ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Biktarvy 30 mg/120 mg/15 mg film-coated tablets
Biktarvy 50 mg/200 mg/25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Biktarvy 30 mg/120 mg/15 mg film-coated tablets

Each film-coated tablet 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 mg/200 mg/25 mg film-coated tablets

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).

Biktarvy 30 mg/120 mg/15 mg film-coated tablets

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 mg/200 mg/25 mg film-coated tablets

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 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).

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 mg/120 mg/15 mg tablet to be taken once daily.

Adults and paediatric patients weighing at least 25 kg
One 50 mg/200 mg/25 mg 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 patients weighing ≥ 35 kg 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, Biktarvy should be administered 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, 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 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 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 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 ≥ 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.
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.

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
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		
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.
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.

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 (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		
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.

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}: ↔ Norgestrel: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Ethinylestradiol: 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]		
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 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 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]
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]

Frequency	Adverse reaction
Musculoskeletal and connective tissue disorders	
Uncommon:	arthralgia
General disorders and administration site conditions	
Common:	fatigue

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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%

	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]**
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.

The European Medicines Agency has deferred the obligation to submit the results of studies with Biktarvy 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 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)
Macrogol (E1521)
Talc (E553b)
Iron oxide red (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

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.

6.5 Nature and contents of container

The following pack configurations are available:

Bottle
Biktarvy 30 mg/120 mg/15 mg tablets and 50 mg/200 mg/25 mg tablets are packaged in 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.

- Outer carton containing 1 bottle of 30 film-coated tablets
- Outer carton containing 90 (3 bottles of 30) film-coated tablets.

Blister
Biktarvy 50 mg/200 mg/25 mg 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.

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. MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1289/001
EU/1/18/1289/002
EU/1/18/1289/003
EU/1/18/1289/004
EU/1/18/1289/005
EU/1/18/1289/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 June 2018

Date of latest renewal: 10 January 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Gilead Sciences Ireland UC
IDA Business & Technology Park
Carrigtohill
County Cork
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

BOTTLE AND CARTON LABELLING

1. NAME OF THE MEDICINAL PRODUCT

Biktarvy 30 mg/120 mg/15 mg film-coated tablets
bictegravir/emtricitabine/tenofovir alafenamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

90 (3 bottles of 30) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture. **Keep the bottle tightly closed.**

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1289/005 30 film-coated tablets
EU/1/18/1289/006 90 (3 bottles of 30) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Biktarvy 30 mg/120 mg/15 mg [Outer packaging only]

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included. [Outer packaging only]

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

BOTTLE AND CARTON LABELLING

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

90 (3 bottles of 30) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture. **Keep the bottle tightly closed.**

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1289/001 30 film-coated tablets
EU/1/18/1289/002 90 (3 bottles of 30) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Biktarvy 50 mg/200 mg/25 mg [Outer packaging only]

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included. [Outer packaging only]

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}
[Outer packaging only]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF UNIT BLISTER PACK

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1289/003 30 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Biktarvy [Outer packaging only]

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF BLISTER MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 90 (3 blister packs of 30) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1289/004 90 (3 blister packs of 30) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Biktarvy [Outer packaging only]

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF BLISTER MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1289/004 90 (3 blister packs of 30) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Biktarvy [Outer packaging only]

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER (7 tablet blister pack)

1. NAME OF THE MEDICINAL PRODUCT

Biktarvy 50 mg/200 mg/25 mg tablets
bictegravir/emtricitabine/tenofovir alafenamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon.
Tue.
Wed.
Thu.
Fri.
Sat.
Sun.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER (2 tablet blister pack)

1. NAME OF THE MEDICINAL PRODUCT

Biktarvy 50 mg/200 mg/25 mg tablets
bictegravir/emtricitabine/tenofovir alafenamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Day Underlined blank space included.
Day Underlined blank space included.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Biktarvy 30 mg/120 mg/15 mg film-coated tablets
bictegravir/emtricitabine/tenofovir alafenamide

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.

If Biktarvy has been prescribed for your child, please note that all the information in this leaflet is addressed to your child (in this case please read "your child" instead of "you").

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, adolescents and children 2 years of age and older, who weigh at least 14 kg.

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.*

- **If you have had kidney disease or if tests have shown problems with your kidneys.** Your doctor may order blood tests to monitor how your kidneys work when starting and during treatment with 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*.

There is a possibility that you may experience kidney problems when taking Biktarvy over a long period of time (see *Warnings and precautions*).

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 under 2 years of age, or weighing less than 14 kg regardless of age. The use of Biktarvy in children under 2 years of age, or weighing less than 14 kg has not yet been studied. For children and adolescents who weigh 25 kg or more, Biktarvy 50 mg/200 mg/25 mg film-coated tablets are available.

Loss of bone mass has been reported in some children from 3 to less than 12 years of age who received one of the active substances (tenofovir alafenamide) contained in Biktarvy. The effects on long term bone health and future fracture risk in children is uncertain. Your doctor will monitor your child's bone health as needed.

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
- **anticonvulsants** used to treat epilepsy, containing:
  - carbamazepine, oxcarbazepine, phenobarbital or phenytoin
- **immunosuppressants** used to control your body's immune response after a transplant, containing ciclosporin
- **ulcer-healing medicines** containing sucralfate

→ **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 supplements containing aluminium and/or magnesium:** 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.** However, if you are pregnant see *Pregnancy and breast-feeding*.
- **Iron supplements:** you will need to take Biktarvy at least 2 hours **before** iron supplements, or you can take them together with food at any time. However, if you are pregnant see *Pregnancy and breast-feeding*.

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 or pharmacist for advice before taking this medicine.
- Tell your doctor immediately if you become pregnant and ask about the potential benefits and risks of your antiretroviral therapy to you and your child.
- **Antacids and supplements containing aluminium and/or magnesium:** during your pregnancy you will need to take Biktarvy at least 2 hours **before** or 6 hours **after** taking antacids, medicines or supplements containing aluminium and/or magnesium.
- **Supplements or medicines containing calcium and/or iron:** during your pregnancy you will need to take Biktarvy at least 2 hours **before** or 6 hours **after** taking supplements or medicines containing calcium and/or iron. Alternatively, you can take them together with food at any time.

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. Breast-feeding is not recommended in women living with HIV because HIV infection can be passed on to the baby in breast milk. If you are breast-feeding, or thinking about breast-feeding, you should **discuss it with your doctor as soon as possible**.

Driving and using machines

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

Biktarvy contains sodium

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

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.

There are two strengths of Biktarvy tablets. Your doctor will prescribe the appropriate tablet for your age and weight.

The recommended dose is:

Children 2 years of age and older, who weigh at least 14 kg but less than 25 kg: one tablet each day with or without food (one 30 mg/120 mg/15 mg tablet).

Due to the bitter taste, it is recommended not to chew or crush the tablet.
If you have difficulty swallowing the tablet whole, you can split it in half. Take both halves of the tablet one after the other to get the full dose. Do not store the split tablet.

The score line on the tablet is only there to help you break the tablet if your child has difficulty swallowing it whole.

The 90-day multipack contains three 30-day packs together.
→ **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 are on dialysis, take your daily dose of Biktarvy following completion of dialysis.

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 or carton 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 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
- hives (*urticaria*)
- joint pain (*arthralgia*)
- suicidal thoughts and suicide attempt (particularly in patients who have had depression or mental health problems before)
- anxiety
- sleep disorders

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

Rare side effects
(may affect up to 1 in 1000 people)
- Stevens-Johnson syndrome (SJS) is a serious life-threatening condition which usually starts with flu- like symptoms. A few days later other symptoms appear including:
  - Painful red or purple skin that looks burned and peels off
  - Blisters on your skin, mouth, nose, and genitals
  - Red, painful, watery eyes

→ If you have any of these symptoms, stop your medicine immediately and tell your doctor straight away.

→ 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. You can also report side effects directly via the national reporting system listed in Appendix V. 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 or blister strips after {EXP}. The expiry date refers to the last day of that month.

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 30 mg of bictegravir, 120 mg of emtricitabine and tenofovir alafenamide fumarate equivalent to 15 mg of tenofovir alafenamide.

The other ingredients are

Tablet core
Microcrystalline cellulose (E460), croscarmellose sodium (E468), magnesium stearate (E470b).

Film-coating
Polyvinyl alcohol (E203), titanium dioxide (E171), macrogol (E1521), talc (E553b), iron oxide red (E172), iron oxide black (E172).

What Biktarvy looks like and contents of the pack

Biktarvy 30 mg/120 mg/15 mg film-coated tablets are pink, capsule-shaped, film-coated tablets, debossed with “BVY” on one side and a score line on the other side of the tablet.

The tablets are supplied in a bottle. Not all pack sizes may be marketed.

Biktarvy comes in bottles of 30 tablets and in packs made up of 3 bottles, each containing 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.

Marketing Authorisation Holder
Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

Manufacturer
Gilead Sciences Ireland UC
IDA Business & Technology Park
Carrigtohill
County Cork
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Gilead Sciences Belgium SRL-BV
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This leaflet was last revised in .

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Package leaflet: Information for the user

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

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.

If Biktarvy has been prescribed for your child, please note that all the information in this leaflet is addressed to your child (in this case please read "your child" instead of "you").

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, adolescents and children 2 years of age and older, who weigh at least 14 kg.

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.*

- **If you have had kidney disease or if tests have shown problems with your kidneys.** Your doctor may order blood tests to monitor how your kidneys work when starting and during treatment with 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*.

There is a possibility that you may experience kidney problems when taking Biktarvy over a long period of time (see *Warnings and precautions*).

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 weighing less than 25 kg regardless of age. For children 2 years of age and older, who weigh at least 14 kg but less than 25 kg Biktarvy 30 mg/120 mg/15 mg film-coated tablets are available. The use of Biktarvy in children under 2 years of age, or weighing less than 14 kg has not yet been studied.

Loss of bone mass has been reported in some children from 3 to less than 12 years of age who received one of the active substances (tenofovir alafenamide) contained in Biktarvy. The effects on long term bone health and future fracture risk in children is uncertain. Your doctor will monitor your child's bone health as needed.

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
- **anticonvulsants** used to treat epilepsy, containing:
  - carbamazepine, oxcarbazepine, phenobarbital or phenytoin
- **immunosuppressants** used to control your body's immune response after a transplant, containing ciclosporin
- **ulcer-healing medicines** containing sucralfate

→ **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 supplements containing aluminium and/or magnesium:** 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.** However, if you are pregnant see *Pregnancy and breast-feeding*.
- **Iron supplements:** you will need to take Biktarvy at least 2 hours **before** iron supplements, or you can take them together with food at any time. However, if you are pregnant see *Pregnancy and breast-feeding*.

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 or pharmacist for advice before taking this medicine.
- Tell your doctor immediately if you become pregnant and ask about the potential benefits and risks of your antiretroviral therapy to you and your child.
- **Antacids and supplements containing aluminium and/or magnesium:** during your pregnancy you will need to take Biktarvy at least 2 hours **before** or 6 hours **after** taking antacids, medicines or supplements containing aluminium and/or magnesium.
- **Supplements or medicines containing calcium and/or iron:** during your pregnancy you will need to take Biktarvy at least 2 hours **before** or 6 hours **after** taking supplements or medicines containing calcium and/or iron. Alternatively, you can take them together with food at any time.

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. Breast-feeding is not recommended in women living with HIV because HIV infection can be passed on to the baby in breast milk. If you are breast-feeding, or thinking about breast-feeding, you should **discuss it with your doctor as soon as possible**.

Driving and using machines

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

Biktarvy contains sodium

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

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.

There are two strengths of Biktarvy tablets. Your doctor will prescribe the appropriate tablet for your age and weight.

The recommended dose is:

Adults, adolescents and children who weigh at least 25 kg: one tablet each day with or without food (one 50 mg/200 mg/25 mg tablet).

Due to the bitter taste, it is recommended not to chew or crush the tablet.
If you have difficulty swallowing the tablet whole, you can split it in half. Take both halves of the tablet one after the other to get the full dose. Do not store the split tablet.

The Biktarvy 30-day blister pack contains four 7-blister strips and one 2-blister strip. To help track taking your medication over 30 days, the 7-blister strips have days of the week printed and you can write the relevant days of the week on the 2-blister strip.
The 90-day multipack contains three 30-day packs together.

→ **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 are on dialysis, take your daily dose of Biktarvy following completion of dialysis.

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 or carton 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 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
- hives (*urticaria*)
- joint pain (*arthralgia*)
- suicidal thoughts and suicide attempt (particularly in patients who have had depression or mental health problems before)
- anxiety
- sleep disorders

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

Rare side effects
(may affect up to 1 in 1000 people)
- Stevens-Johnson syndrome (SJS) is a serious life-threatening condition which usually starts with flu- like symptoms. A few days later other symptoms appear including:
  - Painful red or purple skin that looks burned and peels off
  - Blisters on your skin, mouth, nose, and genitals
  - Red, painful, watery eyes

→ If you have any of these symptoms, stop your medicine immediately and tell your doctor straight away.

→ 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. You can also report side effects directly via the national reporting system listed in Appendix V. 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 or blister strips after {EXP}. The expiry date refers to the last day of that month.

Bottle
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.

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

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 50 mg/200 mg/25 mg 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 (E460), croscarmellose sodium (E468), magnesium stearate (E470b).

Film-coating
Polyvinyl alcohol (E203), titanium dioxide (E171), macrogol (E1521), talc (E553b), iron oxide red (E172), iron oxide black (E172).

What Biktarvy looks like and contents of the pack

Biktarvy 50 mg/200 mg/25 mg film-coated tablets are purplish-brown, capsule-shaped, film-coated tablets debossed on one side with “GSI” and “9883” on the other side.

The tablets may be supplied either in a bottle or in a blister pack. Not all pack sizes may be marketed.

Bottle
Biktarvy comes in bottles of 30 tablets and in packs made up of 3 bottles, each containing 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.

Blister
Biktarvy 50 mg/200 mg/25 mg tablets also come in blister packs of 30 tablets and in multipacks comprising 3 cartons, each containing 30 tablets. Each individual pack contains 4 x blister strips containing 7 tablets and 1 x blister strip containing 2 tablets. Each blister cavity contains a desiccant, which should not be removed or swallowed.

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Manufacturer
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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.