STRIBILD®

(elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil (as fumarate))
Film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Stribild®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (equivalent to 300 mg of tenofovir disoproxil fumarate or 136 mg of tenofovir).

Excipients with known effect

Each tablet contains 10.4 mg lactose (as monohydrate) (equiv. to 10.9 mg lactose monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Green, capsule-shaped, film-coated tablet of dimensions 20 mm x 10 mm, debossed on one side with "GSI" and the number "1" surrounded by a square box on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Stribild is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years and over who are antiretroviral treatment-naïve or are infected with HIV-1 without known mutations associated with resistance to any of the three antiretroviral agents in Stribild (see sections 4.2, 4.4 and 5.1).

4.2 Posology and method of administration

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

Posology
One tablet to be taken once daily with food (see section 5.2).

If the patient misses a dose of Stribild within 18 hours of the time it is usually taken, the patient should take Stribild with food as soon as possible and resume the normal dosing schedule. If a patient misses a dose of Stribild by more than 18 hours and it is almost time for the next dose, the patient should not take the missed dose and simply resume the usual dosing schedule.

If the patient vomits within 1 hour of taking Stribild another tablet should be taken.

Special populations

Elderly
No data are available on which to make a dose recommendation for patients over the age of 65 years (see sections 4.4 and 5.1). Stribild should be administered with caution to elderly patients (see section 4.4).

Renal impairment
Stribild should not be initiated in patients with creatinine clearance below 70 mL/min (see sections 4.4 and 5.2). See section 4.4 regarding initiation of Stribild in patients with creatinine clearance below 90 mL/min.

Stribild should be discontinued if creatinine clearance declines below 50 mL/min during treatment with Stribild as dose interval adjustment is required for emtricitabine and tenofovir disoproxil and this cannot be achieved with the fixed-dose combination tablet (see sections 4.4 and 5.2). See section 4.4 regarding patients with creatinine clearance that falls below 70 mL/min while on treatment with Stribild.

Hepatic impairment
No dose adjustment of Stribild is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Stribild has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, Stribild is not recommended for use in patients with severe hepatic impairment (see sections 4.4 and 5.2).

If Stribild is discontinued in patients co-infected with HIV and hepatitis B virus (HBV), these patients should be closely monitored for evidence of exacerbation of hepatitis (see section 4.4).

Paediatric population
The safety and efficacy of Stribild in children aged 6 to less than 18 years have not yet been established. Currently available data are described in section 5.2 but no recommendation on a posology can be made.

Stribild should not be used in children aged 0 to less than 6 years because of safety/efficacy concerns.

Method of administration

Stribild should be taken orally, once daily with food (see section 5.2). There is no information available regarding the crushing/splitting of the product. The film-coated tablet should not be chewed, crushed, or split.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Patients who have previously discontinued treatment with tenofovir disoproxil due to renal toxicity, with or without reversal of the effects post-discontinuation.

Co-administration is contraindicated with medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. Therefore, Stribild should not be co-administered with medicinal products that include, but are not limited to, the following (see section 4.5):

- alpha 1-adrenoreceptor antagonists: alfuzosin
- antiarrhythmics: amiodarone, quinidine
- ergot derivatives: dihydroergotamine, ergometrine, ergotamine
- gastrointestinal motility agents: cisapride
- HMG Co-A reductase inhibitors: lovastatin, simvastatin

- neuroleptics/antipsychotics: pimozide, lurasidone
- PDE-5 inhibitors: sildenafil for treatment of pulmonary arterial hypertension
- sedatives/hypnotics: orally administered midazolam, triazolam

Co-administration is contraindicated with medicinal products that are strong inducers of CYP3A due to the potential for loss of virologic response and possible resistance to Stribild. Therefore, Stribild should not be co-administered with medicinal products that include, but are not limited to, the following (see section 4.5):

- anticonvulsants: carbamazepine, phenobarbital, phenytoin
- antimycobacterials: rifampicin
- herbal products: St. John's wort (*Hypericum perforatum*)

Co-administration with dabigatran etexilate, a P-glycoprotein (P-gp) substrate, is contraindicated (see section 4.5).

4.4 Special warnings and precautions for use

Renal and bone effects in adults

Renal effects
Emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil (see section 4.8).

There are currently inadequate data to determine whether co-administration of tenofovir disoproxil and cobicistat is associated with a greater risk of renal adverse reactions compared with regimens that include tenofovir disoproxil without cobicistat.

Patients who have previously discontinued treatment with tenofovir disoproxil due to renal toxicity, with or without reversal of the effects post-discontinuation, should not be treated with Stribild (see section 4.3).

Renal monitoring
Before initiating treatment with Stribild
Creatinine clearance should be calculated and urine glucose and urine protein should be determined in all patients. Stribild should not be initiated in patients with creatinine clearance < 70 mL/min. It is recommended that Stribild is not initiated in patients with creatinine clearance < 90 mL/min unless, after review of the available treatment options, it is considered that Stribild is the preferred treatment for the individual patient.

During treatment with Stribild
Creatinine clearance, serum phosphate, urine glucose and urine protein should be monitored every four weeks during the first year and then every three months during Stribild therapy. In patients at risk for renal impairment a more frequent monitoring of renal function is required.

Cobicistat inhibits the tubular secretion of creatinine and may cause modest increases in serum creatinine and modest declines in creatinine clearance (see section 4.8). Patients who experience a confirmed increase in serum creatinine of greater than 26.5 µmol/L (0.3 mg/dL) from baseline should be closely monitored for renal safety.

See also under *Co-administration of other medicinal products* below.

Renal management
If serum phosphate is < 0.48 mmol/L (1.5 mg/dL) or creatinine clearance is decreased to < 70 mL/min, renal function should be re-evaluated within one week, including measurements of blood glucose,

blood potassium and urine glucose concentrations (see section 4.8). It is recommended that Stribild is discontinued in patients with creatinine clearance that falls to < 70 mL/min while on treatment unless it is considered that the potential benefit of this combination of antiretroviral agents for the individual patient outweighs the possible risks of continuing with therapy. Interrupting treatment with Stribild should also be considered in case of progressive decline of renal function when no other cause has been identified.

Stribild should be discontinued in patients with confirmed creatinine clearance that falls to < 50 mL/min (since the required dose interval adjustments are not possible using this fixed dose combination tablet) or with decreases in serum phosphate to < 0.32 mmol/L (1.0 mg/dL) (see sections 4.2 and 5.2).

Bone effects
Bone abnormalities such as osteomalacia which can manifest as persistent or worsening bone pain and, which can infrequently contribute to fractures may be associated with tenofovir disoproxil-induced proximal renal tubulopathy (see section 4.8).

Tenofovir disoproxil may also cause a reduction in bone mineral density (BMD).

In the Phase 3 Study GS-US-236-0103, BMD was assessed in a non-random subset of 120 subjects (Stribild group n = 54; ritonavir-boosted atazanavir (ATV/r) plus emtricitabine (FTC)/tenofovir disoproxil group n = 66). Mean percentage decreases in BMD from baseline to Week 144 in the Stribild group were comparable to the ATV/r+FTC/tenofovir disoproxil group at the lumbar spine (-1.43% *versus* -3.68%, respectively) and at the hip (-2.83% *versus* -3.77%, respectively). In the Phase 3 studies GS-US-236-0102 and GS-US-236-0103, bone fractures occurred in 27 subjects (3.9%) in the Stribild group, 8 subjects (2.3%) in the EFV/FTC/tenofovir disoproxil group, and 19 subjects (5.4%) in the ATV/r+FTC/tenofovir disoproxil group.

In a 144-week controlled clinical study (GS-99-903) that compared tenofovir disoproxil with stavudine in combination with lamivudine and efavirenz in antiretroviral-naïve patients, small decreases in BMD of the hip and spine were observed in both treatment groups. Decreases in BMD of spine and changes in bone biomarkers from baseline were significantly greater in the tenofovir disoproxil treatment group at 144 weeks. Decreases in BMD of hip were significantly greater in this group until 96 weeks. However, there was no increased risk of fractures or evidence for clinically relevant bone abnormalities over 144 weeks in this study.

In other studies (prospective and cross-sectional), the most pronounced decreases in BMD were seen in patients treated with tenofovir disoproxil as part of a regimen containing a boosted protease inhibitor. Overall, in view of the bone abnormalities associated with tenofovir disoproxil and the limitations of long term data on the impact of tenofovir disoproxil on bone health and fracture risk, alternative treatment regimens should be considered for patients with osteoporosis that are at a high risk for fractures.

If bone abnormalities are suspected or detected then appropriate consultation should be obtained.

<u>Patients with HIV and hepatitis B or C virus co-infection</u>

Patients with chronic hepatitis B or C treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

Physicians 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 Summary of Product Characteristics for these medicinal products. Stribild should not be administered concomitantly with other medicinal products containing tenofovir disoproxil, lamivudine or adefovir dipivoxil used for the treatment of hepatitis B virus infection.

Discontinuation of Stribild 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 Stribild should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, initiation of hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Liver disease

The safety and efficacy of Stribild have not been established in patients with significant underlying liver disorders. The pharmacokinetics of emtricitabine have not been studied in patients with hepatic impairment. The pharmacokinetics of elvitegravir, cobicistat and tenofovir have been studied in patients with moderate hepatic impairment. Stribild has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). No dose adjustment of Stribild is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment (see sections 4.2 and 5.2).

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

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Mitochondrial dysfunction following exposure *in utero*

Nucleos(t)ide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or postnatally to nucleoside analogues; these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactatemia, hyperlipasemia). These events have often been transitory. Late onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed *in utero* to nucleos(t)ide analogues, who present with severe clinical findings of unknown aetiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Immune Reactivation Syndrome

In HIV infected patients with severe immune deficiency at the time of institution of CART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples include cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Opportunistic infections

Patients receiving Stribild or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore 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.

Co-administration of other medicinal products

Stribild is indicated for use as a complete regimen for the treatment of HIV-1 infection and must not be administered with other antiretroviral products (see section 4.5).

Stribild should not be administered concomitantly with other medicinal products containing tenofovir disoproxil, lamivudine or adefovir dipivoxil used for the treatment of hepatitis B virus infection, or with other medicinal products containing tenofovir alafenamide.

Concomitant use with nephrotoxic medicinal products
Use of Stribild should be avoided with concurrent or recent use of a nephrotoxic medicinal product, e.g. aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin 2 (also called aldesleukin) (see section 4.5). If concomitant use of Stribild and nephrotoxic agents is unavoidable, renal function must be monitored weekly.

Cases of acute renal failure after initiation of high dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) have been reported in patients treated with tenofovir disoproxil and with risk factors for renal dysfunction. If Stribild is co-administered with an NSAID, renal function should be monitored adequately.

Contraception requirements
Female patients of childbearing potential should use either a hormonal contraceptive containing at least 30 µg ethinyloestradiol and containing drospirenone or norgestimate as the progestogen or should use an alternative reliable method of contraception (see sections 4.5 and 4.6). The use of Stribild with oral contraceptives containing other progestogens should be avoided (see section 4.5). Plasma concentrations of drospirenone are expected to be increased following co-administration with Stribild and clinical monitoring is recommended due to the potential for hyperkalaemia (see section 4.5).

Use with certain hepatitis C virus antiviral agents
Co-administration of tenofovir disoproxil with ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir has been shown to increase plasma concentrations of tenofovir, especially when used together with an HIV regimen containing tenofovir disoproxil and a pharmacokinetic enhancer (ritonavir or cobicistat). The safety of tenofovir disoproxil in the setting of ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with co-administration of ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir with Stribild should be considered, particularly in patients at increased risk of renal dysfunction. Patients receiving Stribild concomitantly with

ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir should be monitored for adverse reactions related to tenofovir disoproxil.

Elderly

Stribild has limited data in patients over the age of 65 years. Elderly patients are more likely to have decreased renal function, therefore caution should be exercised when treating elderly patients with Stribild.

Pregnancy

Treatment with cobicistat and elvitegravir during the second and third trimesters of pregnancy has been shown to result in lower elvitegravir exposures (see section 5.2). Cobicistat levels decrease and may not provide sufficient boosting. The substantial reduction in elvitegravir exposure may result in virological failure and an increased risk of mother-to-child transmission of HIV infection. Therefore, therapy with Stribild should not be initiated during pregnancy, and women who become pregnant during therapy with Stribild should be switched to an alternative regimen (see section 4.6).

Excipients

Stribild contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

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

4.5 Interaction with other medicinal products and other forms of interaction

As Stribild contains elvitegravir, cobicistat, emtricitabine and tenofovir disoproxil, any interactions that have been identified with these active substances individually may occur with Stribild. Stribild is indicated for use as a complete regimen for the treatment of HIV-1 infection and must not be administered with other antiretroviral products. Therefore, information regarding drug-drug interactions with other antiretroviral products (including protease inhibitors and non-nucleoside reverse transcriptase inhibitors) is not provided (see section 4.4). Interaction studies have only been performed in adults.

Cobicistat is a strong mechanism-based CYP3A inhibitor and a CYP3A substrate. Cobicistat is also a weak CYP2D6 inhibitor and is metabolised, to a minor extent, by CYP2D6. The transporters that cobicistat inhibits include P-gp, BCRP, OATP1B1 and OATP1B3.

Co-administration of Stribild with medicinal products that are primarily metabolised by CYP3A or CYP2D6, or are substrates of P-gp, BCRP, OATP1B1 or OATP1B3 may result in increased plasma concentrations of those products, which could increase or prolong their therapeutic effect and adverse reactions (see Concomitant use contraindicated and section 4.3). Co-administration of Stribild with medicinal products that have active metabolite(s) formed by CYP3A may result in reduced plasma concentrations of these active metabolite(s).

Co-administration of Stribild with medicinal products that inhibit CYP3A may decrease the clearance of cobicistat, resulting in increased cobicistat plasma concentrations.

Elvitegravir is a modest inducer and may have the potential to induce CYP2C9 and/or inducible UGT enzymes; as such it may decrease the plasma concentration of substrates of these enzymes. Elvitegravir is metabolised by CYP3A and, to a minor extent, by UGT1A1. Medicinal products that induce CYP3A activity are expected to increase the clearance of elvitegravir, resulting in decreased plasma concentration of elvitegravir which may lead to loss of therapeutic effect of Stribild and development of resistance (see Concomitant use contraindicated and section 4.3).

Concomitant use contraindicated

Co-administration of Stribild and some medicinal products that are primarily metabolised by CYP3A may result in increased plasma concentrations of these products, which are associated with the potential for serious and/or life-threatening reactions such as peripheral vasospasm or ischaemia (e.g., dihydroergotamine, ergotamine, ergometrine), or myopathy, including rhabdomyolysis (e.g., simvastatin, lovastatin), or prolonged or increased sedation or respiratory depression (e.g., orally administered midazolam or triazolam). Co-administration of Stribild and other medicinal products primarily metabolised by CYP3A such as amiodarone, quinidine, cisapride, pimozide, lurasidone, alfuzosin and sildenafil for pulmonary arterial hypertension is contraindicated (see section 4.3).

Co-administration of Stribild and some medicinal products that induce CYP3A such as St. John's wort (*Hypericum perforatum*), rifampicin, carbamazepine, phenobarbital and phenytoin may result in significantly decreased cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance (see section 4.3).

Concomitant use not recommended

Renally eliminated medicinal products
Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of Stribild with medicinal products that reduce renal function or compete for active tubular secretion (e.g. cidofovir) may increase serum concentrations of emtricitabine, tenofovir and/or the co-administered medicinal products.

Use of Stribild should be avoided with concurrent or recent use of nephrotoxic medicinal products. Some examples include, but are not limited to, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2 (also called aldesleukin).

Other interactions

Interactions between the components of Stribild and potential co-administered medicinal products are listed in Table 1 below (increase is indicated as "↑", decrease as "↓", no change as "↔"). The interactions described are based on studies conducted with the components of Stribild as individual agents and/or in combination, or are potential drug interactions that may occur with Stribild.

Table 1: Interactions between the individual components of Stribild and other medicinal products

Medicinal product by therapeutic areas	**Effects on drug levels Mean percent change in AUC, C_{max}, C_{min}[1]**	**Recommendation concerning co-administration with Stribild**
ANTI-INFECTIVES		
Antifungals		
Ketoconazole (200 mg twice daily)/Elvitegravir (150 mg once daily)[2]	Elvitegravir: AUC: ↑ 48% C_{min}: ↑ 67% C_{max}: ↔ Concentrations of ketoconazole and/or cobicistat may increase with co-administration of Stribild.	When administering with Stribild, the maximum daily dose of ketoconazole should not exceed 200 mg per day. Caution is warranted and clinical monitoring is recommended during the co-administration.

Medicinal product by therapeutic areas	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min}[1]	Recommendation concerning co-administration with Stribild
Itraconazole[3] Voriconazole[3] Posaconazole[3] Fluconazole	Interaction not studied with any of the components of Stribild. Concentrations of itraconazole, fluconazole and posaconazole may be increased when co-administered with cobicistat. Concentrations of voriconazole may increase or decrease when co-administered with Stribild.	Clinical monitoring should be made upon co-administration with Stribild. When administering with Stribild, the maximum daily dose of itraconazole should not exceed 200 mg per day. An assessment of benefit/risk ratio is recommended to justify use of voriconazole with Stribild.
Antimycobacterials		
Rifabutin (150 mg every other day)/Elvitegravir (150 mg once daily)/Cobicistat (150 mg once daily)	Co-administration of rifabutin, potent CYP3A inducer, may significantly decrease cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Rifabutin: AUC: ↔ C_{min}: ↔ C_{max}: ↔ 25-O-desacetyl-rifabutin AUC: ↑ 525% C_{min}: ↑ 394% C_{max}: ↑ 384% Elvitegravir: AUC: ↓ 21% C_{min}: ↓ 67% C_{max}: ↔	Co-administration of Stribild and rifabutin is not recommended. If the combination is needed, the recommended dose of rifabutin is 150 mg 3 times per week on set days (for example Monday-Wednesday-Friday). Increased monitoring for rifabutin-associated adverse reactions including neutropenia and uveitis is warranted due to an expected increase in exposure to desacetyl-rifabutin. Further dose reduction of rifabutin has not been studied. It should be kept in mind that a twice weekly dose of 150 mg may not provide an optimal exposure to rifabutin thus leading to a risk of rifamycin resistance and a treatment failure.
Hepatitis C virus (HCV) antiviral agents		
Ledipasvir/Sofosbuvir	Interaction not studied with Stribild. Co-administration with Stribild may lead to increased tenofovir exposure.	Increased plasma concentrations of tenofovir resulting from co-administration of Stribild and ledipasvir/sofosbuvir may increase

Medicinal product by therapeutic areas	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min}[1]	Recommendation concerning co-administration with Stribild
Ledipasvir/Sofosbuvir (90 mg/400 mg once daily) + Elvitegravir/Cobicistat (150 mg/150 mg once daily)	Observed: Ledipasvir: AUC: ↑ 78% C_{min}: ↑ 91% C_{max}: ↑ 63% Sofosbuvir: AUC: ↑ 36% C_{min}: N/A C_{max}: ↑ 33% GS-331007[5]: AUC: ↑ 44% C_{min}: ↑ 53% C_{max}: ↑ 33% Elvitegravir: AUC: ↔ C_{min}: ↑ 36% C_{max}: ↔ Cobicistat: AUC: ↑ 59% C_{min}: ↑ 325% C_{max}: ↔	adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with ledipasvir/sofosbuvir and a pharmacokinetic enhancer (e.g. cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring, if other alternatives are not available (see section 4.4).
Sofosbuvir/Velpatasvir (400 mg/100 mg once daily) + Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Disoproxil (150 mg/150 mg/200 mg/245 mg once daily)	Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[5]: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 45% Velpatasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 37% Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Cobicistat: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 71% Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 36% C_{min}: ↑ 45%	Increased plasma concentrations of tenofovir resulting from co-administration of Stribild and sofosbuvir/velpatasvir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g. cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring (see section 4.4).

Medicinal product by therapeutic areas	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min}[1]	Recommendation concerning co-administration with Stribild
Sofosbuvir/Velpatasvir/ Voxilaprevir (400 mg/100 mg/ 100 mg+100 mg once daily)[6] + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg once daily)[7]	Co-administration with Stribild may lead to increased tenofovir exposure. Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 39% C_{max}: ↑ 48% C_{min}: ↑ 47%	Increased plasma concentrations of tenofovir resulting from co-administration of Stribild and sofosbuvir/velpatasvir/voxilaprevir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir/voxilaprevir and a pharmacokinetic enhancer (e.g. cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring (see section 4.4).
Sofosbuvir/Velpatasvir/ Voxilaprevir (400 mg/100 mg/ 100 mg+100 mg once daily)[6] + Elvitegravir/Cobicistat (150 mg/150 mg once daily)[8]	Sofosbuvir: AUC: ↔ C_{max}: ↑ 27% C_{min}: N/A GS-331007[5]: AUC: ↑ 43% C_{max}:↔ C_{min}: N/A Velpatasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 46% Voxilaprevir: AUC: ↑ 171% C_{max}:↑ 92% C_{min}: ↑ 350% Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 32% Cobicistat: AUC: ↑ 50% C_{max}: ↔ C_{min}: ↑ 250%	

Medicinal product by therapeutic areas	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min}[1]	Recommendation concerning co-administration with Stribild
Nucleoside reverse transcriptase inhibitors (NRTIs)		
Didanosine	Co-administration of tenofovir disoproxil and didanosine results in a 40-60% increase in systemic exposure to didanosine.	Co-administration of Stribild and didanosine is not recommended. Increased systemic exposure to didanosine may increase didanosine related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co-administration of tenofovir disoproxil and didanosine at a dose of 400 mg daily has been associated with a significant decrease in CD4 cell count, possibly due to an intracellular interaction increasing phosphorylated (i.e. active) didanosine. A decreased dosage of 250 mg didanosine co-administered with tenofovir disoproxil therapy has been associated with reports of high rates of virological failure within several tested combinations for the treatment of HIV-1 infection. However, in case of initiation of Stribild in patients previously taking didanosine or discontinuation of Stribild and change to a regimen including didanosine there could be a short period when measurable plasma levels of didanosine and tenofovir occur.
Macrolide antibiotics		
Clarithromycin	Interaction not studied with any of the components of Stribild. Concentrations of clarithromycin and/or cobicistat may be altered with co-administration of Stribild.	No dose adjustment of clarithromycin is required for patients with normal renal function or mild renal impairment (ClCr 60-90 mL/min). Clinical monitoring is recommended for patients with ClCr < 90 mL/min. For patients with ClCr < 60 mL/min, alternative antibacterials should be considered.
Telithromycin	Interaction not studied with any of the components of Stribild. Concentrations of telithromycin and/or cobicistat may be altered with co-administration of Stribild.	Clinical monitoring is recommended upon co-administration of Stribild.

GLUCOCORTICOIDS		
Corticosteroids		
Corticosteroids primarily metabolised by CYP3A (including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone).	Interaction not studied with any of the components of Stribild. Plasma concentrations of these medicinal products may be increased when co-administered with Stribild, resulting in reduced serum cortisol concentrations.	Concomitant use of Stribild and corticosteroids that are metabolised by CYP3A (e.g. fluticasone propionate or other inhaled or nasal corticosteroids) may increase the risk of development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. Co-administration with CYP3A-metabolised corticosteroids is not recommended unless the potential benefit to the patient outweighs the risk, in which case patients should be monitored for systemic corticosteroid effects. Alternative corticosteroids which are less dependent on CYP3A metabolism e.g. beclomethasone for intranasal or inhalational use should be considered, particularly for long-term use. For coadministration of cutaneously-administered corticosteroids sensitive to CYP3A inhibition, refer to the prescribing information of the corticosteroid for conditions or uses that augment its systemic absorption.
MEDICINAL PRODUCTS or ORAL SUPPLEMENTS CONTAINING POLYVALENT CATIONS (e.g. Mg, Al, Ca, Fe, Zn)		
Magnesium/aluminium-containing antacid suspension (20 mL single dose)/Elvitegravir (50 mg single dose)/Ritonavir (100 mg single dose)	Elvitegravir (antacid suspension after ± 2 hours): AUC: ↔ C_{min}: ↔ C_{max}: ↔ Elvitegravir (simultaneous administration): AUC: ↓ 45% C_{min}: ↓ 41% C_{max}: ↓ 47% Elvitegravir plasma concentrations are lower with antacids due to local complexation in the gastrointestinal tract and not to changes in gastric pH.	It is recommended to separate Stribild and administration of antacids, medicinal products or oral supplements containing polyvalent cations by at least 4 hours. For information on other acid reducing agents (e.g. H_2-receptor antagonists and proton pump inhibitors), see Studies conducted with other medicinal products.
Calcium or iron supplements (including multivitamins) Other cation-containing antacids Cation-containing laxatives Sucralfate Buffered medicinal products	Interaction not studied with any of the components of Stribild. Elvitegravir plasma concentrations are expected to be lower with antacids, medicinal products or oral supplements containing polyvalent cations, due to local complexation in the gastrointestinal tract and not to changes in gastric pH.	

ORAL ANTI-DIABETICS		
Metformin	Interaction not studied with any of the components of Stribild. Cobicistat reversibly inhibits MATE1, and concentrations of metformin may be increased when co-administered with Stribild.	Careful patient monitoring and dose adjustment of metformin is recommended in patients who are taking Stribild.
NARCOTIC ANALGESICS		
Methadone/Elvitegravir/Cobicistat	Methadone: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Cobicistat: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Elvitegravir: AUC: ↔ C_{min}: ↔ C_{max}: ↔	No dose adjustment of methadone is required.
Methadone/Tenofovir disoproxil	Methadone: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Tenofovir: AUC: ↔ C_{min}: ↔ C_{max}: ↔	
Buprenorphine/Naloxone/ Elvitegravir/Cobicistat	Buprenorphine: AUC: ↑ 35% C_{min}: ↑ 66% C_{max}: ↔ Naloxone: AUC: ↓ 28% C_{max}: ↓ 28% Cobicistat: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Elvitegravir: AUC: ↔ C_{min}: ↔ C_{max}: ↔	No dose adjustment of buprenorphine/naloxone is required.

ORAL CONTRACEPTIVES		
Drospirenone/Ethinyloestradiol (3 mg/0.02 mg single dose)/Cobicistat (150 mg once daily)	Interaction not studied with Stribild. *Expected* Drospirenone: AUC: ↑	Plasma concentrations of drospirenone may be increased when co-administered with cobicistat-containing products. Clinical monitoring is recommended due to the potential for hyperkalemia.
Norgestimate (0.180/0.215 mg once daily)/Ethinyloestradiol (0.025 mg once daily)/ Elvitegravir (150 mg once daily)/Cobicistat (150 mg once daily)[4]	Norgestimate: AUC: ↑ 126% C_{min}: ↑ 167% C_{max}: ↑ 108% Ethinyloestradiol: AUC: ↓ 25% C_{min}: ↓ 44% C_{max}: ↔ Elvitegravir: AUC: ↔ C_{min}: ↔ C_{max}: ↔	Caution should be exercised when co-administering Stribild and a hormonal contraceptive. The hormonal contraceptive should contain at least 30 µg ethinyloestradiol and contain drospirenone or norgestimate as the progestogen or patients should use an alternative reliable method of contraception (see sections 4.4 and 4.6). The long-term effects of substantial increases in progestogen exposure are unknown.
ANTIARRHYTHMICS		
Digoxin (0.5 mg single dose)/Cobicistat (150 mg multiple doses)	Digoxin: AUC: ↔ C_{max}: ↑ 41%	It is recommended that digoxin levels be monitored when digoxin is combined with Stribild.
Disopyramide Flecainide Systemic lidocaine Mexiletine Propafenone	Interaction not studied with any of the components of Stribild. Concentrations of these antiarrhythmic drugs may be increased when co-administered with cobicistat.	Caution is warranted and clinical monitoring is recommended upon co-administration with Stribild.
ANTI-HYPERTENSIVES		
Metoprolol Timolol	Interaction not studied with any of the components of Stribild. Concentrations of beta-blockers may be increased when co-administered with cobicistat.	Clinical monitoring is recommended and a dose decrease may be necessary when these agents are co-administered with Stribild.
Amlodipine Diltiazem Felodipine Nicardipine Nifedipine Verapamil	Interaction not studied with any of the components of Stribild. Concentrations of calcium channel blockers may be increased when co-administered with cobicistat.	Clinical monitoring of therapeutic and adverse effects is recommended when these medicinal products are concomitantly administered with Stribild.
ENDOTHELIN RECEPTOR ANTAGONISTS		
Bosentan	Interaction not studied with any of the components of Stribild. Co-administration with Stribild may lead to decreased elvitegravir and/or cobicistat exposures and loss of therapeutic effect and development of resistance.	Alternative endothelin receptor antagonists may be considered.

ANTICOAGULANTS		
Dabigatran	Interaction not studied with any of the components of Stribild. Co-administration with Stribild may increase dabigatran plasma concentrations with similar effects as seen with other strong P-gp inhibitors.	Co-administration of Stribild with dabigatran is contraindicated.
Apixaban Rivaroxaban Edoxaban	Interaction not studied with any of the components of Stribild. Co-administration with Stribild may result in increased plasma concentrations of the DOAC, which may lead to an increased bleeding risk.	Co-administration of apixaban, rivaroxaban or edoxaban is not recommended with Stribild.
Warfarin	Interaction not studied with any of the components of Stribild. Concentrations of warfarin may be affected upon co-administration with Stribild.	It is recommended that the international normalised ratio (INR) be monitored upon co-administration of Stribild. INR should continue to be monitored during the first weeks following ceasing treatment with Stribild.
ANTIPLATELETS		
Clopidogrel	Interaction not studied with any of the components of Stribild. Co-administration of clopidogrel with cobicistat is expected to decrease clopidogrel active metabolite plasma concentrations, which may reduce the antiplatelet activity of clopidogrel.	Co-administration of clopidogrel with Stribild is not recommended.
Prasugrel	Interaction not studied with any of the components of Stribild. Stribild is not expected to have a clinically relevant effect on plasma concentrations of the active metabolite of prasugrel.	No dose adjustment of prasugrel is required.

ANTICONVULSANTS		
Carbamazepine (200 mg twice daily)/Elvitegravir (150 mg once daily)/Cobicistat (150 mg once daily)	Co-administration of carbamazepine, a potent CYP3A inducer, may significantly decrease cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Carbamazepine: AUC: ↑ 43% C_{min}: ↑ 51% C_{max}: ↑ 40% Elvitegravir: AUC: ↓ 69% C_{min}: ↓ 97% C_{max}: ↓ 45% Cobicistat: AUC: ↓ 84% C_{min}: ↓ 90% C_{max}: ↓ 72% Carbamazepine-10,11-epoxide: AUC: ↓ 35% C_{min}: ↓ 41% C_{max}: ↓ 27%	Co-administration of Stribild with carbamazepine, phenobarbital, or phenytoin is contraindicated (see section 4.3).
INHALED BETA AGONIST		
Salmeterol	Interaction not studied with any of the components of Stribild. Co-administration with Stribild may result in increased plasma concentrations of salmeterol, which is associated with the potential for serious and/or life-threatening reactions.	Concurrent administration of salmeterol and Stribild is not recommended.
HMG CO-A REDUCTASE INHIBITORS		
Rosuvastatin (10 mg single dose)/Elvitegravir (150 mg single dose)/Cobicistat (150 mg single dose)	Elvitegravir: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Rosuvastatin: AUC: ↑ 38% C_{min}: N/A C_{max}: ↑ 89%	Concentrations of rosuvastatin are transiently increased when administered with elvitegravir and cobicistat. Dose modifications are not necessary when rosuvastatin is administered in combination with Stribild.
Atorvastatin (10 mg single dose)/ Elvitegravir (150 mg once daily)/ Cobicistat (150 mg once daily)/ Emtricitabine (200 mg once daily)/ Tenofovir alafenamide (10 mg once daily)	Atorvastatin: AUC: ↑160% C_{min}: NC C_{max}: ↑132% Elvitegravir: AUC: ↔ C_{min}: ↔ C_{max}: ↔	Concentrations of atorvastatin are increased when co-administered with elvitegravir and cobicistat. Start with the lowest possible dose of atorvastatin with careful monitoring upon co-administration with Stribild.
Pitavastatin	Interaction not studied with any of the components of Stribild. Concentrations of pitavastatin may be increased when administered with elvitegravir and cobicistat.	Caution should be exercised when co-administering Stribild with pitavastatin.

Pravastatin Fluvastatin	Interaction not studied with any of the components of Stribild. Concentrations of these HMG Co-A reductase inhibitors are expected to transiently increase when administered with elvitegravir and cobicistat.	Dose modifications are not necessary when administered in combination with Stribild.
Lovastatin Simvastatin	Interaction not studied with any of the components of Stribild.	Co-administration of Stribild and lovastatin and simvastatin is contraindicated (see section 4.3).
PHOSPHODIESTERASE TYPE 5 (PDE-5) INHIBITORS		
Sildenafil Tadalafil Vardenafil	Interaction not studied with any of the components of Stribild. PDE-5 inhibitors are primarily metabolised by CYP3A. Co-administration with Stribild may result in increased plasma concentrations of sildenafil and tadalafil, which may result in PDE-5 inhibitor-associated adverse reactions.	Co-administration of Stribild and sildenafil for the treatment of pulmonary arterial hypertension is contraindicated. Caution should be exercised, including consideration of dose reduction, when co-administering Stribild with tadalafil for the treatment of pulmonary arterial hypertension. For the treatment of erectile dysfunction, it is recommended that a single dose of sildenafil no more than 25 mg in 48 hours, vardenafil no more than 2.5 mg in 72 hours, or tadalafil no more than 10 mg in 72 hours be co-administered with Stribild.
ANTIDEPRESSANTS		
Escitalopram Trazodone	Interaction not studied with any of the components of Stribild. Concentrations of trazodone may increase upon co-administration with cobicistat.	Careful dose titration of the antidepressant and monitoring for antidepressant response is recommended.
IMMUNOSUPPRESSANTS		
Ciclosporin Sirolimus Tacrolimus	Interaction not studied with any of the components of Stribild. Concentrations of these immunosuppressant agents may be increased when administered with cobicistat.	Therapeutic monitoring is recommended upon co-administration with Stribild.
SEDATIVES/HYPNOTICS		
Buspirone Clorazepate Diazepam Estazolam Flurazepam Orally administered midazolam Triazolam Zolpidem	Interaction not studied with any of the components of Stribild. Midazolam and triazolam are primarily metabolised by CYP3A. Co-administration with Stribild may result in increased plasma concentrations of these drugs, which is associated with the potential for serious and/or life-threatening reactions.	Co-administration of Stribild and orally administered midazolam and triazolam is contraindicated (see section 4.3). With other sedatives/hypnotics, dose reduction may be necessary and concentration monitoring is recommended.

ANTI-GOUT		
Colchicine	Interaction not studied with any of the components of Stribild. Co-administration with Stribild may result in increased plasma concentrations of this drug.	Dose reductions of colchicine may be required. Stribild should not be co-administered with colchicine to patients with renal or hepatic impairment.

N/A = not applicable
NC = not calculated
DOAC = direct oral anticoagulant
[1] When data available from drug interaction studies.
[2] Studies performed with ritonavir boosted elvitegravir.
[3] These are drugs within class where similar interactions could be predicted.
[4] Study conducted using Stribild.
[5] The predominant circulating metabolite of sofosbuvir.
[6] Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.
[7] Study conducted with emtricitabine/tenofovir disoproxil + darunavir (800 mg) + ritonavir (100 mg).
[8] Study conducted with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fixed dose combination tablet.

Studies conducted with other medicinal products

Based on drug interaction studies conducted with the components of Stribild, no clinically significant drug interactions have been either observed or are expected between the components of Stribild and the following medicinal products: entecavir, famciclovir, famotidine, omeprazole, ribavirin and sertraline.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / contraception in males and females

The use of Stribild must be accompanied by the use of effective contraception (see section 4.5).

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of Stribild in pregnant women. However, a large amount of data in pregnant women (more than 1,000 pregnancy outcomes) indicate no malformations or foetal/neonatal toxicity associated with emtricitabine and tenofovir disoproxil.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Treatment with cobicistat and elvitegravir during the second and third trimesters of pregnancy has been shown to result in lower elvitegravir exposure (see section 5.2). Cobicistat levels decrease and may not provide sufficient boosting. The substantial reduction in elvitegravir exposure may result in virological failure and an increased risk of mother-to-child transmission of HIV infection. Therefore, therapy with Stribild should not be initiated during pregnancy, and women who become pregnant during therapy with Stribild should be switched to an alternative regimen (see section 4.4).

Breast-feeding

It is not known whether elvitegravir or cobicistat are excreted in human milk. Emtricitabine and tenofovir have been shown to be excreted in human milk. In animal studies it has been shown that elvitegravir, cobicistat and tenofovir are excreted in milk. There is insufficient information on the effects of elvitegravir, cobicistat, emtricitabine and tenofovir disoproxil in newborns/infants. Therefore Stribild should not be used during breast-feeding.

In order to avoid transmission of HIV to the infant it is recommended that women living with HIV do not breast-feed their infants.

Fertility

No human data on the effect of Stribild on fertility are available. Animal studies do not indicate harmful effects of elvitegravir, cobicistat, emtricitabine or tenofovir disoproxil on fertility.

4.7 Effects on ability to drive and use machines

Stribild has no or negligible influence on the ability to drive and use machines. However, patients should be informed that dizziness, fatigue and insomnia have been reported during treatment with Stribild.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions considered possibly or probably related to Stribild in clinical studies through 144 weeks in treatment-naïve adult patients were nausea (16%) and diarrhoea (12%).

The most frequently reported adverse reactions to Stribild in clinical studies through 48 weeks in virologically-suppressed adult patients were nausea (3% to 5%) and fatigue (6%).

In patients receiving tenofovir disoproxil, rare events of renal impairment, renal failure and uncommon events of proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have been reported. Monitoring of renal function is recommended for patients receiving Stribild (see section 4.4).

Discontinuation of Stribild therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis (see section 4.4).

Tabulated summary of adverse reactions

Adverse reactions to Stribild from Phase 3 clinical studies GS-US-236-0102 and GS-US-236-0103 and adverse reactions to treatment with emtricitabine and tenofovir disoproxil from clinical studies and post-marketing experience, when used with other antiretrovirals, are listed in Table 2, below, by body system organ class and highest frequency observed. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) or rare (≥ 1/10,000 to < 1/1,000).

Table 2: Tabulated summary of adverse reactions associated with Stribild based on experience from Phase 3 studies GS-US-236-0102 and GS-US-236-0103 and adverse reactions to treatment with emtricitabine and tenofovir disoproxil from clinical studies and post-marketing experience, when used with other antiretrovirals

Frequency	Adverse reaction
Blood and lymphatic system disorders:	
Common:	neutropenia[1]
Uncommon:	anaemia[1,2]
Immune system disorders:	
Common:	allergic reaction[1]
Metabolism and nutrition disorders:	
Very common:	hypophosphataemia[1,3]
Common:	hyperglycaemia[1], hypertriglyceridaemia[1], decreased appetite
Uncommon:	hypokalaemia[1,3]
Rare:	lactic acidosis[1]

Frequency	Adverse reaction
Psychiatric disorders:	
Common:	insomnia, abnormal dreams
Uncommon:	suicidal ideation and suicide attempt (in patients with a pre-existing history of depression or psychiatric illness), depression
Nervous system disorders:	
Very common:	headache, dizziness
Gastrointestinal disorders:	
Very common:	diarrhoea, vomiting, nausea
Common:	elevated amylase including elevated pancreatic amylase[1], elevated serum lipase[1], abdominal pain, dyspepsia, constipation, abdominal distension[1], flatulence
Uncommon:	pancreatitis[1]
Hepatobiliary disorders:	
Common:	increased transaminases[1], hyperbilirubinaemia[1]
Rare:	hepatic steatosis[1], hepatitis[1]
Skin and subcutaneous tissue disorders:	
Very common:	rash
Common:	vesiculobullous rash[1], pustular rash[1], maculopapular rash[1], pruritus[1], urticaria[1], skin discolouration (increased pigmentation)[1,2]
Uncommon:	angioedema[1]
Musculoskeletal and connective tissue disorders:	
Very common:	elevated creatine kinase[1]
Uncommon:	rhabdomyolysis[1,3], muscular weakness[1,3]
Rare:	osteomalacia (manifested as bone pain and infrequently contributing to fractures)[1,3,5], myopathy[1,3]
Renal and urinary disorders:	
Common:	increased blood creatinine[4]
Uncommon:	renal failure[4], proximal renal tubulopathy including Fanconi syndrome acquired[4], proteinuria
Rare:	acute tubular necrosis[1], nephritis (including acute interstitial nephritis)[1,5], nephrogenic diabetes insipidus[1]
General disorders and administration site conditions:	
Very common:	asthenia[1]
Common:	pain[1], fatigue

1 This adverse reaction was not observed in the Phase 3 clinical studies for Stribild but identified from clinical studies or post-marketing experience for emtricitabine or tenofovir disoproxil when used with other antiretrovirals.

2 Anaemia was common and skin discolouration (increased pigmentation) was very common when emtricitabine was administered to paediatric patients.

3 This adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil in the absence of this condition.

4 See section 4.8, Description of selected adverse reactions for more details.

5 This adverse reaction was identified through post-marketing surveillance for emtricitabine or tenofovir disoproxil but not observed in randomised, controlled clinical studies in adults or paediatric HIV clinical studies for emtricitabine or in randomised controlled clinical studies or the tenofovir disoproxil expanded access program for tenofovir disoproxil. The frequency category was estimated from a statistical calculation based on the total number of patients exposed to emtricitabine in randomised controlled clinical studies (n = 1,563) or tenofovir disoproxil in randomised controlled clinical studies and the expanded access program (n = 7,319).

Description of selected adverse reactions

Renal impairment

Proximal renal tubulopathy generally resolved or improved after tenofovir disoproxil discontinuation. However, in some patients, declines in creatinine clearance did not completely resolve despite tenofovir disoproxil discontinuation. Patients at risk of renal impairment (such as patients with baseline renal risk factors, advanced HIV disease, or patients receiving concomitant nephrotoxic medications) are at increased risk of experiencing incomplete recovery of renal function despite tenofovir disoproxil discontinuation (see section 4.4).

In the clinical studies of Stribild over 144 weeks, 13 (1.9%) subjects in the Stribild group (n = 701) and 8 (2.3%) subjects in the ATV/r+FTC/tenofovir disoproxil group (n = 355) discontinued study drug due to a renal adverse reaction. Of these discontinuations, 7 in the Stribild group and 1 in the ATV/r+FTC/tenofovir disoproxil group occurred during the first 48 weeks. The types of renal adverse reactions seen with Stribild were consistent with previous experience with tenofovir disoproxil. Four (0.6%) of the subjects who received Stribild developed laboratory findings consistent with proximal tubulopathy leading to discontinuation of Stribild during the first 48 weeks. No additional proximal renal tubular dysfunction cases were reported from Week 48 to Week 144. Two of the four subjects had renal impairment (i.e. estimated creatinine clearance less than 70 mL/min) at baseline. The laboratory findings in these 4 subjects with evidence of proximal tubulopathy improved without clinical consequence upon discontinuation of Stribild, but did not completely resolve in all subjects. Three (0.8%) subjects who received ATV/r+FTC/tenofovir disoproxil developed laboratory findings consistent with proximal renal tubular dysfunction leading to discontinuation of ATV/r+FTC/tenofovir disoproxil after Week 96 (see section 4.4).

The cobicistat component of Stribild has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting renal glomerular function. In studies GS-US-236-0102 and GS-US-236-0103, decreases in estimated creatinine clearance occurred early in treatment with Stribild, after which they stabilised. The mean change in estimated glomerular filtration rate (eGFR) by Cockcroft-Gault method after 144 weeks of treatment was -14.0 ± 16.6 mL/min for Stribild, -1.9 ± 17.9 mL/min for EFV/FTC/tenofovir disoproxil, and -9.8 ± 19.4 mL/min for ATV/r+FTC/tenofovir disoproxil.

Lactic acidosis
Cases of lactic acidosis have been reported with tenofovir disoproxil alone or in combination with other antiretrovirals. Patients with predisposing factors such as patients with decompensated liver disease, or patients receiving concomitant medications known to induce lactic acidosis are at increased risk of experiencing severe lactic acidosis during tenofovir disoproxil treatment, including fatal outcomes.

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).

<u>Other special population(s)</u>

Patients with renal impairment
Since tenofovir disoproxil can cause renal toxicity, close monitoring of renal function is recommended in any patient with renal impairment treated with Stribild (see sections 4.2, 4.4 and 5.2).

Exacerbations of hepatitis after discontinuation of treatment
In HIV infected patients co-infected with HBV, clinical and laboratory evidence of hepatitis have occurred after discontinuation of treatment (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

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

You can also report any side effects directly to the registration holder via email: DrugSafety.Israel@gilead.com

4.9 Overdose

If overdose occurs the patient must be monitored for evidence of toxicity (see section 4.8), and standard supportive treatment applied as necessary.

There is no specific antidote for overdose with Stribild. As elvitegravir and cobicistat are highly bound to plasma proteins it is unlikely that elvitegravir and cobicistat will be significantly removed by haemodialysis or peritoneal dialysis. Up to 30% of the emtricitabine dose and approximately 10% of the tenofovir dose can be removed by haemodialysis. It is not known whether emtricitabine or tenofovir can be removed by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use; antivirals for treatment of HIV infections, combinations. ATC code: J05AR09

Mechanism of action and pharmacodynamic effects

Elvitegravir is an HIV-1 integrase strand transfer inhibitor (INSTI). Integrase is an HIV-1 encoded enzyme that is required for viral replication. Inhibition of integrase prevents the integration of HIV-1 DNA into host genomic DNA, blocking the formation of the HIV-1 provirus and propagation of the viral infection.

Cobicistat is a selective, mechanism-based inhibitor of cytochromes P450 of the CYP3A subfamily. Inhibition of CYP3A-mediated metabolism by cobicistat enhances the systemic exposure of CYP3A substrates, such as elvitegravir, where bioavailability is limited and half-life is shortened by CYP3A-dependent metabolism.

Emtricitabine is a nucleoside analogue of cytidine. Tenofovir disoproxil is converted *in vivo* to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate. Both emtricitabine and tenofovir have activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2) and hepatitis B virus.

Emtricitabine and tenofovir are phosphorylated by cellular enzymes to form emtricitabine triphosphate and tenofovir diphosphate, respectively. *In vitro* studies have shown that both emtricitabine and tenofovir can be fully phosphorylated when combined together in cells. Emtricitabine triphosphate and tenofovir diphosphate competitively inhibit HIV-1 reverse transcriptase, resulting in DNA chain termination.

Both emtricitabine triphosphate and tenofovir diphosphate are weak inhibitors of mammalian DNA polymerases and there was no evidence of toxicity to mitochondria *in vitro* and *in vivo*.

Antiviral activity *in vitro*

The dual-drug combinations and the triple combination of elvitegravir, emtricitabine and tenofovir demonstrated synergistic activity in cell culture. Antiviral synergy was maintained for elvitegravir, emtricitabine, and tenofovir when tested in the presence of cobicistat. No antagonism was observed for any of these combinations.

The antiviral activity of elvitegravir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cells, monocyte/macrophage cells, and peripheral blood lymphocytes and the 50% effective concentration (EC_{50}) values were in the range of 0.02 to 1.7 nM. Elvitegravir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values ranged from 0.1 to 1.3 nM) and activity against HIV-2 (EC_{50} of 0.53 nM).

Cobicistat has no detectable anti-HIV activity and does not antagonise or enhance the antiviral effects of elvitegravir, emtricitabine, or tenofovir.

The antiviral activity of emtricitabine against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The EC_{50} values for emtricitabine were in the range of 0.0013 to 0.64 μM. Emtricitabine displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007 to 0.075 μM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.007 to 1.5 μM).

The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC_{50} values for tenofovir were in the range of 0.04 to 8.5 μM. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values ranged from 0.5 to 2.2 μM) and strain specific activity against HIV-2 (EC_{50} values ranged from 1.6 to 5.5 μM).

Resistance

In cell culture
Resistance to emtricitabine or tenofovir has been seen *in vitro* and in the HIV-1 from some patients due to the development of the M184V or M184I emtricitabine resistance substitution in reverse transcriptase or the K65R tenofovir resistance substitution in reverse transcriptase. In addition, a K70E substitution in HIV-1 reverse transcriptase has been selected clinically by tenofovir disoproxil and results in low-level reduced susceptibility to abacavir, emtricitabine, tenofovir, and lamivudine.

Emtricitabine-resistant viruses with the M184V/I substitution were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir and zidovudine. The K65R substitution can also be selected by abacavir, stavudine or didanosine and results in reduced susceptibility to these agents plus lamivudine, emtricitabine and tenofovir. Tenofovir disoproxil should be avoided in patients with HIV-1 harbouring the K65R substitution.

In patients, HIV-1 expressing three or more thymidine analogue associated mutations (TAMs) that included either the M41L or L210W reverse transcriptase mutation showed reduced susceptibility to tenofovir disoproxil.

HIV-1 isolates with reduced susceptibility to elvitegravir have been selected in cell culture. Reduced susceptibility to elvitegravir was most commonly associated with the integrase substitutions T66I, E92Q and Q148R. Additional integrase substitutions observed in cell culture selection included H51Y, F121Y, S147G, S153Y, E157Q, and R263K. HIV-1 with the raltegravir-selected substitutions T66A/K, Q148H/K, and N155H showed cross-resistance to elvitegravir. Primary mutations for raltegravir/elvitegravir do not affect the *in vitro* susceptibility of dolutegravir as single mutations, and the additional presence of secondary mutations (except Q148) also does not result in relevant fold changes in experiments with site directed mutants.

No development of resistance to cobicistat can be demonstrated in HIV-1 *in vitro* due to its lack of antiviral activity.

Substantial cross-resistance was observed between most elvitegravir-resistant HIV-1 isolates and raltegravir, and between emtricitabine-resistant isolates and lamivudine. Patients who failed treatment with Stribild and who had HIV-1 with emergent Stribild resistance substitutions harboured virus that remained susceptible to all PIs, NNRTIs, and most other NRTIs.

In treatment-naïve patients
In a pooled analysis of antiretroviral-naïve patients receiving Stribild in Phase 3 studies GS-US-236-0102 and GS-US-236-0103 through Week 144, genotyping was performed on plasma HIV-1 isolates from all patients with confirmed virologic failure or who had HIV-1 RNA > 400 copies/mL at virologic failure, at Week 48, at Week 96, at Week 144 or at the time of early study drug discontinuation. As of Week 144, the development of one or more primary elvitegravir, emtricitabine, or tenofovir resistance-associated substitutions was observed in 18 of the 42 patients with evaluable genotypic data from paired baseline and Stribild treatment-failure isolates (2.6%, 18/701 patients). Of the 18 patients with viral resistance development, 13 occurred through Week 48, 3 occurred between Week 48 to Week 96, and 2 occurred between Week 96 to Week 144 of treatment. The substitutions that emerged were M184V/I (n = 17) and K65R (n = 5) in reverse transcriptase and E92Q (n = 9), N155H (n = 5), Q148R (n = 3), T66I (n = 2), and T97A (n = 1) in integrase. Other substitutions in integrase that occurred in addition to a primary INSTI resistance substitution each in single cases were H51Y, L68V, G140C, S153A, E157Q, and G163R. Most patients who developed resistance substitutions to elvitegravir developed resistance substitutions to both emtricitabine and elvitegravir. In phenotypic analyses of isolates from patients in the resistance analysis population, 13 patients (31%) had HIV-1 isolates with reduced susceptibility to elvitegravir, 17 patients (40%) had reduced susceptibility to emtricitabine, and 2 patients (5%) had reduced susceptibility to tenofovir.

In Study GS-US-236-0103, 27 patients treated with Stribild had HIV-1 with the NNRTI-associated K103N substitution in reverse transcriptase at baseline and had virologic success (82% at Week 144) similar to the overall population (78%), and no emergent resistance to elvitegravir, emtricitabine, or tenofovir in their HIV-1.

In virologically-suppressed patients
No emergent resistance to Stribild was identified in clinical studies of virologically-suppressed patients who switched from a regimen containing a ritonavir-boosted protease inhibitor (PI+RTV) (Study GS-US-236-0115), an NNRTI (Study GS-US-236-0121) or raltegravir (RAL) (Study GS-US-236-0123).

Twenty patients from these studies who switched to Stribild had the NNRTI-associated K103N substitution in their historical genotype prior to starting initial antiretroviral therapy. Eighteen of these 20 patients maintained virologic suppression through 48 weeks. Due to protocol violation, two patients with historical K103N substitutions discontinued early with HIV-1 RNA < 50 copies/mL.

Clinical experience

The efficacy of Stribild in HIV-1 infected treatment-naïve adult patients is based on the analyses of 144-week data from 2 randomised, double-blinded, active-controlled, Phase 3 studies, GS-US-236-0102 and GS-US-236-0103 (n = 1,408). The efficacy of Stribild in HIV-1 infected virologically-suppressed adult patients is based on the analyses of 48-week data from two randomised, open-label studies (Studies GS-US-236-0115 and GS-US-236-0121) and a single group open-label study (Study GS-US-236-0123) (n = 910; 628 receiving Stribild).

Treatment-naïve HIV-1 infected adult patients
In Study GS-US-236-0102 HIV-1 infected antiretroviral treatment-naïve adult patients received once-daily treatment of Stribild or once-daily treatment of fixed-dose combination of EFV/FTC/tenofovir disoproxil. In Study GS-US-236-0103 HIV-1 infected antiretroviral treatment-naïve adult patients

received once daily treatment of Stribild or ritonavir-boosted atazanavir (ATV/r) plus fixed-dose combination of emtricitabine(FTC)/tenofovir disoproxil. For both studies at 48 weeks, the virologic response rate was evaluated in both treatment arms. Virologic response was defined as achieving an undetectable viral load (< 50 HIV-1 RNA copies/mL, snapshot analysis).

Baseline characteristics and treatment outcomes for both Studies GS-US-236-0102 and GS-US-236-0103 are presented in Tables 3 and 4, respectively.

Table 3: Demographic and baseline characteristics of antiretroviral treatment-naïve HIV-1 infected adult subjects in studies GS-US-236-0102 and GS-US-236-0103

	Study GS-US-236-0102		**Study GS-US-236-0103**	
	Stribild n = 348	EFV/FTC/tenofovir disoproxil n = 352	Stribild n = 353	ATV/r + FTC/ tenofovir disoproxil n = 355
Demographic characteristics				
Mean age, years (range)	38.0 (18-67)		38.0 (19-72)	
Sex				
Male	89%		90%	
Female	11%		10%	
Ethnicity				
White	63%		74%	
Black/African American	28%		17%	
Asian	2%		5%	
Other	7%		4%	
Baseline disease characteristics[a]				
Mean baseline plasma HIV-1 RNA (range) log_{10} copies/mL	4.8 (2.6-6.5)		4.8 (1.7-6.6)	
Percentage of subjects with viral load > 100,000 copies/mL	33		40	
Mean baseline CD4+ cell count (range), x 10^6 cells/L	386 (3-1,348)		370 (5-1,132)	
Percentage of subjects with CD4+ cell counts ≤ 200 cells/mm^3	13		13	

a Patients were stratified by baseline HIV-1 RNA in both studies.

Table 4: Virologic outcome of randomised treatment of studies GS-US-236-0102 and GS-US-236-0103 at Week 48 (snapshot analysis)[a] and Week 144[b]

	Week 48				Week 144			
	Study GS-US-236-0102		Study GS-US-236-0103		Study GS-US-236-0102		Study GS-US-236-0103	
	Stribild n = 348	EFV/ FTC/ tenofovir disoproxil n = 352	Stribild n = 353	ATV/r + FTC/ tenofovir disoproxil n = 355	Stribild n = 348	EFV/ FTC/ tenofovir disoproxil n = 352	Stribild n = 353	ATV/r + FTC/ tenofovir disoproxil n = 355
Virologic success HIV-1 RNA < 50 copies/mL	88%	84%	90%	87%	80%	75%	78%	75%
Treatment difference	3.6% (95% CI = -1.6%, 8.8%)		3.0% (95% CI = -1.9%, 7.8%)		4.9% (95% CI = -1.3%, 11.1%)		3.1% (95% CI = -3.2%, 9.4%)	
Virologic failure[c]	7%	7%	5%	5%	7%	10%	8%	7%
No virologic data at Week 48 or 144 window								
Discontinued study drug due to AE or death[d]	3%	5%	3%	5%	6%	8%	6%	8%
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[e]	2%	3%	2%	3%	5%	7%	8%	9%
Missing data during window but on study drug	0%	0%	0%	0%	1%	0%	1%	1%

a Week 48 window is between Day 309 and 378 (inclusive).
b Week 144 window is between Day 967 and 1,050 (inclusive).
c Includes subjects who had ≥ 50 copies/mL in the Week 48 or Week 144 window, subjects who discontinued early due to lack or loss of efficacy, subjects who discontinued for reasons other than an adverse event, death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.
d Includes patients who discontinued due to adverse event or death at any time point from day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
e Includes subjects who discontinued for reasons other than an adverse event, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

Stribild met the non-inferiority criteria in achieving HIV-1 RNA < 50 copies/mL when compared to efavirenz/emtricitabine/tenofovir disoproxil and when compared to atazanavir/ritonavir + emtricitabine/tenofovir disoproxil.

In Study GS-US-236-0102, the mean increase from baseline in CD4+ cell count at Week 48 was 239 cells/mm^3 in the Stribild-treated patients and 206 cells/mm^3 in the EFV/FTC/tenofovir disoproxil -treated patients. At Week 144, the mean increase from baseline in CD4+ cell count was 321 cells/mm^3 in the Stribild-treated patients and 300 cells/mm^3 in the EFV/FTC/ tenofovir disoproxil -treated patients. In Study GS-US-236-0103, the mean increase from baseline in CD4+ cell count at Week 48 was 207 cells/mm^3 in the Stribild-treated patients and 211 cells/mm^3 in the ATV/r+FTC/ tenofovir disoproxil -treated patients. At Week 144, the mean increase from baseline in CD4+ cell count was 280 cells/mm^3 in the Stribild-treated patients and 293 cells/mm^3 in the ATV/r+FTC/ tenofovir disoproxil -treated patients.

Virologically-suppressed HIV-1 infected patients
In Study GS-US-236-0115 and Study GS-US-236-0121, patients had to be on either their first or second antiretroviral regimen with no history of virologic failure, have no current or past history of resistance to the antiretroviral components of Stribild and must have been suppressed on a PI+RTV or an NNRTI in combination with FTC/ tenofovir disoproxil (HIV-1 RNA < 50 copies/mL) for at least six months prior to screening. Patients were randomised in a 2:1 ratio to either switch to Stribild or stay on their baseline antiretroviral regimen (SBR) for 48 weeks. In Study GS-US-236-0115, virologic success rates were: Stribild 93.8% (272 of 290 patients); SBR 87.1% (121 of 139 patients). The mean increase from baseline in CD4+ cell count at Week 48 was 40 cells/mm^3 in the Stribild-treated patients and 32 cells/mm^3 in the PI+RTV+FTC/ tenofovir disoproxil -treated patients. In Study GS-US-236-0121, virologic success rates were: Stribild 93.4% (271 of 290 patients) and SBR 88.1% (126 of 143 patients). The mean increase from baseline in CD4+ cell count at Week 48 was 56 cells/mm^3 in the Stribild-treated patients and 58 cells/mm^3 in the NNRTI+FTC/ tenofovir disoproxil -treated patients.

In Study GS-US-236-0123, patients had to have previously only received RAL in combination with FTC/ tenofovir disoproxil as their first antiretroviral regimen for at least six months. Patients had to be stably suppressed for at least six months prior to study entry, have no current or past history of resistance to the antiretroviral components of Stribild, and have HIV-1 RNA < 50 copies/mL at screening. All 48 patients who received at least one dose of Stribild remained suppressed (HIV-1 RNA < 50 copies/mL) through Week 48. The mean increase from baseline in CD4+ cell count at Week 48 was 23 cells/mm^3.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of Stribild with food in HIV-1 infected subjects, peak plasma concentrations were observed 4 hours post-dose for elvitegravir, 3 hours post-dose for cobicistat, 3 hours post-dose for emtricitabine, and 2 hours for tenofovir following the rapid conversion of tenofovir disoproxil. The steady-state mean C_{max}, AUC_{tau}, and C_{trough} (mean ± SD) following multiple doses of Stribild in HIV-1 infected subjects, respectively, were 1.7 ± 0.39 µg/mL, 23 ± 7.5 µg•h/mL, and 0.45 ± 0.26 µg/mL for elvitegravir, which provides inhibitory quotient of ~ 10 (ratio of C_{trough}: protein binding-adjusted IC_{95} for wild-type HIV-1 virus). Corresponding steady-state mean C_{max}, AUC_{tau}, and C_{trough} (mean ± SD) were 1.1 ± 0.40 µg/mL, 8.3 ± 3.8 µg•h/mL, and 0.05 ± 0.13 µg/mL for cobicistat, 1.9 ± 0.5 µg/mL, 13 ± 4.5 µg•h/mL, and 0.14 ± 0.25 µg/mL for emtricitabine, and 0.45 ± 0.16 µg/mL, 4.4 ± 2.2 µg•h/mL, and 0.1 ± 0.08 µg/mL for tenofovir.

Relative to fasting conditions, the administration of Stribild with a light meal (~373 kcal, 20% fat) or high-fat meal (~800 kcal, 50% fat) resulted in increased exposures of elvitegravir and tenofovir. For elvitegravir, C_{max} and AUC increased 22% and 36% with a light meal, while increasing 56% and 91% with a high-fat meal, respectively. The C_{max} and AUC of tenofovir increased 20% and 25% respectively with a light meal, while the C_{max} was unaffected and AUC increased 25% with a high fat meal. Cobicistat exposures were unaffected by a light meal and although there was a modest decrease of 24% and 18% in C_{max} and AUC respectively with a high-fat meal, no difference was observed in its pharmacoenhancing effect on elvitegravir. Emtricitabine exposures were unaffected with light or high-fat meal.

Distribution

Elvitegravir is 98-99% bound to human plasma proteins and binding is independent of drug concentration over the range of 1 ng/mL to 1,600 ng/mL. The mean plasma to blood drug concentration ratio was 1.37. Cobicistat is 97-98% bound to human plasma proteins and the mean plasma to blood drug concentration ratio was 2.

Following intravenous administration the volume of distribution of emtricitabine and tenofovir was approximately 1,400 mL/kg and 800 mL/kg, respectively. After oral administration of emtricitabine

or tenofovir disoproxil, emtricitabine and tenofovir are widely distributed throughout the body. *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 drug concentration ratio was ~ 1.0 and the mean semen to plasma drug concentration ratio was ~ 4.0. *In vitro* protein binding of tenofovir to plasma or serum protein was less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 µg/mL.

Biotransformation

Elvitegravir undergoes oxidative metabolism by CYP3A (major route), and glucuronidation by UGT1A1/3 enzymes (minor route). Following oral administration of boosted [^{14}C]elvitegravir, elvitegravir was the predominant species in plasma, representing ~94% of the circulating radioactivity. Aromatic and aliphatic hydroxylation or glucuronidation metabolites are present in very low levels, display considerably lower anti-HIV activity and do not contribute to the overall antiviral activity of elvitegravir.

Cobicistat is metabolised via CYP3A and/or CYP2D6-mediated oxidation and does not undergo glucuronidation. Following oral administration of [^{14}C]cobicistat, 99% of circulating radioactivity in plasma was unchanged cobicistat.

In vitro studies indicate that emtricitabine is not an inhibitor of human CYP450 enzymes. Following administration of [^{14}C]emtricitabine, complete recovery of the emtricitabine dose was achieved in urine (~ 86%) and faeces (~ 14%). Thirteen percent of the dose was recovered in the urine as three putative metabolites. The biotransformation of emtricitabine includes oxidation of the thiol moiety to form the 3'-sulfoxide diastereomers (~ 9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (~ 4% of dose). No other metabolites were identifiable.

In vitro studies have determined that neither tenofovir disoproxil nor tenofovir are substrates for the CYP450 enzymes. Moreover, at concentrations substantially higher (approximately 300-fold) than those observed *in vivo*, tenofovir did not inhibit *in vitro* drug metabolism mediated by any of the major human CYP450 isoforms involved in drug biotransformation (CYP3A4, CYP2D6, CYP2C9, CYP2E1, or CYP1A1/2). Tenofovir disoproxil had no effect on any of the CYP450 isoforms, except CYP1A1/2, where a small (6%) but statistically significant reduction in metabolism of a CYP1A1/2 substrate was observed.

Elimination

Following oral administration of [^{14}C]elvitegravir/ritonavir, 94.8% of the dose was recovered in faeces, consistent with the hepatobiliary elimination of elvitegravir; 6.7% of the administered dose was recovered in urine. The median terminal plasma half-life of elvitegravir following administration of Stribild is approximately 12.9 hours.

Following oral administration of [^{14}C]cobicistat, 86% and 8.2% of the dose were recovered in faeces and urine, respectively. The median terminal plasma half-life of cobicistat following administration of Stribild is approximately 3.5 hours and the associated cobicistat exposures provide elvitegravir C_{trough} approximately 10-fold above the protein-binding adjusted IC_{95} for wild-type HIV-1 virus.

Emtricitabine is primarily excreted by the kidneys with complete recovery of the dose achieved in urine (approximately 86%) and faeces (approximately 14%). Thirteen percent of the emtricitabine dose was recovered in urine as three metabolites. The systemic clearance of emtricitabine averaged 307 mL/min. Following oral administration, the elimination half-life of emtricitabine is approximately 10 hours.

Tenofovir is primarily excreted by the kidney by both filtration and an active tubular transport system (human organic anion transporter [hOAT1]) with approximately 70-80% of the dose excreted unchanged in urine following intravenous administration. The apparent clearance of tenofovir averaged approximately 307 mL/min. Renal clearance has been estimated to be approximately

210 mL/min, which is in excess of the glomerular filtration rate. This indicates that active tubular secretion is an important part of the elimination of tenofovir. Following oral administration, the elimination half-life of tenofovir is approximately 12 to 18 hours.

Elderly

Pharmacokinetics of elvitegravir, cobicistat, emtricitabine and tenofovir have not been evaluated in the elderly (over 65 years).

Gender

No clinically relevant pharmacokinetic differences due to gender have been identified for cobicistat-boosted elvitegravir, emtricitabine and tenofovir disoproxil.

Ethnicity

No clinically relevant pharmacokinetic differences due to ethnicity have been identified for cobicistat-boosted elvitegravir, emtricitabine and tenofovir disoproxil.

Paediatric population

The pharmacokinetics of elvitegravir or cobicistat in paediatric subjects have not been fully established. In general, elvitegravir pharmacokinetics in paediatric patients (12 to < 18 years of age) and emtricitabine pharmacokinetics in children (aged 4 months to 18 years of age) are similar to those seen in adults. Tenofovir exposure achieved in 8 paediatric patients (12 to < 18 years of age) receiving oral daily doses of tenofovir disoproxil fumarate 300 mg (tablet) was similar to exposures achieved in adults receiving once-daily doses of 300 mg.

Renal impairment

A study of pharmacokinetics of cobicistat-boosted elvitegravir was performed in non-HIV-1 infected subjects with severe renal impairment (creatinine clearance below 30 mL/min). No clinically relevant differences in elvitegravir or cobicistat pharmacokinetics were observed between subjects with severe renal impairment and healthy subjects. No dose adjustment of elvitegravir or cobicistat is necessary for patients with renal impairment. The pharmacokinetics of emtricitabine and tenofovir are altered in subjects with renal impairment. In subjects with creatinine clearance below 50 mL/min or with end stage renal disease requiring dialysis, C_{max}, and AUC of emtricitabine and tenofovir were increased (see section 4.4).

Hepatic impairment

Both elvitegravir and cobicistat are primarily metabolised and eliminated by the liver. A study of pharmacokinetics of cobicistat-boosted elvitegravir was performed in non-HIV-1 infected subjects with moderate hepatic impairment. No clinically relevant differences in elvitegravir or cobicistat pharmacokinetics were observed between subjects with moderate impairment and healthy subjects. No dose adjustment of elvitegravir or cobicistat is necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of elvitegravir or cobicistat has not been studied. The pharmacokinetics of emtricitabine have not been studied in subjects with hepatic impairment; however, emtricitabine is not significantly metabolised by liver enzymes, so the impact of liver impairment should be limited. Clinically relevant changes in tenofovir pharmacokinetics in patients with hepatic impairment were not observed. Therefore, no tenofovir disoproxil dose adjustment is required in patients with hepatic impairment.

Hepatitis B and/or hepatitis C virus co-infection

Pharmacokinetics of emtricitabine and tenofovir disoproxil have not been fully evaluated in hepatitis B and/or C virus co-infected patients. Limited data from population pharmacokinetic

analysis (n = 24) indicated that hepatitis B and/or C virus infection had no clinically relevant effect on the exposure of boosted elvitegravir.

Pregnancy and postpartum

The results reported from a prospective study (IMPAACT P1026s) showed that treatment with cobicistat and elvitegravir-containing regimens during pregnancy results in lower elvitegravir and cobicistat exposures (Table 5).

Table 5: Changes in pharmacokinetic parameters from the IMPAACT P1026s study for elvitegravir and cobicistat in women receiving cobicistat and elvitegravir-containing regimens during the second and third trimesters of pregnancy compared to paired postpartum data

Comparison to paired postpartum data, n	Mean % change of elvitegravir pharmacokinetic parameters[a]			Mean % change of cobicistat pharmacokinetic parameters[a]		
	AUC_{24}	C_{max}	C_{24}	AUC_{24}	C_{max}	C_{24}
2T/PP, n = 14	↓ 24%[b]	↓ 8%	↓ 81%[b]	↓ 44%[b]	↓ 28%[b]	↓ 60%[b]
3T/PP, n = 24	↓ 44%[b]	↓ 28%[b]	↓ 89%[b]	↓ 59%[b]	↓ 38%[b]	↓ 76%[b]

2T = second trimester; 3T = third trimester; PP =postpartum

a paired comparisons

b P<0.10 compared with postpartum

5.3 Preclinical safety data

Elvitegravir was negative in an *in vitro* bacterial mutagenicity test (Ames test) and negative in an *in vivo* rat micronucleus assay at doses up to 2,000 mg/kg. In an *in vitro* chromosomal aberration test, elvitegravir was negative with metabolic activation; however, an equivocal response was observed without activation.

Cobicistat was not mutagenic or clastogenic in conventional genotoxicity assays. *Ex vivo* rabbit studies and *in vivo* dog studies suggest that cobicistat has a low potential for QT prolongation, and may slightly prolong the PR interval and decrease left ventricular function at concentrations at least 11-fold higher than the human exposure at the recommended 150 mg daily dose. In a human clinical study of 35 healthy subjects, echocardiograms performed at baseline and after receiving 150 mg cobicistat once daily for at least 15 days indicated no clinically significant change in left ventricular function.

Reproductive toxicity studies in rats and rabbits with cobicistat showed no effects on mating, fertility, pregnancy or foetal parameters. However increased postimplantation loss and decreased foetal weights were observed in rats associated with significant decreases in maternal body weights at 125 mg/kg/day.

Long term oral carcinogenicity studies with elvitegravir and cobicistat did not show any carcinogenic potential in mice and rats.

Non-clinical data on emtricitabine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction and development.

Non-clinical data on tenofovir disoproxil reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential, and toxicity to reproduction and development. Findings in repeat-dose toxicity studies in rats, dogs and monkeys at exposure levels greater than or equal to clinical exposure levels and with possible relevance to clinical use included kidney and bone changes and a decrease in serum phosphate concentration. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (rats and dogs). Reproductive toxicity studies in rats and rabbits showed no effects on mating, fertility, pregnancy or foetal

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

The active substances elvitegravir, cobicistat and tenofovir disoproxil are persistent in the environment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose (E460)
Croscarmellose sodium (E468)
Magnesium stearate (E572)
Silicon dioxide (E551)
Sodium lauryl sulfate
Lactose monohydrate
Hydroxypropyl cellulose (E463)

Film-coating
Polyvinyl alcohol (partially hydrolysed) (E1203)
Indigo carmine (FD&C Blue #2) aluminium lake (E132)
Polyethylene glycol (E1521)
Titanium dioxide (E171)
Talc (E553b)
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

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

6.4 Special precautions for storage

Store in the original package in order to protect from moisture. Keep the bottle tightly closed. Store at a temperature below 30°C.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with a polypropylene child-resistant closure containing 30 film-coated tablets and a silica gel desiccant.

The following pack size is available: outer carton 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. MANUFACTURER

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Ireland

8. REGISTRATION HOLDER

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Revised in April 2023 in accordance with MoH guidelines.
Reference: EU SmPC from January 2023.

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