Product Monograph

PrSTRIBILD®

(elvitegravir/cobicistat/emtricitabine/ tenofovir disoproxil fumarate) tablets

150 mg elvitegravir
150 mg cobicistat
200 mg emtricitabine
300 mg tenofovir disoproxil fumarate

Antiretroviral Agent

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HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet elvitegravir 150 mg / cobicistat 150 mg / emtricitabine 200 mg / tenofovir disoproxil fumarate 300 mg	Lactose monohydrate *For a complete listing, see the **DOSAGE FORMS, COMPOSITION, AND PACKAGING** section.*

INDICATIONS AND CLINICAL USE

STRIBILD (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) is indicated for use as a complete regimen for the treatment of adults aged 18 years and older infected with HIV-1 with no known mutations to the integrase inhibitor class, tenofovir or emtricitabine.

The safety and efficacy of STRIBILD has not been established in patients with a prior history of virologic failure.

Geriatrics (>65 years of age):

Clinical studies of STRIBILD did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from adult patients < 65 years of age.

Pediatrics (<18 years of age):

Safety and effectiveness in children less than 18 years of age have not been established.

CONTRAINDICATIONS

STRIBILD is contraindicated in patients with known hypersensitivity to any of the components of the product. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

Coadministration of STRIBILD 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. Coadministration with the drugs listed in Table 1 is contraindicated due to the potential for serious and/or life-threatening events or loss of virologic response and possible resistance to STRIBILD. See also **DRUG INTERACTIONS, Drug-Drug Interactions.**

Table 1. Drugs That Are Contraindicated with STRIBILD

Drug Class	Drugs within class that are contraindicated with STRIBILD	Clinical Comment
Alpha 1-adrenoreceptor antagonists	alfuzosin	Potential for increased alfuzosin concentrations, which can result in hypotension.
Anticonvulsants	carbamazepine, phenobarbital, phenytoin	Potential for decreased cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance.
Antihistamines	astemizole*, terfenadine*	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimycobacterials	rifampin	Rifampin is a potent inducer of CYP450 metabolism. STRIBILD should not be used in combination with rifampin, as this may cause significant decrease in the plasma concentration of elvitegravir and cobicistat. This may result in loss of therapeutic effect and development of resistance to STRIBILD.
Antipsychotics	lurasidone pimozide	Potential for serious and/or life-threatening reactions. Potential for serious and/or life-threatening events such as cardiac arrhythmias.
Benzodiazepines	orally administered midazolam*, triazolam	Triazolam and orally administered midazolam are extensively metabolized by CYP3A4. Coadministration of triazolam or orally administered midazolam with STRIBILD may cause large increases in the concentration of these benzodiazepines. The potential exists for serious and/or life threatening events such as prolonged or increased sedation or respiratory depression.
Beta 2-adrenoceptor agonist	salmeterol	Coadministration of salmeterol with STRIBILD may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Direct oral anticoagulants	apixaban, rivaroxaban	Apixaban and rivaroxaban are primarily metabolized by CYP3A4 and transported by P-gp. Coadministration with STRIBILD may result in increased plasma concentrations of apixaban or rivaroxaban, which may lead to an increased bleeding risk.
Ergot derivatives	dihydroergotamine, ergonovine, ergotamine, methylergonovine*	Potential for serious and/or life-threatening events such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI motility agents	cisapride*	Potential for serious and/or life-threatening events such as cardiac arrhythmias.
Herbal products	St. John's Wort (*Hypericum perforatum*)	Patients taking STRIBILD should not use products containing St. John's wort because coadministration may result in reduced plasma concentrations of elvitegravir and cobicistat. This may result in loss of therapeutic effect and development of resistance.

Drug Class	Drugs within class that are contraindicated with STRIBILD	Clinical Comment
HMG-CoA reductase inhibitors	lovastatin, simvastatin	Potential for serious reactions such as myopathy, including rhabdomyolysis.
PDE-5 inhibitors	sildenafil†	A safe and effective dose in combination with STRIBILD has not been established for sildenafil (REVATIO®) when used for the treatment of pulmonary hypertension. There is increased potential for sildenafil-associated adverse events (which include visual disturbances, hypotension, priapism, and syncope).

*Not marketed in Canada.
†For the treatment of pulmonary arterial hypertension

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Lactic Acidosis and Severe Hepatomegaly with Steatosis**

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs including tenofovir disoproxil fumarate (tenofovir DF), a component of STRIBILD, in combination with other antiretrovirals (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/ Pancreatic**).

- **Post-Treatment Exacerbation of Hepatitis**

STRIBILD is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of STRIBILD have not been established in patients coinfected with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV after the discontinuation of emtricitabine or tenofovir DF, two of the components of STRIBILD. Hepatic function should be closely monitored with both clinical and laboratory follow-up for at least several months in patients who discontinue STRIBILD and are coinfected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted (see **WARNINGS AND PRECAUTIONS, Special populations**).

- **Nephrotoxicity**

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia) has been reported with the use of STRIBILD (see **WARNINGS AND PRECAUTIONS, Renal**).

General

Avoid Use with other Antiretroviral Agents:

STRIBILD is a fixed dose combination of elvitegravir, cobicistat, emtricitabine and tenofovir DF. It should not be co-administered with any other antiretroviral agents because:

- **STRIBILD is indicated for use as a complete antiretroviral regimen for the treatment of HIV-1 infection.**
- **Potential for over-exposure when combined with other antiretroviral products containing the components of STRIBILD.**

- **Potential for drug-drug interactions, and**
- **As a fixed dose combination formulation, no dosage adjustments for STRIBILD are possible.**

STRIBILD is not recommended to be used with the following:

- **Products containing elvitegravir (GENVOYA®).**
- **Products containing cobicistat (Evotaz™, GENVOYA®, Prezcobix® or TYBOST®).**
- **Products containing emtricitabine or tenofovir DF (ATRIPLA®, COMPLERA®, DESCOVY®, EMTRIVA®, GENVOYA®, ODEFSEY™, TRUVADA® or VIREAD®).**
- **Products containing tenofovir alafenamide (DESCOVY, GENVOYA®, ODEFSEY™, or VEMLIDY™).**
- **Products containing lamivudine (Combivir®, 3TC®, Heptovir®, Kivexa®, Triumeq® or Trizivir®).**
- **adefovir dipivoxil (HEPSERA®).**
- **ritonavir or ritonavir-containing products (Holkira™ Pak, Kaletra®, Norvir®) or regimens due to similar effects of cobicistat and ritonavir on cytochrome P450 (CYP3A).**

Use with Certain Hepatitis C Virus (HCV) Regimens:

The safety of increased tenofovir concentrations when STRIBILD is coadministered with HARVONI® (ledipasvir/sofosbuvir) has not been established. Coadministration is not recommended (see **DRUG INTERACTIONS**).

Coadministration of STRIBILD with EPCLUSA® (sofosbuvir/velpatasvir) has been shown to increase tenofovir exposure. Patients receiving STRIBILD concomitantly with EPCLUSA, particularly those at risk for renal dysfunction, should be monitored for adverse reactions associated with tenofovir disoproxil fumarate (see **DRUG INTERACTIONS**).

Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions with CYP3A Substrates or Inducers:

Coadministration of STRIBILD with drugs that are primarily metabolized by CYP3A may result in increased plasma concentrations of such drugs, which may lead to serious and/or life-threatening events. Drugs that induce CYP3A activity may decrease plasma concentrations of cobicistat and elvitegravir, which may lead to loss of therapeutic effect of STRIBILD and development of resistance (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS**).

Endocrine and Metabolism

Fat Redistribution:

Redistribution/accumulation of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Hepatic/ Biliary/Pancreatic

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 analogs 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 analogs 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).

Hepatic Impairment:

Limited data on the use of STRIBILD in patients with mild or moderate hepatic impairment (Child-Pugh Class A and B, respectively) suggests that no dose adjustment of STRIBILD is required in these patients. No pharmacokinetic or safety data are available regarding the use of STRIBILD in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, STRIBILD is not recommended for use in patients with severe hepatic impairment.

Elvitegravir and cobicistat are primarily metabolized and eliminated by the liver. A study of the pharmacokinetics of cobicistat-boosted elvitegravir in non-HIV-1 infected patients with moderate hepatic impairment (Child-Pugh Class B) and healthy patients did not reveal any clinically relevant differences in elvitegravir or cobicistat pharmacokinetics. The pharmacokinetics of elvitegravir or cobicistat has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

Tenofovir and tenofovir disoproxil are not metabolized by liver enzymes. Clinically relevant pharmacokinetic changes in patients with hepatic impairment are not observed. Emtricitabine has not been evaluated in patients with hepatic impairment since it is not metabolized by liver enzymes.

The safety and efficacy of STRIBILD have not been studied specifically in patients with underlying liver disorders. Patients with chronic hepatitis B or C and treated with antiretroviral

therapy are at increased risk for severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products **(**see **WARNINGS AND PRECAUTIONS, Special Populations)**.

Pancreatitis:

Caution should be exercised in the use of STRIBILD in patients with a history of pancreatitis or risk factors for the development of pancreatitis. Pancreatitis has occurred during the use of nucleoside analogues including tenofovir DF. Therapy should be suspended in patients with suspected pancreatitis.

Immune

Immune Reconstitution Inflammatory Syndrome:

Immune reconstitution inflammatory syndrome has been reported in patients treated with combination antiretroviral therapy, including the components of STRIBILD. During the initial phase of combination antiretroviral treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infections, cytomegalovirus, *Pneumocystis jiroveci* pneumonia (PCP), and tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.

Musculoskeletal

Bone Effects

Assessment of bone mineral density (BMD) should be considered for HIV infected patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. If bone abnormalities are suspected then appropriate consultation should be obtained.

Tenofovir DF (VIREAD) has been associated with decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C telopeptide, and urinary N telopeptide), suggesting increased bone turnover. Serum parathyroid hormone levels and 1.25 Vitamin D levels were also higher in patients receiving VIREAD. The effects of tenofovir DF-associated changes in BMD on future fracture risk are unknown. For additional information, please consult the VIREAD Product Monograph.

In Study 103, BMD was assessed by DEXA in a non-random subset of 120 patients (STRIBILD group: N=54 at Week 48, N=47 at Week 96 and N=40 at Week 144; ATV + RTV + TRUVADA group: N=66 at Week 48, N=53 at Week 96 and N=47 at Week 144). Mean percentage decreases in BMD from baseline to Week 144 in the STRIBILD group were comparable to the

ATV + RTV +TRUVADA group at the lumbar spine (-2.6% versus -3.3%, respectively, at Week 48, -2.0% versus -3.5%, respectively, at Week 96, and -1.43% versus -3.68%, respectively at Week 144) and at the hip (-3.1% versus -3.9%, respectively, at Week 48 , -3.2% versus -4.2%, respectively, at Week 96, and -2.8% versus 3.8%, respectively at Week 144).

In Studies 102 and 103 (STRIBILD group: N = 701; ATRIPLA group: N = 352; ATV + RTV + TRUVADA group: N = 355), bone fractures occurred in 9 patients (1.3%) in the STRIBILD group, 6 patients (1.7%) in the ATRIPLA group, and 6 patients (1.7%) in the ATV + RTV + TRUVADA group at Week 48 and in 14 patients (2.0%) in the STRIBILD group, 8 patients (2.3%) in the ATRIPLA group, and 14 patients (3.9%) in the ATV + RTV +TRUVADA group at Week 96 and in 27 patients (3.9%) in the STRIBILD group, 8 patients (2.3%) in the ATRIPLA group, and 19 patients (5.4%) in the ATV + RTV + TRUVADA group at Week 144. These findings were consistent with data from a 144 week study of treatment-naïve patients that received tenofovir DF + lamivudine + efavirenz.

Cases of osteomalacia (associated with proximal renal tubulopathy and which may contribute to fractures) have been reported in association with the use of tenofovir DF (see **ADVERSE REACTIONS, Post Market Adverse Drug Reactions: Tenofovir DF**).

For additional information, please consult the VIREAD Product Monograph.

Neurologic

Effects on Ability to Drive and Use Machines

Patients should be informed that cases of dizziness have been reported during treatment with STRIBILD. Patients who experience dizziness, trouble concentrating or drowsiness should avoid driving or operating machinery.

Renal

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported in association with the use of STRIBILD **(**see **ADVERSE REACTIONS, Adverse Drugs Reactions Overview** and **Post Market Adverse Drug Reactions).**

The following should be considered prior to initiation of, and during therapy with STRIBILD:

- Estimated creatinine clearance, urine glucose and urine protein levels should be documented in all patients prior to initiating therapy with STRIBILD and STRIBILD should not be initiated in patients with estimated creatinine clearance <70 mL/minute.
- Routine monitoring of estimated creatinine clearance, urine glucose and urine protein levels should be performed in all patients during therapy with STRIBILD.
- STRIBILD should be discontinued if estimated creatinine clearance declines to <50 mL/minute during treatment.

- Serum phosphorus should be monitored in patients at risk for renal impairment.

- STRIBILD should be avoided with concurrent or recent use of other nephrotoxic agents. Examples of nephrotoxic agents include but are not limited to aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir, or interleukin-2.

Although cobicistat may cause modest increases in serum creatinine and modest declines in estimated creatinine clearance without affecting renal glomerular function (see **ADVERSE REACTIONS**, **Laboratory Abnormalities**) patients who experience a confirmed increase in serum creatinine of greater than 0.4 mg per dL (35.36 µmol/L) from baseline should be closely monitored for renal safety, including measuring serum phosphorus, urine glucose, and urine protein.

In the clinical trials of STRIBILD over 144 weeks, 13 (1.9%) patients in the STRIBILD group (N=701), 8 (2.3%) patients in the ATV + RTV + TRUVADA group (N=355) and no patients in the ATRIPLA group (N=352) discontinued study drug due to a renal adverse reaction. Of these discontinuations, 8 in the STRIBILD group and 1 in the ATV + RTV + TRUVADA group occurred during the first 48 weeks. 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 of treatment. Two of the four patients had renal impairment (i.e. estimated creatinine clearance less than 70 mL per minute) at baseline. The laboratory findings in these 4 patients improved but did not completely resolve in all patients upon discontinuation of STRIBILD. One (0.3%) patient who received ATV + RTV + TRUVADA developed laboratory findings consistent with proximal renal tubular dysfunction leading to discontinuation of ATV + RTV + TRUVADA after Week 96.

Special Populations

Patients Co-infected with HIV and HBV:

STRIBILD is not approved for the treatment of chronic HBV infection and the safety and efficacy of STRIBILD have not been established in patients co-infected with HBV and HIV. It is recommended that all patients with HIV be tested for the presence of HBV before initiating antiretroviral therapy.

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV after the discontinuation of emtricitabine and tenofovir DF, two of the components of STRIBILD. In some patients infected with HBV and treated with EMTRIVA, the exacerbations of hepatitis B were associated with liver decompensation and liver failure.

Hepatic function should be closely monitored with both clinical and laboratory follow-up for at least several months in patients who discontinue STRIBILD and are co-infected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, post-treatment exacerbation of hepatitis may lead to hepatic decompensation. Therefore, in these patients, discontinuation of treatment without initiation of alternative anti-hepatitis B therapy is not recommended.

Patients with Mild to Moderate Renal Impairment:

In Study 118, 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. 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 118 in patients with mild to moderate renal impairment was consistent with the overall renal findings in Studies 102 and 103.

Pregnant Women:

There are not sufficient data to recommend the routine initiation of STRIBILD in women during pregnancy. STRIBILD should not be used in pregnant women unless the potential benefits outweigh the potential risks to the fetus and mother. Lower exposures of elvitegravir and cobicistat have been reported during pregnancy compared to postpartum. Closely monitor viral load during pregnancy, if STRIBILD is continued to be used.

Tenofovir DF: Reduced pup body weights, survival and delay in sexual maturation was observed in a peri- and postnatal toxicity study in rats at the maternally toxic doses of 450 and 600 mg/kg (approximately 14 and 19 times the human dose based on body surface area comparisons).

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to ART (antiretroviral therapy) including STRIBILD, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients,
http://www.apregistry.com
Telephone: (800) 258–4263
Fax: (800) 800-1052

Nursing Women:

HIV-1 infected mothers should not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that elvitegravir, cobicistat and tenofovir are secreted in milk. It is not known whether elvitegravir or cobicistat is excreted in human milk. In humans, samples of breast milk obtained from five HIV-1 infected mothers show that emtricitabine is 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} achieved from oral administration of emtricitabine; tenofovir is secreted in human milk at low levels (estimated neonatal concentrations 128 to 266 times lower than the tenofovir IC_{50}). 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. Tenofovir-associated risks, including the risk of developing viral resistance to tenofovir, in infants breastfed by mothers being treated with

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

Pediatrics (<18 years of age): Safety and effectiveness in children less than 18 years of age have not been established.

Geriatrics (>65 years of age): Clinical studies of STRIBILD did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than adult patients < 65 years of age. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Monitoring and Laboratory Tests:

It is recommended that estimated creatinine clearance, urine glucose and urine protein be documented in all patients prior to initiating therapy. STRIBILD should not be initiated in patients with estimated creatinine clearance below 70 mL/minute. Routine monitoring of estimated creatinine clearance, urine glucose and urine protein should be performed during STRIBILD therapy in all patients and additionally serum phosphorus should be measured during STRIBILD therapy in patients at risk for renal impairment. Although cobicistat may cause modest increases in serum creatinine and modest declines in estimated creatinine clearance without affecting renal glomerular function (see **ADVERSE REACTIONS, Laboratory Abnormalities**) patients who experience a confirmed increase in serum creatinine of greater than 0.4 mg per dL (35.36 μmol/L) from baseline should be closely monitored for renal safety, including measuring serum phosphorus, urine glucose, and urine protein. STRIBILD should be discontinued if estimated creatinine clearance declines below 50 mL/minute during therapy as dose interval adjustment required for emtricitabine and tenofovir DF cannot be achieved with the fixed-dose combination tablet.

Assessment of bone mineral density (BMD) should be considered for HIV infected patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Drug Reaction Overview

The following adverse drug reactions are discussed in other sections of the labeling:

• Lactic Acidosis/Severe Hepatomegaly with Steatosis [See **Boxed Warning, WARNINGS AND PRECAUTIONS**].

• Severe Acute Exacerbations of Hepatitis B [See **Boxed Warning, WARNINGS AND PRECAUTIONS**].

• New Onset or Worsening Renal Impairment [See **Boxed Warning, WARNINGS AND PRECAUTIONS**].

• Decreases in Bone Mineral Density [See **WARNINGS AND PRECAUTIONS**].

• Immune Reconstitution Inflammatory Syndrome [See **WARNINGS AND PRECAUTIONS**].

In Treatment-Naïve HIV-1 Infected Patients

The safety assessment of STRIBILD at Week 48 and Week 144 is based on the pooled data from 1408 patients in two Phase 3 trials, Study 102 and Study 103, in antiretroviral treatment-naïve HIV-1 infected adult patients. A total of 701 patients received STRIBILD once daily in these two studies.

The proportion of patients who discontinued treatment with STRIBILD, ATRIPLA (efavirenz 600 mg/emtricitabine 200 mg/tenofovir DF 300 mg) or ATV + RTV + TRUVADA (emtricitabine 200 mg/tenofovir DF 300 mg) due to adverse events, regardless of severity, was 3.7%, 5.1%, and 5.1% through Week 48; and 6.0%, 7.4%, 8.5% through Week 144 respectively. The most common adverse reaction (incidence greater than or equal to 2%) occurring in patients receiving STRIBILD in Studies 102 and 103 through Week 48 and Week 144 is diarrhea. The safety profile of STRIBILD at Week 144 was consistent with that at Week 48. See also Table 2 for the frequency of adverse reactions (Grades 2-4) occurring in at least 2% of patients in any treatment arm in Studies 102 and 103.

Table 2. Treatment-Emergent Adverse Drug Reactions[a] (Grades 2-4) Reported in ≥ 2% of Patients in Any Treatment Arm in Studies 102 and 103 (Week 48 and Week 144 analyses[b])

	Week 48			Week 144		
	STRIBILD	**ATRIPLA**	**Atazanavir/r +RTV + TRUVADA**	**STRIBILD**	**ATRIPLA**	**Atazanavir +RTV + TRUVADA**
	N=701	**N=352**	**N=355**	**N=701**	**N=352**	**N=355**
EYE DISORDERS						
Ocular icterus	0%	0%	2%	0%	0%	2%
GASTROINTESTINAL DISORDERS						
Diarrhea	2%	1%	3%	2%	2%	3%
Nausea	2%	1%	2%	2%	1%	2%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
Fatigue	1%	3%	3%	1%	3%	3%
NERVOUS SYSTEM DISORDERS						
Dizziness	<1%	3%	1%	<1%	3%	1%
Headache	2%	1%	1%	2%	1%	1%
PSYCHIATRIC DISORDERS						
Abnormal dreams	<1%	4%	<1%	<1%	4%	<1%
Depression	<1%	3%	0%	<1%	3%	0%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
Rash	<1%	3%	<1%	<1%	3%	<1%

a Frequencies of adverse reactions are based on Grade 2-4 treatment-emergent adverse events, attributed to study drugs

b The cumulative results are reported for each analysis (i.e., results from Week 0 to Week 48 are reported for Week 48 analysis and results from Week 0 to Week 144 are reported for Week 144 analysis).

Additional treatment-emergent adverse drug reactions of at least moderate intensity (≥ Grade 2) that occurred in less than 2% of patients treated with STRIBILD in Studies 102 and 103 include vomiting, abdominal pain, dyspepsia, flatulence, insomnia, asthenia, pyrexia, chest pain, myalgia, somnolence, renal failure, Fanconi syndrome, and increased blood creatinine.

Adverse drug reactions of suicidal ideation and suicide attempt occurred in less than 1% of patients receiving elvitegravir or STRIBILD, all of whom had a pre-existing history of depression or psychiatric illness.

Of the 701 patients who received STRIBILD for 144 weeks in Studies 102 and 103, renal events with laboratory findings consistent with proximal renal tubular injury leading to STRIBILD discontinuation were reported in 4 patients during the first 48 weeks. These findings largely reversed upon discontinuation of STRIBILD without clinical sequelae. All 4 patients had renal impairment at baseline or were at risk for renal impairment. No additional proximal renal tubular dysfunction cases were reported from Week 48 to Week 144 (see **WARNINGS AND PRECAUTIONS:** Renal).

In Virologically-Suppressed HIV-Infected Patients

No new adverse drug reactions to STRIBILD through Week 48 were identified in 584 virologically stably suppressed patients switching to STRIBILD from a regimen containing a ritonavir-boosted protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). In a combined analysis of Studies 115 and 121, the frequency of adverse reactions (all grades) was 24% in patients switching to STRIBILD compared to 6% of patients in either group who stayed on their baseline antiretroviral regimen, RTV-boosted PI + TRUVADA or NNRTI + TRUVADA. Common adverse reactions that occurred in greater than or equal to 2% of patients switching to STRIBILD were nausea (4%), flatulence (2%), and headache (2%). The proportion of patients who discontinued treatment with STRIBILD, the RTV-boosted PI, or the NNRTI due to adverse events, was 2%, 3% and 1%, respectively.

Adverse Reactions from Clinical Trials of the Components of STRIBILD

For information on the safety profiles of EMTRIVA, TYBOST, or VIREAD, consult the Product Monographs for these products.

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

Table 3. Laboratory Abnormalities (Grades 3-4) Reported in ≥ 2% of Patients Receiving STRIBILD in Studies 102 and 103 (Week 48 and Week 144 analyses[a])

	Week 48			Week 144		
	STRIBILD	**ATRIPLA**	**Atazanavir +RTV + TRUVADA**	**STRIBILD**	**ATRIPLA**	**Atazanavir +RTV + TRUVADA**
Laboratory Parameter Abnormality	N=701	N=352	N=355	N=701	N=352	N=355
AST (> 5.0 x ULN)	2%	3%	4%	3%	6%	6%
ALT (>5.0 x ULN)	1%	3%	2%	2%	5%	4%
Amylase[b] (> 2.0 x ULN)	2%	2%	4%	3%	3%	5%
Creatine Kinase (≥ 10.0 x ULN)	5%	11%	7%	8%	15%	11%
Urine RBC (Hematuria) (> 75 RBC/HPF)	3%	1%	2%	4%	2%	4%

a The cumulative results are reported for each analysis (i.e., results from Week 0 to Week 48 are reported for Week 48 analysis and results from Week 0 to Week 144 are reported for Week 144 analysis).

b 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 ATV + RTV + TRUVADA (N=38) was 17%, 15%, and 24%, respectively, to Week 144.

Proteinuria (all grades) occurred in 52% of patients receiving STRIBILD, 41% of patients receiving ATRIPLA, and 42% of patients receiving ATV + RTV + TRUVADA. Proteinuria was predominantly Grade 1 in severity. The cobicistat component of STRIBILD has been shown to increase serum creatinine and decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting renal glomerular function. The effect of cobicistat on serum creatinine was investigated in a Phase I study in patients with normal renal function (eGFR ≥ 80 mL/minute, N=18) and mild to moderate renal impairment (eGFR 50-79 mL/minute, N=12). A statistically significant change of estimated glomerular filtration rate calculated by Cockcroft-Gault method ($eGFR_{CG}$) from baseline was observed after 7 days of treatment with cobicistat 150 mg among patients with normal renal function (-9.9 ± 13.1 mL/minute) and mild to moderate renal impairment (-11.9 ± 7.0 mL/minute). These decreases in $eGFR_{CG}$ were reversible after cobicistat was discontinued. The actual glomerular filtration rate, as determined by the clearance of probe drug iohexol, was not altered from baseline following treatment of cobicistat among patients with normal renal function and mild to moderate renal impairment, indicating cobicistat inhibits tubular secretion of creatinine, reflected as a reduction in $eGFR_{CG}$, without affecting the actual glomerular filtration rate.

In Studies 102 and 103, increases in serum creatinine and decreases in estimated creatinine clearance occurred early in treatment with STRIBILD, after which they stabilized.

Table 4 displays the mean changes in serum creatinine and eGFR levels at Week 48 and Week 144 and the percentage of patients with elevations in serum creatinine (All Grades).

Table 4. Change from Baseline in Serum Creatinine and eGFR and Incidence of Elevated Serum Creatinine (All Grades) in Studies 102 and 103 at Week 48 and Week 144

	Week 48			Week 144		
	STRIBILD (N=701)	**ATRIPLA (N=352)**	**ATV + RTV + TRUVADA (N=355)**	**STRIBILD (N=701)**	**ATRIPLA (N=352)**	**ATV + RTV + TRUVADA (N=355)**
Serum Creatinine (mg/dL)[a]	0.14 (±0.13)	0.01 (±0.12)	0.09 (±0.13)	0.14 (± 0.14)	0.01 (±0.12)	0.09 (±0.15)
eGFR by Cockcroft-Gault (mL/minute)[a]	-13.9 (±14.9)	-1.6 (±16.5)	-9.3 (±15.8)	- 14.0 (±16.6)	- 1.9 (±17.9)	- 9.8 (±19.4)
Patients with Elevations in Serum Creatinine (All Grades) (%)	7	1	4	12	2	6

a Mean change ±SD

Emtricitabine and Tenofovir DF: In addition to the laboratory abnormalities described with STRIBILD (Table 3), Grade 3/4 laboratory abnormalities of ALT (>215 U/L in males and > 170 U/L in females) Grade 3/4 elevations of bilirubin (> 2.5 x ULN), serum glucose (< 40 or > 250 mg/dL), alkaline phosphatase (> 550 U/L), neutrophils (< 750/mm^3), fasting cholesterol (> 240 mg/dL), and urine glucose (≥ 3+) occurred in up to 3% of patients treated with emtricitabine or tenofovir DF with other antiretroviral agents in other clinical trials. For detailed information, please consult the respective Product Monographs.

Serum Lipids: In the clinical trials of STRIBILD, a similar percentage of patients receiving STRIBILD, ATRIPLA, and ATV + RTV + TRUVADA were on lipid lowering agents at baseline (11%, 11%, and 12%, respectively). While receiving study drug through Week 144, an additional 11% of STRIBILD patients were started on lipid lowering agents, compared to 13% of ATRIPLA and 12% of ATV + RTV + TRUVADA patients.

During 144 weeks of study drug exposure, Grade 3 or 4 elevations in fasting cholesterol (greater than 300 mg per dL) were reported in 1.8% of STRIBILD patients, compared to 3% in ATRIPLA and less than 1% in ATV + RTV + TRUVADA patients. In addition, Grade 3 or 4 elevations in fasting triglycerides (greater than 750 mg per dL) during 144 weeks of study drug exposure were reported in less than 1% of STRIBILD patients, compared to 2% in ATRIPLA and 2% in ATV + RTV + TRUVADA patients.

Changes from baseline in total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides are presented in (Table 5).

Table 5. Lipid Values, Mean Change from Baseline, Reported in Patients Receiving STRIBILD or Comparator in Studies 102 and 103 (Week 48 and Week 144 analyses)

	STRIBILD N=701			ATRIPLA N=352			Atazanavir + RTV + TRUVADA N=355		
	Baseline	**Week 48**	**Week 144**	**Baseline**	**Week 48**	**Week 144**	**Baseline**	**Week 48**	**Week 144**
	mg/dL	**Change from baseline [a] (mg/dL)**	**Change from baseline [a] (mg/dL)**	**mg/dL**	**Change from baseline [a] (mg/dL)**	**Change from baseline [a] (mg/dL)**	**mg/dL**	**Change from baseline [a] (mg/dL)**	**Change from baseline [a] (mg/dL)**
Total Cholesterol (fasted)	166 [N=675]	+11 [N=606]	+ 17 [N=535]	161 [N=343]	+19 [N=298]	+ 22 [N=262]	168 [N=337]	+9 [N=287]	+ 16 [N=243]
HDL-cholesterol (fasted)	43 [N=675]	+6 [N=605]	+ 7 [N=535]	43 [N=343]	+8 [N=298]	+ 9 [N=262]	42 [N=335]	+5 [N=284]	+ 7 [N=242]
LDL-cholesterol (fasted)	100 [N=675]	+10 [N=606]	+ 15 [N=535]	97 [N=343]	+17 [N=298]	+ 19 [N=262]	101 [N=337]	+11 [N=288]	+ 18 [N=242
Triglycerides (fasted)	122 [N=675]	+13 [N=606]	+ 12 [N=535]	121 [N=343]	+13 [N=298]	+ 5 [N=262]	132 [N=337]	+29 [N=287]	+ 22 [N=242

a The change from baseline at Week 48 (or Week 144) is the mean of within-patient changes for patients with both baseline and Week 48 (or Week 144) values.

Post Market Adverse Drug Reactions

In addition to the adverse reaction reports from clinical trials, the following possible adverse reactions have been identified during post-approval use of emtricitabine or tenofovir DF. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been considered possible adverse reactions due to a combination of their seriousness, frequency of reporting or potential causal relationship with treatment.

Emtricitabine:

The following adverse experiences have been reported in post-marketing experience without regard to causality; some events represent a single report.

Blood and lymphatic system disorders:	Thrombocytopenia
Gastrointestinal disorders:	Pancreatitis
General disorders and administrative site conditions:	Pyrexia
Metabolism and nutrition disorders:	Lactic acidosis

Tenofovir DF:

Immune system disorders:	Allergic reaction (including angioedema)
Metabolism and nutrition disorders:	Lactic acidosis, hypokalemia, hypophosphatemia
Respiratory, thoracic and mediastinal disorders:	Dyspnea
Gastrointestinal disorders:	Pancreatitis, increased amylase, abdominal pain
Hemic and lymphatic system disorders:	Thrombocytopenia
Hepatobiliary disorders:	Hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT, GGT)
Skin and Subcutaneous Tissue Disorders:	Rash
Musculoskeletal and Connective Tissue Disorders:	Rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), muscular weakness, myopathy

Renal and urinary disorders:	Acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria
General disorders and administrative site conditions:	Asthenia

The following adverse reactions, listed under the body system headings above, sometimes appeared to be concurrent with proximal renal tubulopathy: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), hypokalemia, muscular weakness, myopathy, hypophosphatemia.

There have been three post marketing reports of acute renal failure in patients on concomitant NSAIDS therapy where a relationship to tenofovir DF could not be excluded.

DRUG INTERACTIONS

Serious Drug Interactions

Cobicistat, a component of STRIBILD, is a strong inhibitor of cytochrome P450 (CYP3A) and a CYP3A substrate. Coadministration of STRIBILD with drugs that are primarily metabolized by CYP3A may result in increased plasma concentrations of such drugs, which may lead to serious and/or life-threatening events. Elvitegravir, a component of STRIBILD, is metabolized by CYP3A. Drugs that induce CYP3A activity may decrease plasma concentrations of cobicistat and elvitegravir, which may lead to loss of therapeutic effect of STRIBILD and development of resistance (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS**, **Table 7 – Established and Other Potentially Significant Drug Interactions**).

Drug-Drug Interactions

STRIBILD is indicated for use as a complete regimen for the treatment of HIV-1 infection; therefore STRIBILD should not be coadministered with other antiretroviral medications for treatment of HIV-1 infection. Complete information regarding potential drug-drug interactions with other antiretrovirals products is not provided (See **WARNINGS AND PRECAUTIONS, General).**

The drug interactions described in Table 6 are based on studies conducted with STRIBILD or the components of STRIBILD (elvitegravir, cobicistat, emtricitabine or tenofovir DF), as individual agents or are potential drug-drug interactions. The table includes potentially clinically relevant interactions, but is not comprehensive.

Potential of STRIBILD to Affect Other Drugs

Cobicistat, a component of STRIBILD, is a strong inhibitor of cytochrome P450 (CYP3A) and CYP2D6. The transporters that cobicistat inhibits include 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 (see **CONTRAINDICATIONS**). Elvitegravir is a modest inducer of CYP2C9 and may decrease the plasma concentrations of CYP2C9 substrates.

Potential for Other Drugs to Affect One or More Components of STRIBILD

Elvitegravir and cobicistat, components of STRIBILD, are metabolized by CYP3A. Cobicistat is also metabolized, to a minor extent, by CYP2D6. Drugs that induce CYP3A activity are expected to increase the clearance of elvitegravir and cobicistat, resulting in decreased plasma concentration of cobicistat, and thus that of elvitegravir, which may lead to loss of therapeutic effect of STRIBILD and development of resistance (see **CONTRAINDICATIONS**).

Coadministration of STRIBILD with other drugs that inhibit CYP3A may decrease the clearance and increase the plasma concentration of cobicistat (see **DRUG INTERACTIONS**, **Table 6**).

Drugs Affecting Renal Function

Since emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of STRIBILD with drugs that are eliminated by active tubular secretion may increase concentrations of emtricitabine, tenofovir, and/or the coadministered drug. Some examples include, but are not limited to acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, and valganciclovir. Tenofovir and cobicistat have distinct, non-overlapping transport pathways in the renal proximal tubules. Tenofovir, as an organic anion, is a substrate of renal organic anion transporters OAT1/3 and MRP4. Cobicistat does not affect these transporters and is not expected to exacerbate potential renal toxicity of tenofovir.

Established and Other Potentially Significant Drug Interactions

The drug interactions described are based on studies conducted with the components of STRIBILD (elvitegravir, cobicistat, emtricitabine, and tenofovir DF) as individual agents and/or in combination, or are potential drug interactions that may occur with STRIBILD.

The table is not all-inclusive (see also **CONTRAINDICATIONS**).

Table 6. Established and Other Potentially Significant[a] Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[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. No dose adjustment is needed when STRIBILD is combined with either H2 receptor antagonists or proton pump inhibitors. For information on other acid reducing agents (e.g. H_2-receptor antagonists and proton pump inhibitors), see **DRUG INTERACTIONS: Drugs without Clinically Significant Interactions with STRIBILD.**
Analeptics:		
modafinil	↓ elvitegravir ↓ cobicistat	Coadministration of modafinil, a CYP3A inducer, may significantly decrease cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Alternative analeptics should be considered.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Antiarrhythmics:		
amiodarone bepridil* digoxin disopyramide flecainide systemic lidocaine mexilitine propafenone quinidine	↑ antiarrhythmics	Concentrations of these antiarrhythmic drugs may be increased when coadministered with STRIBILD. 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/minute). Clinical monitoring is recommended for patients with CLcr <90 ml/minute. For patients with CLcr <60 mL/minute, alternative antibacterials should be considered. Concentrations of telithromycin and/or cobicistat may be altered with coadministration of STRIBILD. Clinical monitoring is recommended upon coadministration with STRIBILD.
Anticoagulants:		
warfarin	↑ or ↓ warfarin	Concentrations of warfarin may be affected upon coadministration with STRIBILD. It is recommended that the international normalized ratio (INR) be monitored upon coadministration with STRIBILD.
Direct Oral Anticoagulants (DOACs): apixaban rivaroxaban dabigatran edoxaban	↑ DOACs	DOACs are primarily metabolized by CYP3A4 and/or transported by P-gp. Coadministration 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 contraindicated 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 Product Monograph of the coadministered DOAC.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Anticonvulsants:		
carbamazepine oxcarbazepine phenobarbital phenytoin	↑ carbamazepine ↓ 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.
clonazepam ethosuximide	↑ clonazepam ↑ ethosuximide	Coadministration of oxcarbazepine a CYP3A inducer with STRIBILD may significantly decrease cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Alternative anticonvulsants should be considered. Concentrations of clonazepam and ethosuximide may be increased when coadministered with STRIBILD. Clinical monitoring is recommended upon coadministration with STRIBILD.
Antidepressants:		
Selective Serotonin Reuptake Inhibitors (SSRIs) paroxetine Tricyclic Antidepressants (TCAs) amitryptyline desipramine imipramine nortriptyline bupropion trazodone	↑ SSRIs (except sertraline) ↑ TCAs ↑ trazodone	Concentrations of these antidepressant agents may be increased when coadministered with STRIBILD. Careful dose titration of the antidepressant and monitoring for antidepressant response are recommended.
Antifungals:		
itraconazole ketoconazole voriconazole	↑ antifungals ↑ cobicistat	Concentrations of ketoconazole, itraconazole, and/or cobicistat may increase with coadministration of STRIBILD. When administering with STRIBILD, the maximum daily dose of ketoconazole and itrazonazole 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.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Anti-gout:		
colchicine	↑ colchicine	STRIBILD should not be coadministered with colchicine to patients with renal or hepatic impairment. Treatment of gout-flares – coadministration of colchicine in patients receiving STRIBILD: 0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Treatment course to be repeated no earlier than 3 days. Prophylaxis of gout-flares – coadministration of colchicine in patients receiving STRIBILD: If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day. If the original regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day. Treatment of familial Mediterranean fever – coadministration of colchicine in patients receiving STRIBILD: Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
Antimycobacterial:		
Rifabutin rifapentine*	↓ elvitegravir ↓ cobicistat ↑ rifabutin and rifabutin metabolite	Coadministration of rifabutin and rifapentine may 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.
Antipsychotic:		
quetiapine	↑ quetiapine	STRIBILD should not be used in combination with quetiapine. Due to CYP3A4 inhibition by cobicistat, concentrations of quetiapine are expected to increase, which can result in serious and/or life-threatening adverse reactions. If coadministration is necessary, monitoring and quetiapine dose reduction may be required.
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.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Calcium Channel Blockers:		
amlodipine diltiazem felodipine nicardipine* 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.
Corticosteroids:		
Systemic Corticosteroids: dexamethasone	↓ elvitegravir ↓ cobicistat	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.
Corticosteroids (all routes, excluding cutaneous): betamethasone budesonide dexamethasone fluticasone mometasone triamcinolone	↑ corticosteroids	Coadministration of inhaled or nasal corticosteroids and STRIBILD is not recommended unless the potential benefit to the patient outweighs the risks. Coadministration of STRIBILD 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.
Endothelin Receptor Antagonists:		
bosentan	↑ bosentan	Coadministration of bosentan in patients on STRIBILD: In patients who have been receiving STRIBILD for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability. Coadministration of STRIBILD in patients on bosentan: Discontinue use of bosentan at least 36 hours prior to initiation of STRIBILD. After at least 10 days following the initiation of STRIBILD, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability.
Hepatitis C Virus Antiviral Agents:		
ledipasvir/sofosbuvir	↑ tenofovir	The safety of increased tenofovir concentrations when STRIBILD is coadministered with HARVONI (ledipasvir/sofosbuvir) has not been established. Coadministration is not recommended (see **WARNINGS AND PRECAUTIONS**).
sofosbuvir/velpatasvir	↑ tenofovir	Coadministration of STRIBILD with EPCLUSA (sofosbuvir/velpatasvir) has been shown to increase tenofovir exposure. Patients receiving STRIBILD concomitantly with EPCLUSA should be monitored for adverse reactions associated with tenofovir disoproxil fumarate (see **WARNINGS AND PRECAUTIONS**).

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
HMG CoA Reductase Inhibitors:		
atorvastatin rosuvastatin	↑ HMG-CoA reductase inhibitors	Concentrations of atorvastatin are increased when coadministered with elvitegravir and cobicistat. Start with the lowest dose of atorvastatin and titrate carefully while monitoring for safety (e.g., myopathy). Do not exceed a dosage of atorvastatin 20 mg daily. Concentrations of rosuvastatin are transiently increased when coadministered with elvitegravir and cobicistat. Dose modifications are not necessary when rosuvastatin is administered in combination with STRIBILD.
Hormonal Contraceptives:		
drospirenone/ethinyl estradiol[#] norgestimate/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. Coadministration of STRIBILD and a norgestimate/ethinyl estradiol-containing hormonal oral contraceptive resulted in decreased plasma concentrations of ethinyl estradiol and an increase in norgestimate. The effects of increases in the concentration of the progestational component norgestimate are not fully known and can include increased risk of insulin resistance, dyslipedemia, acne and venous thrombosis. The potential unknown 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 oral contraceptives containing progestogens other than drospirenone or norgestimate or with other hormonal contraceptives (e.g. contraceptive patch, contraceptive vaginal ring), has not been studied; therefore alternative non-hormonal methods of contraception should be considered.
Immunosuppressants:		
cyclosporine rapamycin* sirolimus tacrolimus	↑ immunosuppressants	Concentrations of these immunosuppressant agents may be increased when coadministered with STRIBILD. Therapeutic monitoring is recommended upon coadministration with STRIBILD.

Concomitant Drug Class: Drug Name	Effect on Concentration[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.
Neuroleptics:		
perphenazine risperidone thioridazine*	↑ neuroleptics	Coadministration with STRIBILD may result in increased plasma concentrations of these drugs. 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, tadalafil and vardenafil, which may result in PDE5 inhibitor-associated adverse reactions. Coadministration of STRIBILD with sildenafil for the treatment of pulmonary arterial hypertension is contraindicated while coadministration 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, or no more than 10 mg tadalafil in 72 hours be coadministered with STRIBILD. Vardenafil should not be coadministered with STRIBILD.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Sedative/hypnotics:		
buspirone clorazepate diazepam estazolam* flurazepam zolpidem*	↑ sedatives/hypnotics	Coadministration with STRIBILD may result in increased plasma concentrations of these drugs. Dose reduction may be necessary and concentration monitoring is recommended.

CL_{cr}=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

* Not marketed in Canada

# Indicates that a drug-drug interaction trial was conducted.

Drugs without Clinically Significant Interactions with STRIBILD:

Based on drug interaction studies conducted with the components of STRIBILD, no clinically significant drug interactions have been either observed or are expected between the components of STRIBILD and the following drugs: entecavir, famciclovir, famotidine, R/S-methadone, omeprazole, sertraline, 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 **WARNINGS AND PRECAUTIONS**).

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 **CONTRAINDICATIONS**).

The effects of coadministered drugs on the exposure of elvitegravir are shown in Table 7a and Table 7b. The effects of the individual components of STRIBILD on the exposure of coadministered drugs are shown in Table 8.

Table 7a. Drug Interactions: Changes in Pharmacokinetic Parameters for Elvitegravir when Boosted with Ritonavir in the Presence of the Coadministered Drug[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose (mg)	Ritonavir Booster Dose (mg)	N	% Change of Elvitegravir Pharmacokinetic Parameters (90% CI)		
					C_{max}	AUC	C_{min}
Antacids	20 mL single dose given 4 hours before elvitegravir	50 single dose	100 single dose	10	↓5 (↓16 to ↑7)	↓4 (↓12 to ↑4)	↑4 (↓7 to ↑17)
	20 mL single dose 4 hours after elvitegravir			8	↓2 (↓12 to ↑10)	↓2 (↓9 to ↑6)	0 (↓10 to ↑11)
	20 mL single dose given 2 hours before elvitegravir			10	↓18 (↓26 to ↓9)	↓15 (↓21 to ↓9)	↓10 (↓18 to ↓1)
	20 mL single dose given 2 hours after elvitegravir			11	↓21 (↓29 to ↓12)	↓20 (↓25 to ↓14)	↓20 (↓27 to ↓11)
	20 mL single dose simultaneously administered with elvitegravir	50 single dose	100 single dose	13	↓47 (↓53 to ↓40)	↓45 (↓50 to ↓40)	↓41 (↓48 to ↓33)
Ketoconazole	200 twice daily	150 once daily	100 once daily	18	↑17 (↑4 to ↑33)	↑48 (↑36 to ↑62)	↑67 (↑48 to ↑88)
Omeprazole	40 once daily given 2 hours before elvitegravir	50 once daily	100 once daily	9	↓7 (↓17 to ↑4)	↓1 (↓9 to ↑7)	↓6 (↓15 to ↑4)

↑ = Increase; ↓ = Decrease; NA = Not Applicable

a All interaction studies conducted in healthy volunteers.

Table 7b. Drug Interactions: Changes in Pharmacokinetic Parameters for Elvitegravir when Boosted with Cobicistat in the Presence of the Coadministered Drug[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose (mg)	Cobicistat Booster Dose	N	% Change of Elvitegravir Pharmacokinetic Parameters (90% CI)		
					C_{max}	AUC	C_{min}
Atorvastatin[b]	10 single dose	150 once daily	150 once daily	16	↓9 (↓15 to ↓2)	↓8 (↓13 to ↓2)	↓12 (↓19 to ↓4)
Carbamazepine	200 twice daily	150 once daily	150 once daily	12	↓45 (↓51 to ↓39)	↓69 (↓72 to ↓67)	↓97 (↓98 to ↓96)
Famotidine	40 once daily given 12 hours after elvitegravir	150 once daily	150 once daily	10	↑2 (↓11 to ↑17)	↑3 (↓ 5 to ↑13)	↑18 (↑5 to ↑32)
	40 once daily given simultaneously with elvitegravir			16	0 (↓8 to ↑10)	↑3 (↓2 to ↑8	↑7 (↓2 to ↑17)
Ledipasvir/Sofosbuvir[c]	90/400 once daily	150 once daily	150 once daily	29	↓12 (↓18 to ↓5)	↑2 (↓5 to ↑9)	↑36 (↑23 to ↑49)
Sofosbuvir/Velpatasvir[def]	400/100 mg once daily	150 once daily	150 once daily	24	↓ 7 (↓ 14 to 0)	↓ 7 (↓ 13 to ↓1)	↓ 3 (↓ 9 to↑ 4)
Omeprazole	20 once daily given 2 hours before elvitegravir	50 once daily	150 once daily	11	↑16 (↑4 to ↑30)	↑10 (↑2 to ↑19)	↑13 (↓4 to ↑34)
	20 once daily given 12 hours after elvitegravir	150 once daily	150 once daily	11	↑3 (↓8 to ↑15)	↑5 (↓7 to ↑18)	↑10 (↓8 to ↑32)

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose (mg)	Cobicistat Booster Dose	N	% Change of Elvitegravir Pharmacokinetic Parameters (90% CI)		
					C_{max}	AUC	C_{min}
Rifabutin	150 once every other day	150 once daily	150 once daily	12	↓9 (↓16 to ↓1)	↓21 (↓26 to ↓15)	↓67 (↓73 to ↓60)
Rosuvastatin	10 single dose	150 once daily	150 once daily	10	↓6 (↓17 to ↑7)	↑2 (↓9 το ↑14)	↓2 (↓17 to ↑16)
Sertraline[b]	50 single dose	150 once daily	150 once daily	19	↓12 (↓18 to ↓7)	↓6 (↓11 to ↓2)	↓1 (↓7 to ↑5)

↑ = Increase; ↓ = Decrease; N/A = Not Applicable

a All interaction studies conducted in healthy volunteers.

b Study conducted with GENVOYA

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 Percent change of cobicistat PK parameters (90% CI) was ↑11 (↑6 to ↑17) for C_{max}, ↑23 (↑17 to ↑29) for AUC, and ↑71 (↑54 to ↑90) for C_{min}

e Percent change of tenofovir PK parameters (90% CI) was ↑36 (↑25 to ↑47) for C_{max}, ↑35 (↑29 to ↑42) for AUC, and ↑45 (↑39 to ↑51) for C_{min}.

f Study conducted with STRIBILD

In drug interaction studies conducted with elvitegravir, neither famotidine, methadone (R/S-methadone), or omeprazole had a clinically significant effect on the C_{max}, AUC, or C_{min} of elvitegravir.

Table 8. 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 Booster Dose	N	% Change of Coadministered Drug Pharmacokinetic Parameters (90% CI)		
					C_{max}	AUC	C_{min}
Atorvastatin[b]	10 single dose	150 once daily	150 once daily	16	↑132 (↑91 to ↑182)	↑160 (↑131 to ↑193)	NC
Buprenorphine	16 - 24 once daily	150 once daily	150 once daily	17	↑12 (↓2 to ↑27)	↑35 (↑18 to ↑55)	↑66 (↑43 to ↑93)
Norbuprenorphine					↑24 (↑3 to ↑49)	↑42 (↑22 to ↑67)	↑57 (↑31 to ↑88)

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose (mg)	Cobicistat Booster Dose	N	% Change of Coadministered Drug Pharmacokinetic Parameters (90% CI)		
					C_{max}	AUC	C_{min}
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	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)
R-Methadone	80-120 daily	150 once daily	150 once daily	11	↑1 (↓9 to ↑13)	↑7 (↓4 to ↑19	↑10 (↓5 to ↑28)
S-Methadone					↓4 (↓13 to ↑6)	0 (↓11 to ↑12)	↑2 (↓11 to ↑17)
Digoxin	0.5 single dose	N/A	150 once daily	22	↑41 ↑29 to ↑ 55	↑8 (0 to ↑17)	NC
Ledipasvir	90/400 once daily	150 once daily	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)	NA
GS-331007[c]					↑33 (↑22 to ↑44)	↑44 (↑41 to ↑48)	↑53 (↑47 to ↑59)
Sofosbuvir	400/100 mg once daily	150 once daily[d]	150 once daily[d]	24	↑ 1 (↓15 to ↑ 19)	↑ 24 (↑ 13 to↑37)	NA
GS-331007[c]					↑ 13 (↑ 7 to ↑ 18)	↑ 35 (↑ 30 to ↑ 40)	↑ 45 (↑ 38 to ↑ 52)
Velpatasvir					↑ 5 (↓ 7 to↑ 19)	↑ 19 (↑ 7 to ↑ 34)	↑ 37 (↑ 22 to ↑ 54)
Norgestimate/ Ethinyl Estradiol	0.180/0.215/ 0.250 norgestimate once daily	150 once daily[d]	150 once daily[d]	13	↑108 (↑100 to ↑117)	↑126 (↑115 to ↑137)	↑167 (↑143 to ↑192)
	0.025 ethinyl estradiol once daily				↓6 (↓14 to ↑4)	↓25 (↓31 to ↓19)	↓44 (↓48 to ↓39)

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose (mg)	Cobicistat Booster Dose	N	% Change of Coadministered Drug Pharmacokinetic Parameters (90% CI)		
					C_{max}	AUC	C_{min}
Rifabutin	150 once every other day	150 once daily	150 once daily	12	↑9 (↓2 to ↑20)[e]	↓8 (↓17 to ↑3)[e]	↓6 (↓15 to ↑4)[e]
25-O-desacetyl-rifabutin				12	↑384 (↑309 to ↑474)	↑525 (↑408 to ↑669)	↑394 (↑304 to ↑504)
Rosuvastatin	10 single dose	150 once daily	150 once daily	10	↑89 (↑48 to ↑142)	↑38 (↑14 to ↑67)	↑43 (↑8 to ↑89)
Sertraline[b]	50 single dose	150 once daily	150 once daily	19	↑14 (↓6 to ↑38)	↓7 (↓23 to ↑13)	N/A

↑ = Increase; ↓ = Decrease; N/A = Not Applicable; NC = Not Calculated
a All interaction studies conducted in healthy volunteers.
b Study conducted with GENVOYA.
c The predominant circulating nucleoside metabolite of sofosbuvir.
d Study conducted with STRIBILD.
e Comparison based on rifabutin 300 mg once daily.

Drug-Food Interactions

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

Drug-Herb Interactions

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 with St. John's wort is contraindicated.

Drug-Laboratory Interactions

Interactions of STRIBILD with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

The recommended dose of STRIBILD is one tablet (containing 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine and 300 mg of tenofovir DF) taken orally once daily with food.

Geriatrics (>65 years of age)

No data are available on which to make a dose recommendation for patients over 65 years of age.

Pediatrics (<18 years of age)

STRIBILD is not indicated for use in pediatric patients <18 years of age.

Dosage in Patients with Renal Impairment

STRIBILD should not be initiated in patients with estimated creatinine clearance below 70 mL/minute. STRIBILD should be discontinued if estimated creatinine clearance declines below 50 mL/minute during treatment with STRIBILD as dose interval adjustment required for emtricitabine and tenofovir DF cannot be achieved with the fixed-dose combination tablet (see **WARNINGS AND PRECAUTIONS**).

Dosage in Patients with Hepatic Impairment

Limited data on the use of STRIBILD in patients with mild or moderate hepatic impairment (Child-Pugh Class A and B, respectively) suggests that no dose adjustment of STRIBILD is required in these patients. STRIBILD has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

Missed Dose

If a patient misses a dose of STRIBILD within 12 hours of the time it is usually taken, the patient should take STRIBILD with a meal as soon as possible, and then take the next dose of STRIBILD at the regularly scheduled time.

If a patient misses a dose of STRIBILD by more than 12 hours, the patient should not take the missed dose, but resume the usual dosing schedule.

OVERDOSAGE

For management of a suspected drug overdose, please contact your Regional Poison Control Centre.

If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary including monitoring of vital signs and observation of

the patient's clinical status. Hemodialysis can remove both emtricitabine and tenofovir DF (refer to information below).

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 patients. 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 hemodialysis or peritoneal dialysis.

Cobicistat:

Limited clinical experience is available at doses higher than the therapeutic dose of cobicistat. In two studies, a single dose of cobicistat 400 mg was administered to a total of 60 healthy patients. 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 hemodialysis or peritoneal dialysis.

Emtricitabine:

Hemodialysis 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/minute and a dialysate flow rate of 600 mL/minute), however, a single treatment does not significantly affect emtricitabine C_{max} or AUC. It is not known whether emtricitabine can be removed by peritoneal dialysis.

Tenofovir DF:

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

Elvitegravir:

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

Cobicistat:

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.

Emtricitabine:

Emtricitabine is phosphorylated to form emtricitabine 5'-triphosphate which inhibits the activity of the HIV-1 RT by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination (see **DETAILED PHARMACOLOGY**).

Tenofovir DF:

Tenofovir DF is hydrolyzed and phosphorylated 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 DNA, by DNA chain termination (see **DETAILED PHARMACOLOGY**).

Effects on Electrocardiogram:

The electrocardiographic effects of cobicistat were determined in a study of 48 healthy adult patients. Cobicistat did not prolong the QTcF interval at exposures 2- and 4-fold above the recommended therapeutic dose. Prolongation of the PR interval was noted in patients receiving cobicistat in the same study. The maximum mean (95% upper confidence bound) difference in PR from placebo after baseline-correction was 9.5 (12.1) msec for 250-mg dose and 20.2 (22.8) for 400-mg dose cobicistat. Because the 150 mg cobicistat dose used in the STRIBILD fixed-dose combination tablet is lower than the lowest dose studied in the thorough QT study, it is unlikely that treatment with STRIBILD will result in clinically relevant PR prolongation.

In a thorough QT/QTc study in 126 healthy patients, ritonavir-boosted elvitegravir at therapeutic or supratherapeutic dose approximately 2-fold the recommended therapeutic dose did not affect the QT/QTc interval and did not prolong the PR interval.

Pharmacokinetics

Absorption:

Following oral administration of STRIBILD with food in HIV-1 infected patients, peak plasma concentrations were observed 4.0 hours post dose for elvitegravir, 3 hours post dose for cobicistat, 3 hours post dose for emtricitabine, and 2 hours for tenofovir following the rapid conversion of tenofovir DF. The pharmacokinetics of STRIBILD are listed in Table 9.

Table 9. Pharmacokinetic Parameters of Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir Exposure Following Oral Administration of STRIBILD in HIV-Infected Patients

Parameter Mean ± SD [range: min:max]	Elvitegravir[a]	Cobicistat[b]	Emtricitabine[b]	Tenofovir[b]
C_{max} (microgram per mL)	1.7 ± 0.4 [0.4:3.7]	1.1 ± 0.4 [0.1:2.1]	1.9 ± 0.5 [0.6:3.6]	0.45 ± 0.2 [0.2:1.2]
AUC_{tau} (microgram•hour per mL)	23.0 ± 7.5 [4.4:69.8]	8.3 ± 3.8 [0.5:18.3]	12.7 ± 4.5 [5.2:34.1]	4.4 ± 2.2 [2.1:18.2]
C_{trough} (microgram per mL)	0.45 ± 0.26[c] [0.05:2.34]	0.05 ± 0.13 [0.01:0.92]	0.14 ± 0.25 [0.04:1.94]	0.10 ± 0.08 [0.04:0.58]

SD = Standard Deviation

a From Population Pharmacokinetic analysis, N=419

b From Intensive Pharmacokinetic analysis, N=61-62, except cobicistat C_{trough} N=53

c Provides an inhibitory quotient (IQ_{95}) of ~ 10 (ratio of C_{trough}: protein binding-adjusted IC_{95} for wild-type HIV-1 virus (0.045 µg/mL)

Elvitegravir plasma exposures are non-linear and less than dose proportional, likely due to solubility-limited absorption. Cobicistat exposures are non-linear and greater than dose-proportional over the range of 50 mg to 400 mg, consistent with a mechanism-based CYP3A inhibitor. The multiple dose pharmacokinetics of emtricitabine are dose proportional over the dose range of 25 to 200 mg. The pharmacokinetics of tenofovir were dose proportional over the dose range 75 to 600 mg and were not affected by repeated dosing at any dose level.

Distribution:

Elvitegravir: Elvitegravir is 98-99% bound to human plasma proteins and binding is independent of drug concentrations over the range of 1 ng/mL to 1.6 µg/mL. The mean plasma to blood drug concentration ratio was 1.37.

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

Emtricitabine: *In vitro* binding of emtricitabine to human plasma proteins is less than 4% and is independent of drug concentration over the range of 0.02 to 200 micrograms per mL.

Tenofovir DF: *In vitro* binding of tenofovir to human plasma proteins is less than 0.7% and is independent of drug concentration over the range of 0.01 to 25 micrograms per mL.

Metabolism:

Elvitegravir: Elvitegravir undergoes primarily oxidative metabolism via CYP3A, and is secondarily glucuronidated via UGT1A1/3 enzymes.

Cobicistat*:* Cobicistat is metabolized via CYP3A (major)- and CYP2D6 (minor)-mediated oxidation and does not undergo glucuronidation.

Emtricitabine and tenofovir*:* Emtricitabine and tenofovir are not significantly metabolized.

Elimination:

Elvitegravir: The median terminal plasma half-life of elvitegravir following administration of STRIBILD is approximately 12.9 hours. After single dose administration of ritonavir-boosted [^{14}C]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.

Cobicistat*:* The median terminal plasma half-life of cobicistat following administration of STRIBILD is approximately 3.5 hours. With single dose administration of [^{14}C] cobicistat after multiple dosing of cobicistat for 6 days, 86% and 8.2% of the administered dose were recovered in feces and urine, respectively.

Emtricitabine and tenofovir*:* Emtricitabine and tenofovir are primarily excreted in the urine by a combination of glomerular filtration and active tubular secretion.

Special Populations and Conditions

Pediatrics: STRIBILD is not recommended for pediatric administration. The pharmacokinetics of STRIBILD has not been studied in pediatric patients <18 years of age.

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

Race:

Elvitegravir: Population pharmacokinetics analysis of elvitegravir in HIV-1 infected patients indicated that race had no clinically relevant effect on the exposure of cobicistat-boosted elvitegravir.

Cobicistat: Population pharmacokinetics analysis of cobicistat in HIV-1 infected patients indicated that race had no clinical relevant effect on the exposure of cobicistat.

Emtricitabine*:* No pharmacokinetic differences due to race have been identified following the administration of emtricitabine.

Tenofovir DF*:* There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations following administration of tenofovir DF.

Gender: No clinically relevant pharmacokinetic differences due to gender have been identified for cobicistat-boosted elvitegravir, cobicistat, emtricitabine or tenofovir DF. There was insufficient pharmacokinetic data in clinical trials to determine the effect of gender on the pharmacokinetics of cobicistat.

Hepatic Insufficiency:

Elvitegravir and Cobicistat: The pharmacokinetics of STRIBILD has not been studied specifically in patients with hepatic insufficiency. Both elvitegravir and cobicistat are primarily metabolized and eliminated by the liver. A study of the pharmacokinetics of cobicistat-boosted elvitegravir was performed in non-HIV-1 infected patients with moderate hepatic impairment. No clinically relevant differences in elvitegravir or cobicistat pharmacokinetics were observed between patients with moderate impairment (Child-Pugh Class B) and healthy patients. No dosage adjustment of elvitegravir or cobicistat is necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of elvitegravir or cobicistat has not been studied.

Emtricitabine: The pharmacokinetics of emtricitabine have not been studied in patients with hepatic impairment; however, emtrictabine is not significantly metabolized by liver enzymes.

Tenofovir DF: The pharmacokinetics of tenofovir following a 300 mg single dose of tenofovir DF 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.

Renal Insufficiency:

Elvitegravir and Cobicistat: The pharmacokinetics of STRIBILD has not been studied specifically in patients with renal insufficiency. A study of the pharmacokinetics of cobicistat-boosted elvitegravir in non-HIV-1 infected patients with severe renal impairment (estimated creatinine clearance below 30 mL/minute) and healthy patients was performed. No clinically relevant differences in elvitegravir or cobicistat pharmacokinetics were observed between patients with severe renal impairment and healthy patients.

Emtricitabine and Tenofovir DF: The pharmacokinetics of emtricitabine and tenofovir are altered in patients with renal insufficiency **(**see **WARNINGS AND PRECAUTIONS, Renal, Nephrotoxicity)**. In patients with creatinine clearance <50 mL/minute, C_{max} and $AUC_{0-\infty}$ of emtricitabine and tenofovir were increased. Because STRIBILD is a fixed dose combination, it should not be prescribed for patients requiring dosage adjustment such as those with moderate to severe renal impairment (creatinine clearance < 50 mL/minute).

Hepatitis B and/or Hepatitis C Virus Coinfection: Limited data from population pharmacokinetic analysis (N=24) indicated that hepatitis B and/or C virus infection had no clinically relevant effect on the exposure of boosted elvitegravir. The pharmacokinetics of emtricitabine and tenofovir DF have not been fully evaluated in patients coinfected with hepatitis B and/or C virus.

STORAGE AND STABILITY

Store at 15–30° C (59–86° F).

- Keep container tightly closed

- Dispense only in original container
- Do not use if seal over bottle opening is broken or missing.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

STRIBILD is available as tablets. Each tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate (which is equivalent to 245 mg of tenofovir disoproxil), as active ingredients. The tablets also include the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, sodium lauryl sulfate and magnesium stearate. The tablets are coated with a coating material containing indigo carmine (FD&C blue #2) aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide and yellow iron oxide. STRIBILD tablets are green, capsule-shaped, film-coated, and debossed with "GSI" on one side and the number "1" surrounded by a square box (1) on the other side. Each bottle contains 30 tablets and a silica gel desiccant and closed with a child-resistant closure.

PART II. SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

STRIBILD tablet is a single tablet regimen containing elvitegravir, cobicistat, emtricitabine and tenofovir DF. Elvitegravir is an HIV-1 integrase strand transfer inhibitor. Cobicistat is a mechanism-based inhibitor of cytochrome P450 (CYP) enzymes of the CYP3A family. Emtricitabine is a synthetic nucleoside analog of cytidine. Tenofovir DF, which is converted *in vivo* to tenofovir, is an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate.

STRIBILD tablets are for oral administration. Each tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate (which is equivalent to 245 mg of tenofovir disoproxil), as active ingredients. The tablets also include the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, sodium lauryl sulfate, and magnesium stearate. The tablets are film-coated with a coating material containing indigo carmine (FD&C blue #2) aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and yellow iron oxide.

Elvitegravir:

Drug Substance

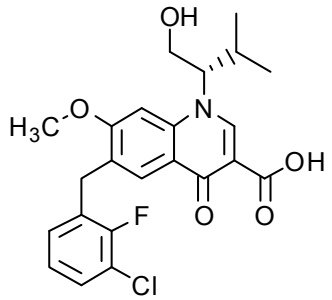
Common Name: elvitegravir (USAN)

Chemical Name: 3-quinolinecarboxylic acid, 6-[(3-chloro-2-fluorophenyl)methyl]-1,4-dihydro-1-[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]-7-methoxy-4-oxo-

Empirical Formula: $C_{23}H_{23}ClFNO_5$

Molecular Weight: 447.9

Structural Formula:



Physicochemical Properties:

Description: Elvitegravir is a white to pale yellow powder.

Solubility: The solubility is approximately 0.0003 mg/mL in water at 20 °C. The partition coefficient (log P) cannot be determined due to its low solubility in aqueous media and the pKa is 6.6 (carboxylic acid).

Cobicistat:

Drug Substance

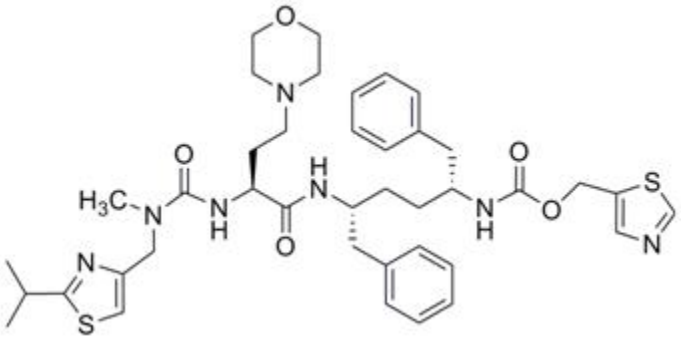
Common Name: cobicistat (USAN)

Chemical Name: 1,3-Thiazol-5-ylmethyl [(2R,5R)-5-{[(2S)-2-[(methyl{[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl}carbamoyl)amino]-4-(morpholin-4-yl)butanoyl]amino}-1,6-diphenylhexan-2-yl]carbamate

Empirical Formula: $C_{40}H_{53}N_7O_5S_2$

Molecular Weight: 776.0

Structural Formula:



Physicochemical Properties:

Description: Cobicistat is adsorbed onto silicon dioxide. Cobicistat is a white to pale yellow solid.

Solubility: The solubility is approximately 0.1 mg/mL in water at 20 °C. The partition coefficient (log P) is 4.3 (*n*-octanol/phosphate buffer pH 8.5) and the pKa is pKa1 = 1.8 (thiazole group), pKa2 = 2.5 (alkylthiazole group), pKa3 = 6.4 (morpholino group).

Emtricitabine:

Drug Substance

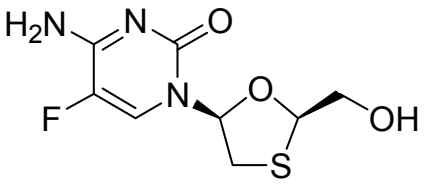
Common Name: emtricitabine (USAN)

Chemical Name: 5-fluoro-1-(2*R*,5*S*)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine

Empirical Formula: $C_8H_{10}FN_3O_3S$

Molecular Weight: 247.24

Structural Formula:



Physicochemical Properties:

Description: Emtricitabine is a white to off-white crystalline powder.

Solubility: The solubility is approximately 112 mg/mL in water at 25 °C. The partition coefficient (log P) is –0.43 and the pKa is 2.65.

Tenofovir DF:

Drug Substance

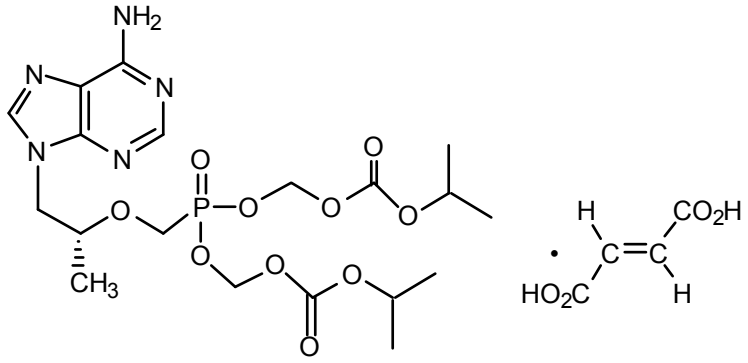
Common Name: tenofovir disoproxil fumarate (USAN)

Chemical Name: 9-[(*R*)-2-[[bis[[(isopropoxycarbonyl)oxy]methoxy]phosphinyl]-methoxy]propyl]adenine fumarate (1:1)

Empirical Formula: $C_{19}H_{30}N_5O_{10}P \bullet C_4H_4O_4$

Molecular Weight: 635.52

Structural Formula:



Physicochemical Properties:

Description: Tenofovir disoproxil fumarate is a white to off-white crystalline powder.

Solubility: The solubility is 13.4 mg/mL in water at 25 °C. The partition coefficient (log P) is 1.25 and the pKa is 3.75.

CLINICAL TRIALS

Study Demographics and Trial Design

Description of Clinical Studies

The efficacy of STRIBILD is based on the analyses of 144-week data from two randomized, double-blind, active-controlled studies, Study GS-US-236-0102 and Study GS-US-236-0103 in treatment- naïve, HIV-1 infected patients (N=1408) with baseline estimated creatinine clearance > 70 mL/minute.

The efficacy of STRIBILD in HIV-1 infected virologically suppressed patients is based on the analyses of 48-week data from two randomized, open-label studies, Study GS-US-236-0115 and Study GS-US-236-0121. Patients in all studies had estimated creatinine clearance > 70 mL/min at screening.

Treatment-Naïve HIV-1 Infected Patients

In Study 102, patients were randomized in a 1:1 ratio to receive either STRIBILD (elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir DF 300 mg; N=348) once daily or ATRIPLA (efavirenz 600 mg/ emtricitabine 200 mg/tenofovir DF 300 mg; N=352) once daily.

In Study 103, patients were randomized in a 1:1 ratio to receive either STRIBILD (elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir DF 300 mg; N=353) once daily or ATV + RTV (atazanavir 300 mg + ritonavir 100 mg) + TRUVADA (emtricitabine 200 mg/tenofovir DF 300 mg) (N=355) once daily.

For demographic and baseline characteristics for Study 102 and 103, see Table 10.

Table 10. Demographic and Baseline Characteristics of Antiretroviral Treatment-naïve HIV-1 Infected Adult Patients in Studies GS-US-236-0102 and GS-US-236-0103

Study	Dosage, Route of Administration	Demographics	
		Treatment Arm	**Control Arm**
Study GS-US-236-0102	**STRIBILD (elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir DF 300 mg) once daily (Treatment arm)** **or** **ATRIPLA (efavirenz 600 mg/ emtricitabine 200 mg/tenofovir DF 300 mg) once daily. (Comparator arm)**	**N=348** **Gender: n (%)** Male 307 (88.2) Female 41 (11.8) **Age: median (range)** 37.0 (18–63) **Race:** White – 214 (61.5) Black/ African Heritage –106 (30.5) Asian – 6 (1.7) Other – 16 (4.6) American Indian/Alaska Native – 2 (0.6) Native Hawaiian/Pacific Islander – 4 (1.1)	**N=352** **Gender: n (%)** Male 316 (89.8) Female 36 (10.2) **Age: median (range)** 38.0 (18–67) **Race:** White – 227 (64.5) Black/ African Heritage –91 (25.9) Asian – 10 (2.8) Other – 19 (5.4) American Indian/Alaska Native – 4 (1.1) Native Hawaiian/Pacific Islander – 1 (0.3)
		Baseline Body Mass Index - kg/m^2	
		25.5 (16.5-53.2)	25.1 (16.5-53.3)
		Baseline disease characteristics	
		Plasma HIV-1 RNA log_{10} copies/ml	
		4.75 (2.64-6.42)	4.78 (3.03-6.54)
		Patients with viral load < 100,000 copies/ml	
		66.1 %	67.0 %
		Patients with viral load > 100,000 copies/ml	
		33.9	33.0
		CD4+ cell count /µL	
		376 (14-1348)	383 (3-1003)
		Patients with CD4+ cell counts ≤200 cells/mm^3	
		12.3 %	14.5 %

All data are presented as median (range).

Study	Dosage, Route of Administration	Demographics	
		Treatment Arm	**Control Arm**
Study GS-US-236-0103	**STRIBILD (elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir DF 300 mg) once daily (Treatment arm)** **or** **ATV + RTV (atazanavir 300 mg + ritonavir 100 mg) + TRUVADA (emtricitabine 200 mg/tenofovir DF 300 mg) once daily. (Comparator arm)**	**N=353** **Gender: n (%)** Male 324 (91.8) Female 29 (8.2) **Age: median (range)** 37.0 (19-72) **Race:** White – 250 (70.8) Black/ African Heritage –72 (20.4) Asian – 17 (4.8) Other – 11 (3.1) American Indian/Alaska Native – 2 (0.6) Native Hawaiian/Pacific Islander –1 (0.3)	**N=355** **Gender: n (%)** Male 316 (89.0) Female 39 (11.0) **Age: median (range)** 39.0 (19-69) **Race:** White – 277 (78.0) Black/ African Heritage –47 (13.2) Asian – 17 (4.8) Other – 9 (2.5) American Indian/Alaska Native – 3 (0.9) Native Hawaiian/Pacific Islander –2 (0.6)
		Body Mass Index - kg/m^2	
		24.4 (15.8-53.2)	25.0 (17.8-51.4)
		Baseline disease characteristics	
		HIV-1 RNA (range) log$_{10}$ copies/ml	
		4.88 (1.69-6.58)	4.86 (2.98-6.63)
		Patients with viral load < 100,000 copies/ml	
		57.5 %	60.3 %
		Patients with viral load > 100,000 copies/ml	
		42.5 %	39.7 %
		Baseline CD4+ cell count /µL	
		351 (5-1132)	366 (10-963)
		Patients with CD4+ cell counts ≤200 cells/mm^3	
		15.3 %	11.0 %

All data are presented as median (range).

Clinical Efficacy
In Study 102, virologic success (HIV-1 RNA <50 copies/mL) at Week 48 was 88% in the STRIBILD-treated patients and 84% in the ATRIPLA-treated patients, respectively. In Study 103, virologic success (HIV-1 RNA <50 copies/mL) at Week 48 was 90% in the STRIBILD-treated patients and 87% in the ATV + RTV + TRUVADA-treated patients, respectively.

Treatment outcome of Study 102 and 103 through 144 weeks are presented in Table 11.

Table 11. Virologic Outcome of Randomized Treatment of Study GS-US-236-102 and Study GS-US-236-103 at Week 48[a] and Week 144[c]

	Week 48				Week 144			
	Study GS-US-236-102		Study GS-US-236-103		Study GS-US-236-102		Study GS-US-236-103	
	STRIBILD (N=348)	ATRIPLA (N=352)	STRIBILD (N=353)	ATV/r + 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[c]	7%	7%	5%	5%	7%	10%	8%	7%
No Virologic Data in Week 48, 96 or 144 Window								
Discontinued Study Drug Due to AE or Death[d]	3%	5 %	3%	5 %	6%	8%	6%	8%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[e]	2%	3%	2%	3%	5%	7%	8%	9%
Missing Data During Window but on Study Drug	0%	0%	0%	0%	1%	0%	1%	1%

a Week 48 window is between Day 309 and 378 (inclusive).
b Week 144 window is between Day 967 and 1050 (inclusive).
c Includes patients who had ≥50 copies/mL in the Week 48 and Week 144 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.
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 102, the mean increase from baseline in CD4+ cell count at Week 48 and Week 144 was 239 and 321 cells/mm^3 in the STRIBILD-treated patients, 206 and 300 cells/mm^3 in the comparator-treated patients, respectively. In Study 103, the mean increase from baseline in CD4+ cell count at Week 48 and Week 144 was 207 and 280 cells/mm^3 in the STRIBILD-treated patients, 211 and 293 cells/mm^3 in the comparator-treated patients, respectively.

In Virologically-Suppressed HIV-1 Infected 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 randomized in a 2:1 ratio to either switch to STRIBILD (STRIBILD arm, N = 293; randomized and dosed) or stay on their baseline antiretroviral regimen for 48 weeks (PI + RTV + TRUVADA arm, N = 140; randomized and dosed).

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 randomized in a 2:1 ratio to either switch to STRIBILD (STRIBILD arm, N = 291; randomized and dosed), or stay on their baseline antiretroviral regimen for 48 weeks (NNRTI +TRUVADA arm, N = 143; randomized and dosed).

For demographic and baseline characteristics for Study 115 and 121, see Table 12.

Table 12. Demographic and Baseline Characteristics of Virologically Suppressed HIV-1 Infected Adult Patients with No History of Virologic Failure in Studies GS-US-236-0115 and GS-US-236-0121

Study	Dosage, Route of Administration	Demographics	
		Treatment Arm	**Control Arm**
Study GS-US-236-0115	**STRIBILD (elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir DF 300 mg) once daily (Treatment arm)** **or** **PI + RTV + TRUVADA arm, (Comparator arm)**	**N=293** **Gender: n (%)** Male 250 (85.3) Female 43 (14.7) **Age: median (range)** 41.0 (22-76) **Race:** White – 234 (79.9) Black/ African Heritage – 43 (14.7) Asian – 7 (2.4) Other – 5 (1.7) American Indian/Alaska Native – 2 (0.7) Native Hawaiian/Pacific Islander – 0 (0.0)	**N=140** **Gender: n (%)** Male 121 (86.4) Female 19 (13.6) **Age: median (range)** 40.0 (21-62) **Race:** White – 113 (80.7) Black/ African Heritage – 20 (14.3) Asian – 2 (1.4) Other – 2 (1.4) American Indian/Alaska Native – 1 (0.7) Native Hawaiian/Pacific Islander – 0 (0.0)
		Baseline Body Mass Index - kg/m^2	
		25.6 (17.4-56.5)	25.3 (18.6-38.4)
		Baseline disease characteristics	
		CD4+ cell count /mm^3	
		610 cells/mm^3 (74-1919)	
		Plasma HIV-1 RNA ≤200 copies/ml	
		293	135
		CD4 cell count /µL	
		564 (74-1919)	585 (106-1533)
		Patients with CD4 cell counts ≤200 count /µL	
		3.1%	4.3 %

Study	Dosage, Route of Administration	Demographics	
		Treatment Arm	**Control Arm**
Study GS-US-236-0121	**STRIBILD arm; randomized and dosed), or stay on their baseline antiretroviral regimen for 48 weeks. (Treatment arm)** **or** **NNRTI + TRUVADA arm; randomized and dosed (Comparator arm)**	**N=291** **Gender: n (%)** Male 268 (92.1) Female 23 (7.9) **Age: median (range)** 43.0 (20-70) **Race:** White – 231 (79.4) Black/ African Heritage – 49 (16.8) Asian – 4 (1.4) Other – 4 (1.4) American Indian/Alaska Native – 2 (0.7) Native Hawaiian/Pacific Islander – 1 (0.3)	**N=143** **Gender: n (%)** Male 134 (94.7) Female 9 (6.3) **Age: median (range)** 39.0 (22-64) **Race:** White – 109 (76.2) Black/ African Heritage – 23 (16.1) Asian – 9 (6.3) Other – 2 (1.4) American Indian/Alaska Native – 0 (0.0) Native Hawaiian/Pacific Islander – 0 (0.0)
		Baseline Body Mass Index - kg/m^2	
		25.6 (15.6-41.0)	24.7 (18.4-51.6)
		Baseline disease characteristics	
		Baseline CD4+ cell count /mm^3	
		588 cells/mm^3 (100-1614)	
		Baseline plasma HIV-1 RNA (range) ≤200 copies/ml	
		289	143
		Baseline CD4 cell count /µL (range)	
		561 (100-1614)	562 (181-1286)
		Patients with CD4 cell counts ≤200 count /µL	
		1.4	0.7

All data are presented as median (range).

Virologic outcomes of Study GS-US-236-0115 and Study GS-US-236-0121 are presented in Table 13. Five treated patients were excluded from the efficacy analysis and were not included in Table 12. In 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 GS-US-236-0121, one STRIBILD patient had protocol-prohibited documented resistance.

Table 13. Virologic Outcomes of Randomized Treatment in Study GS-US-236-0115 and 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)**	**NNRTI+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 Window	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/mm^3 in the STRIBILD-treated patients and 32 cells/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/mm^3 in the NNRTI + TRUVADA-treated patients.

DETAILED PHARMACOLOGY

Mechanism of Action

Elvitegravir: Elvitegravir is a HIV-1 integrase strand transfer inhibitor (INSTI), 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.

Emtricitabine: Emtricitabine, a synthetic nucleoside analog 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 and 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.

Tenofovir DF: Tenofovir DF is an acyclic nucleoside phosphonate diester analog 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 DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Antiviral Activity

Elvitegravir, Cobicistat, Emtricitabine and Tenofovir: The triple combination of elvitegravir, emtricitabine and tenofovir was not antagonistic in cell culture combination antiviral activity assays and was not affected by the addition of cobicistat.

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/nucleotide reverse transcriptase inhibitors (NRTIs) (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, or zidovudine); non-nucleoside reverse transcriptase inhibitors (NNRTIs) (efavirenz, etravirine,

nevirapine or rilpivirine); protease inhibitors (PIs) (amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, or tipranavir); the integrase strand transfer inhibitor 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 antagonize the antiviral effects of elvitegravir, emtricitabine, or tenofovir.

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. The EC_{50} values for emtricitabine were in the range of 0.0013–0.64 μM (0.0003–0.158 μg/mL). In drug combination studies of emtricitabine with nucleoside reverse transcriptase inhibitors (abacavir, lamivudine, stavudine, zalcitabine, and zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, and nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, and saquinavir), additive to synergistic effects were observed. Most of these drug combinations have not been studied in humans. Emtricitabine displayed antiviral activity *in vitro* against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007–0.075 μM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.007–1.5 μM).

Tenofovir DF: 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 EC_{50} values for tenofovir were in the range of 0.04–8.5 μM. In drug combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, and zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, and nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, and saquinavir), additive to synergistic effects were observed. Most of these drug combinations have not been studied in humans. Tenofovir displayed antiviral activity *in vitro* against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values ranged from 0.5–2.2 μM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 1.6 μM to 4.9 μM).

Resistance

In Cell Culture:

Elvitegravir: HIV-1 isolates with reduced susceptibility to elvitegravir have been selected in cell culture. Reduced susceptibility to elvitegravir was associated with the primary integrase substitutions T66A/I, E92G/Q, S147G, and Q148R Additional integrase substitutions observed in cell culture selection included D10E, S17N, H51Y, F121Y, S153F/Y, E157Q, D232N, R263K, and V281M.

Emtricitabine and Tenofovir: HIV-1 isolates with reduced susceptibility to emtricitabine or tenofovir have been selected in cell culture. Reduced susceptibility to emtricitabine was

associated with M184V/I substitutions in HIV-1 reverse transcriptase. HIV-1 isolates selected by tenofovir expressed a K65R substitution in HIV-1 reverse transcriptase and showed a 2-4 fold reduction in susceptibility to tenofovir. In addition, a K70E mutation in HIV-1 RT has been selected by tenofovir DF and results in low-level reduced susceptibility to abacavir, emtricitabine, tenofovir, and lamivudine.

In Treatment-Naïve HIV-1 Infected Patients:

In a pooled analysis of antiretroviral-naïve patients receiving STRIBILD in Study GS-US-236-102 and Study GS-US-236-103, genotyping was performed on plasma HIV-1 isolates from all patients with confirmed virologic failure or who had HIV-1 RNA > 400 copies/mL at Week 48, Week 96 and Week 144 or at the time of early study drug discontinuation.

As of Week 48, the development of one or more primary elvitegravir, emtricitabine, or tenofovir resistance-associated mutation was observed in 13 out of 25 patients with evaluable genotypic data from paired baseline and STRIBILD treatment-failure isolates (1.9 %, 13/701 patients). As of Week 96, the development of one or more primary elvitegravir, emtricitabine, or tenofovir resistance-associated mutation was observed in 44% (16/36) patients with evaluable genotypic data from paired baseline and STRIBILD treatment-failure isolates (2.3%, 16/701 patients). As of Week 144, the development of one of 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 E92Q (N=9), N155H (N=5), Q148R (N=3), T66I (N=2), and T97A (N=1) in integrase. Other mutations in integrase that occurred in addition to a primary INSTI resistance mutation each in single cases were H51Y, L68V, G140C, S153A, E157Q, V165I, H183P and G163R. Most patients who developed resistance mutations to elvitegravir developed 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 Week 144) similar to the overall population (78%), and no emergent resistance to elvitegravir, emtricitabine, or tenofovir DF.

In Virologically Suppressed HIV-1 Infected Patients:

No emergent resistance to STRIBILD was identified in clinical trials of virologically suppressed patients who switched from a regimen containing a ritonavir-boosted PI (GS-US-236-0115, N=290), an NNRTI (GS-US-236-0121, N=290) or raltegravir (GS-US-236-0123, N=48).

Twenty patients from these studies who switched to STRIBILD had the NNRTI-associated K103N mutation in their historical genotype prior to starting initial antiretroviral therapy.

Eighteen of these 20 patients maintained virologic suppression through 48 weeks. Due to protocol violation, two patients with historical K103N mutations discontinued early with HIV-1 RNA <50 copies/mL.

Cross-resistance

STRIBILD: STRIBILD-treatment failure subject isolates exhibited varying degrees of cross resistance within the INSTI and NRTI drug classes depending on the specific substitutions observed. These isolates remained susceptible to all NNRTIs and protease inhibitors.

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.

Elvitegravir: Cross-resistance has been observed among INSTIs. Elvitegravir-resistant viruses showed varying degrees of cross-resistance in cell culture to raltegravir depending on the type and number of substitutions in HIV-1 integrase. Among the four primary elvitegravir resistance-associated substitutions detected in the STRIBILD-treatment virologic failure isolates, E92Q, Q148R, and N155H individually conferred reduced susceptibility both to elvitegravir (greater than 32-fold) and raltegravir (greater than 5-fold) when introduced into a wild-type virus by site-directed mutagenesis. The T66I substitution conferred greater than 14-fold reduced susceptibility to elvitegravir but less than 3-fold to raltegravir. Among the three primary raltegravir resistance-associated substitutions (Y143C/H/R, Q148H/K/R, and N155H), all but Y143C/H conferred significant reductions in susceptibility to elvitegravir (greater than 5-fold). Most viruses expressing elvitegravir or raltegravir resistance mutations maintain susceptibility to dolutegravir.

Emtricitabine: Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine and zalcitabine but retained susceptibility *in vitro* to didanosine, stavudine, tenofovir, zidovudine, and NNRTIs (delavirdine, efavirenz, and nevirapine). Isolates from heavily treatment-experienced patients containing the M184V/I amino acid substitution in the context of other NRTI resistance-associated substitutions may retain susceptibility to tenofovir. HIV-1 isolates containing the K65R substitution, selected *in vivo* by abacavir, didanosine, tenofovir, and zalcitabine, demonstrated reduced susceptibility to inhibition by emtricitabine. Viruses harboring mutations conferring reduced susceptibility to stavudine and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to emtricitabine. HIV-1 containing the K103N substitution associated with resistance to NNRTIs was susceptible to emtricitabine.

Tenofovir DF: The K65R and K70E mutations result in reduced susceptibility to abacavir, didanosine, lamivudine, emtricitabine, tenofovir and zalcitabine, but retain sensitivity to zidovudine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors the K65R or K70E mutation. HIV-1 isolates from patients (N=20) whose HIV-1 expressed a mean of 3 zidovudine-associated RT amino acid substitutions (M41L, D67N, K70R,

L210W, T215Y/F, or K219Q/E/N) showed a 3.1-fold decrease in the susceptibility to tenofovir. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the RT showed reduced susceptibility to tenofovir.

TOXICOLOGY

General

No toxicology studies have been conducted with STRIBILD tablets. The toxicology information is based on studies conducted with elvitegravir, cobicistat, emtricitabine or tenofovir DF as individual agents.

Elvitegravir*:* The nonclinical safety profile of elvitegravir has been studied in mice, rats, rabbits and dogs. Elvitegravir has demonstrated minimal acute toxicity after oral dosing to rats and dogs (lethal dose > 2000 mg/kg and > 1000 mg/kg in rats and dogs, respectively). There were no significant adverse effects in mice treated for 13 weeks at doses up to 2000 mg/kg/day. No adverse target organ toxicity has been observed in studies up to 26 weeks in rats and 39 weeks in dogs at dose levels up to 2000 mg/kg/day and 100 mg/kg/day, respectively. Two nonadverse findings, not considered clinically relevant, were observed in rats and dogs. Lipid-like vacuoles were observed in the lamina propria, mainly in the upper small intestine (duodenum and/or jejunum) in rats and dogs, but there were no toxic or reactive changes associated with these vacuoles. Increased cecal weight and dilatation with whitish loose contents in rats were not accompanied by histopathologic changes or adverse clinical observations. The NOAELs for elvitegravir are considered to be 2000 mg/kg/day for mice and rats, and 100 mg/kg/day for dogs – the highest doses evaluated in the 13-week, 26-week, and 39-week repeat-dose studies, respectively.

Cobicistat: The nonclinical safety profile of cobicistat has been studied in mice, rats, rabbits and dogs. The single dose toxicity of COBI was low; the maximum tolerated dose was 100 mg/kg in mice; no adverse effects were noted in rats at 500 mg/kg. In repeat-dose studies (up to 13 weeks in mice, up to 26 weeks in rats; up to 39 weeks in dogs), target organs identified were liver (mouse, rat, and dog) and thyroid (rat). The liver effects in mice and rats are considered adaptive changes, are commonly seen in rodents with microsomal enzyme inducers, and are considered secondary to microsomal enzyme induction. In dogs, hepatic changes were considered an adaptive response, and not adverse based on their minimal severity, the absence of degeneration, and their reversibility after cessation of dosing. The thyroid changes in rats are considered adaptive changes, secondary to hepatic microsomal enzyme induction and thyroid hormone imbalance. The thyroid effects are considered rodent specific and predispose rats, but not humans, to thyroid neoplasms. The NOAELs for cobicistat are considered to be 5 (males) and 50 (females) mg/kg/day for mice, 30 mg/kg/day for rats, and 10 mg/kg/day for dogs in the 13-week, 26-week, and 39-week repeat-dose studies, respectively.

Safety Pharmacology – QT prolongation

Cobicistat: Ex vivo rabbit studies and *in vivo* dog studies suggest that cobicistat has a low potential for QT prolongation, and may slightly prolong the PR interval and decrease left

ventricular function at mean concentrations at least 11-fold higher than the human exposure at the recommended 150 mg daily dose (see **ACTION AND CLINICAL PHARMACOLOGY, Effects on Electrocardiogram**).

In a human clinical study of 35 healthy patients, echocardiograms performed at baseline and after receiving 150 mg cobicistat once daily for at least 15 days indicated no clinically significant change in left ventricular function.

For additional information on toxicology, reproductive toxicology, mutagenicity and carcinogenicity, please consult the Product Monographs for EMTRIVA and VIREAD.

Carcinogenesis

Elvitegravir: In long-term carcinogenicity studies of elvitegravir, no drug-related increases in tumor incidence were found in mice at doses up to 2000 mg/kg/day alone or in combination with 25 mg/kg/day ritonavir (3 and 14 times, respectively, the human systemic exposure at the therapeutic 150 mg daily dose), or in rats at doses up to 2000 mg/kg/day (20 times the human systemic exposure at the therapeutic daily dose).

Cobicistat: In a long-term carcinogenicity study in mice, no drug-related increases in tumor incidence were observed at doses up to 50 and 100 mg/kg/day (males and females, respectively). Cobicistat exposures at these doses were approximately 9 (male) and 21 (females) times, respectively, the human systemic exposure at the therapeutic daily dose. In a long-term carcinogenicity study of cobicistat in rats, an increased incidence of follicular cell adenomas and/or carcinomas in the thyroid gland was observed at doses of 25 and 50 mg/kg/day in males, and at 30 mg/kg/day in females. The follicular cell findings are considered to be rat-specific, secondary to hepatic microsomal enzyme induction and thyroid hormone imbalance, and are not relevant for humans. At the highest doses tested in the rat carcinogenicity study, systemic exposures were approximately 2.6 times the human systemic exposure at the therapeutic daily dose.

Emtricitabine: In long-term oral carcinogenicity studies of emtricitabine, no drug-related increase in tumor incidence was found in mice at doses up to 750 mg/kg/day (23 times the human systemic exposure at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (28 times the human systemic exposure at the therapeutic dose).

Tenofovir DF: Long-term oral carcinogenicity studies were conducted in mice and rats receiving tenofovir DF. In the mouse study, one male and two female mice in the 600 mg/kg/day group (10 times the human systemic exposure at the recommended human dose of 300 mg/day) had duodenal tumors. The mechanism underlying this effect is uncertain but may relate to high local drug concentrations in the gastrointestinal tract. No treatment-related tumors were seen in mice in the 100 or 300 mg/kg/day groups. In the rat study at doses of 30, 100, and 300 mg/kg/day (approximately 4 times human exposure), no treatment-related increase in tumor incidence was observed.

Mutagenesis

Elvitegravir: Elvitegravir was not genotoxic in the reverse mutation bacterial test (Ames test) and the rat micronucleus assay. In an *in vitro* chromosomal aberration test, elvitegravir was negative with metabolic activation; however, an equivocal response was observed without activation.

Cobicistat: Cobicistat was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or mouse micronucleus assays.

Emtricitabine: Emtricitabine was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or mouse micronucleus assays.

Tenofovir DF: Tenofovir DF was not mutagenic in the *in vitro* bacterial mutation (Ames) assay (*Salmonella-Eschericia coli*/Mammalian-Microsome Reverse Mutation Assay) but was mutagenic in the *in vitro* mouse lymphoma assay (L5178Y TK +/– Forward Mutation Assay), with and without metabolic activation. Tenofovir DF was not clastogenic in the *in vivo* mouse micronucleus assay at plasma exposure levels of more than 10x the human exposure.

Reproductive Toxicology

Elvitegravir: Reproductive studies were conducted in rats and rabbits. Animal studies do not indicate direct or indirect harmful effects of elvitegravir with respect to pregnancy, fetal development, parturition or postnatal development. There were no effects on mating or fertility parameters.

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-fetal 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 daily dose of 150 mg.

Elvitegravir did not affect fertility in male and female rats at approximately 16- and 30-fold higher exposures (AUC), respectively, than in humans at 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: Reproductive studies were conducted in rats and rabbits. Animal studies do not indicate direct or indirect harmful effects of cobicistat with respect to pregnancy, fetal development, parturition or postnatal development. There were no effects on mating and fertility parameters.

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-fetal 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.

Cobicistat did not affect fertility in male or female rats at daily exposures (AUC) approximately 4-fold higher than human exposures at the recommended 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.

Emtricitabine: The incidence of fetal variations and malformations was not increased in embryofetal toxicity studies performed with emtricitabine in mice at exposures (AUC) approximately 60-fold higher and in rabbits at approximately 120-fold higher than human exposures at the recommended daily dose.

Emtricitabine did not affect fertility in male rats at approximately 140-fold or in male and female mice at approximately 60-fold higher exposures (AUC) than in humans given the recommended 200 mg daily dose. Fertility was normal in the offspring of mice exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 60-fold higher than human exposures at the recommended 200 mg daily dose.

Tenofovir DF: Tenofovir DF had no adverse effects on fertility or embryo-fetal development in rats at doses 450 mg/kg/day and in rabbits at doses up to 300 mg/kg/day (14 and 19 times the human dose based on body surface area comparisons).

Tenofovir DF had no adverse effects on fertility or general reproductive performance in rats at doses up to 600 mg/kg/day. In a study of effects on peri- and postnatal development in rats, reduced pup body weights, survival and delay in sexual maturation was in rats at the maternally toxic doses of 450 and 600 mg/kg (approximately 14 and 19 times the human dose based on body surface area comparisons). There were no adverse effects on growth, development, behavior, or reproductive parameters at non-maternally toxic doses (150 mg/kg/day).

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PART III. CONSUMER INFORMATION

PrSTRIBILD®
(elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) tablets

This leaflet is Part III of a three-part "Product Monograph" published when STRIBILD was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about STRIBILD. Contact your healthcare professional if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
STRIBILD contains 4 medicines, elvitegravir, cobicistat, EMTRIVA® (emtricitabine) and VIREAD® (tenofovir DF), combined in one single tablet regimen.

STRIBILD is used as a complete regimen to treat people with HIV infection. STRIBILD is for adults age 18 and older. STRIBILD is for people who do not have an HIV virus that is resistant to STRIBILD. STRIBILD has not been studied in children under age 18 or adults over age 65.

What it does:
STRIBILD lowers the amount of HIV in the blood (viral load).

HIV infection destroys CD4+ (T) cells, which are important to the immune system. The immune system helps fight infection. After a large number of T cells are destroyed, acquired immune deficiency syndrome (AIDS) develops.

STRIBILD may help increase the count of CD4+ (T) white blood cells that help fight off other infections. Lowering the amount of HIV in the blood and increasing the CD4+ (T) lowers the chance of getting infections that happen when your immune system is weak (opportunistic infections).

STRIBILD does not cure HIV infection or AIDS. The long-term effects of STRIBILD are not known at this time. People taking STRIBILD may still get opportunistic infections or other conditions that happen with HIV infection. Opportunistic infections are infections that develop because the immune system is weak. Some of these conditions are pneumonia, herpes virus infections, and *Mycobacterium avium* complex (MAC) infections. **It is very important that you see your healthcare professional regularly while taking STRIBILD.**
STRIBILD has not been shown to reduce the risk of passing HIV to others through sexual contact or blood contamination. Continue to practice safe sex. Use latex or polyurethane condoms to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood. Do not re-use or share needles.

When it should not be used:
Together with your healthcare professional you need to decide whether STRIBILD is right for you.

Do not take STRIBILD if:
- you are taking any medication that is listed in this pamphlet under **"Drugs that should not be taken with STRIBILD" (**see **INTERACTIONS WITH THIS MEDICATION).**
- you are allergic to STRIBILD or any of its ingredients. The medicinal ingredients are elvitegravir, cobicistat, emtricitabine and tenofovir DF **(**see: **What the important nonmedicinal ingredients are).**

What the medicinal ingredients are:
elvitegravir
cobicistat
emtricitabine
tenofovir disoproxil fumarate (tenofovir DF)

What the important nonmedicinal ingredients are:
lactose monohydrate, microcrystalline cellulose, silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, sodium lauryl sulfate, magnesium stearate, indigo carmine FD&C Blue #2 aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide and yellow iron oxide.

What dosage forms it comes in:
STRIBILD is available as tablets. Each tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate (which is equivalent to 245 mg of tenofovir disoproxil), as active ingredients. The tablets are green, modified capsule-shaped, film-coated, debossed with "GSI" on one side and 1 on the other side. Each bottle contains 30 tablets and a silica gel desiccant and is closed with a child-resistant closure.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- The class of medicines to which emtricitabine and tenofovir DF, two of the components of STRIBILD, belongs (NRTIs) can cause a condition called lactic acidosis (build-up of acid in the blood). The symptoms that may be signs of lactic acidosis include: feeling very weak, tired or uncomfortable; unusual or unexpected stomach discomfort; feeling cold; feeling dizzy or lightheaded; suddenly developing a slow or irregular heartbeat. This rare but serious side effect has occasionally been fatal. Lactic acidosis occurs more often in women, particularly if they are very overweight.
- Severe liver problems can happen in people who take STRIBILD or similar medicines. You may develop an enlarged liver (hepatomegaly) or a fatty liver (steatosis). Non-specific symptoms such as yellowing of the skin and eyes, nausea, vomiting and stomach pain might indicate the development of liver problems. If you notice the above symptoms of either lactic acidosis or severe liver problems, stop taking STRIBILD and consult a healthcare professional immediately.
- **"Flare-ups" of Hepatitis B Virus infection,** in which the disease suddenly returns in a worse way than before, can occur if you have hepatitis B and stop taking STRIBILD. Do not stop taking STRIBILD without your healthcare professional's advice. If you stop taking STRIBILD, tell your healthcare professional immediately about any new, unusual or worsening symptoms that you notice after stopping treatment. After you stop taking STRIBILD, your healthcare professional will still need to check your health and take blood tests to check your liver. STRIBILD is not approved for the treatment of hepatitis B virus infection.
- The most serious possible side effect is harm to the kidneys, including damage to kidney cells, kidney tissue inflammation and kidney failure. Your healthcare professional may monitor your kidney function before beginning and while receiving STRIBILD. Some patients treated with tenofovir DF (a component of STRIBILD) have had kidney problems. Your healthcare professional may need to perform additional blood tests if you have had kidney problems in the past or need to take another drug that can cause kidney problems.
- In animal studies, tenofovir DF, a component of STRIBILD, caused harm to the bones of animals. If you notice bone pain, or suffer a bone fracture, or other bone problem, consult your healthcare professional. **If you have bone problems, you may wish to discuss calcium and/or vitamin D supplementation with your healthcare professional. The effect of supplementation with calcium and/or vitamin D is unknown.**
- Patients who experience dizziness, trouble concentrating, or drowsiness should avoid driving or operating machinery.
- If you have advanced HIV infection (AIDS) and have an infection, you may develop symptoms of infection and inflammation or worsening of the symptoms of an existing infection once treatment with STRIBILD is started. These symptoms may indicate that your body's improved immune system is fighting infection. If you notice signs of inflammation or infection, tell your healthcare professional at once.

BEFORE you use STRIBILD (elvitegravir/cobicistat /emtricitabine/tenofovir DF) talk to your healthcare professional:

If you are pregnant or plan to become pregnant: It is not known if STRIBILD can harm your unborn child.

Pregnancy Registry. There is a pregnancy registry for women who take antiviral medicines during pregnancy. This registry collects information about your health and your baby's health. If you become pregnant while taking STRIBILD, talk with your healthcare professional about taking part in this registry.

If you are breast-feeding or plan to breast-feed: Do not breast-feed if you have HIV because of the chance of passing the HIV virus to your baby. Two of the components of STRIBILD, emtricitabine and tenofovir DF, can be passed to your baby in your breast milk and may cause harm to your baby. If you are a woman who has or will have a baby, talk with your healthcare professional about the best way to feed your baby.

If you have other medical conditions: Let your healthcare professional know if you have other medical conditions, especially liver problems (including hepatitis B or C virus infection), kidney problems, or have or are at risk for bone disease or bone related problems or pancreatitis (inflammation of the pancreas).

If you are taking other medicines: Some medicines can interact when taken together, including prescription and non-prescription medicines, herbal products and dietary supplements **(**see: **INTERACTIONS WITH THIS MEDICATION).**

INTERACTIONS WITH THIS MEDICATION

Drugs that <u>must</u> not be taken with STRIBILD:

- alfuzosin hydrochloride (Xatral®)
- apixaban (Eliquis®), rivaroxaban (Xarelto®)
- astemizole* (Hismanal®) or terfenadine (Seldane®)
- cisapride* (Prepulsid®)
- carbamazepine (Carbatrol®, Epitol®, Equetro®, Tegretol®)
- ergot-containing medicines: dihydroergotamine, ergonovine, ergotamine, methylergonovine, such as Cafergot®, Migranal®, D.H.E. 45®*, Ergotrate®, Methergine®*, Migergot®*, Ergomar®*, and others
- lovastatin (Advicor®, Altoprev®*, Mevacor®)
- lurasidone (Latuda®)
- midazolam* (Versed®), when taken by mouth
- phenobarbital (Luminal®)
- phenytoin (Dilatin®, Phenytek®)
- pimozide (Orap®)
- rifampin (Rifadin®, Rifamate®*, Rifater®, Rofact®)
- salmeterol (Advair®, Serevent®)
- sildenafil (Revatio®), when used for treating lung problems
- simvastatin (Simcor®*, Vytorin®*, Zocor®)
- St. John's wort *(Hypericum perforatum)* or products containing St. John's wort
- triazolam (Halcion®*)

*Not available in Canada

If you are taking STRIBILD, you should not take:

- Do not take STRIBILD if you are on other medications that may affect your kidneys and have not discussed this with your healthcare professional.
- Any other medicines to treat HIV infection.
- Medicines that contain the same active components, elvitegravir (GENVOYA®), cobicistat (Evotaz™, GENVOYA®, Prezcobix® or TYBOST®), emtricitabine or tenofovir DF (ATRIPLA®, COMPLERA®, DESCOVY®, EMTRIVA®, GENVOYA®, ODEFSEY™, TRUVADA®, or VIREAD®)
- Medicines that contain lamivudine (Combivir®, 3TC® Heptovir®, Kivexa®, Triumeq® or Trizivir®)
- Medicines that contain tenofovir alafenamide (DESCOVY, GENVOYA®, ODEFSEY™, or VEMLIDY™)
- ritonavir (Holkira™ Pak, Kaletra®, Norvir®)
- adefovir (HEPSERA®)
- ledipasvir/sofosbuvir (HARVONI®)

Also tell your healthcare professional if you take:

- An antacid medicine that contains aluminum, magnesium hydroxide, or calcium carbonate. Take antacids at least 2 hours before or after you take STRIBILD.
- Antidepressants such as trazodone
- Antifungals such as ketoconazole (Nizoral®), itraconazole (Sporanox®) and voriconazole (Vfend®)
- Antiarrhythmics such as amiodarone (Cordarone®), flecainide (Tambacor®) and quinidine (Neudexta®)
- Antibacterials such as clarithromycin (Biaxin®) and telithromycin (Ketek®)
- Antimycobacterials such as rifabutin (Mycobutin®)
- Anticoagulants such as warfarin (Coumadin®), dabigatran (Pradaxa®), edoxaban (Lixiana®)
- Antigout (colchicine)
- Antipsychotics such as quetiapine (Seroquel®)
- Beta-blockers such as metoprolol (Lopressor®) and timolol
- Calcium channel blockers such as amlodipine (Norvasc®), diltiazem (Cardizem®), and felodipine
- Cholesterol lowering agents such as atorvastatin (Lipitor®)
- Corticosteroids such as betamethasone, budesonide, dexamethasone, fluticasone (Flonase®), mometasone, and triamcinolone
- Endothelial receptor antagonists such as bosentan (Tracleer®)
- Hormonal contraceptives such as norgestimate/ethinyl estradiol and drospirenone/ethinyl estradiol
- Immunosuppressants such as cyclosporine (Neoral®), sirolimus (Rapamune®) and tacrolimus (Prograf®)
- Neuroleptics such as risperidone (Risperdal®) and perphenazine (Trilafon®)
- PDE-5 inhibitors such as sildenafil (Viagra®), tadalafil (Cialis®, Adcirca®), and vardenafil (Levitra®)
- Sedative/hypnotics such as diazepam (Valium®), flurazepam and buspirone
- Sofosbuvir/velpatasvir (EPCLUSA®)

These are not all the medicines that may cause problems if you take STRIBILD. Be sure to tell your healthcare professional about all the medicines you take.

Keep a complete list of all the prescription and non-prescription medicines as well as any herbal medicines that you are taking, how much you take and how often you take them. Make a new list when medicines or herbal medicines are added or stopped, or if the dose changes. Give copies of this list to all your healthcare professionals **every** time you visit them or fill a prescription. This will give your healthcare professional

a complete picture of the medicines you use. Then he or she can decide the best approach for the situation.

PROPER USE OF THIS MEDICATION

Stay under a healthcare professional's care when taking STRIBILD. Do not change your treatment or stop treatment without first talking with your healthcare professional.

Take STRIBILD every day exactly as your healthcare professional prescribed it. Follow the directions from your healthcare professional, exactly as written on the label. Set up a dosing schedule and follow it carefully.

When your STRIBILD supply starts to run low, get more from your healthcare professional. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. If STRIBILD is not taken regularly, as prescribed, the virus may develop resistance to STRIBILD and become harder to treat.

Only take medicine that has been prescribed specifically for you. Do not give STRIBILD to others or take medicine prescribed for someone else. Do not use if seal over bottle opening is broken or missing.

Usual Adult Dose:

- The usual dose of STRIBILD is one tablet orally (by mouth) once a day, preferably at the same time each day. Swallow with plenty of water.
- Take STRIBILD with food. Taking STRIBILD with food helps get the right amount of medicine in your body.

Overdosage:

In case of drug overdose, contact your healthcare professional, hospital emergency department or Regional Poison Control Centre, even if there are no symptoms.

Missed Dose:

It is important that you do not miss any doses. If you miss a dose of STRIBILD and it is less than 12 hours from the time you usually take STRIBILD, then take the dose. If more than 12 hours have passed from the time you usually take STRIBILD, then wait until the next scheduled daily dose. **Do not** take more than 1 dose of STRIBILD in a day. **Do not** take 2 doses at the same time. Call your healthcare professional if you are not sure what to do.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The common side effects of STRIBILD are:

- Diarrhea
- Nausea
- Headache

Additional side effects may include:

- Depression
- Vomiting
- Tiredness
- Stomach pain
- Upset stomach
- Gas
- Dizziness
- Trouble sleeping
- Abnormal dreams
- Serious kidney problems
- Rash
- Suicidal ideation (suicidal thoughts) and suicide attempt (in patients who have had depression or previous mental health problems). If you have these thoughts, contact your healthcare professional.

Other common side effects reported for EMTRIVA and VIREAD are:

- Allergic reaction (including skin rash, redness, irritation, swelling of the face, lips, tongue or throat)
- Pancreatitis (inflammation of the pancreas)
- Shortness of breath
- Skin discoloration (small spots or freckles)
- Sinusitis (inflammation of the sinuses)
- Nasopharyngitis (inflammation of the nasal cavity and throat area)
- Somnolence (feeling sleepy)
- Upper respiratory tract infection
- Back pain
- Weakness
- Pain

Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amounts of fat in the upper back and neck ("buffalo hump"), breast, and around the trunk. Loss of fat from the legs, arms and face may also happen. The cause and long term health effects of these conditions are not known at this time.

Changes in your immune system (Immune Reconstitution Inflammatory Syndrome) can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time, or

you could develop an autoimmune disease in which your immune system reacts against your own body (e.g. Grave's disease (which affects the thyroid gland), Guillain-Barré syndrome (which affects the nervous system) or polymyositis (which affects the muscles) and it may develop at any time, sometimes months later after the start of HIV therapy). Sometimes symptoms can be severe, so if you develop high temperature (fever), joint or muscle pain, redness, rash, swelling or fatigue, or any new symptoms, contact your healthcare professional right away.

Tell your healthcare professional if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of STRIBILD. For more information, ask your healthcare professional.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

	Symptoms/Effect	Talk with your healthcare professional		Stop taking drug and call your healthcare professional
		Only if severe	In all cases	
Rare	**Effect: Lactic acidosis** **Symptoms** • Feeling very weak or tired • Unusual muscle pain • Stomach pain with nausea and vomiting • Feeling cold, especially in arms and legs • Feeling dizzy or lightheaded • Fast or irregular heartbeat • Fast and deep breathing		✓ ✓ ✓ ✓ ✓ ✓ ✓	
Very Rare	**Effect: Hepatotoxicity (severe liver problems) with hepatomegaly (liver enlargement) and steatosis (fat in the liver)** **Symptoms** • Jaundice (skin or the white part of eyes turns yellow) • Urine turns dark • Bowel movements (stools) turn light in color • Loss of appetite for several days or longer • Feeling sick to your stomach (nausea) • Lower stomach pain		✓ ✓ ✓ ✓ ✓ ✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

	Symptoms/Effect	Talk with your healthcare professional		Stop taking drug and call your healthcare professional
		Only if severe	In all cases	
Very Rare	**Effect: Flare-ups of hepatitis B virus infection following drug discontinuation** **Symptoms** • Jaundice (skin or the white part of eyes turns yellow) • Urine turns dark • Bowel movements (stools) turn light in color • Loss of appetite for several days or longer • Feeling sick to your stomach (nausea) • Lower stomach pain		✓ ✓ ✓ ✓ ✓ ✓	
Rare	**Effect: Kidney problems** **Symptoms** • You may have increased or decreased urination as well as increased thirst • You may have swelling of your legs and feet • You may feel listless and tired		✓ ✓ ✓	

Lactic acidosis is a medical emergency and must be treated in the hospital. You may be more likely to get lactic acidosis or serious liver problems if you are female, very overweight (obese) or have been taking nucleoside analog medicines, like STRIBILD, for a long time.

Muscle pain, muscle weakness, bone pain and softening of the bone (infrequently contributing to fractures) have also been reported due to tenofovir DF (a component of STRIBILD).

There have been other side effects in patients taking EMTRIVA or VIREAD. This is **not** a complete list of side effects. If you have questions about side effects, ask your healthcare professional. You should report any new or continuing symptoms to your healthcare professional right away. Your healthcare professional may be able to help you manage these side effects.

HOW TO STORE IT

- Keep STRIBILD and all other medications out of reach and sight of children.

- STRIBILD should be stored at 15–30 °C (59–86 °F). It should remain stable until the expiration date printed on the label.
- Do not keep your medicine in places that are too hot or cold.
- Do not keep medicine that is out of date or that you no longer need. If you throw any medicines away, make sure that children will not find them.
- Keep STRIBILD in its original container and keep the container tightly closed.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 1908C
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the Medeffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, please contact your healthcare professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for healthcare professionals can be found at: www.gilead.ca or by contacting the sponsor, Gilead Sciences Canada, Inc., at: 1-866-207-4267

This leaflet was prepared by Gilead Sciences Canada, Inc.

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