters of tenofovir alafenamide were C_{max} = 0.121 mcg/mL (15.4%), and AUC_{tau} = 0.142 mcg•h/mL (17.3%).

Distribution

In vitro binding of bictegravir to human plasma proteins was > 99% (free fraction ~0.25%). The *in vitro* human blood to plasma bictegravir concentration ratio was 0.64.

In vitro binding of emtricitabine to human plasma proteins was < 4% and independent of concentration over the range of 0.02 to 200 mcg/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 less than 0.7% and is independent of concentration over the range of 0.01-25 mcg/mL. *Ex-vivo* binding of tenofovir alafenamide to human plasma proteins in samples collected during clinical studies was approximately 80%.

Biotransformation

Metabolism is the major clearance pathway for bictegravir in humans. *In vitro* phenotyping studies showed that bictegravir is primarily metabolized by CYP3A and UGT1A1. Following a single dose oral administration of [^{14}C]-bictegravir, ~60% of the dose from faeces included unchanged parent, desfluoro-hydroxy- BIC-cysteine-conjugate, and other minor oxidative metabolites. Thirty five percent of the dose was recovered from urine and consisted primarily of the glucuronide of bictegravir and other minor oxidative metabolites and their phase II conjugates. Renal clearance of the unchanged parent was minimal.

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 25 mg oral dose of tenofovir alafenamide resulted in tenofovir diphosphate concentrations > 4-fold higher in PBMCs and > 90% lower concentrations of tenofovir in plasma as compared to a 300 mg oral dose of tenofovir disoproxil fumarate.

Elimination

Bictegravir is primarily eliminated by hepatic metabolism. Renal excretion of intact bictegravir is a minor pathway (~1% of dose). The plasma bictegravir half-life was 17.3 hours.

Emtricitabine is primarily excreted by the kidneys by both glomerular filtration and active tubular secretion. The plasma emtricitabine half-life was approximately 10 hours.

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 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.

Linearity

The multiple dose pharmacokinetics of bictegravir are dose proportional over the dose range of 25 to 100 mg. The multiple dose pharmacokinetics of emtricitabine are dose proportional over the dose range of 25 to 200 mg. Tenofovir alafenamide exposures are dose proportional over the dose range of 8 mg to 125 mg.

Other special populations

Renal impairment
No clinically relevant differences in bictegravir, tenofovir alafenamide, or tenofovir pharmacokinetics were observed between healthy subjects and subjects with severe renal impairment (estimated CrCl < 30 mL/min). There are no pharmacokinetic data on bictegravir or tenofovir alafenamide in patients with creatinine clearance less than 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
Clinically relevant changes in the pharmacokinetics of bictegravir were not observed in subjects with moderate 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 the pharmacokinetics of tenofovir alafenamide or its metabolite tenofovir were not observed in patients with mild, moderate, or severe hepatic impairment.

Age, gender and race
Pharmacokinetics of bictegravir, emtricitabine, and tenofovir have not been fully evaluated in the elderly (≥ 65 years of age). Population analyses using pooled pharmacokinetic data from adult trials did not identify any clinically relevant differences due to age, gender or race on the exposures of bictegravir, emtricitabine, or tenofovir alafenamide.

5.3 Preclinical safety data

Bictegravir was not mutagenic or clastogenic in conventional genotoxicity assays.

Bictegravir was not carcinogenic in a 6-month rasH2 transgenic mouse study (at doses of up to 100 mg/kg/day in males and 300 mg/kg/day in females, which resulted in exposures of approximately 15 and 23 times, in males and females, respectively, the exposure in humans at the recommended human dose) nor in a 2-year rat study (at doses of up to 300 mg/kg/day, which resulted in exposures of approximately 31 times the exposure in humans).

Studies of bictegravir in monkeys revealed the liver as the primary target organ of toxicity. Hepatobiliary toxicity was described in a 39-week study at a dosage of 1000 mg/kg/day, which resulted in exposures of approximately 16 times the exposure in humans at the recommended human dose, and was partially reversible after a 4-week recovery period.

Studies in animals with bictegravir have shown no evidence of teratogenicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with bictegravir during pregnancy, there were no toxicologically significant effects on developmental endpoints.

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 bone mineral density in rats and dogs at tenofovir exposures at least 43-times greater than those expected after administration of B/F/TAF.

A minimal infiltration of histiocytes was present in the eye in dogs at tenofovir alafenamide and tenofovir exposures of approximately 14- and 43-times greater, respectively, than those expected after administration of B/F/TAF.

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 foetal 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
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate

Film-coating
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol
Talc
Iron oxide red (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.4 Special precautions for storage

Store below 30°C (86°F). Store in the original package in order to protect from moisture. Keep the bottle tightly closed. Do not use if seal over bottle opening is broken or missing.

6.5 Nature and contents of container

White, 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.

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 for:
Gilead Sciences, Inc.
Foster City, CA 94404

Registration Number:

KEN-AUG18-EU-JUN18

Package leaflet: Information for the user

Biktarvy 50 mg/200 mg/25 mg film-coated tablets
bictegravir/emtricitabine/tenofovir alafenamide

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Biktarvy is and what it is used for

Biktarvy contains three active substances:
- **bictegravir**, an antiretroviral medicine known as an integrase strand transfer inhibitor (INSTI)
- **emtricitabine**, an antiretroviral medicine of a type known as a nucleoside reverse transcriptase inhibitor (NRTI)
- **tenofovir alafenamide**, an antiretroviral medicine of a type known as a nucleotide reverse transcriptase inhibitor (NtRTI)

Biktarvy is a single tablet for the treatment of human immunodeficiency virus 1 (HIV-1) infection in adults.

Biktarvy reduces the amount of HIV in your body. This will improve your immune system and reduce the risk of developing illnesses linked to HIV infection.

2. What you need to know before you take Biktarvy

Do not take Biktarvy:

- **If you are allergic to bictegravir, emtricitabine, tenofovir alafenamide** or any of the other ingredients of this medicine (listed in section 6).

- **If you are currently taking any of the following medicines:**
  - **rifampicin** used to treat some bacterial infections such as tuberculosis
  - **St John's wort** (*Hypericum perforatum)*, a herbal remedy used for depression and anxiety, or products that contain it.

→ If any of these apply to you, **do not take Biktarvy and tell your doctor immediately.**

Warnings and precautions

Talk to your doctor before taking Biktarvy:

- **If you have liver problems or a history of liver disease, including hepatitis.** Patients with liver disease including chronic hepatitis B or C, who are treated with antiretrovirals, have a higher risk of severe and potentially fatal liver complications. If you have hepatitis B infection, your doctor will carefully consider the best treatment regimen for you.

- **If you have hepatitis B infection.** Liver problems may become worse after you stop taking Biktarvy.

→ Do not stop taking Biktarvy if you have hepatitis B. Talk to your doctor first. For more details, see section 3, *Do not stop taking Biktarvy.*

While you are taking Biktarvy

Once you start taking Biktarvy, look out for:

- **Signs of inflammation or infection**
- **Joint pain, stiffness** or **bone problems**

→ **If you notice any of these symptoms, tell your doctor immediately.** For more information see section 4, *Possible side effects*.

It is possible that in the future, long-term users of Biktarvy may get kidney problems.

You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your doctor the precautions needed to avoid infecting other people. This medicine is not a cure for HIV infection. While taking Biktarvy you may still develop infections or other illnesses associated with HIV infection.

Children and adolescents

Do not give this medicine to children and adolescents under 18 years of age. The use of Biktarvy in children and adolescents under 18 years of age has not yet been studied.

Other medicines and Biktarvy

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Biktarvy may interact with other medicines. As a result, the amounts of Biktarvy or other medicines in your blood may change. This may stop your medicines from working properly, or may make any side effects worse. In some cases, your doctor may need to adjust your dose or check your blood levels.

Medicines that must never be taken with Biktarvy:
- **rifampicin** used to treat some bacterial infections such as tuberculosis
- **St John's wort** (*Hypericum perforatum)*, a herbal remedy used for depression and anxiety, or products that contain it.

→ If you are taking any of these medicines, **do not take Biktarvy and tell your doctor immediately.**

Talk to your doctor if you are taking:

- **medicines used for treating HIV and/or hepatitis B**, containing:
  - adefovir dipivoxil, atazanavir, bictegravir, emtricitabine, lamivudine, tenofovir alafenamide, or tenofovir disoproxil
- **antibiotics used to treat bacterial infections,** containing:
  - azithromycin, clarithromycin, rifabutin or rifapentine
- **antiviral medicines used to treat hepatitis C**, containing boceprevir
- **anticonvulsants** used to treat epilepsy, containing:
  - carbamazepine, oxcarbazepine, phenobarbital and phenytoin
- **immunosuppressants** used to control your body's immune response after a transplant, containing ciclosporin
- **ulcer-healing medicines** containing sucralfate
- **medicines to treat opioid addiction,** containing methadone.

→ **Tell your doctor if you are taking any of these medicines.** Do not stop your treatment without contacting your doctor.

Get advice from a doctor or pharmacist if you are taking:

- **antacids** to treat stomach ulcers, heartburn, or acid reflux, containing aluminium and/or magnesium hydroxide
- **mineral supplements** or **vitamins** containing magnesium or iron

→ **Get advice from your doctor or pharmacist before taking Biktarvy** if you are taking any of these medicines.
Antacids and magnesium supplements: you will need to take Biktarvy at least 2 hours **before** antacids or supplements containing aluminium and/or magnesium. Or you can take Biktarvy with food at least 2 hours **after**.
Iron supplements: you will need to take Biktarvy at least 2 hours **before** iron supplements, or you can take them together with food.

Pregnancy and breast-feeding

- If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Ask your doctor or pharmacist for advice before taking any medicine when pregnant.

If you have taken Biktarvy during your pregnancy, your doctor may request regular blood tests and other diagnostic tests to monitor the development of your child. In children whose mothers took nucleoside reverse transcriptase inhibitors (NRTIs) during pregnancy, the benefit from the protection against HIV outweighed the risk of side effects.

Do not breast-feed during treatment with Biktarvy. This is because some of the active substances in this medicine pass into human breast milk. It is also recommended that you do not breast-feed to avoid passing the virus to the baby in breast milk. If you really want to breastfeed, talk to your doctor first.

Driving and using machines

Biktarvy can cause dizziness. If you feel dizzy when taking Biktarvy, do not drive and do not use any tools or machines.

3. How to take Biktarvy

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is:

Adults: one tablet each day with or without food

Do not chew, crush or split the tablet.

→Get advice from a doctor or pharmacist if you are taking:
- **antacids** to treat stomach ulcers, heartburn, or acid reflux, containing aluminium and/or magnesium hydroxide
- **mineral supplements** or **vitamins** containing magnesium or iron

→See section 2 for more information on taking these medicines with Biktarvy.

If you take more Biktarvy than you should

If you take more than the recommended dose of Biktarvy you may be at higher risk of side effects of this medicine (see section 4, *Possible side effects*).

Contact your doctor or nearest emergency department immediately for advice. Keep or take the tablet bottle with you so that you can easily describe what you have taken.

If you forget to take Biktarvy

It is important not to miss a dose of Biktarvy.

If you do miss a dose:
- **If you notice within 18 hours** of the time you usually take Biktarvy, you must take the tablet as soon as possible. Then take the next dose as usual.
- **If you notice 18 hours or more** after the time you usually take Biktarvy, then do not take the missed dose. Wait and take the next dose at your usual time.

If you vomit less than 1 hour after taking Biktarvy, take another tablet. If you vomit more than 1 hour after taking Biktarvy you do not need to take another tablet until your next regularly scheduled tablet.

Do not stop taking Biktarvy

Do not stop taking Biktarvy without talking to your doctor. Stopping Biktarvy can seriously affect how future treatment works. If Biktarvy is stopped for any reason, speak to your doctor before you restart taking Biktarvy tablets.

When your supply of Biktarvy starts to run low, get more from your doctor or pharmacist. This is very important because the amount of virus may start to increase if the medicine is stopped for even a short time. The disease may then become harder to treat.

If you have both HIV infection and hepatitis B, it is especially important not to stop your Biktarvy treatment without talking to your doctor first. You may require blood tests for several months after stopping treatment. In some patients with advanced liver disease or cirrhosis, stopping treatment is not recommended as this may lead to worsening of your hepatitis, which may be life-threatening.

→ **Tell your doctor immediately** about new or unusual symptoms after you stop treatment, particularly symptoms you associate with hepatitis B infection.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Possible side effects: tell a doctor immediately

- **Any signs of inflammation or infection.** In some patients with advanced HIV infection (AIDS) and a history of opportunistic infections (infections that occur in people with a weak immune system), signs and symptoms of inflammation from previous infections may occur soon after HIV treatment is started. It is thought that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms.

- **Autoimmune disorders**, when the immune system attacks healthy body tissue, may also occur after you start taking medicines for HIV infection. Autoimmune disorders may occur many months after the start of treatment. Look out for any symptoms of infection or other symptoms such as:
  - muscle weakness
  - weakness beginning in the hands and feet and moving up towards the trunk of the body
  - palpitations, tremor or hyperactivity

→ If you notice these or any symptoms of inflammation or infection, tell your doctor immediately.

Common side effects
(may affect up to 1 in 10 people)
- depression
- abnormal dreams
- headache
- dizziness
- diarrhoea
- feeling sick (*nausea*)
- tiredness (*fatigue*)

Uncommon side effects
(*may affect up to 1 in 100 people*)
- anaemia
- vomiting
- stomach pain
- problems with digestion resulting in discomfort after meals (*dyspepsia*)
- wind (*flatulence*)
- swelling of the face, lips, tongue or throat (*angioedema*)
- itching (*pruritus*)
- rash
- joint pain (*arthralgia*)
- suicidal behaviour
- anxiety
- sleep disorders

Blood tests may also show:
- higher levels of substances called bilirubin and/or serum creatinine in the blood

→ If any of the side effects get serious, tell your doctor.

Other effects that may be seen during HIV treatment

The frequency of the following side effects is not known (frequency cannot be estimated from the available data).

- **Bone problems.** Some patients taking combination antiretroviral medicines such as Biktarvy may develop a bone disease called *osteonecrosis* (death of bone tissue caused by loss of blood supply to the bone). Taking this type of medicine for a long time, taking corticosteroids, drinking alcohol, having a very weak immune system, and being overweight, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are:
  - joint stiffness
  - joint aches and pains (especially of the hip, knee and shoulder)
  - difficulty with movement

→ If you notice any of these symptoms tell your doctor.

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. To report suspected side effects, contact Gilead Sciences, Inc. at safety_FC@gilead.com.
To received medical information on Biktarvy please contact MedicalInformation@gilead.com. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Biktarvy

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and bottle. The expiry date refers to the last day of that month.

Store below 30° (86°F).

Store in the original package in order to protect from moisture. Keep the bottle tightly closed. Do not use if the seal over the bottle opening is broken or missing.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Biktarvy contains

The active substances are bictegravir, emtricitabine and tenofovir alafenamide. Each Biktarvy tablet contains bictegravir sodium equivalent to 50 mg of bictegravir, 200 mg of emtricitabine and tenofovir alafenamide fumarate equivalent to 25 mg of tenofovir alafenamide.

The other ingredients are

Tablet core
Microcrystalline cellulose, croscarmellose sodium, magnesium stearate

Film-coating
Polyvinyl alcohol, titanium dioxide (E171), macrogol, talc, iron oxide red (E172), iron oxide black (E172).

What Biktarvy looks like and contents of the pack

Biktarvy film-coated tablets are purplish-brown, capsule-shaped, film-coated tablets debossed on one side with "GSI" and "9883" on the other side. Biktarvy comes in bottles of 30 tablets. Each bottle contains a silica gel desiccant that must be kept in the bottle to help protect your tablets. The silica gel desiccant is contained in a separate sachet or canister and should not be swallowed.

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IDA Business and Technology Park
Carrigtohill
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