# Professional Information

## SCHEDULING STATUS

S4

## 1 NAME OF THE MEDICINE

BIKTARVY 50 mg/200 mg/25 mg FILM-COATED TABLETS

**Warnings**

*Lactic acidosis / hyperlactataemia*

Use of BIKTARVY can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction. Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss. In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/ℓ) and the serum bicarbonate and respond as follows:

- Lactate 2-5 mmol/ℓ with minimum symptoms: switch to agents that are less likely to cause lactic acidosis.
- Lactate 5-10 mmol/ℓ with symptoms and/or with reduced standard bicarbonate: Stop nucleoside reverse transcriptase inhibitors (NRTIs) and change treatment option. Once lactate has settled, use medicines that are less likely to cause lactic acidosis. Exclude other causes, (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis and hyperthyroidism.
- Lactate> 10 mmol/ℓ: STOP all therapy (80 % mortality). The above lactate values may not be applicable to paediatric patients. Caution should be exercised when administering BIKTARVY to patients with known risk factors for liver disease. Treatment with BIKTARVY should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

*Mitochondrial dysfunction*

Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or postnatally to nucleoside analogues. Apart from lactic acidosis/hyperlactataemia (see above) other manifestations of mitochondrial dysfunction include haematological disorders (anaemia, neutropenia), and peripheral neuropathy. Some late-onset neurological disorders have been

reported (hypertonia, convulsion, abnormal behaviour). It is not known whether the neurological disorders are transient or permanent. Any foetus exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative infants/children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant sign and symptoms.

*Liver disease*

Use of BIKTARVY can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of BIKTARVY has not been established in patients with significant underlying liver disorders/diseases. In case of concomitant antiviral therapy for hepatitis B or C, please also consult the relevant package inserts for these medicines.

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

*Patients with HIV and hepatitis B or C virus co-infection*

Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV).

In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant package inserts for these medicines.

Patients co-infected with HIV and HBV who discontinue BIKTARVY should be closely monitored with both clinical and laboratory follow-up after stopping treatment. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Only relevant to lamivudine, tenofovir and emtricitabine (FTC): Discontinuation of BIKTARVY therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains bictegravir sodium equivalent to 50 mg of bictegravir, 200 mg of emtricitabine, and tenofovir alafenamide fumarate equivalent to 25 mg of tenofovir alafenamide.
For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

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

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Biktarvy is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults, adolescents and paediatric patients at least 6 years of age and weighing at least 25 kg without any known mutation associated with resistance to the individual components and who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per ml) on a stable antiretroviral regiment for at least 3 months.

### 4.2 Posology and method of administration

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

Posology

*Adults and paediatric patients aged 6 years and older weighing at least 25 kg*
The recommended dose of BIKTARVY is one tablet once daily, with or without food.

*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 the patient does not need to take another tablet 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 6 years of age or weighing less than 25 kg have not been established.

Method of Administration
Biktarvy should be taken orally once daily with or without food.
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 whole 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**
Known hypersensitivity to bictegravir, emtricitabine, tenofovir alafenamide, or to any of the excipients.
Co-administration with dofetilide is contraindicated due to the potential for increased dofetilide plasma concentrations and associated serious and/or life-threatening events.
Co-administration of bictegravir and medicines that potentially induce both CYP3A and UGT1A1, such as rifampicin and or St. John's wort (*Hypericum perforatum),* is contraindicated due to the potential to decrease BIC plasma concentrations, which may result in the loss of therapeutic effect and development of resistance to Biktarvy (see sections 4.4 and 4.5).

**4.4 Special warnings and precautions for use**

Transmission of HIV
While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk remains.

Appropriate prevention measures should be taken to reduce the risk of sexual transmission of HIV.

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 three months after stopping treatment. If appropriate, anti-hepatitis B therapy may be warranted, especially in HBV coinfected patients with advanced liver disease or cirrhosis since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

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), such as Biktarvy, 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 lipid and glucose blood levels may occur during treatment with Biktarvy. Although there is evidence for a treatment effect, such changes may in part be linked to disease control and life style.
Body weight/ body mass index (BMI), lipids and blood glucose levels should be regularly monitored and appropriately managed in patients on treatment with Biktarvy.

Mitochondrial dysfunction

Nucleos(t)ide analogues may impact on mitochondrial function. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or postnatally to nucleoside analogues, as in Biktarvy. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactataemia, hyperlipasaemia). Late onset neurological disorders have been reported (hypertonia, convulsions, abnormal behaviour). These findings should be considered for any child exposed *in utero* to nucleos(t)ide analogues, such as Biktarvy, who present with severe clinical findings of unknown aetiology, particularly neurologic findings.

Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms.

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 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 medical practitioner experienced in the treatment of patients with HIV associated diseases.

Co-administration of Biktarvy in HIV patients currently treated for Tuberculosis (TB) with rifamycin is contraindicated.

The safety and efficacy of Biktarvy in HIV patients treated for Tuberculosis (TB) has not been established.

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, such as Biktarvy. 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 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 medicines 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 medicines 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. (see sections 4.3 and 4.5).

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, essentially 'sodium-free'**.**

**4.5 Interaction with other medicines and other forms of interaction**

Biktarvy is indicated for use as a complete regimen for the treatment of HIV-1 infection. Therefore, comprehensive information regarding interactions with other antiretroviral products is not provided.

Interaction studies have only been performed in adults.

*Bictegravir*

Bictegravir is a substrate of CYP3A and UGT1A1. Co-administration of bictegravir and medicines 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. Co-administration of bictegravir with medicines 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 an inhibitor of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), BSEP, OCT1 and OAT3 *in vitro*.

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 metformin without dose adjustment. Biktarvy should not be co-administered with dofetilide, which is contraindicated due to the potential for increased dofetilide plasma concentrations and associated serious and/or life-threatening events (see section 4.3).

Bictegravir is not an inhibitor or inducer of CYP3A *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 medicines is low. Co-administration of emtricitabine with medicines that are

eliminated by active tubular secretion may increase concentrations of emtricitabine, and/or the co-administered medicines. Medicines that decrease renal function may increase concentrations of emtricitabine.

*Tenofovir alafenamide*

Tenofovir alafenamide is transported by P-gp and BCRP. Co-administration of Biktarvy with medicinal products that strongly affect P-gp and BCRP activity may lead to changes in tenofovir alafenamide absorption. Medicines that induce P-gp activity (e.g. rifabutin, carbamazepine, phenobarbitone) 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 medicines 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 the components of Biktarvy and potential co-administered medicines are listed in Table 1 (where 90 % confidence interval [CI] of the geometric least-squares mean [GLSM] ratio were within "↔", extended above "↑", or extended below "↓" the predetermined equivalence boundaries; a value of 1.00 corresponds to no change of the pharmacokinetic parameters and where twice daily is indicated as "b.i.d." and once daily as "q.d."). The interactions described are based on studies conducted with Biktarvy, or the components of Biktarvy as individual agents and/or in combination or are potential medicine interactions that may occur with Biktarvy.

**Table 1: Interactions between Biktarvy or its individual component(s) and other medicines**

| **Medicines by therapeutic areas/possible mechanism of interaction** | **Effects on medicine levels. Mean percent change in AUC, $C_{max}$, $C_{min}$** | **Recommendation concerning co-administration with Biktarvy** |
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| **HERBAL PRODUCTS** | | |
| St. John's wort (*Hypericum perforatum*)<br><br>(Induction of CYP3A, UGT1A1, and P-gp) | Interaction not studied with any of the components of Biktarvy.<br>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),<br>Bictegravir[1]<br><br>(Induction of CYP3A, UGT1A1, and P-gp) | Bictegravir:<br>AUC: ↓ 75 %<br>$C_{max}$: ↓ 28 %<br><br>Interaction not studied with tenofovir alafenamide.<br>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),<br>Bictegravir[1] | Bictegravir:<br>AUC: ↓ 38 %<br>$C_{min}$: ↓ 56 %<br>$C_{max}$: ↓ 20 % | Co-administration is not recommended due to the expected decrease of tenofovir alafenamide. |

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| (Induction of CYP3A and P-gp) | Interaction not studied with tenofovir alafenamide. Co-administration of rifabutin may decrease tenofovir alafenamide plasma concentrations. | |
| Rifapentine<br><br>(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 MEDICINES** | | |
| Atazanavir (300 mg once daily), Cobicistat (150 mg once daily), Bictegravir[1] (Inhibition of CYP3A, UGT1A1, and P-gp/ BCRP) | Bictegravir:<br>AUC: ↑ 306 %<br>$C_{max}$: ↔ | Co-administration is not recommended. |
| Atazanavir (400 mg once daily), Bictegravir[1]<br><br>(Inhibition of CYP3A and UGT1A1) | Bictegravir:<br>AUC: ↑ 315 %<br>$C_{max}$: ↔ | |
| **HEPATITIS C VIRUS ANTIVIRAL MEDICINES** | | |
| Ledipasvir/ Sofosbuvir (90 mg/400 mg once daily), Bictegravir/Emtricitabine/ Tenofovir alafenamide[2] | Bictegravir:<br>AUC: ↔<br>$C_{min}$: ↔<br>$C_{max}$: ↔<br>Emtricitabine:<br>AUC: ↔ | No dose adjustment is required upon co-administration. |

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| | $C_{min}$: ↔<br>$C_{max}$: ↔<br>Tenofovir alafenamide:<br>AUC: ↔<br>$C_{max}$: ↔<br>Ledipasvir:<br>AUC: ↔<br>$C_{min}$: ↔<br>$C_{max}$: ↔<br>Sofosbuvir:<br>AUC: ↔<br>$C_{max}$: ↔<br>Sofosbuvir metabolite GS-331007:<br>AUC: ↔<br>$C_{min}$: ↔<br>$C_{max}$: ↔ | |
| Sofosbuvir/ Velpatasvir/ Voxilaprevir (400/100/100+100 mg[3] once daily), Bictegravir/Emtricitabine/ Tenofovir alafenamide<br><br>(Inhibition of P-gp/ BCRP) | Bictegravir:<br>AUC: ↔<br>$C_{min}$: ↔<br>$C_{max}$: ↔<br>Emtricitabine:<br>AUC: ↔<br>$C_{min}$: ↔<br>$C_{max}$: ↔<br>Tenofovir alafenamide:<br>AUC: ↑ 57 %<br>$C_{max}$: ↑ 28 %<br>Sofosbuvir:<br>AUC: ↔<br>$C_{max}$: ↔<br>Sofosbuvir metabolite GS-331007: | No dose adjustment is required upon co-administration. |

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| | AUC: ↔<br>$C_{min}$: ↔<br>$C_{max}$: ↔<br>Velpatasvir:<br>AUC: ↔<br>$C_{min}$: ↔<br>$C_{max}$: ↔<br>Voxilaprevir:<br>AUC: ↔<br>$C_{min}$: ↔<br>$C_{max}$: ↔ | |
| **ANTIFUNGALS** | | |
| Voriconazole (300 mg twice daily), Bictegravir[1]<br><br>(Inhibition of CYP3A) | Bictegravir:<br>AUC: ↑ 61 %<br>$C_{max}$: ↔ | No dose adjustment is required upon co-administration. |
| Itraconazole<br>Posaconazole<br><br>(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<br>Clarithromycin<br><br>(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 agents on the bictegravir component of Biktarvy. |

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| **ANTIDYSRHYTHMICS** | | |
| Dofetilide | Effect on dofetilide concentrations unknown | Data are not available on the potential interaction of dofetilide with Biktarvy. Due to the potential for serious and/or life-threatenting events with increased dofetilide plasma concentraions, co-administration of Biktarvy with dofetilide is contraindicated [see section 4.3]. |
| **ANTICONVULSANTS** | | |
| Carbamazepine (titrated from 100 mg to 300 mg twice a day), Emtricitabine/Tenofovir alafenamide[4]<br><br>(Induction of CYP3A, UGT1A1, and P-gp) | Tenofovir alafenamide:<br>AUC: ↓ 54 %<br>$C_{max}$: ↓ 57 %<br><br>Interaction not studied with bictegravir. Co-administration of carbamazepine may decrease bictegravir plasma concentrations. | Co-administration is not recommended. |
| Oxcarbazepine<br>Phenobarbital<br>Phenytoin<br><br>(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 | Co-administration is not recommended. |

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| | decrease bictegravir and tenofovir alafenamide plasma concentrations. | |
| **ANTACIDS, SUPPLEMENTS AND BUFFERED MEDICINAL PRODUCTS** | | |
| Magnesium/aluminium-containing antacid suspension (20 ml single dose[5]), Bictegravir<br><br>(Chelation with polyvalent cations) | Bictegravir (antacid suspension 2 hours prior, fasted):<br>AUC: ↓ 52 %<br>$C_{max}$: ↓ 58 %<br><br>Bictegravir (antacid suspension after 2 hours, fasted):<br>AUC: ↔<br>$C_{max}$: ↔<br>Bictegravir (simultaneous administration, fasted):<br>AUC: ↓ 79 %<br>$C_{max}$: ↓ 80 %<br>Bictegravir (simultaneous administration with food):<br>AUC: ↓ 47 %<br>$C_{max}$: ↓ 49 % | *For non-pregnant patients:*<br>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).<br><br>Biktarvy should be administered at least 2 hours before, or with food 2 hours after antacids or supplements containing magnesium and/or aluminium.<br><br>*For pregnant patients:*<br>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 | Bictegravir (simultaneous | *For non-pregnant patients:* |

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| (Chelation with polyvalent cations) | administration, fasted):<br>AUC: ↓ 63 %<br>$C_{max}$: ↓ 71 %<br>Bictegravir (simultaneous administration with food):<br>AUC: ↔<br>$C_{max}$: ↓ 25 % | Biktarvy should be administered at least 2 hours before oral medications or supplements containing iron, or taken together with food at any time.<br><br>*For pregnant patients:*<br>Biktarvy should be administered at least 2 hours before or 6 hours after taking oral medications or supplements containing iron. Alternatively, Biktarvy and oral medications or supplements containing iron can be taken together with food at any time. |
| Calcium carbonate (1200 mg single dose), Bictegravir (Chelation with polyvalent cations) | Bictegravir (simultaneous administration, fasted):<br>AUC: ↓ 33 %<br>Cmax: ↓ 42 %<br>Bictegravir (simultaneous administration with food):<br>AUC: ↔<br>Cmax: ↔ | *For non-pregnant patients:*<br>Biktarvy and calcium-containing oral medications or supplements can be taken together, without regard to food.<br><br>*For pregnant patients:*<br>Biktarvy should be administered at least 2 hours before or 6 hours after taking oral medications or |

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| | | supplements containing calcium.<br>Alternatively, Biktarvy and oral medications or supplements containing calcium can be taken together with food at any time. |
| Sucralfate<br>(Chelation with polyvalent cations) | Interaction not studied with any of the components of Biktarvy.<br>Co-administration may decrease bictegravir plasma concentrations. | Co-administration not recommended. |
| **ANTIDEPRESSANTS** | | |
| Sertraline (50 mg single dose), Tenofovir alafenamide[6] | Tenofovir alafenamide:<br>AUC: ↔<br>$C_{max}$: ↔<br><br>Sertraline:<br>AUC: ↔<br>$C_{max}$: ↔<br>No interaction is expected with bictegravir and emtricitabine | No dose adjustment is required upon co-administration. |
| **IMMUNOSUPRESSANTS** | | |
| Ciclosporin (IV or oral use)<br>(P-gp inhibition) | Interaction not studied with any of the components of Biktarvy.<br>Co-administration of ciclosporin (IV or oral use) is expected to | Co-administration of ciclosporin (IV or oral use) is not recommended. If the combination is needed, clinical and biological monitoring, notably renal |

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| | increase plasma concentrations of both bictegravir and tenofovir alafenamide. | function, is recommended. |
| **ORAL ANTI-DIABETICS** | | |
| Metformin (500 mg twice daily), Bictegravir/Emtricitabine/ Tenofovir alafenamide<br><br>(Inhibition of OCT2/MATE1) | Metformin:<br>AUC: ↑ 39 %<br>$C_{min}$: ↑ 36 %<br>$C_{max}$: ↔ | No dose adjustment is required upon co-administration in patients with normal renal function.<br><br>In patients with moderate renal impairment, close monitoring should be considered when starting co-administration of bictegravir with metformin, due to the increased risk for lactic acidosis in these patients. A dose adjustment of metformin should be considered if required. |
| **ORAL CONTRACEPTIVES** | | |
| Norgestimate (0.180/0.215/0.250 mg once daily)/ Ethinylestradiol (0.025 mg once daily), Bictegravir[1] | Norelgestromin:<br>AUC: ↔<br>$C_{min}$: ↔<br>$C_{max}$: ↔ | No dose adjustment is required upon co-administration. |
| Norgestimate (0.180/0.215/0.250 mg once daily), Ethinylestradiol (0.025 mg once daily), | Norgestrel:<br>AUC: ↔<br>$C_{min}$: ↔<br>$C_{max}$: ↔ | |

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| Emtricitabine/Tenofovir alafenamide[4] | Ethinylestradiol:<br>AUC: ↔<br>$C_{min}$: ↔<br>$C_{max}$: ↔ | |
| **SEDATIVES/HYPNOTICS** | | |
| Midazolam (2 mg, oral syrup, single dose), Bictegravir/Emtricitabine/ Tenofovir alafenamide | Midazolam:<br>AUC: ↔<br>$C_{max}$: ↔ | 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, itraconazole, ketoconazole, methadone, naloxone, norbuprenorphine or omeprazole.

**4.6 Fertility, pregnancy and lactation**

Pregnancy

Data from an observational study in Botswana showed that use of doultegravir, another intergrase strand transfer inhibitor (INSTI) at the time of contraception and/or early pregnanacy in humans, was associated with an increase in neural tube defects in newborns.

A large amount of data on pregnant women (more than 1,000 exposed outcomes) indicates 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) indicates 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, if Biktarvy is used during pregnancy, viral load should be monitored closely in accordance with established treatment guidelines.

Lactation

Emtricitabine, bictegravir and tenofovir alafenamide are excreted in milk therefore Biktarvy should not be used by mothers breast-feeding their babies because there is insufficient data on the effects of Biktarvy in newborns/ infants.

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*

In animal studies there were no effects of bictegravir, emtricitabine or tenofovir alafenamide on mating or fertility parameters.

**4.7 Effects on ability to drive and use machines**

Treatment with Biktarvy may affect the patient's 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 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: | rash, pruritus |
| *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.

Clinical Trials in Virologically Suppressed Adults

The safety of BIKTARVY in virologically-suppressed adults was based on Week 48 data from 282 subjects in a randomized, double-blind, active-controlled trial (Trial 1844) in which virologically-suppressed subjects were switched from either DTG + ABC/3TC or ABC/DTG/3TC to BIKTARVY; and Week 48 data from 290 subjects in an open-label, active-controlled trial in which virologically-suppressed subjects were switched from a regimen containing atazanavir (ATV) (given with cobicistat or ritonavir) or darunavir (DRV) (given with cobicistat or ritonavir) plus

either FTC/TDF or ABC/3TC, to BIKTARVY (Trial 1878). Overall, the safety profile in virologically suppressed adult subjects in Trials 1844 and 1878 was similar to that in subjects with no antiretroviral treatment history.

**Postmarketing Experience**

In addition to adverse reactions from clinical studies, the following adverse reactions were identified during post-approval use of products containing tenofovir alafenamide (TAF). Because these reactions were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

SKIN AND SUBCUTANEOUS TISSUE DISORDERS
Angioedema, Stevens-Johnson syndrome, urticaria

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 adversereactions through Week 144 in Biktarvy 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[1] 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) and in 50 children aged 6 to < 12 years and weighing ≥ 25 kg through Week 96 (48-week main phase and 48-week extension in an open-label clinical study (GS-US-380-1474). In this study, no new adverse reactions have been observed in paediatric subjects aged 6 years and older weighing at least 25 kg 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).

<u>Other Special Populations</u>

*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).

The safety of emtricitabine+tenofovir alafenamide was evaluated in 72 HIV-suppressed adults co-infected with chronic hepatitis B through Week 48 in an open-label clinical study (GS-US-292-1249) in which patients were switched from another antiretroviral regimen (which included tenofovir disoproxil fumarate [TDF] in 69 of 72 patients) to emtricitabine+tenofovir alafenamide in combination with elvitegravir+cobicistat as a fixed dose combination tablet (elvitegravir/ cobicistat/ emtricitabine/tenofovir alafenamide. Based on these limited data, the safety profile of this regimen in patients co-infected with HIV-1 and chronic hepatitis B 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and Reporting platform (who-umc-org) found on SAHPRA website.

**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 symptomatic and 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 3hour 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**

A 20.2.8 Antiviral Medicines

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.

Emtricitabine triphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there was no evidence of toxicity to mitochondria *in vitro* and *in vivo*.

Tenofovir alafenamide is a nucleotide reverse transcriptase inhibitor (NtRTI) and phosphonamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). Tenofovir alafenamide is permeable into cells and due to increased plasma stability and intracellular activation through hydrolysis by cathepsin A, tenofovir alafenamide is more efficient than tenofovir disoproxil fumarate in loading tenofovir into peripheral blood mononuclear cells (PBMCs) (including lymphocytes and other HIV target cells) and macrophages. Intracellular tenofovir is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV replication through incorporation into viral DNA by the HIV RT, which results in DNA chain-termination. Tenofovir has activity against HIV-1, HIV-2 and HBV.

Antiviral activity *in vitro*

The triple combination of bictegravir, emtricitabine, and tenofovir alafenamide demonstrated synergistic antiviral activity in cell culture.

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 associated with M184V/I mutations in HIV-1 RT.
HIV-1 isolates with reduced susceptibility to tenofovir alafenamide have been selected in cell culture and expressed a 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 = 3).

*Patients with co-infected with HIV-1 and Chronic Hepatitis B*
In a clinical study of patients coinfected with HIV-1 and chronic hepatitis B who received FTC + TAF in combination with EVG+COBI as a fixed-dose combination tablet for 48 weeks (GS-US-292-1249, N = 72), no subject had HIV or HBV emergent resistance to FTC, TAF, or EVG.

*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.

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. Viruses harbouring mutations conferring reduced susceptibility to stavudine and zidovudine - thymidine analogue-associated mutations - TAMs (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E), or didanosine (L74V) remained sensitive to emtricitabine. HIV-1 containing the K103N substitution or other substitutions associated with resistance to NNRTIs was susceptible to emtricitabine.

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 fumarate. HIV-1 containing the K103N or Y181C mutations associated with resistance to NNRTIs were susceptible to tenofovir alafenamide fumarate. HIV-1 containing mutations associated with resistance to PIs, such as M46I, I54V, V82F/T, and L90M were susceptible to tenofovir alafenamide fumarate.

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).

*HIV-1 infected, treatment-naïve patients*

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.

Patients with Renal Impairment

The safety profile of emtrictabine + tenofovir alafenamide in patients with mild to moderate renal impairment was similar to that in patients with normal renal function.

The effect of bictegravir on renal function was evaluated in a randomised, blinded, parallel, placebo-controlled trial in 40 healthy subjects who received bictegravir 75 mg (n=20) or placebo (n=20) once daily with food for 14 days. Mean change from baseline in serum creatinine in the bictegravir group was 0.1 mg/dL (8.84 µmol/L) on Days 7 and 14. Bictegravir did not have a clinically significant effect on the estimated glomerular filtration rate or on the actual glomerular filtration rate (determined by the clearance of probe drug, iohexol) compared with placebo.

Effects on electrocardiogram

In a QT/QTc study in 48 healthy subjects, tenofovir alafenamide at the therapeutic dose or at a supratherapeutic dose 5 times the recommended therapeutic dose did not affect the QT/QTc interval and did not prolong the PR interval.

*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) and between the ages of 6 to < 12 years (≥ 25 kg) (n = 50) 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.

**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 Biktarvy. Relative to fasting conditions, the administration of Biktarvy 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 change is not considered clinically meaningful and Biktarvy can be administered with or without food.

Following oral administration of Biktarvy 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 well absorbed following oral administration with peak plasma concentrations occurring at 1.5-2.0 hours after administration of Biktarvy. The mean absolute bioavailability of emtricitabine from 200 mg hard capsules was 93 %. The mean absolute bioavailability of the emtricitabine 10 mg/ml oral solution was 75 %. Emtricitabine systemic exposure was unaffected when emtricitabine was administered with food and Biktarvy can be administered with or without food.

Following oral administration of Biktarvy 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 well following oral administration with peak plasma concentrations occurring at 0.5-2.0 hours after administration of Biktarvy. 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 Biktarvy can be administered with or without food.

Following oral administration of Biktarvy 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

*Bictegravir*
*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.

*Emtricitabine*
*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.

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

Distribution studies in dogs showed 5.7 to 15-fold higher [$^{14}$C]-radioactivity in lymphoid tissues (iliac, axillary, inguinal and mesenteric lymph nodes, and spleen) 24 hours following administration of an equivalent dose of [$^{14}$C]-TAF relative to [$^{14}$C]-TDF.

Metabolism

*Bictegravir*
Metabolism is the major clearance pathway for bictegravir in humans, accounting for >90 % of an oral dose. *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. No unique metabolites were identifiable. Bictegravir is not an inhibitor or inducer of CYP3A *in vivo.*

*Emtricitabine*

*In vitro* studies indicate that emtricitabine is not an inhibitor of human CYP450 enzymes. Following administration of [$^{14}$C]-FTC, 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.

*Tenofovir alafenamide*

Metabolism is a major elimination pathway for tenofovir alafenamide in humans, accounting for > 80 % of an oral dose. *In vitro* studies have shown that tenofovir alafenamide is metabolised to tenofovir (major metabolite) by cathepsin A in PBMCs (including lymphocytes and other HIV target cells) and macrophages; and by carboxylesterase-1 in hepatocytes. *In vivo*, tenofovir alafenamide is hydrolysed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. In human clinical studies, a 25 mg oral dose of tenofovir alafenamide resulted in tenofovir diphosphate concentrations > 4-fold higher in PBMCs and > 90 % lower concentrations of tenofovir in plasma as compared to a 300 mg oral dose of tenofovir disoproxil fumarate. Tenofovir alafenamide is not an inhibitor or inducer of CYP3A *in vivo*.

Elimination

*Bictegravir*

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*

Emtricitabine is primarily excreted by the kidneys by both glomerular filtration and active tubular secretion. The plasma emtricitabine half-life was approximately 10 hours. Following emtricitabine dosing, the steady state mean intracellular half-life of emtricitabine 5'-triphosphate (the active drug moiety) in PBMCs was 39 hours.

*Tenofovir alafenamide*

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

Linearity

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

Pharmacokinetics in special populations

*Age, gender and ethnicity*

Population analyses using pooled pharmacokinetic data from adult trials did not identify any clinically relevant differences due to age, gender or race on the exposures of bictegravir, emtricitabine, or tenofovir alafenamide.

*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; therefore, 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.

*Hepatitis B and/or Hepatitis C virus Co-infection*

The pharmacokinetics of bictegravir, emtricitabine and tenofovir alafenamide have not been fully evaluated in patients co-infected with hepatitis B and/or C virus.

*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 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 3.

**Table 3: Exposures of Bictegravir, Emtricitabine, Tenofovir Alafenamide and Tenofovir in Children, Adolescents, and Adults**

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

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 = 24
d n = 22
e n = 23
f n = 75
g n = 74
h 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 4).

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 4: 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. [1,2,3]

### 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 revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. Emtricitabine has demonstrated low carcinogenic potential in mice and rats.

Non-clinical studies of tenofovir alafenamide in rats and dogs revealed bone and kidney as the primary target organs of toxicity. Bone toxicity was observed as reduced bone mineral density in rats and dogs at tenofovir exposures at least 43 times greater than those expected after administration of B/F/TAF. A minimal infiltration of histiocytes was present in the eye in dogs at tenofovir alafenamide and tenofovir exposures of approximately 14 and 43 times greater, respectively, than those expected after administration of B/F/TAF.

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

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

tenofovir disoproxil fumarate reduced the viability index and weight of pups in a peri-postnatal toxicity study at maternally toxic doses.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*List of Excipients*

Tablet core:
Microcrystalline cellulose, Croscarmellose sodium, Magnesium stearate.
Film-coating:
Polyvinyl alcohol, Titanium dioxide (E171), Polyethylene glycol, Talc, 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

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

### 6.5 Nature and contents of container

White, high density polyethylene (HDPE) bottle with a polypropylene continuous-thread, child-resistant cap, lined with an induction activated aluminium foil liner containing 30 film-coated tablets. Each bottle contains silica gel desiccant and polyester coil.
The following pack sizes are available: outer cartons containing 1 bottle of 30 film-coated tablets

### 6.6 Special precautions for disposal

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

## 7 HOLDER OF CERTIFICATE OF REGISTRATION

Gilead Sciences South Africa (Pty) Ltd

Ground Floor

Mac Mac Building

Maxwell Office Park

Magwa Crescent

Waterfall, Midrand

Gauteng, 2090

South Africa

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