NEW ZEALAND DATA SHEET

1 STRIBILD® (TENOFOVIR DISOPROXIL FUMARATE/EMTRICITABINE/ELVITEGRAVIR/COBICISTAT) TABLETS

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tenofovir disoproxil fumarate (tenofovir DF) 300 mg /Emtricitabine (FTC) 200 mg/Elvitegravir (EVG) 150 mg/Cobicistat (COBI) 150 mg tablets.

For full list of excipients, see section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Each STRIBILD tablet is capsule shaped, film-coated and green in colour. Each tablet is debossed with 'GSI' on one side and the number "1" surrounded by a square box (1) on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

STRIBILD is indicated as a single tablet regimen for the treatment of HIV infection in treatment-naive adults. STRIBILD is also indicated in certain virologically suppressed (HIV1 RNA <50 copies/mL) adult patients on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen (see section 5.1 Pharmacodynamics under subsection "Clinical Data"). Patients must not have a history of treatment failure or known mutations associated with resistance to the antiretroviral components of STRIBILD (tenofovir DF, emtricitabine or elvitegravir).
STRIBILD is a fixed dose combination of one integrase inhibitor, one pharmacokinetic enhancer and two nucleos(t)ide HIV-1 reverse transcriptase inhibitors.

4.2 Dose and Method of Administration

Adults: The recommended dose of STRIBILD is one tablet once daily taken orally with a meal.

Renal impairment: STRIBILD should not be initiated in patients with estimated creatinine clearance below 70 mL/min. STRIBILD should be discontinued if estimated creatinine clearance declines below 50 mL/min during treatment with STRIBILD as dose interval adjustment required for emtricitabine and tenofovir DF cannot be achieved with the fixed-dose combination tablet (see section 4.4 Special Warnings and Precautions for Use).

4.3 Contraindications

STRIBILD is contraindicated in patients with known hypersensitivity to any of the active substances or any other component of the tablets.

STRIBILD must not be administered to children or adolescents under the age of 18 years.

Coadministration with the following drugs is contraindicated due to the potential for serious and/or life-threatening events or loss of virologic response and possible resistance to STRIBILD (See section 4.5 Interaction with Other Medicines and Other Forms of Interaction.):

Coadministration is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events, and with drugs that are potent inducers of CYP3A due to the potential for loss of virologic response and possible resistance to STRIBILD. Therefore, coadministration is contraindicated with, but not limited to, the following drugs (See Drug Interactions):

- Alpha 1-adrenoreceptor antagonists: alfuzosin
- Anticonvulsants: carbamazepine, phenobarbital, phenytoin
- Antimycobacterials: rifampicin
- Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine
- Gastrointestinal (GI) motility agents: cisapride
- Herbal products: St. John's wort (*Hypericum perforatum*)
- HMG CoA reductase inhibitors: lovastatin, simvastatin
- Neuroleptics: pimozide
- Phosphodiesterase-5 (PDE-5) inhibitors: sildenafil for the treatment of pulmonary arterial hypertension
- Sedative/hypnotics: orally administered midazolam, triazolam

STRIBILD is a fixed-dose combination of tenofovir DF, emtricitabine, elvitegravir and cobicistat. STRIBILD should not be administered concurrently with other medicinal products containing any of the same active components: tenofovir DF, emtricitabine, elvitegravir or cobicistat. STRIBILD should not be administered with adefovir dipivoxil or tenofovir alafenamide.

4.4 Special Warnings and Precautions for Use

General

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.

Patients should be advised that antiretroviral therapies, including STRIBILD, have not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions must continue to be used. Patients should also be informed that STRIBILD is not a cure for HIV infection.

Lactic Acidosis/Severe Hepatomegaly with Steatosis
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported with the use of antiretroviral nucleoside analogues including the tenofovir DF component of STRIBILD, alone or in combination with other antiretrovirals, in the treatment of HIV infection. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogues to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with STRIBILD should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Renal Impairment
The emtricitabine and tenofovir DF components of STRIBILD are primarily excreted by the kidney. Renal failure, renal impairment, elevated creatinine, hypophosphataemia and Fanconi syndrome have been reported with the use of tenofovir DF.

Estimated creatinine clearance, urine glucose, and urine protein should be documented in all patients prior to initiating therapy with STRIBILD. STRIBILD should not be initiated in patients with estimated creatinine clearance below 70 mL/min.

Routine monitoring of estimated creatine clearance should be performed during STRIBILD therapy in patients, additionally, serum phosphorus should be measured in patients at risk for renal impairment. STRIBILD should be discontinued if estimated creatinine clearance declines below 50 mL/min as dose interval adjustment required for tenofovir disoproxil fumarate and emtricitabine cannot be achieved with the fixed-dose combination tablet.

Although cobicistat may cause modest increases in serum creatinine and modest declines in estimated creatinine clearance without affecting renal glomerular function, patients who experience a confirmed increase in serum creatinine of greater than 0.4 mg per dL from baseline should be monitored for renal safety, including measuring serum phosphorus, urine glucose and urine protein (see section 4.8 Undesirable Effects, section 5.1 Pharmacodynamics under subsection “Clinical Data”).

STRIBILD should be avoided with concurrent or recent use of a nephrotoxic agent.

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.

Bone Effects
Bone toxicity including a reduction in bone mineral density (BMD) have been observed in tenofovir DF studies in three animal species. Clinically relevant bone abnormalities have not been seen in long term clinical studies (>3 years) with VIREAD, or in 144 week studies with STRIBILD. However, bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy (see section 4.8 Undesirable Effects). If bone abnormalities are suspected during therapy then appropriate consultation should be obtained.

HIV and Hepatitis B Virus (HBV) Co-infection
The safety and efficacy of STRIBILD have not been established in patients coinfected with HIV and HBV. Discontinuation of STRIBILD therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis due to the emtricitabine and tenofovir DF components of STRIBILD. Patients co-infected with HIV and HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping STRIBILD treatment. If appropriate, initiation of anti-hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, discontinuation of anti-hepatitis B therapy is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation. STRIBILD should not be administered concomitantly with other medicinal products used for the treatment of hepatitis B virus infection (tenofovir disoproxil [as fumarate or alafenamide], lamivudine or adefovir dipivoxil).

Use with Hepatitis C Virus Antiviral Agents
Coadministration of tenofovir disoproxil fumarate with HARVONI® (ledipasvir/sofosbuvir),EPCLUSA (sofosbuvir/velpatasvir), or VOSEVI (sofosbuvir/velpatasvir/voxilaprevir has been shown to increase plasma concentrations of tenofovir, especially when used together with an HIV regimen containing tenofovir DF and a pharmacokinetic enhancer (ritonavir or cobicistat). The safety of tenofovir DF in the setting of HARVONI, EPCLUSA, or VOSEVI and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with coadministration of HARVONI with STRIBILD should be considered, particularly in patients at increased risk of renal dysfunction. Patients receiving STRIBILD concomitantly with HARVONI, EPCLUSA, or VOSEVI should be monitored for adverse reactions related to tenofovir DF.

Use with Other Antiretroviral Products
STRIBILD is indicated for use as a complete regimen for the treatment of HIV-1 infection and should not be coadministered with other antiretroviral products. STRIBILD should not be used in conjunction with protease inhibitors or non-nucleoside reverse transcriptase inhibitors due to potential drug-drug interactions including altered and/or suboptimal pharmacokinetics of cobicistat, elvitegravir, and/or the coadministered antiretroviral products.

STRIBILD should not be coadministered with products containing any of the same active components, emtricitabine, tenofovir disoproxil fumarate, elvitegravir or cobicistat; or with products containing lamivudine. STRIBILD should not be administered concurrently with ritonavir or ritonavir-containing products or regimens due to similar effects of cobicistat and ritonavir on CYP3A. STRIBILD should not be administered with adefovir dipivoxil or tenofovir alafenamide.

Lipodystrophy
Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors and lipoatrophy and nucleoside reverse transcriptase inhibitors has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the

measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Immune Reconstitution Syndrome
Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including tenofovir DF and emtricitabine. In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy, 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 antiretroviral therapy. Relevant examples are 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 have also been reported to occur in the setting of immune reconstitution; however, the reported time to onset is more variable, and these events can occur many months after initiation of treatment.

Use in Children
STRIBILD is not recommended for use in children or adolescents below 18 years of age due to insufficient data on safety and efficacy.

Use in the Elderly
Clinical studies of STRIBILD did not contain sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. Caution should be exercised when prescribing STRIBILD to the elderly, keeping in mind the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Genotoxicity
No genotoxicity studies have been conducted with tenofovir DF, emtricitabine, elvitegravir and cobicistat in combination.

Tenofovir disoproxil fumarate was mutagenic in an in vitro mouse L5178Y lymphoma cell assay (tk locus) and in an *ex vivo* assay for unscheduled DNA synthesis in rat hepatocytes, but it was negative in *in vitro* bacterial assays for gene mutation and an *in vivo* mouse micronucleus test for chromosomal damage.

Emtricitabine was not mutagenic in bacteria or mouse lymphoma cell assays *in vitro* nor clastogenic in the mouse micronucleus test *in vivo*.

Elvitegravir showed an equivocal response in an *in vitro* chromosomal aberration assay in Chinese hamster lung cells, but only in the absence of metabolic activation. No genotoxicity was observed in a test for bacterial reverse mutation *in vitro,* or *in vivo* rat micronucleus test.

Cobicistat was not genotoxic in *in vitro* tests for bacterial reverse gene mutation or gene mutation in mouse lymphoma L5178Y cells (tk locus), or in an *in vivo* rat micronucleus test.

Carcinogenicity
No carcinogenicity studies have been conducted with tenofovir DF, emtricitabine, elvitegravir and cobicistat in combination.

Tenofovir disoproxil fumarate: In a long-term carcinogenicity study conducted in mice with tenofovir DF there was a low incidence of duodenal tumours with the highest dose of 600 mg/kg/day. These were associated with a high incidence of duodenal mucosal hyperplasia, which was also observed with a dose of 300 mg/kg/day. These findings may be related to high local drug concentrations in the gastro-intestinal tract, likely to result in much higher exposure margins than that based on the AUC. At therapeutic doses the risk of these duodenal effects occurring in humans is likely to be low. The systemic drug exposure (AUC) with the 600 mg/kg/day dose was approximately 15 times the human exposure at the therapeutic dose of 300 mg/day. No tumourigenic response was observed in rats treated with doses of up to 300 mg/kg/day (5 times the human systemic exposure at the therapeutic dose based on AUC).

Emtricitabine: In long-term oral carcinogenicity studies conducted with emtricitabine, no drug-related increases in tumour incidence were found in mice at doses up to 750 mg/kg/day (32 times the human systemic exposure (AUC) at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (38 times the human systemic exposure at the therapeutic dose).

Elvitegravir: In a long-term carcinogenicity study in mice, no tumourigenic response was seen with doses of up to 2000 mg/kg/day, with the highest dose also being given together with 25 mg/kg/day ritonavir. Respective elvitegravir exposures (AUC) with this dose were approximately 3.1 and 14 times the human exposure with the 150 mg/day dose. No tumourigenic response was seen in a long-term study in rats with doses up to 2000 mg/kg/day (12 times in males and 27 times in females the human exposure (AUC) with the therapeutic dose).

Cobicistat: In a long term study in mice with doses of up to 50 mg/kg/day in males and 100 mg/kg/day in females (9-21 times the human exposure (AUC) at 150mg daily), cobicistat treatment did not result in any increased tumour incidences. In a corresponding study, with doses of up to 50 mg/kg/day in males and 30 mg/kg/day in females (1.9-2.6 times the human exposure with 150 mg daily), treatment resulted in increased incidence of thyroid follicular cell tumours. Hepatocyte hypertrophy was also observed, and this oncogenic response is most likely related to alterations in thyroid hormones and to be specific to species.

4.5 Interaction with Other Medicines and Other Forms of Interaction

General
As STRIBILD contains tenofovir DF, emtricitabine, elvitegravir and cobicistat, any interactions that have been identified with these agents individually may occur with STRIBILD.

CYP3A Associated Drug-Drug Interactions
Cobicistat, a component of STRIBILD, is a strong inhibitor of cytochrome P450 (CYP3A) and a CYP3A substrate. Thus, coadministration of STRIBILD with drugs that are primarily metabolized by CYP3A may result in increased plasma concentrations of such drugs (see section 4.3 Contraindications). Coadministration of STRIBILD with drugs that inhibit CYP3A may decrease the clearance of cobicistat, resulting in increased plasma concentration of cobicistat. Cobicistat, is also an inhibitor of CYP2D6. The transporters that cobicistat inhibits included p-glycoprotein (P-gp), BCRP, OATP1B1 and OATP1B3. Thus, coadministration of STRIBILD

with drugs that are primarily metabolized by CYP3A or CYP2D6, or are substrates of P-gp, BCRP, OATP1B1 or OATP1B3 may result in increased plasma concentrations of such drugs.

Elvitegravir, a component of STRIBILD, is metabolized by CYP3A. Drugs that induce CYP3A activity are expected to increase the clearance of elvitegravir and cobicistat, resulting in decreased plasma concentration of elvitegravir and cobicistat, which may lead to loss of therapeutic effect of STRIBILD and development of resistance (see section 4.3 Contraindications).

Drugs Affecting Renal Functions
Tenofovir and emtricitabine and are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No drug-drug interactions due to competition for renal excretion have been observed; however, coadministration of STRIBILD with drugs that are eliminated by active tubular secretion may increase concentrations of Tenofovir and emtricitabine, and/or the coadministered drug. Some examples include, but are not limited to acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, and valganciclovir. Drugs that decrease renal function may increase concentrations of tenofovir and / or emtricitabine.

Co-administration of other medicinal products
Exposure to didanosine is significantly increased following co-administration with tenofovir DF that may increase the risk of didanosine-related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported (see 4.5 Interaction with Other Medicines and Other Forms of Interaction)**.**

Established and Other Potentially Significant Interactions

STRIBILD is indicated for use as a complete regimen for the treatment of HIV-1 infection and should 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. Drug interaction information for STRIBILD with potential concomitant drugs is summarized in Table 1. The drug interactions described are based on studies conducted with STRIBILD or the components of STRIBILD, (tenofovir DF, emtricitabine, elvitegravir and cobicistat) as individual agents and/or in combination, or are potential drug interactions that may occur with STRIBILD.
The table is not all-inclusive (see section 4.3 Contraindications).

Table 1 Established Significant [a] Drug Interactions

Concomitant Drug Class: Drug Name	Effect[b]	Clinical Comment
Acid Reducing Agents: antacids	↓ elvitegravir	Elvitegravir plasma concentrations are lower with antacids due to local complexation in the GI tract and not to changes in gastric pH. It is recommended to separate STRIBILD and antacid administration by at least 2 hours. For information on other acid reducing agents (e.g. H_2-receptor antagonists and proton pump inhibitors), see *section 4.5 Interaction with Other Medicines and Other Forms of Interaction.*
Alpha 1-Adrenoreceptor Antagonist: alfuzosin	↑ alfuzosin	Alfuzosin is primarily metabolized by CYP3A. Coadministration with STRIBILD may result in increased plasma concentrations of alfuzosin, which is associated with the potential for serious and/or life-threatening reactions. Coadministration of STRIBILD and alfuzosin is contraindicated.
Antiarrhythmics: amiodarone disopyramide flecainide systemic lidocaine propafenone digoxin	↑ antiarrhythmics ↑ digoxin	Concentrations of these antiarrhythmic drugs may be increased when coadministered with cobicistat. Caution is warranted and clinical monitoring is recommended upon coadministration of these agents with STRIBILD.
Antibacterials: clarithromycin telithromycin	↑ clarithromycin ↑ telithromycin ↑ cobicistat	Concentrations of clarithromycin and/or cobicistat may be altered with coadministration 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 when administering STRIBILD. Concentrations of telithromycin and/or cobicistat may be altered with co-administration of STRIBILD. Clinical monitoring is recommended upon co-administration with STRIBILD.

Concomitant Drug Class: Drug Name	Effect[b]	Clinical Comment
Anticoagulants: Warfarin	↑ or ↓ warfarin	Concentrations of warfarin may be affected upon coadministration with STRIBILD. It is recommended that the INR be monitored upon coadministration of STRIBILD.
Direct Oral Anticoagulants (DOACs): apixaban rivaroxaban dabigatran edoxaban	↑ DOACs	Coadministration of DOACs with STRIBILD may result in increased plasma concentrations of the DOAC, which may lead to an increased bleeding risk. Coadministration of a DOAC affected by both P-gp and CYP3A4, including apixaban and rivaroxaban, is not recommended with STRIBILD. Clinical monitoring and/or dose adjustment is recommended when a DOAC transported by P-gp, including dabigatran or edoxaban, is coadministered with STRIBILD. Refer to the prescribing information of the coadministered DOAC.
Anticonvulsants: carbamazepine oxcarbazepine phenobarbital phenytoin	↓ elvitegravir ↓ cobicistat	Carbamazepine, a potent CYP3A inducer, decreases cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Coadministration of STRIBILD with carbamazepine, phenobarbital, or phenytoin is contraindicated. Coadministration of oxcarbazepine, a CYP3A inducer, may decrease cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Alternative anticonvulsants should be considered when administering with STRIBILD.
clonazepam ethosuximide	↑ clonazepam ↑ ethosuximide	Concentrations of clonazepam and ethosuximide may be increased when coadministered with cobicistat. Clinical monitoring is recommended upon coadministration of STRIBILD.
Antidepressants: Selective Serotonin Reuptake Inhibitors sertaline trazodone	↑ SSRIs ⇔ sertraline ↑ trazodone	Concentrations of sertraline are not expected to be affected upon coadministration with STRIBILD. No dose adjustment is required upon coadministration. Concentrations of other antidepressant agents may be increased when coadministered with cobicistat. Dose titration may be required for most drugs of the SSRI class. Concentrations of trazodone may increase upon coadministration with cobicistat. Dose reduction should be considered when administering trazodone with STRIBILD.
Antifungals: itraconazole ketoconazole voriconazole	↑ antifungals ↑ cobicistat	Concentrations of ketoconazole and/or cobicistat may increase with coadministration of STRIBILD. When administering with STRIBILD, the maximum daily dose of ketoconazole and itraconazole should not exceed 200 mg/ day. Concentrations of voriconazole may be increased when coadministered with cobicistat. Clinical monitoring may be needed upon coadministration with STRIBILD.
Anti-gout: colchicine	↑ colchicine	Dose reductions of colchicine may be required. STRIBILD should not be coadministered with colchicine in patients with renal or hepatic impairment.

Concomitant Drug Class: Drug Name	Effect[b]	Clinical Comment
Antihistamines: astemizole terfenadine	↑ astemizole ↑ terfenadine	Concentrations of astemizole and terfenadine may be increased when coadministered with cobicistat. Clinical monitoring is recommended when these agents are coadministered with STRIBILD.
Antimycobacterial: rifabutin rifapentine	↓ elvitegravir ↓ cobicistat	Coadministration of, rifabutin, and rifapentine with STRIBILDmay significantly decrease cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Coadministration of STRIBILD with rifabutin or rifapentine is not recommended.
Beta-Blockers: metoprolol timolol	↑ beta-blockers	Concentrations of beta-blockers may be increased when coadministered with cobicistat. Clinical monitoring is recommended and a dose decrease may be necessary when these agents are coadministered with STRIBILD.
Calcium Channel Blockers: amlodipine diltiazem felodipine nifedipine verapamil	↑ calcium channel blockers	Concentrations of calcium channel blockers may be increased when coadministered with cobicistat. Caution is warranted and clinical monitoring is recommended upon coadministration with STRIBILD.
Corticosteroid **(all routes excluding cutaneous):** Dexamethasone (oral) betamethasone budesonide fluticasone mometasone triamcinolone	↓ elvitegravir(with oral dexamethasone) ↓ cobicistat (with oral dexamethasone) ↑ corticosteroids	Coadministration of dexamethasone, a CYP3A inducer, may significantly decrease cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Alternative corticosteroids should be considered. Coadministration with corticosteroids that are sensitive to CYP3A inhibition can increase the risk for Cushing's syndrome and adrenal suppression, which have been reported during postmarketing use of cobicistat-containing products. Consider the risk of systemic corticosteroid effects if STRIBILD is coadministered with corticosteroids that are sensitive to CYP3A inhibition. Alternative corticosteroids should be considered, particularly for long term use.
Endothelin Receptor Antagonists: bosentan	↑ bosentan ↓ elvitegravir ↓ cobicistat	Coadministration with STRIBILD may lead to decreased elvitegravir and/or cobicistat exposures and loss of therapeutic effect. Coadministration is not recommended.

Concomitant Drug Class: Drug Name	Effect[b]	Clinical Comment
Ergot Derivatives: dihydroergotamine ergotamine ergonovine methylergonovine	↑ ergot derivatives	Ergot derivatives are primarily metabolized by CYP3A. Coadministration with STRIBILD may result in increased plasma concentrations of these drugs, which is associated with the potential for serious and/or life-threatening reactions. Coadministration of STRIBILD and dihydroergotamine, ergotamine, ergonovine and methylergonovine are contraindicated.
Hepatitis C Virus Antiviral Agents: ledipasvir/sofosbuvir sofosbuvir/velpatasvir sofosbuvir/velpatasvir/ voxilaprevir	↑ tenofovir	Increased plasma concentrations of tenofovir resulting from co-administration of STRIBILD and HARVONI (ledipasvir/sofosbuvir), EPCLUSA (sofosbuvir/velpatasvir) or VOSEVI (sofosbuvir/velpatasvir/voxilaprevir) may increase adverse reactions related to tenofovir DF, including renal disorders. The safety of tenofovir DF when used with HARVONI, EPCLUSA (sofosbuvir/velpatasvir) or VOSEVI (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, if other alternatives are not available.
Herbal Products: St. John's wort (Hypericum perforatum)	↓ elvitegravir ↓ cobicistat	Coadministration of St. John's wort, a potent CYP3A inducer, may significantly decrease cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Coadministration of STRIBILD and St. John's wort is contraindicated.
HMG CoA Reductase Inhibitors: atorvastatin lovastatin rosuvastatin simvastatin	↑ HMG-CoA reductase inhibitors	HMG CoA reductase inhibitors are primarily metabolized by CYP3A. Coadministration with STRIBILD may result in increased plasma concentrations of lovastatin or simvastatin, which are associated with the potential for serious and/or life-threatening reactions. Coadministration of STRIBILD and lovastatin and simvastatin are contraindicated. Concentrations of atorvastatin are increased when administered with elvitegravir and cobicistat. Start with the lowest possible dose of atorvastatin with careful monitoring upon coadministration with STRIBILD. 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.
Immunosuppressants: cyclosporine sirolimus tacrolimus	↑ immunosuppresants	Concentrations of these immunosuppressant agents may be increased when administered with cobicistat. Therapeutic monitoring is recommended upon coadministration with STRIBILD.

Concomitant Drug Class: Drug Name	Effect[b]	Clinical Comment
Narcotic Analgesics: Methadone	⇔ R- Methadone ⇔ S- Methadone	Methadone exposures are unaffected upon coadministration with elvitegravir and cobicistat. No dose adjustment of methadone is required upon coadministration with STRIBILD.
Buprenorphine/naloxone	↑buprenorphine ↑norbuprenorphine ↓naloxone	Concentrations of buprenorphine and norbuprenorphine are modestly increased and concentrations of naloxone are modestly decreased when coadministered with elvitegravir and cobicistat, with no changes on opioid pharmacodynamics. Accordingly, the observed concentration changes are not considered clinically relevant and no dose adjustment of buprenorphine/naloxone is required upon coadministration with STRIBILD.
Inhaled Beta Agonist: salmeterol	↑ salmeterol	Coadministration 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.
Neuroleptics: perphenazine risperidone	↑ neuroleptics	For-neuroleptics, consider reducing the dose of the neuroleptic upon coadministration with STRIBILD.
Phosphodiesterase-5 (PDE5) Inhibitors: sildenafil tadalafil vardenafil	↑ PDE5 inhibitors	PDE5 inhibitors are primarily metabolized by CYP3A. Coadministration with STRIBILD may result in increased plasma concentrations of sildenafil and tadalafil, which may result in PDE5 inhibitor-associated adverse reactions. Coadministration of STRIBILD and sildenafil for the treatment of pulmonary arterial hypertension are contraindicated while co administration of STRIBILD with tadalafil is not recommended. For the treatment of erectile dysfunction, it is recommended that a single dose of no more than 25 mg sildenafil in 48 hours no more than 10 mg tadalafil in 72 hours or no more than 2.5 mg vardenafil in 72 hours be coadministered with STRIBILD.
Sedative/hypnotics: buspirone clorazepate diazepam orally-administered midazolam triazolam zolpidem	↑ sedatives/hypnotics	Midazolam and triazolam are primarily metabolized by CYP3A. Coadministration with STRIBILD may result in increased plasma concentrations of these drugs, which are associated with the potential for serious and/or life-threatening reactions. Coadministration of STRIBILD and orally administered midazolam and triazolam are contraindicated. With other sedative/hypnotics, dose reduction may be necessary and concentration monitoring is recommended.

Concomitant Drug Class: Drug Name	Effect[b]	Clinical Comment
Hormonal Contraceptives: drospirenone/ethinyl estradiol	↑ drospirenone ↑ norgestimate ↓ ethinyl estradiol	Plasma concentrations of drospirenone may be increased when coadministered with cobicistat-containing products. Clinical monitoring is recommended due to the potential for hyperkalemia.
norgestimate/ ethinyl estradiol		The effects of increases in the concentration of the progestational component of norgestimate are not fully known and can include increased risk of insulin resistance, dysipidemia, acne and venous thrombosis. The potential risks and benefits associated with coadministration of norgestimate/ethinyl estradiol with STRIBILD should be considered, particularly in women who have risk factors for these events. Coadministration of STRIBILD with other hormonal contraceptives (e.g., contraceptive patch, contraceptive vaginal ring, or injectable contraceptives) or oral contraceptive containing progesterones other than drospirenone and norgestimate, or <25 µg of ethinyl estradiol, has not been studied; therefore alternative (non hormonal) method of contraception can be considered. Please see the local prescribing information for drospirenone/ethinyl estradiol for contraception advice.

CLcr = creatinine clearance; HMG-CoA = 3-hydroxy-3-methyl-glutaryl-CoA; INR = international normalized ratio; PDE-5 = Phosphodiesterase-5; SSRI = selective serotonin reuptake inhibitor

a. This table is not all inclusive.

b. ↑ = increase, ↓ = decrease, ↔ = no effect

Drugs Without Clinically Significant Interactions with STRIBILD

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

Assessment of Drug Interactions

The drug interaction studies described were conducted with STRIBILD, elvitegravir (coadministered with cobicistat or ritonavir), emtricitabine, or tenofovir DF.

As STRIBILD is indicated for use as a complete regimen for the treatment of HIV-1 infection and should not be administered with other antiretroviral medications, information regarding drug-drug interactions with other antiretrovirals agents is not provided (see section 4.4 Special Warnings and Precautions for Use).

Elvitegravir: Elvitegravir is primarily metabolized by cytochrome CYP3A, and drugs that induce or inhibit CYP3A may affect the exposure of elvitegravir. Coadministration of STRIBILD with drugs that induce CYP3A may result in decreased plasma concentrations of elvitegravir and reduce the therapeutic effect of STRIBILD (see section 4.3 Contraindications).

The effects of coadministered drugs on the exposure of elvitegravir are shown in Table 2. The effects of the individual components of STRIBILD on the exposure of coadministered drugs are shown in Table 3.

Table 2 Drug Interactions: Changes in Pharmacokinetic Parameters for Elvitegravir in the Presence of the Coadministered Drug[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose (mg)	Cobicistat or Ritonavir Booster Dose (mg)	N	% Change of Elvitegravir Pharmacokinetic Parameters[b] (90% CI)		
					C_{max}	AUC	C_{min}
Antacids	20 mL single dose ± 2 hours or ± 4 hours from elvitegravir administration	50 single dose	Ritonavir 100 single dose	39	⇔	⇔	⇔
	20 mL single dose simultaneously administered with elvitegravir	50 single dose	Ritonavir 100 single dose	13	↓47 (↓53 to ↓40)	↓45 (↓50 to ↓40)	↓41 (↓48 to ↓33)
atorvastatin	10 single dose	150 once daily[b]	Cobicistat 150 once daily[b]	16	⇔	⇔	⇔
carbamazepine	200 twice daily	150 once daily	Cobicistat 150 once daily	12	↓45 (↓51 to ↓39)	↓69 (↓72 to ↓67)	↓97 (↓98 to ↓96)
ledipasvir/ sofosbuvir	90/400 once daily	150 once daily	Cobicistat 150 once daily [c]	29	⇔	⇔	↑36 (↑23 to ↑49)
ketoconazole	200 twice daily	150 once daily	Ritonavir 100 once daily	18	⇔	↑48 (↑36 to ↑62)	↑67 (↑48 to ↑88)
Rifabutin	150 once every other day	150 once daily	Cobicistat 150 once daily	12	⇔	↓21 (↓26 to ↓15)	↓67 (↓73 to ↓60)
Rosuvastatin	10 single dose	150 once daily	Cobicistat 150 once daily	10	⇔	⇔	⇔
sertraline	50 single dose	150 once daily[b]	Cobicistat 150 once daily[b]	19	⇔	⇔	⇔
sofosbuvir/ velpatasvir voxilaprevir	400/100/100 + 100 voxilaprevir[d] once daily	150 once daily[b]	cobicistat 150 once daily[b]	29	⇔	⇔	↑32 (↑17 to ↑49)

↑ = Increase; ↓ = Decrease; ⇔ = No Effect; NA = Not Applicable

a. All interaction studies conducted in healthy volunteers

b. Study conducted with GENVOYA® (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide).

c. Percent change of cobicistat PK parameters (90% CI) was ↑25 (↑18 to ↑32) for C_{max}, ↑59 (↑49 to ↑70) for AUC, and ↑325 (↑247 to ↑422) for C_{min}.

d. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Table 3 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of the Individual Components of STRIBILD[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose (mg)	Cobicistat or Ritonavir Booster Dose	N	% Change of Coadministered Drug Pharmacokinetic Parameters[b] (90% CI)		
					C_{max}	AUC	C_{min}
atorvastatin	10 single dose	150 once daily [b]	Cobicistat 150 once daily [b]	16	↑132 (↑91 to ↑182)	↑160 (↑131 to ↑193)	NC
buprenorphine	16-24 once daily	150 once daily	150 once daily	17	⇔	↑35 (↑18 to ↑55)	↑66 (↑43 to ↑93)
norbuprenorphine					↑24 (↑3 to ↑49)	↑42 (↑22 to ↑67)	↑57 (↑31 to ↑88)
naloxone	4-6 once daily	150 once daily	150 once daily	17	↓28 (↓39 to ↓15)	↓28 (↓41 to ↓13)	N/A
carbamazepine	200 twice daily	150 once daily	Cobicistat 150 once daily	12	↑40 (↑32 to ↑49)	↑43 (↑36 to ↑52)	↑51 (↑41 to ↑62)
carbamazepine-10,11-epoxide					↓27 (↓30 to ↓22)	↓35 (↓37 to ↓34)	↓41 (↓43 to ↓39)
norgestimate/ ethinyl estradiol	0.180/0.215/ 0.250 norgestimate once daily	150 once daily[c]	Cobicistat 150 once daily[c]	13	↑108 (↑100 to ↑117)	↑126 (↑115 to ↑137)	↑167 (↑143 to ↑192)
	0.025 ethinyl estradiol once daily				⇔	↓25 (↓31 to ↓19)	↓44 (↓48 to ↓39)
ledipasvir	90/400 once daily	150 once daily	Cobicistat 150 once daily	29	↑63 (↑51 to ↑75)	↑78 (↑64 to ↑94)	↑91 (↑76 to ↑108)
sofosbuvir					↑33 (↑14 to ↑56)	↑36 (↑21 to ↑52)	N/A
GS-331007[d]					↑33 (↑22 to ↑44)	↑44 (↑41 to ↑48)	↑53 (↑47 to ↑59)
rifabutin	150 once every other day	150 once daily	Cobicistat 150 once daily	12	⇔	⇔	⇔
25-O-desacetyl-rifabutin				12	↑384 (↑309 to ↑474)	↑525 (↑408 to ↑669)	↑394 (↑304 to ↑504)

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose (mg)	Cobicistat or Ritonavir Booster Dose	N	% Change of Coadministered Drug Pharmacokinetic Parameters[b] (90% CI)		
					C_{max}	AUC	C_{min}
rosuvastatin[c]	10 single dose	150 single dose	Cobicistat 150 single dose	10	↑89 (↑48 to ↑142)	↑38 (↑13 to ↑67)	N/A
sertraline	50 single dose	150 once daily[b]	Cobicistat 150 once daily[b]	19	⇔	⇔	N/A
sofosbuvir	400/100/100 + 100 voxilaprevir[e] once daily	150 once daily[b]	cobicistat 150 once daily[b]	29	↑27 (↑9 to ↑48)	⇔	NC
GS-331007[d]					⇔	↑43 (↑39 to ↑47)	NC
velpatasvir					⇔	⇔	↑46 (↑30 to ↑64)
voxilaprevir					↑92 (↑63 to ↑126)	↑171 (↑130 to ↑ 219)	↑350 (↑268 to ↑450)

↑ = Increase; ↓ = Decrease; ⇔ = No Effect; NA = Not Applicable; NC = not calculated

a. All interaction studies conducted in healthy volunteers
b. Study conducted with GENVOYA
c. Study conducted with STRIBILD
d. The predominant circulating nucleoside metabolite of sofosbuvir
e. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients

In drug interaction studies conducted with elvitegravir, there was no clinically significant effect on the C_{max}, AUC, or C_{min} of R/S-methadone or telaprevir.

Cobicistat: Cobicistat is an inhibitor of cytochrome P450 (CYP3A), and is also a CYP3A substrate. Agents that are highly dependent on CYP3A metabolism and have high first pass metabolism are the most susceptible to large increases in exposure when coadministered with cobicistat. Agents that inhibit CYP3A may decrease the clearance of cobicistat, resulting in increased plasma concentration of cobicistat (see section 4.3 Contraindications).

Cobicistat is an inhibitor of the following transporter: p-glycoprotein (P-gp), BCRP, OATP1B1 and OATP1B3. Co-administration of STRIBILD with drugs that are substrates of P-gp, BCRP, OATP1B1 and OATP1B3 may result in increased plasma concentrations of such drugs.

Tenofovir disoproxil fumarate and emtricitabine: *In vitro* and clinical pharmacokinetic drug-drug interaction studies have shown that the potential for CYP mediated interactions involving emtricitabine and tenofovir with other medicinal products is low.
Emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No drug-drug interactions due to competition for renal excretion have been observed; however, coadministration of emtricitabine and tenofovir DF with drugs that are eliminated by active tubular secretion may increase concentrations of emtricitabine, tenofovir, and/or the coadministered drug.

Drugs that decrease renal function may increase concentrations of emtricitabine and/or tenofovir.

In drug interaction studies conducted with emtricitabine and with tenofovir DF, coadministration of emtricitabine and famciclovir had no effect on the C_{max} or AUC of either drug, coadministration of tenofovir and entecavir had no effect on the C_{max} or AUC of either drug, and coadministration of tenofovir and ribavirin had no effect on the C_{max} and AUC of entecavir or ribavirin.

STRIBILD: A drug interaction study for STRIBILD was performed with EPCLUSA® (sofosbuvir/velpatasvir).

The changes in pharmacokinetic parameters for sofosbuvir, GS-331007, and velpatasvir in the presence of STRIBILD are presented in Table 4.

Table 4 Drug Interactions: Changes in Pharmacokinetic Parameters for Sofosbuvir, its Predominant Circulating Metabolite GS-331007, and Velpatasvir in the Presence of STRIBILD[a]

Co-administered Drug	Dose of Co-administered Drug (mg)	Velpatasvir Dose (mg)	Sofosbuvir Dose (mg)	N	Mean Ratio (90% CI) of Sofosbuvir, GS-331007 and Velpatasvir PK With/Without Coadministered Drug No Effect=1.00			
						C_{ma}	AUC	C_{mi}
Elvitegravir/ cobicistat/ emtricitabine / tenofovir DF[b]	150/150/200/ 300 once daily	100 once daily	400 once daily	24	sofosbuvir	1.01 (0.85, 1.19)	1.24 (1.13, 1.37)	NA
					GS-331007	1.13 (1.07, 1.18)	1.35 (1.30, 1.40)	1.45 (1.38, 1.52)
					velpatasvir	1.05 (0.93, 1.19)	1.19 (1.07, 1.34)	1.37 (1.22, 1.54)

NA = not available/not applicable.
a. All interaction studies conducted in healthy volunteers.
b. Administered as STRIBILD (elvitegravir, cobicistat, emtricitabine and tenofovir DF fixed-dose combination).

The changes in pharmacokinetic parameters for STRIBILD in the presence of EPCLUSA are presented in Table 5.

Table 5 Changes in Pharmacokinetic Parameters for STRIBILD in the Presence of EPCLUSA[a]

	Dose of Co-administered Drug (mg)	Velpatasvir Dose (mg)	Sofosbuvir Dose (mg)	N	Mean Ratio (90% CI) of Coadministered Drug PK With/Without Sofosbuvir, Velpatasvir or EPCLUSA No Effect=1.00		
					C_{max}	AUC	C_{min}
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir DF[b]	elvitegravir 150 once daily	100 once daily	400 once daily	24	0.93 (0.86, 1.00)	0.93 (0.87, 0.99)	0.97 (0.91, 1.04)
	Cobicistat 150 once daily				1.11 (1.06, 1.17)	1.23 (1.17, 1.29)	1.71 (1.54, 1.90)
	emtricitabine 200 once daily				1.02 (0.97, 1.08)	1.01 (0.98, 1.04)	1.06 (1.01, 1.11)
	tenofovir DF 300 once daily				1.36 (1.25, 1.47)	1.35 (1.29, 1.42)	1.45 (1.39, 1.51)

NA = not available/not applicable.
a. All interaction studies conducted in healthy volunteers.
b. Administered as STRIBILD (elvitegravir, cobicistat, emtricitabine and tenofovir DF fixed-dose combination).

4.6 Fertility, Pregnancy and Lactation

Impairment of Fertility
No reproductive toxicity studies have been conducted with tenofovir DF, emtricitabine, and elvitegravir and cobicistat in combination.

Tenofovir disoproxil fumarate: Male and female rat fertility and mating performance or early embryonic development were unaffected by an oral tenofovir DF dose (600 mg/kg/day) that achieved systemic drug exposures that were in excess of the expected value in humans receiving the therapeutic dose (5-fold based on plasma AUC). There was, however, an alteration of the oestrous cycle in female rats.

Emtricitabine: Emtricitabine did not affect fertility in male rats or in female and male mice at respective approximate exposures (AUC) of 130 and 50 to 80 times the exposure in humans. The fertility of offspring was unaffected by treatment of mice from early gestation to the end of lactation (50 times the human exposure).

Elvitegravir: Elvitegravir did not affect fertility in male and female rats at a dose achieving greater than 10 fold higher exposures (AUC), than in humans with the therapeutic 150 mg daily dose.

Fertility was normal in the offspring of rats exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 18-fold higher than human exposures at the recommended 150 mg daily dose.

Cobicistat: Cobicistat did not affect fertility in male or female rats at daily exposures (AUC) greater than 4-fold higher than human exposures with the 150 mg daily dose.

Fertility was normal in the offspring of rats exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 1.2-fold higher than human exposures at the recommended 150 mg daily dose.

Use in Pregnancy
Pregnancy Category B3.

There are no well controlled clinical studies of STRIBILD in pregnant women. Because animal reproductive studies are not always predictive of human response, STRIBILD should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus and mother. Lower exposures of elvitegravir and cobicistat have been reported during pregnancy compared to postpartum. Closely monitor viral load during pregnancy.

Tenofovir disoproxil fumarate: Reproductive toxicity studies performed in rats and rabbits did not reveal any evidence of harm to the fetus due to tenofovir at respective exposures (AUC) of 4-13 and 66-fold the human exposure. Subcutaneous treatment of pregnant rhesus monkeys with a dose of 30 mg/kg/day of the tenofovir base during the last half of pregnancy resulted in reduced foetal serum phosphorus concentrations.

Emtricitabine: No evidence of embryofoetal toxicity or teratogenicity was observed in mice or rabbits at respective emtricitabine exposures (AUC) of 50 and 130 fold the clinical exposure. Impaired weight gain observed in pregnant rabbits at doses resulting in emtricitabine exposures (AUC) at least 33 times the clinical exposure was not associated with any adverse foetal effects.

Elvitegravir: Studies in animals have shown no evidence of teratogenicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with elvitegravir during pregnancy, there were no toxicologically significant effects on developmental endpoints. The exposures at the embryo-foetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 23 and 0.2 times higher than the exposure in humans at the recommended dose of 150 mg/day.

Cobicistat Studies in animals have shown no evidence of teratogenicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with cobicistat during pregnancy, there were no toxicologically significant effects on developmental endpoints. The exposures at the embryo-foetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 1.8 and 4.3 times higher than the exposure in humans at the recommended daily dose of 150 mg.

Use in Lactation
It is not known whether elvitegravir and cobicistat are excreted in human milk.
Studies in rats have demonstrated that elvitegravir and cobicistat are secreted into milk.

Tenofovir disoproxil fumarate: In humans, samples of breast milk obtained from five HIV-1 infected mothers show that tenofovir was secreted in human milk at low concentrations (estimated neonatal concentrations 128 to 266 times lower than the tenofovir IC_{50} (50% maximal

inhibitory concentration). Tenofovir associated risks, including the risk of developing viral resistance to tenofovir, in infants breastfed by mothers being treated with tenofovir disoproxil fumarate are unknown.

Emtricitabine: Samples of breast milk obtained from five HIV-1 infected mothers show that emtricitabine was secreted in human milk at estimated neonatal concentrations 3 to 12 times higher than the emtricitabine IC_{50} but 3 to 12 times lower than the C_{min} (minimal expected trough concentrations in adults) achieved from oral administration of emtricitabine. Breastfeeding infants whose mothers are being treated with emtricitabine may be at risk for developing viral resistance to emtricitabine. Other emtricitabine-associated risks in infants breastfed by mothers being treated with emtricitabine are unknown.

Because of the potential for both HIV transmission and for serious adverse events in nursing infants, mothers should be instructed not to breast feed if they are receiving STRIBILD.

4.7 Effects on Ability to Drive and Use Machines

No studies on the effects of STRIBILD on the ability to drive and use machines have been performed. However, patients should be informed that dizziness has been reported during treatment with STRIBILD.

4.8 Undesirable Effects

As STRIBILD contains tenofovir DF, emtricitabine, elvitegravir and cobicistat, adverse events associated with these individual antiretroviral agents may be expected to occur with the fixed combination tablet.

For additional safety information about VIREAD (tenofovir DF), EMTRIVA (emtricitabine) in combination with other antiretroviral agents, consult the Data Sheet for these products.

Treatment Naïve Patients

The safety assessment of STRIBILD is based on pooled data from 1408 patients in the Phase 3 trials Study GS-US-236-0102 and Study GS-US-236-0103 in antiretroviral treatment-naive HIV-1 infected adult patients. A total of 701 patients received STRIBILD once daily for 144 weeks.

The proportion of patients who discontinued treatment with STRIBILD, ATRIPLA or atazanavir/r + TRUVADA due to adverse events, regardless of severity, was 6.0%, 7.4% and 8.5%, respectively. The most common adverse reactions (incidence greater than or equal to 8%) occurring in patients receiving STRIBILD in Studies GS-US-236-0102 and GS-US-236-0103 include diarrhea, upper respiratory tract infection, and depression. See also Table 6 for the frequency of adverse reaction (Grade 2-4) occurring in at least 5% of subjects receiving STRIBILD in Studies GS-US-236-0102 and GS-US-236-0103.

Table 6 Treatment-Emergent Adverse Drug Reactions[a] (Grades 2-4) Reported in ≥ 5% of Patients Receiving STRIBILD in Studies GS-US-236-0102 and GS-US-236-0103 (Week 144 analysis)

	STRIBILD	ATRIPLA	Atazanavir/r + TRUVADA
	N=701	N=352	N=355
GASTROINTESTINAL DISORDERS			
Diarrhea	8%	8%	10%
INFECTIONS AND INFESTATIONS			
Upper respiratory tract infection	8%	7%	7%
Bronchitis	7%	4%	6%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Arthralgia	5%	2%	2%
NERVOUS SYSTEM DISORDERS			
Headache	5%	2%	4%
PSYCHIATRIC DISORDERS			
Depression	8%	10%	9%

a. Frequencies of adverse reactions are based on grade 2- 4 treatment-emergent adverse events, regardless of relationship to study drugs

Treatment-emergent adverse drug reactions of at least moderate intensity (≥ Grade 2) that occurred in less than 5% of patients treated with STRIBILD in Studies GS-US-236-0102 and GS-US-236-0103 include back pain, fatigue, nausea, vomiting, abdominal pain, dyspepsia, flatulence, dizziness, insomnia, abnormal dreams, renal failure, Fanconi syndrome acquired, blood creatinine increased, and rash.

In the clinical trials of STRIBILD over 144 weeks, 13 (1.9%) patients in the STRIBILD group (N=701) and 8 (2.3%) patients in the atazanavir + ritonavir + TRUVADA group (N=355) discontinued study drug due to a renal adverse reaction. Of these discontinuations, 7 in the STRIBILD group and 1 in the atazanavir + ritonavir + TRUVADA group occurred during the first 48 weeks. The renal adverse reactions seen with STRIBILD were consistent with previous experience with tenofovir disoproxil fumarate. Four (0.6%) patients who received STRIBILD developed laboratory findings consistent with proximal renal tubular dysfunction 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 patients had renal impairment (i.e. estimated creatinine clearance less than 70 mL per min) at baseline. The laboratory findings in these 4 patients with evidence of proximal tubulopathy improved without clinical consequence upon discontinuation of STRIBILD but did not completely resolve in all patients. Three (0.8%) patients who received atazanavir + ritonavir + TRUVADA developed laboratory findings consistent with proximal renal tubular dysfunction leading to discontinuation of atazanavir + ritonavir + TRUVADA after Week 96.

Additional adverse drug reactions observed with STRIBILD included suicidal ideation and suicide attempt (0.3%, 2 of 701), these two patients had a pre-existing history of depression or psychiatric illness.

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 102 and 103, decreases in estimated creatinine clearance occurred early in treatment with STRIBILD, after which they stabilized. The mean±SD 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 ATRIPLA, and -9.8±19.4 mL/min for ATV+RTV+TRUVADA.

Clinical Trials in Patients with Mild to Moderate Renal Impairment

In Study GS-US-236-0118, 33 HIV-1 infected treatment-naïve patients with mild to moderate renal impairment (eGFR by Cockcroft-Gault method between 50 and 89 mL/minute) were studied in an open-label clinical trial evaluating the safety of 48 weeks of treatment with STRIBILD. By Week 48 three (9.1%) patients all of whom had baseline eGFR between 50-60 mL/minute discontinued due to a renal adverse event; none developed laboratory findings consistent with proximal renal tubular dysfunction. After 48 weeks of treatment, the mean change in serum creatinine was 0.17 ± 0.14 mg/dL and the mean change in eGFR by Cockcroft-Gault method was -6.9 ± 9.0 mL/minute for STRIBILD. The renal safety of STRIBILD in Study GS-US-236-0118 in patients with mild to moderate renal impairment was consistent with the overall renal findings in Studies GS-US-236-102 and GS-US-236-103.

Virologically Supressed Patients

No new adverse reactions to STRIBILD through Week 48 were identified in virologically stably suppressed patients switching to STRIBILD from a regimen containing a ritonavir-boosted protease inhibitor (PI), a non-nucleoside reverse transcriptase inhibitor (NNRTI) or raltegravir. Overall, most adverse reactions were Grade 1; the frequency of adverse reactions (Grades 2-4) was 4% in the patients switching to STRIBILD (N=293) and 1% in the patients remaining on a ritonavir-boosted PI (N=140) in Study GS-US-236-0115, and 5% in the patients switching to STRIBILD (N=291) and 1% in the patients remaining on an NNRTI (N=143) in Study GS-US-236-0121, and 2% in the patients switching to STRIBILD (N=48) in Study GS-US-236-0123.

Tenofovir disoproxil fumarate and emtricitabine: In addition to the adverse drug reactions observed with STRIBILD, the following adverse drug reactions occurred in at least 5% of treatment-experienced or treatment-naive patients receiving emtricitabine or tenofovir DF with other antiretroviral agents in other clinical trials: fever, pain, nasopharyngitis, pneumonia, sinusitis, , myalgia, paresthesia, peripheral neuropathy (including peripheral neuritis and neuropathy), anxiety, increased cough, and rhinitis.

Skin discoloration has been reported with higher frequency among emtricitabine-treated subjects; it was manifested by hyperpigmentation on the palms and/or soles and was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

Laboratory Abnormalities: The frequency of treatment-emergent laboratory abnormalities (Grade 3-4) occurring in at least 2% ofpatients receiving STRIBILD in Studies 102 and 103 are presented in Table 7.

Table 7: Laboratory Abnormalities (Grades 3-4) Reported in ≥ 2% of Patients Receiving STRIBILD in Studies 102 and 103 (Week 144 analysis)

	STRIBILD	ATRIPLA	Atazanavir/r + TRUVADA
Laboratory Parameter Abnormality	N=701	N=352	N=355
AST (>5.0 x ULN)	3%	6%	6%
ALT (>3.0 x ULN)	2%	5%	4%
Amylase* (>2.0 x ULN)	3%	3%	5%
Creatine Kinase (≥ 10.0 x ULN)	8%	15%	11%
Urine RBC (Hematuria) (> 75 RBC/HPF)	4%	2%	4%

* For patients with serum amylase > 1.5 x upper limit of normal, lipase test was also performed. The frequency of increased lipase (Grade 3-4) occurring in STRIBILD (N=69), ATRIPLA (N=40), and Atazanavir/r + TRUVADA (N=38) was 17%, 15%, and 24%, respectively.

Tenofovir disoproxil fumarate or emtricitabine: In addition to the laboratory abnormalities observed with STRIBILD, the following laboratory abnormalities have been previously reported in patients treated with emtricitabine or tenofovir DF with other antiretroviral agents in other clinical trials: Grade 3 or 4 laboratory abnormalities of ALT (M: >215 U/L; F: >170 U/L), alkaline phosphatase (>550 U/L), bilirubin (>2.5 x ULN), serum glucose (<40 or >250 mg/dL), glycosuria (≥3+), neutrophils (<750/mm^3), fasting cholesterol (>240 mg/dL), and fasting triglycerides (>750 mg/dL).

POST MARKETING SURVEILLANCE

In addition to adverse events reported from clinical trials, the following events have been reported in post marketing surveillance. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Tenofovir disoproxil fumarate
IMMUNE SYSTEM DISORDERS
Allergic reaction (including angioedema), immune reconstitution syndrome

METABOLISM AND NUTRITION DISORDERS
Lactic acidosis, hypokaleamia, hypophosphataemia

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS
Dyspnoea

GASTROINTESTINAL DISORDERS
Increased amylase, abdominal pain, pancreatitis

HEPATOBILIARY DISORDERS
Hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT, gamma GT)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS
Rash

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS
Rhabdomyolysis, muscular weakness, myopathy, osteomalacia (manifested as bone pain and infrequently contributing to fractures).

RENAL AND URINARY DISORDERS
Increased creatinine, renal insufficiency, renal failure, acute renal failure, Fanconi syndrome, proximal renal tubulopathy, nephrogenic diabetes insipidus, proteinuria, acute tubular necrosis, polyuria, interstitial nephritis (including acute cases).

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS
Asthaenia

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), hypokalaemia, muscular weakness, myopathy, hypophosphataemia. These events are not considered to be causally associated with tenofovir DF therapy in the absence of proximal renal tubulopathy.

Exacerbations of Hepatitis after Discontinuation of Treatment
In HIV infected patients co-infected with HBV, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of treatment (see section 4.4 Special Warnings and Precautions for Use).

Emtricitabine
IMMUNE SYSTEM DISORDERS
Immune reconstitution syndrome

4.9 Overdose

If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with STRIBILD consists of general supportive measures including monitoring of vital signs and ECG (QT interval) as well as observation of the clinical status of the patient.
For information on the management of overdose, contact the Poison Information Centre on 0800 764 766.

Tenofovir disoproxil fumarate: Clinical experience of doses higher than the therapeutic dose of VIREAD 300 mg is available from two studies. In one study, intravenous tenofovir, equivalent to 16.7 mg/kg/day of tenofovir DF, was administered daily for 7 days. In the second study, 600 mg of tenofovir DF was administered to patients orally for 28 days. No unexpected or severe adverse reactions were reported in either study. The effects of higher doses are not known.

Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of VIREAD, a four-hour haemodialysis session removed approximately 10% of the administered tenofovir dose.

Emtricitabine: Limited clinical experience is available at doses higher than the therapeutic dose of EMTRIVA. In one clinical pharmacology study single doses of emtricitabine 1200 mg were administered to 11 patients. No severe adverse reactions were reported. The effects of higher doses are not known.

Haemodialysis treatment removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

Elvitegravir: Limited clinical experience is available at doses higher than the therapeutic dose of elvitegravir. In one study, boosted elvitegravir equivalent to 2 times the therapeutic dose of 150 mg once daily for 10 days was administered to 42 healthy subjects. No severe adverse reactions were reported. The effects of higher doses are not known. As elvitegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis**.**

Cobicistat: Limited clinical experience is available at doses higher than the therapeutic dose of cobicistat. In two studies, single dose of cobicistat 400 mg was administered to a total of 60 healthy subjects. No severe adverse reactions were reported. The effects of higher doses are not known. As cobicistat is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis**.**

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations, ATC code: J05AR09.

Mechanism of action

STRIBILD is a fixed-dose combination of antiviral drugs tenofovir DF, emtricitabine and elvitegravir, boosted by the pharmacokinetic enhancer cobicistat.

Tenofovir disoproxil fumarate: is an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate. Tenofovir DF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 RT by competing with the natural substrate deoxyadenosine 5′-triphosphate and, after incorporation into deoxyribonucleic acid (DNA), by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Emtricitabine*:* a synthetic nucleoside analogue of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 RT by competing with the natural substrate deoxycytidine 5'-triphosphate by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5′-triphosphate is a weak inhibitor of mammalian DNA polymerases α, β, ε and mitochondrial DNA polymerase γ.

Elvitegravir: 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. Elvitegravir does not inhibit human topoisomerases I or II.

Cobicistat: Cobicistat is a selective mechanism-based inhibitor of cytochromes P450 of the CYP3A subfamily (primarily CYP3A4 and CYP3A5). 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.

Antiviral activity *in vitro*

Tenofovir disoproxil fumarate, emtricitabine and elvitegravir/cobicistat: The triple combination of tenofovir, emtricitabine, and elvitegravir demonstrated synergistic antiviral activity in cell culture. Antiviral synergy was maintained for tenofovir, emtricitabine, and elvitegravir when tested in the presence of cobicistat.

Tenofovir disoproxil fumarate: The *in vitro* 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 IC_{50} (50% inhibitory concentration) values for tenofovir were in the range of 0.04 to 8.5 µM. In drug combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (NRTIs) (abacavir, didanosine, lamivudine (3TC), stavudine (d4T), zalcitabine, zidovudine (AZT)), non-nucleoside reverse transcriptase inhibitors (NNRTIs) (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Tenofovir displayed antiviral activity *in vitro* against HIV-1 clades A, B, C, D, E, F, G and O (IC_{50} values ranged from 0.5 to 2.2 µM). In addition, tenofovir has also been shown to be active *in vitro* against HIV-2, with similar potency as observed against HIV-1.

Emtricitabine: The *in vitro* antiviral activity of emtricitabine against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells (PMBCs). The IC_{50} value for emtricitabine was in the range of 0.0013 to 0.64 µM (0.0003 to 0.158 µg/mL). In drug combination studies of emtricitabine with NRTIs (abacavir, 3TC, d4T, zalcitabine, AZT), NNRTIs (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Emtricitabine displayed antiviral activity *in vitro* against HIV-1 clades A, C, D, E, F, and G (IC_{50} values ranged from 0.007 to 0.075 µM) and showed strain specific activity against HIV-2 (IC_{50} values ranged from 0.007 to 1.5 µM).

Elvitegravir: 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). The antiviral activity of elvitegravir with antiretroviral drugs in two-drug combination studies was additive to synergistic when combined with nucleoside reverse transcriptase inhibitors (NRTIs abacavir, didanosine, emtricitabine, 3TC, d4T, tenofovir, or AZT); NNRTIs (efavirenz, etravirine, or nevirapine); protease inhibitors (amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, or tipranavir); the INSTI raltegravir; the fusion inhibitor enfuvirtide, or the CCR5 co-receptor antagonist, maraviroc. No antagonism was observed for these combinations.

Elvitegravir did not show inhibition of replication of HBV or HCV *in vitro*.

Cobicistat: Cobicistat has no detectable antiviral activity against HIV-1, HBV or HCV and does not antagonise the antiviral effects of elvitegravir, emtricitabine, or tenofovir.

Drug Resistance

<u>In Cell Culture:</u>

Tenofovir disoproxil fumarate: HIV-1 isolates with reduced susceptibility to tenofovir have been selected *in vitro*. These viruses expressed a K65R mutation in reverse transcriptase and showed a 2 to 4 fold reduction in susceptibility to tenofovir. In addition, a K70E mutation in HIV-RT has been selected clinically by tenofovir disoproxil fumarate and results in low-level reduced susceptibility to abacavir, emtricitabine, tenofovir and lamivudine.

Emtricitabine: Emtricitabine-resistant isolates of HIV have been selected *in vitro.* Genotypic analysis of these isolates showed that the reduced susceptibility to emtricitabine was associated with a mutation in the HIV reverse transcriptase gene at codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I).

Elvitegravir: HIV-1 isolates with reduced susceptibility to elvitegravir have been selected in cell culture. Reduced susceptibility to elvitegravir was most commonly associated with the primary integrase substitutions T66I, E92Q, and Q148R. Additional integrase substitutions observed in cell culture selection included H51Y, F121Y, S147G, S153Y, E157Q, and R263K.
Elvitegravir showed cross-resistance in vitro to the raltegravir selected mutations T66A/K, Q148H/K, and N155H.

Cobicistat: No *in vitro* resistance can be demonstrated with cobicistat due to its lack of antiviral activity.

<u>In Clinical Studies:</u>

In Treatment-Naïve Patients

Tenofovir disoproxil fumarate, emtricitabine and elvitegravir/cobicistat:
In a pooled analysis of antiretroviral-naïve patients receiving STRIBILD in clinical trials GS-US-236-0102 and GS-US-236-0103, genotyping was performed on plasma HIV-1 isolates from all patients with confirmed virologic failure or had HIV-1 RNA > 400 copies/mL at virologic failure at Week 48, Week 96 and 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 mutations 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 resistance development, 13 occurred through Week 48, 3 between Week 48-Week 96, and 2 between Week 96-Week 144 of treatment. The mutations that emerged were M184V/I (N=17) and K65R (N=5) in reverse transcriptase; and T66I (n=2), E92Q (N=9), Q148R (N=3), T97A (N=1) and N155H (N=5) in integrase. Other mutations 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 mutations to elvitegravir developed resistance mutations to both emtricitabine and elvitegravir. In phenotypic analyses of patients in the resistance analysis population, 13/42 (31%) patients had HIV-1

isolates with reduced susceptibility to elvitegravir, 17/42 (40%) had reduced susceptibility to emtricitabine, and 2/42 (5%) had reduced susceptibility to tenofovir.

In Study GS-US-236-0103, 27 patients treated with STRIBILD had the NNRTI-associated K103N substitution in RT at baseline and had virologic success (82% at Week144) similar to the overall population (78%), and no emergent resistance to elvitegravir, emtricitabine or tenofovir DF.

In Virologically Supressed Patients

Through Week 48, no patients who switched to STRIBILD in Study GS-US-236-0115 (0 of 290 subjects), Study GS-US-236-0121 (0 of 290 patients), or Study GS-US-236-0123 (0 of 48 subjects) developed genotypic or phenotypic resistance to STRIBILD.

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

Cross-resistance:

Tenofovir disoproxil fumarate, emtricitabine, elvitegravir / cobicistat: No significant cross-resistance has been demonstrated for elvitegravir-resistant HIV-1 isolates and emtricitabine or tenofovir, or for emtricitabine- or tenofovir-resistant isolates and elvitegravir. Substantial cross-resistance was observed between elvitegravir-resistant HIV-1 isolates and raltegravir, and between emtricitabine-resistant isolates and lamivudine. These patient isolates remained susceptible to PIs, NNRTIs, and most other NRTIs.

Tenofovir disoproxil fumarate: The K65R and K70E mutations selected by tenofovir also show reduced susceptibility to abacavir, didanosine, emtricitabine and 3TC. Therefore, cross-resistance among these drugs may occur in patients whose virus harbours the K65R mutation. Patients with 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 DF. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the reverse transcriptase showed reduced susceptibility to tenofovir.

Emtricitabine: Emtricitabine-resistant isolates (M184V/I) were cross-resistant to 3TC and zalcitabine but retained sensitivity to abacavir, didanosine, d4T, tenofovir, AZT and NNRTIs (delavirdine, efavirenz, and nevirapine). HIV-1 isolates containing the K65R mutation, selected *in vivo* by abacavir, didanosine and tenofovir demonstrated reduced susceptibility to inhibition by emtricitabine. Viruses harbouring mutations conferring reduced susceptibility to d4T and AZT (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to emtricitabine. HIV-1 containing the K103N mutation or substitutions associated with resistance to NNRTI were susceptible to emtricitabine.

Elvitegravir: Elvitegravir-resistant viruses show varying degrees of cross-resistance to the integrase strand transfer inhibitor raltegravir depending on the type and number of mutations. Viruses expressing the T66I/A mutations maintain susceptibility to raltegravir, while most other patterns showed reduced susceptibility to raltegravir.

Pharmacodynamics

Effects on Electrocardiogram
The electrocardiographic effects of cobicistat were determined in a study of 48 healthy adult subjects. Cobicistat did not prolong QTcF interval at exposures two- and four-fold above the recommended therapeutic dose. A modest increase in PR interval (+9.6 msec) occurred around C_{max}, three to five hours after dosing with 250 mg of cobicistat. This finding was not considered to be clinically significant.

In a thorough QT/QTc study in 126 healthy subjects, elvitegravir at the therapeutic or supratherapeutic approximately two times the recommended therapeutic dose did not affect the QT/QTc interval and did not prolong the PR interval. Viruses expressing elvitegravir or raltegravir resistance mutations maintain susceptibility to dolutegravir.

Clinical Data

CLINICAL TRIALS

The efficacy of STRIBILD in HIV-1 infected treatment-naïve patients is based on the analyses of 144 week data from two randomised, double-blind, active-controlled trials Study GS-US-236-0102 and Study GS-US-236-0103 (N=1408). The efficacy of STRIBILD in HIV-1 infected virologically-suppressed patients is based on the analyses of 48-week data from two randomised, open-label, controlled studies, Study GS-US-236-0115, Study GS-US-236-0121, and a single-group open-label study, Study GS-US-236-0123, (N=910) 628 receiving STRIBILD). Patients in all five studies had estimated creatinine clearance > 70 mL/min at screening.

Treatment Naïve Patients
In Study GS-US-236-0102, subjects were randomised in a 1:1 ratio to receive either STRIBILD (tenofovir DF 300 mg /emtricitabine 200 mg/elvitegravir 150 mg/cobicistat 150 mg N=348) once daily or ATRIPLA® (tenofovir DF 300 mg/emtricitabine 200 mg/ efavirenz 600 mg N=352) once daily. The mean age was 38 years (range 18-67), 89% were male, 63% were White, and 28% were Black. The mean baseline plasma HIV-1 RNA was 4.8 $\log_{10}$ copies/mL (range 2.6–6.5). The mean baseline CD4+ cell count was 386 cells/mm^3 (range 3–1348) and 13% had CD4+ cell counts <200 cells/mm^3. Thirty-three percent of subjects had baseline viral loads >100,000 copies/mL.

In Study GS-US-236-0103, patients were randomised in a 1:1 ratio to receive either STRIBILD (tenofovir DF 300 mg /emtricitabine 200 mg/elvitegravir 150 mg/cobicistat150 mg, N=353) once daily or ATV/r (atazanavir 300 mg + ritonavir 100 mg) + TRUVADA (tenofovir DF 300 mg/emtricitabine 200 mg) (N=355) once daily. The mean age was 38 years (range 19-72), 90% were male, 74% were White, 17% were Black, and 5% were Asian. The mean baseline plasma HIV-1 RNA was 4.8 $\log_{10}$ copies/mL (range 1.7-6.6). The mean baseline CD4+ cell count was 370 cells/mm^3 (range 5-1132) and 13% had CD4+ cell count <200 cells/mm^3. Forty percent of subjects had baseline viral loads >100,000 copies/mL.

In both studies, patients were stratified by baseline HIV-1 RNA (≤ 100,000 copies/mL or >100,000 copies/mL).

Treatment outcomes of Study GS-US-236-0102 and Study GS-US-236-0103 through 144 weeks are presented in Table 8.

Table 8 Virologic Outcome of Randomised Treatment of Study GS-US-236-0102 and Study GS-US-236-0103 at Week 48[a] and Week 144[b]

	At Week 48				At 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)	ATRIPLA (N=352)	STRIBILD (N=353)	ATV+RTV + TRUVADA (N=355)	STRIBILD (N=348)	ATRIPLA (N=352)	STRIBILD (N=353)	ATV+RTV + TRUVADA (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	7%	7%	5%	5%	7%	10%	8%	7%
No Virologic Data in Week 48 or 144 Window								
Discontinued Study Drug Due to AE or Death[b]	3%	5 %	3%	5%	6%	8%	6%	8%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[c]	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 1050 (inclusive).
c. Includes patients who had ≥50 copies/mL in the Week 48 or 144 windows, patients who discontinued early due to lack or loss of efficacy, patients 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 patients 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 noninferiority criteria in achieving HIV-1 RNA < 50 copies/mL when compared to ATRIPLA and when compared to ATV + RTV + TRUVADA.

In Study GS-US-236-0102, the mean increase from baseline in CD4+ cell count at Week 144 was 321 cells/mm^3 in the STRIBILD treated patients and 300 cells/mm^3 in the ATRIPLA-treated patients. In Study GS-US-236-0103, the mean increase from baseline in CD4+ cell count at

Week 144 was 280 cells/mm^3 in the STRIBILD-treated patients and 293 cells/mm^3 in the ATV + RTV + TRUVADA-treated patients.

Virologically Supressed Patients

In Study GS-US-236-0115 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 (HIV-1 RNA <50 copies/mL) on a ritonavir-boosted PI in combination with TRUVADA for at least 6 months prior to screening. Patients were randomised in a 2:1 ratio to either switch to STRIBILD (STRIBILD arm, N = 293, randomised or dosed) or stay on their baseline antiretroviral regimen for 48 weeks (PI + RTV + TRUVADA arm, N = 140, randomised or dosed). Patients had a mean age of 41 years (range 21-76), 86% were male, 80% were White, and 15% were Black. The mean baseline CD4+ cell count was 610 cells per mm^3 (range 74-1919). At screening patients were receiving atazanavir (40%), darunavir (40%), lopinavir (17%), fosamprenavir (3%), or saquinavir (<1%) as the PI in their regimen.

In 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 (HIV-1 RNA <50 copies/mL) on a NNRTI in combination with TRUVADA for at least 6 months prior to screening. Patients were randomised in a 2:1 ratio to either switch to STRIBILD (STRIBILD arm, N = 291, randomised and dosed), or stay on their baseline antiretroviral regimen for 48 weeks (NNRTI +TRUVADA arm, N = 143, randomised and dosed). Patients had a mean age of 41 years (range 20-72), 93% were male, 78% were White, and 17% were Black. The mean baseline CD4+ cell count was 588 cells per mm^3 (range 100-1614). Randomisation was stratified by use of efavirenz in the baseline regimen. At screening patients were receiving efavirenz (78%) (predominantly as ATRIPLA [74%]), nevirapine (17%), rilpivirine (4%) (as EVIPLERA [4%]), or etravirine (1%) as the NNRTI in their regimen.

Virologic outcomes of Study GS-US-236-0115 and Study GS-US-236-0121 are presented in Table 9. Five treated patients were excluded from the efficacy analysis: in Study GS-US-236-0115, three STRIBILD patients had protocol-prohibited documented resistance and one PI + RTV + TRUVADA patient was not on a protease inhibitor-based regimen at screening; in Study GS-US-236-0121, one STRIBILD patient had protocol-prohibited documented resistance.

Table 9 Virologic Outcomes of Randomised Treatment in Study GS-US-236-0115 and Study GS-US-236-0121 at Week 48

	Study GS-US-236-0115[a]		Study GS-US-236-0121[a]	
	STRIBILD (N=290)	**PI+RTV+TRUVADA** (N=139)	**STRIBILD** (N=290)	**NNTRI+TRUVADA** (N=143)
Virologic Success HIV-1 RNA < 50 copies/mL	94%	87%	93%	88%
Treatment Difference	6.7% (95% CI, 0.4%, 13.7%)		5.3% (95% CI, -0.5%, 12.0%)	
Virologic Failure[b]	1%	1%	1%	1%
No Virologic Data in Week 48	6%	12%	6%	11%
Discontinued Study Drug Due to AE or Death[c]	2%	1%	2%	1%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[d]	4%	10%	4%	9%
Missing Data During Window but on Study Drug	0%	0%	0%	1%

a. Week 48 window is between Day 295 and 378 (inclusive).
b. Includes patients who had ≥ 50 copies/mL in the Week 48 window, patients who discontinued early due to lack or loss of efficacy, patients who discontinued for reasons other than an adverse event, death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥50 copies/mL.
c. 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.
d. Includes patients who discontinued for reasons other than an adverse event, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up.

In Study GS-US-236-0115, the mean increase from baseline in CD4+ cell count at Week 48 was 40 cells per mm^3 in the STRIBILD-treated patients and 32 cells per mm^3 in the PI + RTV + TRUVADA-treated patients. In Study GS-US-236-0121, 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 per mm^3 in the NNTRI + TRUVADA-treated patients.

In Study GS-US-236-0123 patients had to have previously only received raltegravir in combination with TRUVADA as their first antiretroviral regimen for at least six months. Patients had to be stably suppressed for at least 6 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

Solubility
Tenofovir DF is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in water at 25 °C. The partition coefficient (*log p*) for tenofovir disoproxil is 1.25 and the pKa is 3.75.

Emtricitabine is a white to off-white crystalline powder with a solubility of approximately 112 mg/mL in water at 25 ^{o}C. The partition coefficient (*log p*) for emtricitabine is -0.43 and the pKa is 2.65.

Elvitegravir is a white to pale yellow solid with a solubility of less than 0.5 µg/mL in water at 20 °C. The partition coefficient (*log p*) for elvitegravir is 4.5 and the pKa is 6.6.

Cobicistat is a white to pale yellow solid with a solubility of 0.08 mg/mL in water with pH 6.8 phosphate buffer at 25 °C. The partition coefficient (*log p*) for cobicistat is 4.3 and the pKa is 6.4.

Tenofovir disoproxil fumarate, emtricitabine and elvitegravir/cobicistat: Following oral administration of STRIBILD with food in healthy subjects, peak plasma concentrations were observed 4.0 to 4.5 hours post-dose for elvitegravir and cobicistat, 2.5 hours post-dose for emtricitabine, and three hours for tenofovir following the rapid conversion of tenofovir DF. The steady-state mean C_{max}, AUC_{tau}, and C_{trough} (mean ± standard deviation [SD]) following multiple doses of STRIBILD in HIV-1 infected subjects, respectively, were 1.7 ± 0.39 µg/mL, 23 ± 7.5 µg•hr/mL, and 0.45 ± 0.26 µg/mL, respectively for elvitegravir, which provided an 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•hr/mL, and 0.05 ± 013 µg/mL respectively for cobicistat, 1.9 ± 0.5 µg/mL, 13 ± 4.5 µg•hr/mL, and 0.14 ± 0.25 µg/mL respectively for emtricitabine, and 0.45 ± 0.16 µg/mL, 4.4 ± 2.2 µg•hr/mL, and 0.1 ± 0.08 µg/mL respectively for tenofovir.

Tenofovir disoproxil fumarate: The pharmacokinetic properties of tenofovir DF are summarized in Table 1. Following oral administration of VIREAD, maximum tenofovir serum concentrations are achieved in 1.0 ± 0.4 hour. *In vitro* binding of tenofovir to human plasma proteins is <0.7% and is independent of concentration over the range of 0.01 to 25 µg/mL. Approximately 70 to 80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of VIREAD, the terminal elimination half-life of tenofovir is approximately 17 hours.

Emtricitabine: The pharmacokinetic properties of emtricitabine are summarized in Table 10. Following oral administration of EMTRIVA, emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1 to 2 hours post-dose. *In vitro* binding of emtricitabine to human plasma proteins is <4% and is independent of concentration over the range of 0.02 to 200 µg/mL. Following administration of radiolabelled emtricitabine approximately 86% is recovered in the urine and 13% is recovered as metabolites. The metabolites of emtricitabine include 3′-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of EMTRIVA, the plasma emtricitabine half-life is approximately 10 hours.

Table 10. Single Dose Pharmacokinetic Parameters for Tenofovir and Emtricitabine in Adults[1]

	Tenofovir	Emtricitabine
Fasted Oral Bioavailability (%)	25	93
Plasma Terminal Elimination Half-Life (hr)	17	10
C_{max} (µg/mL)	0.30 ± 0.09	1.8 ± 0.7[2]
AUC (µg*hr/mL)	2.29 ± 0.69	10.0 ± 3.1[2]
CL/F (mL/min)	1043 ± 115	302 ± 94
CL_{renal} (mL/min)	243 ± 33	213 ± 89

1. Data presented as mean values.
2. Data presented as steady state values.

Elvitegravir: Elvitegravir is 98% to 99% bound to human plasma proteins and binding is independent of drug concentration over the range of 1 ng/mL to 1.6 µg/mL. The mean plasma to blood drug concentration ratio was 1.37. Elvitegravir undergoes primarily oxidative metabolism via CYP3A, and is secondarily glucuronidated via uridine disphosphate glucuronyosyltransferase (UGT) 1A1/3 enzymes. 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. 94.8% of the dose was recovered in feces, consistent with the hepatobiliary excretion of elvitegravir; 6.7% of the administered dose was recovered in urine as unchanged elvitegravir. The median terminal plasma half-life of elvitegravir following administration of STRIBILD is approximately 12.9 hours. Elvitegravir plasma exposures are non-linear and less than dose proportional, likely due to solubility-limited absorption.

Cobicistat: Cobicistat is 97% to 98% bound to human plasma proteins and the mean plasma to blood drug concentration ratio was 2.

Cobicistat is metabolized via CYP3A (major)- and CYP2D6 (minor)-mediated oxidation and does not undergo glucuronidation. Following oral administration of [14C]cobicistat, 99% of circulating radioactivity in plasma was unchanged cobicistat. Low levels of metabolites are observed in urine and feces and do not contribute to the CYP3A inhibitory activity of cobicistat. Eighty-six percent and 8.2% of the dose were recovered in feces 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 IC95 for wild-type HIV-1 virus. Cobicistat exposures are non-linear and greater than dose-proportional over the dose range of 50 to 400 mg, consistent with a mechanism-based CYP3A inhibitor.

Effect of food

Tenofovir disoproxil fumarate, emtricitabine, elvitegravir / cobicistat: 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 the C_{max} and AUC increased 22% and 36% respectively with a light meal and 56% and 91% respectively 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.

Age, Gender and Ethnicity
No clinically relevant pharmacokinetic differences due to gender or ethnicity have been identified for cobicistat-boosted elvitegravir, emtricitabine, or tenofovir DF (see section 4.4 Special Warnings and Precautions for Use).

The pharmacokinetics of elvitegravir or cobicistat in paediatric patients have not been established. Pharmacokinetics of elvitegravir, cobicistat, emtricitabine and tenofovir have not been fully evaluated in the elderly (65 years of age and older).

No clinically relevant pharmacokinetic differences have been observed between men and women for cobicistat-boosted elvitegravir, emtricitabine and tenofovir DF.

Patients with Impaired Renal Function

Tenofovir disoproxil fumarate and emtricitabine: 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 (ESRD) requiring dialysis, C_{max}, and $AUC_{0-\infty}$ of emtricitabine and tenofovir were increased (see section 4.4 Special Warnings and Precautions for Use).

Elvitegravir and cobicistat: A study of the pharmacokinetics of cobicistat-boosted elvitegravir was performed in non-HIV-1 infected subjects with severe renal impairment (estimated 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.

Patients with Hepatic Impairment
The pharmacokinetics of STRIBILD have not been studied in patients with hepatic impairment.

Tenofovir disoproxil fumarate and emtricitabine: The pharmacokinetics of tenofovir following a 300 mg dose of VIREAD have been studied in non-HIV infected patients with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. The pharmacokinetics of emtricitabine have not been studied in patients with hepatic impairment; however, emtricitabine is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.

Elvitegravir and cobicistat: Both elvitegravir and cobicistat are primarily metabolized 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 dosage 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.

Hepatitis B and/or hepatitis C virus co-infection
The pharmacokinetics of tenofovir DF and emtricitabine was not fully evaluated in hepatitis B (HBV) and/or C (HCV) co-infected patients. Limited data from population pharmacokinetic analysis with 24 patients indicated that HBV and/or HCV infection had no clinically relevant effect on the exposure of boosted elvitegravir.

5.3 Preclinical Safety Data

Tenofovir disoproxil fumarate: Tenofovir and tenofovir DF administered in toxicology studies to rats, dogs and monkeys at exposures (based on AUCs) greater than or equal to 6-fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

Evidence of renal toxicity was noted in 4 animal species. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2 to 20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablet core: lactose monohydrate, cellulose-microcrystalline (E460), silicon dioxide, croscarmellose sodium, hyprolose, magnesium stearate (E572), sodium lauryl sulphate.

Film-coating: indigo carmine (FD&C blue #2) aluminum lake, macrogol 3350, polyvinyl alcohol, talc, titanium dioxide (E171), yellow iron oxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

3 years

6.4 Special Precautions for Storage

STRIBILD should be stored below 30°C.

6.5 Nature and Contents of Container

STRIBILD is supplied in high density polyethylene (HDPE) bottles containing 30 tablets and a silica gel desiccant, polyester coil and is closed with a child resistant closure.

6.6 Special Precautions for Disposal

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

7 MEDICINE SCHEDULE

Prescription Only Medicine

8 SPONSOR

Gilead Sciences (NZ)

Grant Thornton New Zealand Limited
L4, 152 FanshaweStreet,
Auckland1010
New Zealand

Tel: 0800 443 933

9 DATE OF FIRST APPROVAL

22 February 2013

10 DATE OF REVISION OF THE TEXT

05 February 2019

Summary table of changes

Section changed	Summary of new information
All	Reformatted Data Sheet to new template
4.3	Revised to clarify the mechanism of interaction (CYP3A) for drugs contraindicated with cobicistat.
4.4	Addition of VOSEVI (sofosbuvir/velpatasvir/voxilaprevir) to special warning and precautions for Use with Hepatitis C Virus Antiviral Agents
4.5	Update of drug interaction information with direct oral anticoagulants, corticosteroids and with sofosbuvir/velpatasvir/voxilaprevir
4.5	Add drug interaction information for Sertraline, Corticosteroid, Hepatitis C Virus Antiviral Agents and Hormel Contraceptives
4.6	Pregnancy: Addition of elvitegravir and cobicistat exposure during pregnancy information.
6.1	Revised ingredient name to hyprolose and lactose monohydrate
8	Update NZ sponsor address and add telephone number