BIKTARVY® 30/120/15 mg
BIKTARVY® 50/200/25 mg
(Bictegravir/emtricitabine/tenofovir alafenamide fumarate)
Film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Biktarvy® 30/120/15 mg
Biktarvy® 50/200/25 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Biktarvy® 30/120/15 mg
Each film-coated tablet of Biktarvy® 30/120/15 mg contains bictegravir sodium equivalent to 30 mg of bictegravir, 120 mg of emtricitabine, and tenofovir alafenamide fumarate equivalent to 15 mg of tenofovir alafenamide.

Biktarvy® 50/200/25 mg
Each film-coated tablet of Biktarvy® 50/200/25 mg 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).

Biktarvy® 30/120/15 mg
Pink, capsule-shaped, film-coated tablet, debossed with “BVY” on one side and a score line on the other side of the tablet. Each tablet is approximately 14 mm x 6 mm. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Biktarvy® 50/200/25 mg
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 30/120/15 mg is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and paediatric patients at least 2 years of age and weighing at least 14 kg without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir (see section 5.1).

Biktarvy 50/200/25 mg is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and paediatric patients at least 6 years of age and weighing at least 25 kg 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
Paediatric patients at least 2 years of age and weighing at least 14 kg to less than 25 kg
One 30/120/15 mg tablet to be taken once daily.

Adults and paediatric patients weighing at least 25 kg
One 50/200/25mg 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.

Special populations

Elderly
No dose adjustment of Biktarvy is required in patients aged ≥ 65 years (see sections 4.8 and 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).

Renal impairment
No dose adjustment of Biktarvy 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.

No dose adjustment of Biktarvy is required in adult patients with end stage renal disease (estimated creatinine clearance < 15 mL/minute) who are receiving chronic haemodialysis. However, Biktarvy should generally be avoided and only be used in these patients if the potential benefits are considered to outweigh the potential risks (see sections 4.4 and 5.2). On days of haemodialysis, administer the daily dose of Biktarvy after completion of haemodialysis treatment.

Initiation of Biktarvy should be avoided in patients with estimated creatinine clearance ≥15 mL/min and < 30 mL/min, or < 15 mL/min who are not receiving chronic haemodialysis, as the safety of Biktarvy has not been established in these populations (see section 5.2).

No data are available to make dose recommendations in patients weighing < 35 kg with renal impairment or in paediatric patients less than 18 years with end stage renal disease.

Paediatric population
The safety and efficacy of Biktarvy in children less than 2 years of age or weighing less than 14 kg 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).
Due to the bitter taste, it is recommended that the film-coated tablets should not be chewed or crushed. For patients who are unable to swallow the tablet whole, the tablet may be split in half and both halves taken one after the other, ensuring that the full dose is taken immediately.

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

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 lifestyle. For lipids and weight, there is in some cases evidence for a treatment effect. 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 aetiology, 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 and autoimmune hepatitis) 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

Post-marketing cases of renal impairment, including acute renal failure and proximal renal tubulopathy have been reported with tenofovir alafenamide-containing products. 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).

It is recommended that renal function is assessed in all patients prior to, or when initiating, therapy with Biktarvy and that it is also monitored during therapy in all patients as clinically appropriate. In patients who develop clinically significant decreases in renal function, or evidence of proximal renal tubulopathy, discontinuation of Biktarvy should be considered.

Patients with end stage renal disease on chronic haemodialysis

Biktarvy should generally be avoided but may be used in adults with end stage renal disease (estimated CrCl < 15 mL/min) on chronic haemodialysis if the potential benefits outweigh the potential risks (see section 4.2). In a study of emtricitabine + tenofovir alafenamide in combination with elvitegravir + cobicistat as a fixed-dose combination tablet (E/C/F/TAF) in HIV-1 infected adults with end stage renal disease (estimated CrCl < 15 mL/min) on chronic haemodialysis, efficacy was maintained through 96 weeks but emtricitabine exposure was significantly higher than in patients with

normal renal function. Efficacy was also maintained in the extension phase of the study in which 10 patients switched to Biktarvy for 48 weeks. Although no additional adverse reactions were identified, the implications of increased emtricitabine exposure remain uncertain (see sections 4.8 and 5.2).

Co-administration of other medicinal products or supplements

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

In pregnant patients, dosage adjustments are recommended for co-administration of polyvalent cation-containing antacids, oral medications or supplements (see section 4.5).

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

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

Paediatric population

Reductions in bone mineral density (BMD $\geq$ 4%) of the spine and total body less head (TBLH) have been reported in patients aged between 3 to < 12 years who received tenofovir alafenamide-containing products for 48 weeks (see section 4.8). The long-term effects of changes in BMD on the growing bone, including the risk of fracture, are uncertain. A multidisciplinary approach is recommended to decide the appropriate monitoring during treatment.

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

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.

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
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.

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
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		
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)	Interaction not studied. Co-administration of azithromycin or clarithromycin may increase bictegravir plasma concentrations.	Caution is recommended due to the potential effect of these medicinal products 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%	*For non-pregnant patients:* Biktarvy should not be taken simultaneously with antacids or 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 or supplements containing magnesium and/or aluminium. *For pregnant patients:* Biktarvy should be administered at least 2 hours before or 6 hours after taking antacids or supplements containing aluminium and/or magnesium without regard to food.
Zinc (Chelation with polyvalent cations)	Interaction not studied with any of the components of Biktarvy. Co-administration may decrease bictegravir plasma concentrations.	*For non-pregnant patients:* Biktarvy should be administered at least 2 hours before oral medications or supplements containing zinc, or taken together with food at any time. *For pregnant patients:* Biktarvy should be administered at least 2 hours before or 6 hours after taking oral medications or supplements containing zinc. Alternatively, Biktarvy and oral medications or supplements containing zinc can be taken together with food at any time.

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
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%	*For non-pregnant patients:* Biktarvy should be administered at least 2 hours before oral medications or supplements containing iron, or taken together with food at any time. *For pregnant patients:* Biktarvy should be administered at least 2 hours before or 6 hours after taking oral medications or supplements containing iron. Alternatively, Biktarvy and oral medications or supplements containing iron can be taken together with food at any time.
Calcium carbonate (1,200 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}: ↔	*For non-pregnant patients:* Biktarvy and calcium-containing oral medications or supplements can be taken together, without regard to food. *For pregnant patients:* Biktarvy should be administered at least 2 hours before or 6 hours after taking oral medications or supplements containing calcium. Alternatively, Biktarvy and oral medications or supplements containing calcium can be taken together with food at any time.
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.
ORAL ANTI-DIABETICS		

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
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 co-administration 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.
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, methadone, naloxone, norbuprenorphine, omeprazole or rosuvastatin.

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of data on pregnant women (more than 1,000 exposed outcomes) indicate no malformative or foeto/neonatal toxicity associated with emtricitabine or tenofovir alafenamide. A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or foeto/neonatal toxicity associated with bictegravir.

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).

In a study performed in pregnant women receiving Biktarvy, exposures of bictegravir, emtricitabine and tenofovir alafenamide were lower during pregnancy (see section 5.2).

Therefore, Biktarvy may be used during pregnancy if the potential benefit justifies the potential risk to the foetus. Moreover, viral load should all the more be monitored closely in accordance with established treatment guidelines.

Breast-feeding

It is not known whether bictegravir is excreted in human milk. Emtricitabine is excreted in human milk. Based on published data, tenofovir alafenamide is excreted in human milk at low levels. The relative infant dose (RID) is estimated to be below 0.1% of the maternal weight-adjusted dose. 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.

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 women living with HIV do not breast-feed their infants.

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

Biktarvy may have minor influence on the 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

In clinical studies of treatment-naïve patients receiving Biktarvy, the most frequently reported adverse reactions in the double-blind phase (Week 144) were headache (5%), diarrhoea (5%) and nausea (4%).

Tabulated list of adverse reactions

The assessment of adverse reactions is based on safety data from across all Phase 2 and 3 studies with Biktarvy and from post-marketing experience. The adverse reactions in Table 2 are listed by system organ class and frequency. Frequencies are defined as follows: common (≥ 1/100 to < 1/10) uncommon (≥ 1/1 000 to < 1/100) and rare (≥1/10 000 to <1/1 000).

Table 2: Tabulated list of adverse reactions[1]

Frequency	**Adverse reaction**
Blood and lymphatic system disorders	
Uncommon:	anaemia[2]

Frequency	Adverse reaction
Psychiatric disorders	
Common:	depression, abnormal dreams
Uncommon:	suicidal ideation, suicide attempt (particularly in patients with a pre-existing history of depression or psychiatric illness), 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[3,4], rash, pruritus, urticaria[4]
Rare:	Stevens-Johnson syndrome[5]
Musculoskeletal and connective tissue disorders	
Uncommon:	arthralgia
General disorders and administration site conditions	
Common:	fatigue
Investigations	
Common:	weight increased

1 With the exception of angioedema, anaemia, urticaria and Stevens-Johnson syndrome (see footnotes 2-5), all adverse reactions were identified from Biktarvy clinical studies. The frequencies were derived from the double-blind phase (Week 144) of Phase 3 Biktarvy clinical studies in treatment-naïve patients (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-containing products.
4 This adverse reaction was identified through post-marketing surveillance for tenofovir alafenamide-containing products.
5 This adverse reaction was identified through post-marketing surveillance for Biktarvy. The frequency has been calculated using 3/X, where X represent the cumulative number of subjects exposed to Biktarvy in clinical trials (N=3963).

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 and autoimmune hepatitis) 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 144. In Studies GS-US-380-1489 and GS-US-380-1490, median (Q1, Q3) serum creatinine increased by 0.11 (0.03, 0.19) mg/dL (9.7 [2.7, 16.8] µmol/L), 0.11 (0.04, 0.19)mg/dL (9.7 [3.5, 16.8] µmol/L), and 0.12 (0.06, 0.21) mg/dL (10.6 [5.3, 18.6] µmol/L) from baseline to Week 144 in the Biktarvy,

abacavir/dolutegravir/lamivudine, and dolutegravir + emtricitabine/tenofovir alafenamide groups, respectively. There were no discontinuations due to renal adverse reactions through Week 144 in patients administered Biktarvy in clinical studies.

Changes in bilirubin
In Studies GS-US-380-1489 and GS-US-380-1490, total bilirubin increases were observed in 17% of treatment-naïve patients administered Biktarvy through Week 144. Increases were primarily Grade 1 (12%) and Grade 2 (4%) (≥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. Five patients administered Biktarvy (1%) had grade 3 bilirubin increases that were not considered related to study drug. There were no discontinuations due to hepatic adverse reactions through Week 144 in Biktarvy clinical studies.

Paediatric population
The safety of Biktarvy was evaluated in 50 HIV-1 infected adolescents aged 12 to < 18 years and weighing ≥ 35 kg through Week 96 (48-week main phase and 48-week extension), in 50 children aged 6 to < 12 years and weighing ≥ 25 kg through Week 96 (48-week main phase and 48-week extension), and in 22 children ≥ 2 years of age and weighing ≥ 14 to < 25 kg through Week 24 in an open-label clinical study (GS-US-380-1474). In this study, no new adverse reactions have been observed in paediatric subjects aged 2 years and older living with HIV-1 as compared to adult subjects living with HIV-1. Bone mineral density data were not collected in this study. Reductions in BMD of the spine and of the TBLH ≥ 4% have been reported in paediatric patients receiving other tenofovir alafenamide containing products for 48 weeks (see section 4.4).

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).

Elderly
Studies GS-US-380-1844, GS-US-380-1878 and the dedicated Study GS-US-380-4449 in patients ≥ 65 years old (evaluation of 86 HIV-1 infected, virologically-suppressed subjects ≥ 65 years old) included 111 patients aged ≥ 65 years who received Biktarvy. In these patients, no differences in the safety profile of Biktarvy were observed.

Patients with renal impairment
The safety of emtricitabine + tenofovir alafenamide was evaluated in a single arm, open-label clinical study (GS-US-292-1825), in which 55 virologically-suppressed HIV-1 infected patients with end stage renal disease ($eGFR_{CG}$ < 15 mL/min) on chronic haemodialysis received emtricitabine + tenofovir alafenamide in combination with elvitegravir + cobicistat as a fixed-dose combination tablet for 96 weeks. In an extension phase of Study GS-US-292-1825, 10 patients switched to Biktarvy for 48 weeks. No additional adverse reactions were identified in patients with end stage renal disease on chronic haemodialysis in this study (see sections 4.4 and 5.2).

Pregnancy
Biktarvy was evaluated in a clinical study of 33 HIV-1 infected virologically suppressed (HIV-1 RNA < 50 copies/mL) pregnant adults administered 50 mg/200 mg/25 mg Biktarvy once daily from the second or third trimester through postpartum. There were no new safety findings compared to the known safety profile of Biktarvy in HIV-1 infected adults.

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.

You can report any side effects to the Ministry of Health by clicking on the link "Report side effects due to medical treatment" that is located on the Ministry of Health homepage (www.health.gov.il) which redirects to the online form for reporting side effects or by clicking on the link: https://sideeffects.health.gov.il.

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 haemodialysis or peritoneal dialysis. 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: 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 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 µg/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 to 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 vivo
In treatment-naïve patients (Studies GS-US-380-1489 and GS-US-380-1490), through Week 144 of the double-blind phase or 96 weeks of the open-label extension phase, no patient receiving Biktarvy, with HIV-1 RNA ≥ 200 copies/mL at the time of confirmed virologic failure or early study drug discontinuation, had HIV-1 with treatment-emergent genotypic or phenotypic resistance to bictegravir, emtricitabine, or tenofovir alafenamide in the final resistance analysis population (n = 11 with data). At the time of study entry, one treatment-naïve patient had pre-existing INSTI resistance-associated mutations Q148H + G140S and had HIV-1 RNA < 50 copies/mL at Week 4 through Week 144. In addition, 6 patients had the pre-existing INSTI resistance-associated mutation T97A; all had HIV-1 RNA < 50 copies/mL at Week 144 or the last visit.

In virologically-suppressed patients (Studies GS-US-380-1844 and GS-US-380-1878), no patients receiving Biktarvy, with HIV-1 RNA ≥ 200 copies/mL at the time of confirmed virologic failure, Week 48, or early study drug discontinuation, had HIV-1 with treatment-emergent genotypic or phenotypic resistance to bictegravir, emtricitabine, or tenofovir alafenamide in the final resistance analysis population (n = 2).

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 a separate study, 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 nonnucleoside reverse transcriptase inhibitor (NNRTI)-resistant, 3 NRTI-resistant, and 4 protease inhibitor (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 and 144-week data from two randomised, double-blind, active-controlled studies, GS-US-380-1489 (n = 629) and GS-US-380-1490 (n = 645). Furthermore, additional efficacy and safety data are available from adults who received open-label Biktarvy for an additional 96 weeks after Week 144 in an optional extension phase of these studies (n = 1025).

The efficacy and safety of Biktarvy in virologically-suppressed HIV-1 infected adults are based on 48-week data from a randomised, double-blind, active-controlled study, GS-US-380-1844 (n = 563); and a randomised, 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 randomised in a 1:1 ratio to receive either bictegravir/emtricitabine/tenofovir alafenamide (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 randomised 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. Twenty-four percent (24%) 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 0-1,636) 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+ cell 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 Weeks 48 and 144 are presented in Table 3.

Table 3: Pooled virologic outcomes of Studies GS-US-380-1489 and GS-US-380-1490 at Weeks 48[a] and 144[b]

	Week 48			Week 144		
	B/F/TAF (n = 634)[c]	**ABC/DTG/ 3TC (n = 315)[d]**	**DTG + F/TAF (n = 325)[e]**	**B/F/TAF (n = 634)[c]**	**ABC/DTG /3TC (n = 315)[d]**	**DTG + F/TAF (n = 325)[e]**
HIV-1 RNA < 50 copies/mL	91%	93%	93%	82%	84%	84%
Treatment difference (95% CI) B/F/TAF vs Comparator	-	-2.1% (-5.9% to 1.6%)	-1.9% (-5.6% to 1.8%)	-	-2.7% (-7.8% to 2.4%)	-1.9% (-7.0% to 3.1%)
HIV-1 RNA ≥ 50 copies/mL[f]	3%	3%	1%	3%	3%	3%
No virologic data at week 48 or 144 window	6%	4%	6%	16%	13%	13%
Discontinued study drug due to AE or death[g]	<1%	1%	1%	2%	2%	3%
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[h]	4%	3%	4%	13%	11%	9%
Missing data during window but on study drug	2%	<1%	1%	1%	≤1%	1%
Proportion (%) of patients with HIV-1 RNA < 50 copies/mL by subgroup						
By baseline viral load						
≤ 100,000 copies/mL	92%	94%	93%	82%	86%	84%
> 100,000 copies/mL	87%	90%	94%	79%	74%	83%
By baseline CD4+ cell count						
< 200 cells/mm^3	90%	81%	100%	80%	69%	91%
≥ 200 cells/mm^3	91%	94%	92%	82%	86%	83%
HIV-1 RNA < 20 copies/mL	85%	87%	87%	78%	82%	79%

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

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

b Week 144 window was between Day 967 and 1050 (inclusive).

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

d Study GS-US-380-1489.

e Study GS-US-380-1490.

f Includes patients who had ≥ 50 copies/mL in the Week 48 or 144 window; patients who discontinued early due to lack or loss of efficacy (n = 0); patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy (B/F/TAF n = 12 and 15; ABC/DTG/3TC n = 2 and 7; DTG+F/TAF n = 3 and 6, at Weeks 48 and 144, respectively) and at the time of discontinuation had a viral value of ≥ 50 copies/mL.

g 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.

h 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 in achieving HIV-1 RNA < 50 copies/mL at both Weeks 48 and 144 when compared to abacavir/dolutegravir/lamivudine and to dolutegravir + emtricitabine/tenofovir alafenamide, respectively. Treatment outcomes between treatment groups 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+ cell count at Week 144 was 288, 317, and 289 cells/mm^3 in the pooled B/F/TAF, abacavir/dolutegravir/lamivudine, and dolutegravir + emtricitabine/tenofovir alafenamide groups, respectively.

In the optional 96 week open-label extension phase of Studies GS-US-380-1489 and GS-US-380-1490, high rates of virologic suppression were achieved and maintained.

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 randomised, 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 randomised 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. Seventeen percent (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 124-2,444).

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 randomised, 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 randomised 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. Nineteen percent (19%) of patients identified as Hispanic/Latino. The mean baseline CD4+ cell count was 663 cells/mm^3 (range 62-2,582). 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+ cell 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+ cell 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, 8 patients with HIV/HBV co-infection at baseline were randomised to receive B/F/TAF. At Week 48, 7 patients were HBV suppressed (HBV DNA < 29 IU/mL) and had HIV-1 RNA < 50 copies/mL. One patient had missing HBV DNA data at Week 48. At Week 144, 5 patients were HBV suppressed and had HIV-1 RNA < 50 copies/mL. Three patients had missing HBV DNA data at Week 144 (1 lost to follow-up from Week 48, 1 lost to follow-up after Week 72, and 1 lost to follow-up after Week 120).

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.

Pregnancy
In Study GS-US-380-5310, the pharmacokinetics, efficacy and safety of once-daily B/F/TAF were evaluated in an open-label clinical study of virologically suppressed pregnant adults with HIV-1 from the second or third trimester through postpartum (n = 33). All 32 adult participants who completed the study maintained viral suppression during pregnancy, at delivery, and through Week 18 postpartum. The median (Q1, Q3) CD4+ cell count at baseline was 558 (409, 720) cells/µL, and the median (Q1, Q3) change in CD4+ cell count from baseline to Week 12 postpartum was 159 (27, 296) cells/µL. All 29 neonate participants had negative/nondetectable HIV-1 PCR results at birth and/or 4 to 8 weeks of age.

Paediatric population

In Study GS-US-380-1474, the pharmacokinetics, safety and efficacy of B/F/TAF in virologically-suppressed children and adolescents with HIV between the ages of 12 to < 18 years (≥ 35 kg) (n = 50), between the ages of 6 to < 12 years (≥ 25 kg) (n = 50), and ≥ 2 years of age (≥ 14 to < 25 kg) (n = 22) were evaluated.

Cohort 1: Virologically-suppressed adolescents (n = 50; 12 to < 18 years; ≥ 35 kg)

Patients in Cohort 1 had a mean age of 14 years (range: 12 to 17) and a mean baseline weight of 51.7 kg (range: 35 to 123), 64% were female, 27% were Asian, and 65% were Black. At baseline, median CD4+ cell count was 750 cells/mm^3 (range: 337 to 1207), and median CD4+% was 33% (range: 19% to 45%).

After switching to B/F/TAF, 98% (49/50) of patients in Cohort 1 remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 48. The mean change from baseline in CD4+ cell count at Week 48 was -22 cells/mm^3. Two of 50 subjects met the criteria for inclusion in the resistance analysis population through Week 48. No emergent resistance to B/F/TAF was detected through Week 48.

Cohort 2: Virologically-suppressed children (n = 50; 6 to < 12 years; ≥ 25 kg)

Patients in Cohort 2 had a mean age of 10 years (range: 6 to 11) and a mean baseline weight of 31.9 kg (range: 25 to 69), 54% were female, 22% were Asian and 72% were Black. At baseline, median CD4+ cell count was 898 cells/mm^3 (range 390 to 1991) and median CD4+% was 37% (range: 19% to 53%).

After switching to B/F/TAF, 98% (49/50) of patients in Cohort 2 remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 48. The mean change from baseline in CD4+ cell count at Week 48 was -40 cells/mm^3. No patient qualified for resistance analysis through Week 48.

Cohort 3: Virologically-suppressed children (n = 22; ≥ 2 years; ≥ 14 kg to < 25 kg)
Patients in Cohort 3 had a mean age of 5 years (range: 3 to 9) and a mean baseline weight of 18.8 kg (range: 14 to 24), 50% were female, 23% were Asian and 73% were Black. At baseline, median CD4+ cell count was 962 cells/mm^3 (range 365 to 1986) and median CD4+% was 32% (range: 24% to 46%).

After switching to B/F/TAF, 91% (20/22) of patients in Cohort 3 remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 24. The mean change from baseline in CD4+ cell count at Week 24 was −126 cells/mm^3, and the mean change in CD4+% from baseline to Week 24 was 0.2% (range: -7.7% to 7.5%). No patient qualified for resistance analysis through Week 24.

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 µg/mL (22.9%), AUC_{tau} = 102 µg•h/mL (26.9%), and C_{trough} = 2.61 µg/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 µg/mL (34.7%), AUC_{tau} = 12.3 µg•h/mL (29.2%), and C_{trough} = 0.096 µg/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 µg/mL (15.4%), and AUC_{tau} = 0.142 µg•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 µg/mL. At peak plasma concentration, the mean plasma to blood emtricitabine concentration ratio was ~1.0 and the mean semen to plasma emtricitabine 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

Metabolism is the major clearance pathway for bictegravir in humans. *In vitro* phenotyping studies showed that bictegravir is primarily metabolised 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 245 mg oral dose of tenofovir disoproxil.

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

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.

Renal impairment
Severe Renal Impairment (estimated creatinine clearance ≥ 15 and < 30 mL/minute)
No clinically relevant differences in bictegravir, tenofovir alafenamide, or tenofovir pharmacokinetics were observed between healthy subjects and subjects with severe renal impairment (estimated CrCl ≥ 15 mL/min and < 30 mL/min) in Phase 1 Studies. In a separate Phase 1 study of emtricitabine alone,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). The safety of Biktarvy has not been established in subjects with estimated creatinine clearance ≥ 15 mL/min and < 30 mL/min.

End Stage Renal Disease (estimated creatinine clearance < 15 mL/minute)
Exposures of emtricitabine and tenofovir in 12 patients with end stage renal disease (estimated CrCl < 15 mL/min) on chronic haemodialysis who received emtricitabine + tenofovir alafenamide in combination with elvitegravir + cobicistat as a fixed dose combination tablet in Study GS-US-292-1825 were significantly higher than in patients with normal renal function. No clinically relevant differences in tenofovir alafenamide pharmacokinetics were observed in patients with end stage renal disease on chronic haemodialysis as compared to those with normal renal function. In the extension phase of Study GS-US-292-1825, lower bictegravir C_{trough} was observed in patients with end stage renal disease who received Biktarvy compared to patients with normal renal function, but this difference was not considered clinically relevant. No additional adverse reactions were identified in patients with end stage renal disease on chronic haemodialysis in this study (see section 4.8).

There are no pharmacokinetic data on bictegravir, emtricitabine or tenofovir alafenamide in patients with end stage renal disease (estimated CrCl < 15 mL/min) not on chronic haemodialysis. The safety of Biktarvy has not been established in these patients.

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 studies did not identify any clinically relevant differences due to age, gender or race on the exposures of bictegravir, emtricitabine, or tenofovir alafenamide.

Paediatric population
Mean bictegravir C_{max}, and exposures of emtricitabine and tenofovir alafenamide (AUC and/or C_{max}), achieved in 50 children between the ages of 6 to < 12 years (≥ 25 kg) who received the 50 mg/200 mg/25 mg dose of B/F/TAF and in 22 children ≥ 2 years of age (≥ 14 to < 25 kg) who received the 30 mg/120 mg/15 mg dose of B/F/TAF, in Study GS-US-380-1474 were generally higher than exposures in adults. The exposures of bictegravir, emtricitabine, tenofovir alafenamide and tenofovir in children, adolescents, and adults are presented in Table 5.

Table 5: Exposures of Bictegravir, Emtricitabine, Tenofovir Alafenamide and Tenofovir in Children, Adolescents and Adults

	Children aged ≥ 2 years ≥ 14 to < 25 kg[a]	**Children aged 6 to < 12 years ≥ 25 kg[a]**	**Adolescents aged 12 to < 18 years ≥ 35 kg[a]**	**Adults[b]**
	B/F/TAF (30 mg/120 mg/15 mg)	**B/F/TAF (50 mg/200 mg/25 mg)**		
	n = 12	n = 25	n = 24	n = 77
BIC				
AUC_{tau} (ng•h/mL)	108 364.5 (22.9)	121 034.2 (36.4)	109 668.1 (30.6)	94 227.1 (34.7)
C_{max} (ng/mL)	10 040.0 (19.9)	10 988.8 (28.3)	8 087.1 (29.9)	6 801.6 (30.1)
C_{tau} (ng/mL)	1 924.5 (78.3)[c]	2 366.6 (78.8)[d]	2 327.4 (48.6)	2 256.7 (47.3)[g]
FTC				
AUC_{tau} (ng•h/mL)	14 991.2 (21.9)	17 565.1 (36.9)	13 579.1 (21.7)	12 293.6 (29.2)
C_{max} (ng/mL)	3 849.2 (34.7)	3 888.4 (31.0)	2 689.2 (34.0)	2 127.0 (34.7)
C_{tau} (ng/mL)	210.3 (242.9)[c]	226.7 (322.8) [d]	64.4 (25.0)	96.0 (37.4)[h]
TAF				
AUC_{tau} (ng•h/mL)	305.4 (42.6)	434.5 (94.9)[e]	347.9 (113.2)[f]	229.3 (63.0)
C_{max} (ng/mL)	413.8 (31.0)	581.8 (99.9)[d]	333.9 (110.6)	276.5 (62.4)
C_{tau} (ng/mL)	N/A	N/A	N/A	N/A
TFV				
AUC_{tau} (ng•h/mL)	326.6 (23.8)	427.7 (28.5)	333.5 (31.5)	292.6 (27.4)[i]
C_{max} (ng/mL)	21.9 (29.2)	35.5 (89.0)	24.0 (64.2)	15.2 (26.1)[i]
C_{tau} (ng/mL)	10.3 (30.5)[c]	14.0 (30.2)[d]	11.1 (32.4)	10.6 (28.5)[i]

BIC = bictegravir; FTC = emtricitabine; TAF = tenofovir alafenamide fumarate; TFV = tenofovir
N/A = not applicable; %CV = percentage coefficient of variation
Data are presented as mean (%CV).

a Intensive PK data from Study GS-US-380-1474
b Intensive PK data from Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878 for BIC, FTC and TAF PK exposures and population PK data from Studies GS-US-292-0104 and GS-US-292-0111 for TFV PK exposures
c n = 11
d n = 24
e n = 22
f n = 23
g n = 75
h n = 74
i n = 841

Pregnancy

Plasma exposures of bictegravir, emtricitabine, and tenofovir alafenamide were lower during pregnancy as compared to postpartum, whereas exposures during postpartum were generally higher than in non-pregnant adults (Table 6). Exposures were generally similar between the second and third trimesters of pregnancy; exposures were also generally similar between Weeks 6 and 12 postpartum. Based on exposure-response relationships for bictegravir, emtricitabine, and tenofovir alafenamide, the exposure changes during pregnancy are not considered to be clinically relevant; however, specific dosage adjustments for co-administered oral medications or supplements containing polyvalent cations are recommended in pregnant patients (see section 4.5).

Table 6: Steady-state PK Parameters of bictegravir, emtricitabine, and tenofovir alafenamide in HIV-Infected Virologically Suppressed Pregnant Women in the Third Trimester and Week 12 Postpartum Compared to Historical Data in Non-Pregnant Adults with HIV-1

Parameter Mean (%CV)	Third Trimester (N=30)	Week 12 Postpartum (N=32)	Non-Pregnant Adults with HIV-1
Bictegravir			
C_{max} (µg per mL)	5.37 (25.9)	11.0 (24.9)	6.15 (22.9)[b]
AUC_{tau} (µg•h per mL)	60.2 (29.1)	148 (28.5)	102 (26.9)[b]
Unbound AUC_{tau}[a] (µg•h per mL)	0.219 (33.9)	0.374 (32.2)	NA
C_{trough} (µg per mL)	1.07 (41.7)	3.64 (34.1)	2.61 (35.2)[b]
Emtricitabine			
C_{max} (µg per mL)	2.59 (26.5)	3.36 (26.9)	2.13 (34.7)[c]
AUC_{tau} (µg•h per mL)	10.4 (20.3)	15.3 (21.9)	12.3 (29.2)[c]
C_{trough} (µg per mL)	0.05 (27.2)	0.08 (33.7)	0.096 (37.4)[c]
Tenofovir Alafenamide			
C_{max} (µg per mL)	0.27 (42.1)	0.49 (52.5)	0.121 (15.4)[d]
AUC_{tau} (µg•h per mL)	0.21 (45.0)	0.30 (31.8)	0.142 (17.3)[d]
Unbound AUC_{tau}[a] (µg•h per mL)	0.016 (28.4)	0.017 (23.4)	NA

CV = Coefficient of Variation; NA = Not Available
a Calculated by correcting the individual AUC_{tau} estimates by the %unbound fraction.
b From Population PK analysis in Studies 1489, 1490, 1844, and 1878; N = 1193.
c From Intensive PK analysis in Studies 1489, 1490, 1844, and 1878; N = 77.
d From Population PK analysis in Studies 1489 and 1490; N = 486.

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 1,000 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, carcinogenicity studies and a rat peri-postnatal study were conducted only with tenofovir disoproxil. 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 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 (E460)
Croscarmellose sodium (E468)
Magnesium stearate (E470b)

Film-coating
Polyvinyl alcohol (E203)
Titanium dioxide (E171)
Polyethylene glycol (E1521)
Talc (E553b)
Iron oxide red (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Biktarvy 50/200/25 mg:
No special storage conditions are required. Storage at room temperature is recommended.

Bottle
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.

Blister
Store in the original package in order to protect from moisture. Do not use if foil over blister is broken or pierced.

Biktarvy 30/120/15 mg:

Store below 30°C. 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.

The medicine can be used for up to 30 days after first opening of the bottle but not after the expiry date. After opening, store below 30°C.

6.5 Nature and contents of container

The following pack configurations are available:

Biktarvy 50/200/25 mg:
Bottle
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.

Blister
Outer carton containing 1 bottle of 30 film-coated tablets.
Blister packs consisting of polyvinyl chloride/polyethylene/polychlorotrifluoroethylene (PVC/PE/PCTFE) film, sealed to aluminium foil lidding material fitted with a molecular sieve desiccant within each blister cavity.

- Outer carton containing 30 film-coated tablets (4 x blister strips containing 7 film-coated tablets and 1 x blister strip containing 2 film-coated tablets).
- Outer carton containing 90 (3 blister packs of 30) film-coated tablets.

Biktarvy 30/120/15 mg:
Bottle
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.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MANUFACTURER

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8. REGISTRATION HOLDER

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