Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets
50 mg/200 mg/25 mg

POM | Schedule 3| 2833 P.P.

Prescription only medicine List 1

1. NAME OF THE MEDICINAL PRODUCT

Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets 50 mg/200 mg/25 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains Bictegravir 50mg equivalent to 52.50mg of Bictegravir sodium, Emtricitabine 200 mg and Tenofovir Alafenamide 25 mg equivalent to 28.240mg of Tenofovir alafenamide hemifumarate.
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Dosage Form: Tablet
White to off white, capsule shaped biconvex film coated tablets, debossed with "9" on one side and "B4A" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and pediatric patients at least 2 years of age and weighing at least 12 kg without prior or current evidence of viral resistance to bictegravir or tenofovir.

4.2 Posology and method of administration

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

Posology:

Adults and paediatric patients weighing at least 25 kg Over 50 kg (200 mg/25 mg tablet) to be taken once daily.

Missed dose

If the patient misses a dose of Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets within 18 hours of the time it is usually taken, the patient should take Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets as soon as possible and resume the normal dosing schedule. If a patient misses a dose of Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets by more than 18 hours, the patient should wait for the next dose and then resume the normal dosing schedule.
If the patient vomits within 1 hour of taking Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets another tablet should be taken. If a patient vomits more than 1 hour after taking Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets they do not need to take another dose of Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets and the next regularly scheduled dose.

Special populations

Elderly
No dose adjustment of Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets is required in patients aged ≥ 65 years.

Hepatic impairment
No dose adjustment of Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets is required in patients with mild Child-Pugh Class A or moderate Child-Pugh Class B hepatic impairment. Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets not been studied in patients with severe hepatic impairment. Child-Pugh Class C; therefore Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets is not recommended for use in patients with severe hepatic impairment.

Renal impairment
No dose adjustment of Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets is required in patients weighing ≥ 25 kg with estimated creatinine clearance (CrCl) > 30mL/min.
No dose adjustment of Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets is required in adult patients with end-stage renal disease (estimated creatinine clearance (CrCl) < 15 mL/min) who are receiving chronic hemodialysis. However, Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets should generally be avoided and an alternative HIV-1 antiretroviral regimen recommended. Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets 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 Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets 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 should be considered.

Weight and weight changes
An increase in weight and in blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is evidence for a beneficial effect of treatment to prevent cardiovascular and cerebrovascular disease. For the assessment of changes in 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 to Nucleos(t)ide analogues may be a cause for delayed neurological dysfunction in 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 presented with transient neurological events suspected to be mitochondrial dysfunction-related. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactatemia, hyperglycaemia). These events have often been transitory. Late onset neurological disorders have been reported in infants who have recovered from early mitochondrial dysfunction-related events after exposure to nucleoside analogues in utero. These findings should be considered for any child exposed in utero to nucleoside analogues, who present with severe clinical findings of unknown aetiology, particularly neurologic findings. These findings do not affect current recommendations for antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Immune Reactivation Syndrome
In patients with HIV and with severe immune deficiency at the time of institution of CART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause more critical conditions, or aggravate symptoms, of opportunistic infections. Typically, such reactions have been observed within the first few weeks or months of initiation of CART.
Relevant examples include cytomegalovirus retinitis, generalized and/or focal mycobacterial infections, and *Pneumocystis jiroveci 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 Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets 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.

Osteoporosis
Post-marketing cases of renal impairment, including acute renal failure and proximal renal tubulopathy, have been reported with tenofovir alafenamide-containing products. A prudent medical approach is recommended for patients at risk of renal impairment when initiating a tenofovir alafenamide-containing medicinal product. It is recommended that renal function is assessed in all patients prior to, or when initiating, therapy with Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets and during treatment, to confirm renal function remains stable after 2 weeks of treatment. In patients who develop clinically significant decreases in renal function, or evidence of proximal renal tubulopathy, discontinuation of Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets should be considered.

Patients with end stage renal disease on chronic haemodialysis
Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets should generally be avoided in adults with end stage renal disease (estimated CrCl < 15 mL/min) on chronic haemodialysis if the potential benefits outweigh the potential risks. In a study of emtricitabine +tenofovir alafenamide in combination with elvitegravir + cobicistat in a fixed dose combination tablet: 0/2(n=1)(4) in adults with HIV-1 with end stage renal disease (estimated CrCl < 15 mL/min on chronic haemodialysis, efficacy was maintained through 98 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 Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets for 48 weeks. Although no additional adverse reactions were identified, the implications of increased emtricitabine exposure remain unclear.

Co-administration with other medicinal products or vaccines
Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets should not be co-administered simultaneously with antacids, oral medications or supplements containing magnesium, aluminium or iron under fasted conditions. Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets should be administered at least 2 hours before, or with food 2 hours after antacids, oral medications or supplements containing magnesium and/or aluminium. Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets should be administered at least 2 hours before or 4 hours after taking antacids or supplements containing magnesium and/or aluminium with food.
In pregnant patients, dosage adjustments are recommended for co-administration of polivalent cation containing antacids, oral medications or supplements.
Some medicinal products are not recommended for co-administration with Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets: dasatinib, carbamazepine, citrapofen (Hr or oral use), oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifapentine, or sucralfate.
Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets 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 bone mass(TBBM) have been reported in patients aged between 2 to < 12 years who received tenofovir alafenamide-containing products for 48 weeks. The long-term effects of changes in BMD on the growing bone, including the risk of fracture, are uncertain. A medicinal product 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 drug products and other forms of interaction
Interaction studies have only been performed in adults.
Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets should not be administered concomitantly with medicinal products containing tenofovir alafenamide, tenofovir disoproxil, tenofovir adefovir dipivoxil and/or tenofovir alafenamide for the treatment of HIV 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 Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets and development of resistance, therefore administration is contraindicated. 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 recommended when bictegravir is combined with medicinal products that potently inhibit P-gp and BCRP. Co-administration with medicinal products that potently induce P-gp and BCRP is not recommended.
Bictegravir inhibits organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter 1 (MATE1) in vitro. Co-administration of Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets with the OCT2 and MATE1 substrates metformin did not result in a clinically significant increase in metformin exposure. Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets may be co-administered with substrates of OCT2 and MATE1.
Bictegravir is not an inhibitor or inducer of CYP enzymes.

Emtricitabine
In vitro and clinical pharmacokinetic 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 renal cationic secretion may increase concentrations of emtricitabine, and for this 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 Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets with medicinal products that strongly affect P-gp and BCRP activity may lead to changes in bioavailability of tenofovir alafenamide. Medicinal products that induce P-gp activity (e.g.,rifabutin, carbamazepine, phenobarbital or oxcarbazepine) 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 Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets and development of resistance. Co-administration of Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets with other medicinal products that inhibit P-gp and BCRP may increase the absorption of tenofovir alafenamide, resulting in increased plasma concentrations of tenofovir alafenamide.
Tenofovir alafenamide is not an inhibitor or inducer of CYP3A in vivo.

Other interactions
Interactions between Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets 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 the Effect Boundaries are 70%-143%).

Table 1: Interactions between Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets or its individual component(s) and other medicinal products

Medicinal products by therapeutic area/possible mechanism of interaction	Interaction and recommended dose recommendations regarding co-administration with Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets
HERBAL PRODUCTS	
St. John's wort (*Hypericum perforatum*) Interaction not studied with any of the components of Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets. Induction of CYP3A, UGT1A1, and P-gp	Co-administration with St. John's wort is contraindicated. Due to the effect of St. John's wort on the bictegravir component of Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets, co-administration with other bictegravir containing medicinal products is contraindicated.
ANTI-INFECTIVES	
Antimycobacterial	
Rifampicin (600 mg once daily), Bictegravir Induction of CYP3A, UGT1A1, and P-gp	Bictegravir: AUC: ↓ 75% C_{max}: ↓ 39% Co-administration is contraindicated due to the effect of rifampicin on the bictegravir component of Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets.
Rifabutin (300 mg once daily), Bictegravir Induction or CYP3A and P-gp	Bictegravir: AUC: ↓ 38% C_{max}: ↓ 34% C_{trough}: ↓ 20% Co-administration is not recommended due to the expected decrease of bictegravir exposure.
Rifapentine Induction or CYP3A and P-gp	Interaction not studied with any of the components of Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets. Co-administration of rifapentine may decrease bictegravir and tenofovir alafenamide plasma concentrations.
HIV-1 antiviral agents	
Atazanavir (300 mg once daily), Cobicistat (150 mg once daily), Bictegravir Inhibition of CYP3A, UGT1A1, and P-gp(BCRP)	Bictegravir: AUC: ↑ 200% Co-administration is not recommended.
Atazanavir (400 mg once daily), Bictegravir Inhibition of CYP3A and UGT1A1	Bictegravir: AUC: ↑ 315% Co-administration is not recommended.
Hepatitis C virus antiviral agents	
Ledipasvir/Sofosbuvir (90 mg/400 mg once daily), Bictegravir/Emtricitabine/ Tenofovir alafenamide* Inhibition of P-gp(BCRP)	No dose adjustment is required upon co-administration. Bictegravir: AUC_{tau}: ↔ C_{max}: ↔ C_{trough}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{trough}: ↔ Tenofovir alafenamide: AUC: ↔ C_{max}: ↔ Ledipasvir: AUC: ↔ C_{max}: ↔ C_{trough}: ↔ Sofosbuvir: AUC: ↔ C_{max}: ↔ Sofosbuvir metabolite GS-331007: AUC: ↔ C_{max}: ↔
Sofosbuvir/Velpatasvir/ Voxilaprevir (400/100/100 + 100 mg/ once daily), Bictegravir/Emtricitabine/ Tenofovir alafenamide* Inhibition of P-gp(BCRP)	No dose adjustment is required upon co-administration. Bictegravir: AUC_{tau}: ↔ C_{max}: ↔ C_{trough}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{trough}: ↔ Tenofovir alafenamide: AUC: ↑ 57% C_{max}: ↑ 28% C_{trough}: ↔ Sofosbuvir: AUC: ↔ C_{max}: ↔ Sofosbuvir metabolite GS-331007: AUC: ↔ C_{max}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↔ C_{trough}: ↔ Voxilaprevir: AUC: ↔ C_{max}: ↔ C_{trough}: ↔
Antifungals	
Itraconazole (200 mg twice daily), Bictegravir Inhibition of CYP3A;	No dose adjustment is required upon co-administration. Bictegravir: AUC: ↑ 81% C_{max}: ↔
Posaconazole (Prescription Phenytoin Induction of CYP3A, UGT1A1, and P-gp	Interaction not studied with any of the components of Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets. Co-administration of itraconazole, phenobarbital, or phenytoin may decrease bictegravir and tenofovir alafenamide plasma concentrations.
Macrolides	
Azithromycin Clarithromycin Inhibition of P-gp	Interaction not studied. Co-administration of azithromycin or clarithromycin may increase bictegravir plasma concentrations.
ANTICONVULSANTS	
Carbamazepine (Interval from 100 mg to 300 mg twice a day), Emtricitabine/Tenofovir alafenamide* 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.
Oxcarbazepine (Phenobarbital Phenytoin Induction of CYP3A, UGT1A1, and P-gp	Interaction not studied with any of the components of Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets. Co-administration of oxcarbazepine, phenobarbital, or phenytoin may decrease bictegravir and tenofovir alafenamide plasma concentrations.
ANTACIDS, SUPPLEMENTS AND RUFFIXES MEDICINES	
Magnesium/aluminium-containing antacid suspension (20 mL single dose), Bictegravir Chelation with polivalent cations	Bictegravir (antacid suspension 2 hours prior, fasted): AUC: ↓ 32% C_{max}: ↓ 38% Bictegravir (antacid suspension after 2 hours, fasted): AUC: ↓ 79% C_{max}: ↓ 80% Bictegravir (simultaneous administration, fasted): AUC: ↓ 79% C_{max}: ↓ 80% Bictegravir (simultaneous administration with food): AUC: ↓ 67% C_{max}: ↓ 40% *For management patients:* Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets should be administered at least 2 hours before and medications or supplements containing iron, or taken together with food at any time. *For pregnant patients:* Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets should be administered at least 2 hours before or 6 hours after taking and medications or supplements containing iron. Alternatively, Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets and oral medications or supplements containing iron can be taken together with food at any time.
Calcium carbonate (1,200 mg single dose), Bictegravir Chelation with polivalent cations	Bictegravir (simultaneous administration, fasted): AUC: ↓ 22% C_{max}: ↓ 42% Bictegravir (simultaneous administration with food): AUC: ↔ C_{max}: ↓ 22% *For management patients:* Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets and calcium-containing and medication or supplements can be taken together, without regard to food. *For pregnant patients:* Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets should be administered at least 2 hours before or 6 hours after taking and medications or supplements containing iron. Alternatively, Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets and oral medications or supplements containing iron can be taken together with food at any time.
Sucralfate Chelation with polivalent cations	Interaction not studied with any of the components of Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets. Co-administration may decrease bictegravir plasma concentrations.
ANTIDEPRESSANTS	
Sertraline (50 mg single dose), Tenofovir alafenamide*	Tenofovir alafenamide: AUC_{tau}: ↔ C_{max}: ↔ Sertraline: AUC: ↔ C_{max}: ↔ No interaction is expected with bictegravir and emtricitabine.
IMMUNOSUPPRESSANTS	
Ciclosporin (Fr or oral use) (P-gp inhibitor)	Interaction not studied with any of the components of Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets. Co-administration of ciclosporin (Fr or oral use) is expected to increase plasma concentrations of both bictegravir and tenofovir alafenamide.
ORAL ANTI-DIABETICS	
Metformin (500 mg twice daily), Bictegravir/Emtricitabine/ Tenofovir alafenamide Inhibition of OCT2/MATE1	No dose adjustment is required upon co-administration in patients with normal renal function. In patients with moderate renal impairment, close monitoring should be considered when starting co-administration of bictegravir with metformin, due to the increased risk for lactic acidosis in these patients. A dose adjustment of metformin should be considered if required.
ORAL CONTRACEPTIVES	
Norgestimate (0.180/0.215/0.250 mg/day) and ethinylestradiol (0.025 mg/ oral dosing), Bictegravir*	Norelgestromin: AUC: ↔ C_{max}: ↔ C_{trough}: ↔ Norgestrel: AUC: ↔ C_{max}: ↔ C_{trough}: ↔ Ethinylestradiol: AUC: ↔ C_{max}: ↔ C_{trough}: ↔ No dose adjustment is required upon co-administration.
DERATIVES/OPRETICS	
Midazolam (2 mg, oral syrup, single dose), Bictegravir/Emtricitabine/ Tenofovir alafenamide	Midazolam: AUC: ↔ C_{max}: ↔ No dose adjustment is required upon co-administration.

* This study was conducted using bictegravir 75 mg single dose.
Abbreviations: AUC = area under the plasma concentration-time curve; tenofovir alafenamide 75/200/25 mg once daily.
Effects conducted with additional evaluations of co-administration of Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets with HCV.
A This study was conducted using emtricitabine/tenofovir alafenamide 200/25 mg once daily.
Maximum strength unavailable; Bictegravir 50 mg equivalent to 52.5 mg, 80 mg equivalent to 84 mg, and 0 mg sinecbicoxyl sodium.
B This study was conducted using elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide 150/150/200/10 mg once daily.
Based on drug interactions studies with Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets or the components of Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets, no clinically significant disorderprocesses are expected with: amiodipine, atorvastatin, buprenorphine, droxipromen, fenofibrate, fluvoxamine, methadone, midazolam, mifepristone, ondansetron, orlistat, ranolazine, rosuvastatin, sertraline, simeprevir, telaprevir, telmisartan, vortioxetine.

4.6 Fertility, pregnancy and lactation

Pregnancy
A large amount of data on pregnant women (more than 1,000 exposed outcomes) indicates no malformative or fetotoxic toxicity associated with emtricitabine or tenofovir alafenamide. A number of data on pregnant women (between 200-1000 pregnancy outcomes) indicates no malformative or fetotoxic 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 or fertility impairment to the male or female reproductive organs.
Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets may be used during pregnancy if the potential benefit justifies the potential risk to the foetus. Moreover, trial data should of the more be mentioned clinicly in accordance with established treatment guidelines.

Breastfeeding
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 neonatal pups up to at least 5 days after birth. Bictegravir was also detected in milk of lactating rats. Tenofovir alafenamide was rapidly converted to tenofovir in human milk. Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets should not be taken by women who are breastfeeding.

Fertility
No human data on the effect of Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets on fertility are available. Animal studies indicate no effects of bictegravir, emtricitabine and tenofovir alafenamide on fertility.

4.7 Effects on ability to drive and use machines
Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets 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 Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets.

4.8 Undesirable effects
Tabulated list of adverse reactions
In clinical studies of treatment-naïve adult patients receiving Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets through 144 weeks, the most
commonly reported adverse reactions were nausea (5%), diarrhoea (5%) and insomnia (4%).
Tabulated list of adverse reactions
The following adverse reactions have been observed in safety data from across all Phase 2 and 3 studies with Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets and from post-marketing experience. The adverse reaction in Table 2 are listed by system organ class and frequency. Frequencies are defined as follows: common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100) and rare (≥ 1/10000 to < 1/1000).

Table 2: Tabulated list of adverse reactions†

Frequency	Adverse reaction
Blood and lymphatic system disorders	
Uncommon:	Anaemia*
Nervous system disorders	
Common:	depression, abnormal dreams
Uncommon:	suicidal ideation, suicide attempt (particularly in patients with a pre-existing history of depression or psychotic illness), anxiety, sleep disorders
Nervous system disorders	
Common:	headache, dizziness
Gastrointestinal disorders	
Common:	diarrhoea, nausea
Uncommon:	vomiting, abdominal pain, flatulence
Hepatobiliary disorders	
Uncommon:	hyperbilirubinemia
Skin and subcutaneous tissue disorders	
Uncommon:	Angioedema*#, rash, pruritus, urticaria*
Rare:	Stevens-Johnson syndrome*
Musculoskeletal and connective tissue disorders	
Uncommon:	arthralgia
General disorders and administration site conditions	
Uncommon:	fatigue

† With the exception of angioedema, anemia, urticaria and Stevens-Johnson syndrome (see footnotes 2-3), all adverse reactions were identified from Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets or the clinical studies of emtricitabine + tenofovir alafenamide + bictegravir (Phase 3 Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets clinical studies in treatment-naïve patients through 144 weeks (GS-US-380-1489 and GS-US-380-1490).
2 This adverse reaction was identified through post-marketing surveillance for Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets. The frequency has been calculated using 3/N, where N represent the cumulative number of participants exposed to Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets in clinical trials (N=2083).
3 This adverse reaction was identified through post-marketing surveillance for tenofovir alafenamide containing products.
4 This adverse reaction was identified through post-marketing surveillance for Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets. The frequency has been calculated using 3/N, where N represent the cumulative number of participants exposed to Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets in clinical trials (N=2083).

Description of selected adverse reactions
Renal impairment
Weight and levels of blood lipids and glucose may increase during antiretroviral therapy.
Immune Reactivation Syndrome
In patients with HIV and 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.
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.

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-380-1489/1490 (N=1,065), the mean (SD) change from baseline in serum creatinine was 0.11 (0.0), 0.18 (0.0), 0.12 (0.1), 16 (0.2) and 0.16 (0.0), 0.19 (0.1), 0.18 (0.1), and 0.12 (0.0), 0.21 (0.1), 0.18 (0.2) mg/dL at Week 144 in the Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets, Bictegravir + emtricitabine + tenofovir alafenamide, and Bictegravir + tenofovir alafenamide groups, respectively. There were no discontinuations due to renal adverse events through Week 144 in patients administered Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets.

Changes in lipids
In Studies GS-US-380-1489/1490 (N=1,065), total cholesterol increases were observed in 177 treatment-naïve participants receiving Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets through Week 144. Increases were primarily Grade 1 (72%) and Grade 2 (14%) (≥ 1.2 to 2.5 x Upper Limit of Normal (ULN)), and were not associated with fasting status or adverse reactions. Total cholesterol increases were observed in participants who switched to Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets (76) had grade 3 dislipidemia increases that were not considered related to study drug. There were no discontinuations due to hepatic adverse reactions through Week 144 in participants who switched to Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets.

Paediatric population
The safety of Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets was evaluated in 50 adolescents with HIV-1 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 72 children ≥ 2 years of age and weighing ≥ 14 kg to < 25 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 participants aged 2 years and older with HIV-1 as compared to adult participants with HIV-1. Bone mineral density data were not collected in this study. Reductions in BMD of the spine and of the TBBM ≥ 4% have been reported in Paediatric patients receiving other tenofovir alafenamide containing products for 48 weeks.

Other special populations
Patients with HIV and Hepatitis B virus co-infection
In 10 adults with HIV and HBV co-infection who were administered Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets (8 adults who were HIV/HBV treatment-naïve in Study GS-US-380-1489 and 2 adults with HIV/HBV who were virologically suppressed in Study GS-US-380-1878), the safety profile of Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets was similar to that in patients with HIV-1 Mono-infection.

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 80 participants with virologically suppressed HIV-1) included 111 patients aged ≥ 65 years who received Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets. In these patients, no differences in the safety profile of Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets were observed.

Patients with virologically suppressed HIV-1
The safety of Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets was evaluated in 50 adolescents with HIV-1 aged 12 to < 18 years and weighing ≥ 35 kg through Week 96 (48 week main phase and 48 week extension), 50 children aged 6 to < 12 years and weighing ≥ 25 kg through Week 96 (48 week main phase and 48 week extension), and 72 children ≥ 2 years of age and weighing ≥ 14 kg to < 25 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 participants aged 2 years and older with HIV-1 as compared to adult participants with HIV-1. Bone mineral density data were not collected in this study. Reductions in BMD of the spine and of the TBBM ≥ 4% have been reported in Paediatric patients receiving other tenofovir alafenamide containing products for 48 weeks.

4.9 Overdose
If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with Bictegravir, Emtricitabine and Tenofovir Alafenamide Tablets consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient.
Bictegravir is not expected to be highly bioavailable in the gastrointestinal tract. Elimination of 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
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 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 acts against HIV-1, HIV-2 and HBV.
Tenofovir alafenamide is a nucleotide reverse transcriptase inhibitor (NrtRTI) and phosphonamidate prodrug of tenofovir (2' deoxyadenosine monophosphate analogue). Tenofovir alafenamide requires initial diesterase-mediated conversion to tenofovir monophosphate to exert its antiviral activity. Tenofovir alafenamide is more efficient than Tenofovir disoproxil in leading tenofovir into peripheral blood mononuclear cells (PBMC) 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 reverse transcriptase integrase enzyme and 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 EC50 values for bictegravir against laboratory and clinical isolates of HIV-1 ranged from 0.07 to 2.4 nM. Bictegravir demonstrated EC50 of 0.2 nM against HIV-2 isolates.
The antiviral activity of tenofovir alafenamide against laboratory and clinical isolates of HIV-1 subtype B was assess