STRIBILD- elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate tablet, film coated
Gilead Sciences, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use STRIBILD safely and effectively. See full prescribing information for STRIBILD.

STRIBILD® (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate) tablets, for oral use
Initial U.S. Approval: 2012

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

See full prescribing information for complete boxed warning.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate (DF), a component of STRIBILD. (5.1) STRIBILD is not approved for the treatment of chronic hepatitis B virus (HBV) infection. Severe acute exacerbations of hepatitis B have been reported in patients coinfected with HIV-1 and HBV who have discontinued EMTRIVA or VIREAD, two of the components of STRIBILD. Hepatic function should be monitored closely in these patients. If appropriate, initiation of antihepatitis B therapy may be warranted. (5.2)

RECENT MAJOR CHANGES

Contraindications (4)	09/2016
Warnings and Precautions	
Avoid Use with Other Antiretroviral Products (5.4)	09/2016

INDICATIONS AND USAGE

STRIBILD is a four-drug combination of elvitegravir, an HIV integrase strand transfer inhibitor (HIV-1 INSTI), cobicistat, a CYP3A inhibitor, and emtricitabine and tenofovir DF, both HIV nucleoside analog reverse transcriptase inhibitors (HIV NRTI) and is indicated as a complete regimen for the treatment of HIV-1 infection in adult patients who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of STRIBILD. (1, 14)

DOSAGE AND ADMINISTRATION

- Recommended dosage: One tablet taken once daily with food. (2.1)
- Dosage in renal impairment: Initiation of STRIBILD in patients with estimated creatinine clearance below 70 mL per minute is not recommended. Discontinue in patients with estimated creatinine clearance below 50 mL per minute. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir disoproxil fumarate. (3)

CONTRAINDICATIONS

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 adverse events. (4)
- Strongly induce CYP3A, which may lead to lower exposure of one or more components and loss of efficacy of STRIBILD and possible resistance. (4)

WARNINGS AND PRECAUTIONS

- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Assess creatinine clearance (CLcr), urine glucose, and urine protein before initiating treatment with STRIBILD. Monitor CLcr, urine glucose, and urine protein in all patients. Monitor serum phosphorus in patients at risk for renal impairment. Avoid administering STRIBILD with concurrent or recent use of nephrotoxic drugs. (5.3)
- Avoid coadministration with other antiretroviral products: Do not use with products containing any of the components of STRIBILD (cobicistat, elvitegravir, emtricitabine, and tenofovir disoproxil fumarate) or tenofovir alafenamide,

including ATRIPLA, COMPLERA, DESCOVY, EMTRIVA, GENVOYA, ODEFSEY, TRUVADA, TYBOST, VIREAD, or VITEKTA; with drugs containing lamivudine; or with drugs or regimens containing ritonavir. Do not administer in combination with HEPSERA. (5.4)

- Risk of adverse reactions or loss of virologic response due to drug interactions: The concomitant use of STRIBILD and other drugs may result in known or potentially significant drug interactions, some of which may lead to loss of therapeutic effect of STRIBILD and possible development of resistance; and possible clinically significant adverse reactions from greater exposures of concomitant drugs. (5.5)
- Decreases in bone mineral density (BMD): Consider monitoring BMD in patients with a history of pathologic fracture or other risk factors of osteoporosis or bone loss. (5.6)
- Redistribution/accumulation of body fat: Observed in patients receiving antiretroviral therapy. (5.7)
- Immune reconstitution syndrome: May necessitate further evaluation and treatment. (5.8)

ADVERSE REACTIONS

Most common adverse drug reactions to STRIBILD (incidence greater than or equal to 10%, all grades) are nausea and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- STRIBILD is a complete regimen for the treatment of HIV-1 infection; therefore, STRIBILD should not be administered with other antiretroviral medications for treatment of HIV-1 infection. (5.4, 7.1)
- STRIBILD can alter the concentration of drugs metabolized by CYP3A or CYP2D6. Drugs that induce CYP3A can alter the concentrations of one or more components of STRIBILD. Consult the full prescribing information prior to and during treatment for potential drug-drug interactions. (4, 7.2, 7.3, 12.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Use during pregnancy only if the potential benefit justifies the potential risk. (8.1)
- Nursing mothers: Women infected with HIV should be instructed not to breastfeed due to the potential for HIV transmission. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 9/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POSTTREATMENT ACUTE EXACERBATION OF HEPATITIS B

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate, a component of STRIBILD, in combination with other antiretrovirals *[See Warnings and Precautions (5.1)]*.

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 human immunodeficiency virus-1 (HIV-1). Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued EMTRIVA or VIREAD, which are components of STRIBILD. Hepatic function should be monitored closely, with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue STRIBILD. If appropriate, initiation of antihepatitis B therapy may be warranted *[See Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

STRIBILD® is indicated as a complete regimen for the treatment of HIV-1 infection in adult patients who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of STRIBILD *[See Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage Information

The recommended dosage of STRIBILD is one tablet taken orally once daily with food *[See Clinical Pharmacology (12.3)]*.

2.2 Dosage Adjustment in Patients with Renal Impairment

Initiation of STRIBILD in patients with estimated creatinine clearance below 70 mL per minute is not recommended. Because STRIBILD is a fixed-dose combination tablet, STRIBILD should be discontinued if estimated creatinine clearance declines below 50 mL per minute during treatment with STRIBILD, as the dose interval adjustment required for emtricitabine and tenofovir disoproxil fumarate (DF) cannot be achieved *[See Warnings and Precautions (5.3), Adverse Reactions (6.1), Use in Specific Populations (8.6), Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

2.3 Dosage in Patients with Hepatic Impairment

No dosage adjustment of STRIBILD is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. 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 *[See Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

2.4 Testing Prior to Initiation of STRIBILD

Prior to initiation of STRIBILD, patients should be tested for hepatitis B infection *[See Warnings and Precautions (5.2)]* and estimated creatinine clearance, urine glucose, and urine protein should be documented in all patients *[See Warnings and Precautions (5.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Each STRIBILD tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir DF (equivalent to 245 mg of tenofovir disoproxil).

The 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.

4 CONTRAINDICATIONS

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. These drugs and other contraindicated drugs (which may lead to reduced efficacy of STRIBILD and possible resistance) are listed in Table 1 *[See Drug Interactions (7.5) and Clinical Pharmacology (12.3)]*.

Table 1 Drugs that are Contraindicated with STRIBILD

Drug Class	Drugs within Class that are Contraindicated with STRIBILD	Clinical Comment
Alpha 1-Adrenoreceptor Antagonist	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.
Antimycobacterial	Rifampin	Rifampin is a potent inducer of CYP450 metabolism and may cause significant decrease in the plasma concentration of elvitegravir and cobicistat. This may result in loss of therapeutic effect to STRIBILD.
Antipsychotic	Lurasidone Pimozide	Potential for serious and/or life-threatening reactions. Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Ergot Derivatives	Dihydroergotamine 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 Agent	Cisapride	Potential for serious and/or life-threatening events such as cardiac arrhythmias.
Herbal Products	St. John's wort *(Hypericum perforatum)*	Coadministration of products containing St. John's wort and STRIBILD may result in reduced plasma concentrations of elvitegravir and cobicistat. This may result in loss of therapeutic effect and development of resistance.
HMG-CoA Reductase Inhibitors	Lovastatin Simvastatin	Potential for serious reactions such as myopathy, including rhabdomyolysis.
Phosphodiesterase-5 (PDE-5) Inhibitor	Sildenafil* when dosed as Revatio for the treatment of pulmonary arterial hypertension	There is increased potential for sildenafil-associated adverse events (which include visual disturbances, hypotension, priapism, and syncope).
Sedative/Hypnotics	Triazolam Orally administered midazolam†	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

	midazolam†	benzodiazepines. The potential exists for serious and/or life threatening events such as prolonged or increased sedation or respiratory depression.

* *See Drug Interactions (7), Table 6,* for sildenafil when dosed as Viagra for erectile dysfunction.

† *See Drug Interactions (7), Table 6,* for parenterally administered midazolam.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis/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 DF, a component of STRIBILD, in combination with other antiretrovirals. 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).

5.2 Patients Coinfected with HIV-1 and HBV

It is recommended that all patients with HIV-1 be tested for the presence of chronic HBV before initiating antiretroviral therapy. STRIBILD is not approved for the treatment of chronic HBV infection, and the safety and efficacy of STRIBILD have not been established in patients coinfected with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued emtricitabine or 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. Patients who are coinfected with HIV-1 and HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with STRIBILD. If appropriate, initiation of antihepatitis B therapy may be warranted.

5.3 New Onset or Worsening Renal Impairment

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir DF, a component of STRIBILD, and with the use of STRIBILD *[See Adverse Reactions (6.2)]*.

In the clinical trials of STRIBILD over 144 weeks, 13 (1.9%) subjects in the STRIBILD group (N=701), 8 (2.3%) subjects in the atazanavir (ATV) + ritonavir (RTV) + TRUVADA® (emtricitabine 200 mg/tenofovir DF 300 mg) group (N=355), and no subjects in the ATRIPLA® (efavirenz 600 mg/emtricitabine 200 mg/tenofovir DF 300 mg) 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%) subjects 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 subjects had renal impairment (i.e., estimated creatinine clearance less than 70 mL per minute) at baseline. The laboratory findings in these 4 subjects improved but did not completely resolve in all subjects upon discontinuation of STRIBILD. Renal replacement therapy was not required for these subjects. One (0.3%) subject who received ATV+RTV+TRUVADA developed laboratory findings consistent with proximal renal tubular dysfunction, leading to discontinuation of ATV+RTV+TRUVADA after Week 96.

STRIBILD should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple nonsteroidal anti-inflammatory drugs [NSAIDs]) *[See Drug Interactions (7.4)]*. Cases of acute renal failure after initiation of high-dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on tenofovir DF. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.

Persistent or worsening bone pain, pain in extremities, fractures, and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in at-risk patients.

Estimated creatinine clearance, urine glucose, and urine protein should be documented in all patients prior to initiating therapy. Initiation of STRIBILD in patients with estimated creatinine clearance below 70 mL per minute is not recommended.

Routine monitoring of estimated creatinine clearance, urine glucose, and urine protein should be performed during STRIBILD therapy in all patients. Additionally, serum phosphorus should be measured in patients at risk for renal impairment.

Although cobicistat (a component of STRIBILD) may cause modest increases in serum creatinine and modest declines in estimated creatinine clearance without affecting renal glomerular function *[See Adverse Reactions (6.1)]*, patients who experience a confirmed increase in serum creatinine of greater than 0.4 mg per dL from baseline should be closely monitored for renal safety.

The emtricitabine and tenofovir DF components of STRIBILD are primarily excreted by the kidney. STRIBILD should be discontinued if estimated creatinine clearance declines below 50 mL per minute as dose interval adjustment required for emtricitabine and tenofovir DF cannot be achieved with the fixed-dose combination tablet.

5.4 Avoid Use with Other Antiretroviral Products

STRIBILD is indicated for use as a complete regimen for the treatment of HIV-1 infection, and coadministration with other antiretroviral products is not recommended.

STRIBILD is not recommended for coadministration with the following:

- cobicistat (TYBOST®)
- elvitegravir (VITEKTA®)
- products containing emtricitabine, tenofovir DF, or tenofovir alafenamide (ATRIPLA, COMPLERA, DESCOVY, EMTRIVA, GENVOYA, ODEFSEY, TRUVADA, VIREAD®)
- products containing lamivudine (Combivir, Epivir, Epivir-HBV, Epzicom, Triumeq, Trizivir)
- adefovir dipivoxil (HEPSERA®)
- products containing ritonavir (Norvir, Kaletra).

5.5 Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

The concomitant use of STRIBILD and other drugs may result in known or potentially significant drug interactions, some of which may lead to *[See Contraindications (4) and Drug Interactions (7.5)]:*

- Loss of therapeutic effect of STRIBILD and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs.

See Table 6 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations *[See Drug Interactions (7.5)]*. Consider the potential for drug interactions prior to and during STRIBILD therapy; review concomitant medications during STRIBILD therapy; and monitor for the adverse reactions associated with the concomitant drugs.

5.6 Bone Effects of Tenofovir DF

<u>Bone Mineral Density</u>

In clinical trials in HIV-1-infected adults, tenofovir DF (a component of STRIBILD) was associated with slightly greater decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators. Serum parathyroid hormone levels and 1.25 Vitamin D levels were also higher in subjects receiving tenofovir DF. For additional information, *see Adverse Reactions (6.1)* and consult the VIREAD prescribing information.

The effects of tenofovir DF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Assessment of BMD should be considered for HIV-1-infected patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial in all patients. If bone abnormalities are suspected, then appropriate consultation should be obtained.

Mineralization Defects

Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of tenofovir DF *[See Adverse Reactions (6.2)]*. Arthralgias and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing tenofovir DF *[See Warnings and Precautions (5.3)]*.

5.7 Fat Redistribution

Redistribution/accumulation of body fat 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.

5.8 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including STRIBILD. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or 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.

6 ADVERSE REACTIONS

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

- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[See Boxed Warning and Warnings and Precautions (5.1)]*.
- Severe Acute Exacerbations of Hepatitis B *[See Boxed Warning and Warnings and Precautions (5.2)]*.
- New Onset or Worsening Renal Impairment *[See Warnings and Precautions (5.3)]*.
- Bone Effects of Tenofovir DF *[See Warnings and Precautions (5.6)]*.
- Immune Reconstitution Syndrome *[See Warnings and Precautions (5.8)]*.

6.1 Adverse Reactions from Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In HIV-1-Infected Subjects with No Antiretroviral Treatment History

The safety assessment of STRIBILD is based on the Week-144 pooled data from 1408 subjects in two randomized, double-blind, active-controlled clinical trials, Study 102 and Study 103, in antiretroviral treatment-naïve HIV-1-infected adult subjects *[See Clinical Studies (14)]*. A total of 701 subjects received STRIBILD once daily in these two studies.

The proportion of subjects who discontinued treatment with STRIBILD, ATRIPLA, or ATV+RTV+TRUVADA due to adverse events, regardless of severity, was 6.0%, 7.4%, and 8.5%, respectively. Table 2 displays the frequency of adverse reactions greater than or equal to 5% of subjects in any treatment arm.

Table 2 Adverse Reactions* (All Grades) Reported in ≥5% of Subjects in Any Treatment Arm in Studies 102 and 103 (Week-144 Analysis)

	STRIBILD N=701	**ATRIPLA N=352**	**ATV+RTV+ TRUVADA N=355**
EYE DISORDERS			
Ocularicterus	<1%	0%	13%
GASTROINTESTINAL DISORDERS			
Diarrhea	12%	11%	17%
Flatulence	2%	<1%	8%
Nausea	16%	9%	14%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue	4%	8%	6%
HEPATOBILIARY DISORDERS			
Jaundice	0%	<1%	9%
NERVOUS SYSTEM DISORDERS			
Somnolence	1%	7%	1%
Headache	7%	4%	6%
Dizziness	3%	21%	5%
PSYCHIATRIC DISORDERS			
Insomnia	3%	9%	1%
Abnormal dreams	9%	27%	4%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Rash†	4%	15%	6%

* Frequencies of adverse reactions are based on all treatment-emergent adverse events attributed to study drugs.

† Rash event includes dermatitis, drug eruption, eczema, pruritus, pruritus generalized, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash pruritic, and urticaria.

See Warnings and Precautions (5.3) for a discussion of renal adverse reactions from clinical trials experience with STRIBILD.

Additional adverse reactions observed with STRIBILD included suicidal ideation and suicide attempt (0.3%), all in subjects with a preexisting history of depression or psychiatric illness.

In Virologically Suppressed HIV-1-Infected Subjects

No new adverse reactions to STRIBILD through Week 48 were identified in 584 virologically stably suppressed subjects switching to STRIBILD from a regimen containing a RTV-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 subjects switching to STRIBILD compared to 6% of subjects 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 subjects switching to STRIBILD were nausea (4%), flatulence (2%), and headache (2%). The proportion of subjects 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

Emtricitabine and Tenofovir Disoproxil Fumarate: In addition to the adverse reactions observed with STRIBILD, the following adverse reactions occurred in at least 5% of treatment-experienced or treatment-naïve subjects receiving emtricitabine or tenofovir DF with other antiretroviral agents in other clinical trials: depression, abdominal pain, dyspepsia, vomiting, fever, pain, nasopharyngitis, pneumonia, sinusitis, upper respiratory tract infection, arthralgia, back pain, myalgia, paresthesia, peripheral neuropathy (including peripheral neuritis and neuropathy), anxiety, increased cough, and rhinitis.

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

Laboratory Abnormalities

The frequency of laboratory abnormalities (Grades 3−4) occurring in at least 2% of subjects receiving STRIBILD in studies 102 and 103 are presented in Table 3.

Table 3 Laboratory Abnormalities (Grades 3−4) Reported in ≥2% of Subjects Receiving STRIBILD in Studies 102 and 103 (Week-144 Analysis)

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

* Frequencies are based on treatment-emergent laboratory abnormalities.

† For subjects with serum amylase >1.5 × upper limit of normal (ULN), lipase test was also performed. The frequency of increased lipase (Grades 3−4) occurring in STRIBILD (N=69), ATRIPLA (N=40), and ATV+RTV+TRUVADA (N=38) was 17%, 15%, and 24%, respectively.

In Study 103, BMD was assessed by DEXA in a nonrandom subset of 120 subjects (STRIBILD group, N=54; ATV+RTV+TRUVADA group, N=66). Mean percentage decreases in BMD from baseline to Week 144 in the STRIBILD group were comparable to that in the ATV+RTV+TRUVADA group at the lumbar spine (−1.43% versus −3.68%, respectively) and at the hip (−2.83% versus −3.77%, respectively). In studies 102 and 103, bone fractures occurred in 27 subjects (3.9%) in the STRIBILD group, 8 subjects (2.3%) in the ATRIPLA group, and 19 subjects (5.4%) in the ATV+RTV+TRUVADA group. These findings were consistent with data from an earlier 144-week trial of treatment-naïve subjects receiving tenofovir DF + lamivudine + efavirenz.

Proteinuria (all grades) occurred in 52% of subjects receiving STRIBILD, 41% of subjects receiving ATRIPLA, and 42% of subjects receiving ATV+RTV+TRUVADA.

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. In studies 102 and 103, increases in serum creatinine and decreases in estimated creatinine clearance occurred early in treatment with STRIBILD, after which levels stabilized. Table 4 displays the mean changes in serum creatinine and eGFR levels at Week 144 and the percentage of subjects 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 144

	STRIBILD N=701	**ATRIPLA N=352**	**ATV+RTV+ TRUVADA N=355**
Serum Creatinine (mg/dL)*	0.14 (±0.14)	0.01 (±0.12)	0.09 (±0.15)
eGFR by Cockcroft-Gault (mL/minute)*	−14.0 (±16.6)	−1.9 (±17.9)	−9.8 (±19.4)
Subjects with Elevations in Serum Creatinine (All Grades) (%)	12	2	6

* Mean change ± standard deviation

Emtricitabine or Tenofovir Disoproxil Fumarate: In addition to the laboratory abnormalities observed with STRIBILD, the following laboratory abnormalities have been previously reported in subjects treated with emtricitabine or tenofovir DF with other antiretroviral agents in other clinical trials: Grade 3 or 4 laboratory abnormalities of ALT (M: greater than 215 U per L; F: greater than 170 U per L), alkaline phosphatase (greater than 550 U per L), bilirubin (greater than 2.5 × ULN), serum glucose (less than 40 or greater than 250 mg per dL), glycosuria (greater than or equal to 3+), neutrophils (less than 750 per mm^3), fasting cholesterol (greater than 240 mg per dL), and fasting triglycerides (greater than 750 mg per dL).

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

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 at Week 144 in Subjects Receiving STRIBILD or Comparator in Studies 102 and 103

	STRIBILD N=701		**ATRIPLA N=352**		**ATV+RTV+TRUVADA N=355**	
	Baseline	**Week 144**	**Baseline**	**Week 144**	**Baseline**	**Week 144**
	mg/dL	**Change***	**mg/dL**	**Change***	**mg/dL**	**Change***
Total Cholesterol (fasted)	166 [N=675]	+17 [N=535]	161 [N=343]	+22 [N=262]	168 [N=337]	+16 [N=243]

HDL-cholesterol (fasted)	43 [N=675]	+7 [N=535]	43 [N=343]	+9 [N=262]	42 [N=335]	+7 [N=242]
LDL-cholesterol (fasted)	100 [N=675]	+15 [N=535]	97 [N=343]	+19 [N=262]	101 [N=337]	+18 [N=242]
Triglycerides (fasted)	122 [N=675]	+12 [N=535]	121 [N=343]	+5 [N=262]	132 [N=337]	+22 [N=242]

* The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 144 values.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of tenofovir DF. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. No additional postmarketing adverse reactions specific for emtricitabine have been identified.

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

Hepatobiliary Disorders

hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT, gamma GT)

Skin and Subcutaneous Tissue Disorders

rash

Musculoskeletal and Connective Tissue Disorders

rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute 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 Administration Site Conditions

asthenia

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

7 DRUG INTERACTIONS

See also Contraindications (4) and *Clinical Pharmacology (12.3).*

7.1 Other Antiretroviral Medications

STRIBILD is a complete regimen for the treatment of HIV-1 infection; therefore, STRIBILD should not be administered with other antiretroviral medications for treatment of HIV-1 infection. Complete information regarding potential drug-drug interactions with other antiretroviral medications is not provided.

7.2 Potential for STRIBILD to Affect Other Drugs

Cobicistat, a component of STRIBILD, is an inhibitor of CYP3A and CYP2D6 and an inhibitor of the following transporters: P-glycoprotein (P-gp), BCRP, OATP1B1, and OATP1B3. Thus, coadministration of STRIBILD with drugs that are primarily metabolized by CYP3A or CYP2D6, or are substrates of P-gp, BCRP, OATP1B1, or OATP1B3, may result in increased plasma concentrations of such drugs. Elvitegravir is a modest inducer of CYP2C9 and may decrease the plasma concentrations of CYP2C9 substrates.

7.3 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 elvitegravir, which may lead to loss of therapeutic effect of STRIBILD and development of resistance (See Table 6).

Coadministration of STRIBILD with other drugs that inhibit CYP3A may decrease the clearance and increase the plasma concentration of cobicistat (See Table 6).

7.4 Drugs Affecting Renal Function

Because emtricitabine and tenofovir, components of STRIBILD, are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of STRIBILD with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of emtricitabine, tenofovir, and other renally eliminated drugs and this may increase the risk of adverse reactions. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs *[See Warnings and Precautions (5.3)]*.

7.5 Established and Other Potentially Significant Interactions

Table 6 provides a listing of established or potentially clinically significant drug interactions. The drug interactions described are based on studies conducted with either STRIBILD or the components of STRIBILD (elvitegravir, cobicistat, emtricitabine, and tenofovir DF) as individual agents and/or in combination, or are predicted drug interactions that may occur with STRIBILD [for magnitude of interaction, *See Clinical Pharmacology (12.3)*]. The table includes potentially significant interactions but is not all inclusive.

Table 6 Established and Other Potentially Significant* Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration†	Clinical Comment
Acid Reducing Agents:		

Antacids‡ e.g., aluminum and magnesium hydroxide	↓ elvitegravir	Separate STRIBILD and antacid administration by at least 2 hours.
Antiarrhythmics: e.g., amiodarone bepridil digoxin‡ disopyramide flecainide systemic lidocaine mexiletine propafenone quinidine	↑ antiarrhythmics ↑ digoxin	Therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when coadministered with STRIBILD.
Antibacterials: clarithromycin	↑ clarithromycin ↑ cobicistat	Patients with CLcr greater than or equal to 60 mL/minute: No dose adjustment of clarithromycin is required. Patients with CLcr between 50 mL/minute and 60 mL/minute: The dose of clarithromycin should be reduced by 50%.
Anticoagulants: warfarin	Effect on warfarin unknown	Monitor international normalized ratio (INR) upon coadministration of warfarin with STRIBILD.
Anticonvulsants: oxcarbazepine clonazepam ethosuximide	↓ elvitegravir ↓ cobicistat ↑ clonazepam ↑ ethosuximide	***Contraindicated anticonvulsants [see Contraindications (4)]*** Alternative anticonvulsants should be considered when STRIBILD is coadministered with oxcarbazepine. Clinical monitoring is recommended upon coadministration of clonazepam or ethosuximide with STRIBILD.
Antidepressants: Selective Serotonin Reuptake Inhibitors (SSRIs) e.g., paroxetine Tricyclic Antidepressants (TCAs) e.g., amitriptyline desipramine imipramine nortriptyline bupropion trazodone	↑ SSRIs ↑ TCAs ↑ trazodone	Careful dose titration of the antidepressant and monitoring for antidepressant response are recommended when coadministered with STRIBILD.
Antifungals:	↑ elvitegravir	When coadministered with STRIBILD, the maximum daily dose of ketoconazole

Antifungals: itraconazole ketoconazole‡ voriconazole	↑ cobicistat ↑ itraconazole ↑ ketoconazole ↑ voriconazole	or itraconazole should not exceed 200 mg per day. An assessment of benefit/risk ratio is recommended to justify use of voriconazole with STRIBILD.
Anti-gout: colchicine	↑ colchicine	STRIBILD is not recommended to be coadministered with colchicine to patients with renal or hepatic impairment. <u>Treatment of gout-flares – coadministration of colchicine in patients receiving STRIBILD:</u> 0.6 mg (1 tablet) × 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Treatment course to be repeated no earlier than 3 days. <u>Prophylaxis of gout-flares – coadministration of colchicine in patients receiving STRIBILD:</u> 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. <u>Treatment of familial Mediterranean fever – coadministration of colchicine in patients receiving STRIBILD:</u> Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
Antimycobacterial: rifabutin‡ rifapentine	↓ elvitegravir ↓ cobicistat	***Contraindicated antimycobacterials [see Contraindications (4)]*** Coadministration of STRIBILD with rifabutin or rifapentine is not recommended.
Antipsychotics: e.g., perphenazine risperidone thioridazine	↑antipsychotic	***Contraindicated antipsychotics [see Contraindications (4)]*** A decrease in the dose of antipsychotics that are metabolized by CYP3A4 or CYP2D6 may be needed when coadministered with STRIBILD.
quetiapine	↑ quetiapine	<u>Initiation of STRIBILD in patients taking quetiapine:</u> Consider alternative antiretroviral therapy to avoid increases in quetiapine exposure. If coadministration is necessary, reduce the quetiapine dose to 1/6 of the current dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations on adverse reaction monitoring. <u>Initiation of quetiapine in patients taking</u>

		STRIBILD: Refer to the quetiapine prescribing information for initial dosing and titration of quetiapine.
Beta-Blockers: e.g., metoprolol timolol	↑ beta-blockers	Clinical monitoring is recommended and a dose decrease of the beta-blocker may be necessary when these agents are coadministered with STRIBILD.
Calcium Channel Blockers: e.g., amlodipine diltiazem felodipine nicardipine nifedipine verapamil	↑ calcium channel blockers	Clinical monitoring is recommended upon coadministration of calcium channel blockers with STRIBILD.
Corticosteroid: Systemic: dexamethasone	↓ elvitegravir ↓ cobicistat	Alternative corticosteroids should be considered.
Corticosteroid: Inhaled/Nasal: fluticasone	↑ fluticasone	Concomitant use of STRIBILD with inhaled or nasal fluticasone may reduce serum cortisol concentrations. Alternative corticosteroids should be considered, particularly for long-term use.
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 Antiviral Agents: ledipasvir/sofosbuvir	↑ tenofovir	The safety of increased tenofovir concentrations in the setting of HARVONI® and STRIBILD has not been established. Coadministration is not recommended.
HMG-CoA Reductase Inhibitors: atorvastatin	↑ atorvastatin	***Contraindicated HMG-CoA Reductase Inhibitors [see Contraindications (4)]*** Initiate with the lowest starting dose of atorvastatin and titrate carefully while monitoring for safety.
		The effects of increases in the

Hormonal Contraceptives: norgestimate/ethinyl estradiol‡	↑ norgestimate ↓ ethinyl estradiol	concentration of the progestational component norgestimate are not fully known and can include increased risk of insulin resistance, dyslipidemia, acne, and venous thrombosis. The potential risks and benefits associated with coadministration of norgestimate/ethinyl estradiol with STRIBILD should be considered, particularly in women who have risk factors for these events. Coadministration of STRIBILD with other hormonal contraceptives (e.g., contraceptive patch, contraceptive vaginal ring, or injectable contraceptives) or oral contraceptives containing progestogens other than norgestimate has not been studied; therefore, alternative (nonhormonal) methods of contraception can be considered.
Immuno-suppressants: e.g., cyclosporine sirolimus tacrolimus	↑ immuno-suppressants	Therapeutic monitoring of the immunosuppressive agents is recommended upon coadministration with STRIBILD.
Narcotic Analgesics: buprenorphine/ naloxone‡	↑ buprenorphine ↑ norbuprenorphine ↓ naloxone	Patients should be closely monitored for sedation and cognitive effects.
Inhaled Beta Agonist: salmeterol	↑ salmeterol	Coadministration of salmeterol and STRIBILD is not recommended because it may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
		Contraindicated PDE-5 Inhibitors [see Contraindications (4)] Coadministration with STRIBILD may result in an increase in PDE-5 inhibitor associated adverse reactions, including hypotension, syncope, visual disturbances, and priapism. <u>Use of tadalafil for pulmonary arterial hypertension (PAH):</u> • *Coadministration of tadalafil in patients on STRIBILD:* In patients receiving STRIBILD for at least 1 week, start tadalafil at 20 mg once

Phosphodiesterase-5 (PDE-5) Inhibitors: sildenafil tadalafil vardenafil	↑ PDE-5 inhibitors	daily. Increase tadalafil dose to 40 mg once daily based upon individual tolerability. • *Coadministration of STRIBILD in patients on tadalafil:* Avoid use of tadalafil during the initiation of STRIBILD. Stop tadalafil at least 24 hours prior to starting STRIBILD. After at least one week following initiation of STRIBILD, resume tadalafil at 20 mg once daily. Increase tadalafil dose to 40 mg once daily based upon individual tolerability. <u>Use of PDE-5 inhibitors for erectile dysfunction:</u> The below PDE-5 inhibitors can be used along with increased monitoring for PDE-5-inhibitor associated adverse events: • Sildenafil at a single dose not exceeding 25 mg in 48 hours, or • Tadalafil at a single dose not exceeding 10 mg in 72 hours, or • Vardenafil at a single dose not exceeding 2.5 mg in 72 hours
Sedative/hypnotics: Benzodiazepines: e.g., parenterally administered midazolam clorazepate diazepam estazolam flurazepam buspirone zolpidem	↑ sedatives/hypnotics	***Contraindicated sedative/hypnotics [see Contraindications (4)]*** Coadministration of parenteral midazolam with STRIBILD should be done in a setting that ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered. With other sedative/hypnotics, dose reduction may be necessary and clinical monitoring is recommended.

* This table is not all inclusive.

† ↑=Increase, ↓=Decrease, □=No Effect

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

7.6 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 when STRIBILD is combined with the following drugs: entecavir, famciclovir, H_2 receptor antagonists, methadone, proton pump inhibitors, and ribavirin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to STRIBILD, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, STRIBILD should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

Elvitegravir: Studies in animals have shown no evidence of teratogenicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with elvitegravir during pregnancy, there were no toxicologically significant effects on developmental endpoints. The exposures (AUC) 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.

Cobicistat: Studies in animals have shown no evidence of teratogenicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with cobicistat during pregnancy, there were no toxicologically significant effects on developmental endpoints. The exposures (AUC) 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.

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

Tenofovir Disoproxil Fumarate: Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body-surface-area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir.

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed 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. 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.

Samples of breast milk obtained from five HIV-1-infected mothers show that tenofovir is secreted in human milk. Tenofovir-associated risks, including the risk of 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 breastfeed if they are receiving STRIBILD.**

8.4 Pediatric Use

Safety and effectiveness of STRIBILD in pediatric patients less than 18 years of age have not been established *[See Clinical Pharmacology (12.3)]*.

8.5 Geriatric Use

Clinical studies of STRIBILD did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of STRIBILD in elderly patients, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[See Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

Initiation of STRIBILD in patients with estimated creatinine clearance below 70 mL per min is not recommended. Because STRIBILD is a fixed-dose combination tablet, STRIBILD should be discontinued if estimated creatinine clearance declines below 50 mL per minute during treatment with STRIBILD as dose interval adjustment required for emtricitabine and tenofovir DF cannot be achieved *[See Warnings and Precautions (5.3), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

<u>Clinical Trials in Subjects with Mild to Moderate Renal Impairment</u>

In Study 118, 33 HIV-1-infected treatment-naïve subjects 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. 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 subjects treated with STRIBILD.

Twelve of the 33 subjects studied had baseline eGFR between 50 and 70 mL/minute. Three subjects, all with baseline eGFR between 50−60 mL/minute, discontinued STRIBLD due to a renal adverse event. The safety of STRIBILD among 21 of the 33 subjects with baseline eGFR greater than or equal to 70 mL/minute was consistent with the safety profile in studies 102 and 103.

8.7 Hepatic Impairment

No dose adjustment of STRIBILD is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. 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 *[See Dosage and Administration (2) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

No data are available on overdose of STRIBILD in patients. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with STRIBILD consists of general supportive measures, including monitoring of vital signs as well as observation of the clinical status of the patient.

Elvitegravir: Limited clinical experience is available at doses higher than the therapeutic dose of elvitegravir. In one study, boosted elvitegravir equivalent to 2 times the therapeutic dose of 150 mg once daily for 10 days was administered to 42 healthy subjects. No severe adverse reactions were reported. The effects of higher doses are not known. As elvitegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by 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 (2.7 times the dose in STRIBILD) was administered to a total of 60 healthy subjects. No severe adverse reactions were reported. The effects of higher doses are not known. As cobicistat is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis.

Emtricitabine: Limited clinical experience is available at doses higher than the therapeutic dose of EMTRIVA. In one clinical pharmacology study, single doses of emtricitabine 1200 mg (6 times the dose in STRIBILD) were administered to 11 subjects. No severe adverse reactions were reported. The effects of higher doses are not known.

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 per minute and a dialysate flow rate of 600 mL per minute). It is not known whether emtricitabine can be removed by peritoneal dialysis.

Tenofovir Disoproxil Fumarate: Limited clinical experience at doses higher than the therapeutic dose of VIREAD 300 mg is available. In one study, 600 mg tenofovir DF (2 times the dosage in STRIBILD) was administered to 8 subjects orally for 28 days and no severe adverse reactions were reported. The effects of higher doses are not known. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of VIREAD, a 4-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

11 DESCRIPTION

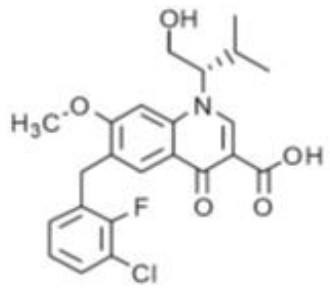
STRIBILD is a fixed-dose combination tablet containing elvitegravir, cobicistat, emtricitabine, and tenofovir DF for oral administration.

- 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. EMTRIVA is the brand name for emtricitabine.
- Tenofovir DF is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate. VIREAD is the brand name for tenofovir DF.

Each tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir DF (equivalent to 245 mg of tenofovir disoproxil). The tablets 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: The chemical name of elvitegravir is 6-(3-Chloro-2-fluorobenzyl)-1-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

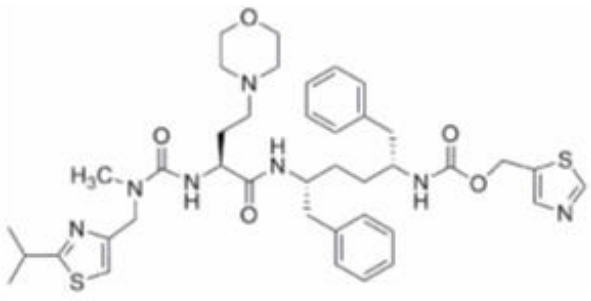
It has a molecular formula of $C_{23}H_{23}ClFNO_5$ and a molecular weight of 447.9. It has the following structural formula:



Elvitegravir is a white to pale-yellow powder with a solubility of less than 0.3 micrograms per mL in water at 20 °C.

Cobicistat: The chemical name for cobicistat is 1,3-thiazol-5-ylmethyl [(2*R*,5*R*)-5-{[(2*S*)-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.

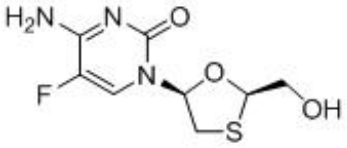
It has a molecular formula of $C_{40}H_{53}N_7O_5S_2$ and a molecular weight of 776.0. It has the following structural formula:



Cobicistat is adsorbed onto silicon dioxide. Cobicistat on silicon dioxide is a white to pale-yellow solid with a solubility of 0.1 mg per mL in water at 20 °C.

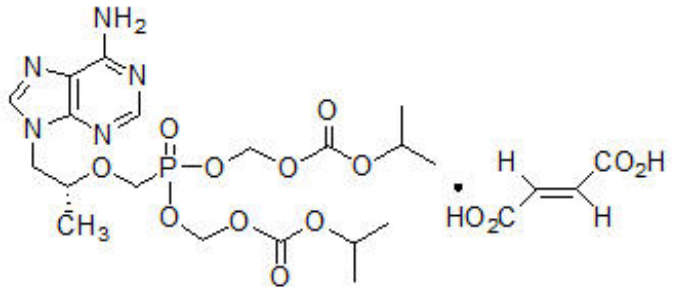
Emtricitabine: The chemical name of emtricitabine is 5-fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. Emtricitabine is the (-)enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5-position.

It has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.25. It has the following structural formula:



Emtricitabine is a white to off-white crystalline powder with a solubility of approximately 112 mg per mL in water at 25 °C.

Tenofovir Disoproxil Fumarate: Tenofovir DF is a fumaric acid salt of the bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. The chemical name of tenofovir DF is 9-[(*R*)-2-[[bis[[(isopropoxycarbonyl)oxy]-methoxy]phosphinyl]methoxy]propyl]adenine fumarate (1:1). It has a molecular formula of $C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$ and a molecular weight of 635.51. It has the following structural formula:



Tenofovir DF is a white to off-white crystalline powder with a solubility of 13.4 mg per mL in water at 25 °C. All dosages are expressed in terms of tenofovir DF except where otherwise noted.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

STRIBILD is a fixed-dose combination of antiretroviral drugs elvitegravir (boosted by the CYP3A inhibitor cobicistat), emtricitabine, and tenofovir DF *[See Microbiology (12.4)]*.

12.2 Pharmacodynamics

Effects on Electrocardiogram

Thorough QT studies have been conducted for elvitegravir and cobicistat. The effect of the other two components, tenofovir and emtricitabine, or the combination regimen STRIBILD on the QT interval is not known.

Elvitegravir: In a thorough QT/QTc study in 126 healthy subjects, elvitegravir (coadministered with 100 mg ritonavir) 125 mg and 250 mg (0.83 and 1.67 times the dose in STRIBILD) did not affect the QT/QTc interval and did not prolong the PR interval.

Cobicistat: In a thorough QT/QTc study in 48 healthy subjects, a single dose of cobicistat 250 mg and 400 mg (1.67 and 2.67 times the dose in STRIBILD) did not affect the QT/QTc interval. Prolongation of the PR interval was noted in subjects receiving cobicistat. The maximum mean (95% upper confidence bound) difference in PR from placebo after baseline-correction was 9.5 (12.1) msec for the 250 mg cobicistat dose and 20.2 (22.8) for the 400 mg cobicistat dose. 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.

Effects on Serum Creatinine

The effect of cobicistat on serum creatinine was investigated in a Phase 1 study in subjects with an eGFR of at least 80 mL per minute (N=18) and with an eGFR of 50 to 79 mL per minute (N=12). A statistically significant change of $eGFR_{CG}$ from baseline was observed after 7 days of treatment with cobicistat 150 mg among subjects with an eGFR of at least 80 mL per minute (-9.9 ± 13.1 mL/min) and subjects with an eGFR of 50 to 79 mL per minute (-11.9 ± 7.0 mL per 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 subjects with an eGFR of at least 50 mL per minute, indicating cobicistat inhibits tubular secretion of creatinine, reflected as a reduction in $eGFR_{CG}$, without affecting the actual glomerular filtration rate.

12.3 Pharmacokinetics

The pharmacokinetic properties of the components of STRIBILD are provided in Table 7. The multiple dose pharmacokinetic parameters of elvitegravir, cobicistat, emtricitabine, and tenofovir are provided in

Table 8.

Table 7 Pharmacokinetic Properties of the Components of STRIBILD

	Elvitegravir	Cobicistat	Emtricitabine	Tenofovir
Absorption				
T_{max} (h)	4	3	3	2
Effect of light meal (relative to fasting)*	↑34% (↑19, ↑51)	↑3% (↓10, ↑17)	↓5% (↓9, 0)	↑24% (↑18, ↑30)
Effect of high fat meal (relative to fasting)*	↑87% (↑66, ↑110)	↓17% (↓27, ↓5)	↓4% (↓8, 0)	↑23% (↑17, ↑29)
Distribution				
% Bound to human plasma proteins	~99	~98	<4	<0.7
Source of protein binding data	Ex vivo	In vitro	In vitro	In vitro
Blood-to-plasma ratio	0.73	0.5	0.6	NC
Metabolism				
Metabolism	CYP3A (major) UGT1A1/3 (minor)	CYP3A (major) CYP2D6 (minor)	Not significantly metabolized	
Elimination				
Major route of elimination	Metabolism		Glomerular filtration and active tubular secretion	
$T_{1/2}$ (h)†	12.9	3.5	10	12−18
% Of dose excreted in urine‡	6.7	8.2	70	70−80
% Of dose excreted in feces‡	94.8	86.2	13.7	NC

NC=Not Calculated

* Values refer to mean systemic exposure (90% confidence interval). STRIBILD light meal=~373 kcal, 20% fat; STRIBILD high fat meal=~800 kcal, 50% fat. Increase = ↑; Decrease = ↓

† $t_{1/2}$ values refer to median terminal plasma half-life.

‡ Dosing in mass balance studies: elvitegravir (single dose administration of [14C] elvitegravir (coadministered with 100 mg RTV); cobicistat (single-dose administration of [^{14}C] cobicistat after multiple dosing of cobicistat for six days); emtricitabine (single dose administration of [^{14}C] emtricitabine after multiple dosing of emtricitabine for ten days); mass balance study not conducted for tenofovir.

Table 8 Pharmacokinetic Parameters of Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir Exposure Following Oral Administration of STRIBILD in HIV-Infected Subjects

Parameter Mean ± SD [range, min:max]	**Elvitegravir***	**Cobicistat†**	**Emtricitabine†**	**Tenofovir†**

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 [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

* From Population Pharmacokinetic analysis, N=419.

† From Intensive Pharmacokinetic analysis, N=61−62, except cobicistat C_{trough} N=53.

Specific Populations

Patients with Renal Impairment

Elvitegravir and Cobicistat: A study of the pharmacokinetics of cobicistat + elvitegravir was performed in healthy subjects and subjects with severe renal impairment (estimated creatinine clearance less than 30 mL per minute). No clinically relevant differences in elvitegravir or cobicistat pharmacokinetics were observed between healthy subjects and subjects with severe renal impairment.

Emtricitabine and Tenofovir Disoproxil Fumarate: The pharmacokinetics of emtricitabine and tenofovir are altered in subjects with estimated creatinine clearance below 50 mL per minute or with end-stage renal disease requiring dialysis *[See Warnings and Precautions (5.3) and Use in Specific Populations (8.6)]*.

Patients with Hepatic Impairment

Elvitegravir and Cobicistat: A study of the pharmacokinetics of cobicistat + elvitegravir was performed in healthy subjects and subjects with moderate hepatic impairment. No clinically relevant differences in elvitegravir or cobicistat pharmacokinetics were observed between subjects with moderate hepatic impairment (Child-Pugh Class B) and healthy subjects. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of elvitegravir or cobicistat has not been studied *[See Use in Specific Populations (8.7)]*.

Emtricitabine: The pharmacokinetics of emtricitabine have not been studied in subjects with hepatic impairment; however, emtricitabine is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.

Tenofovir Disoproxil Fumarate: The pharmacokinetics of tenofovir following a 300 mg dose of VIREAD have been studied in healthy subjects with moderate to severe hepatic impairment. No clinically relevant differences in tenofovir pharmacokinetics were observed between subjects with hepatic impairment and healthy subjects.

Hepatitis B and/or Hepatitis C Virus Coinfection

Elvitegravir: 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 cobicistat-boosted elvitegravir.

Cobicistat: There were insufficient pharmacokinetic data in the clinical trials to determine the effect of hepatitis B and/or C virus infection on the pharmacokinetics of cobicistat.

Emtricitabine and Tenofovir Disoproxil Fumarate: The pharmacokinetics of emtricitabine and tenofovir DF have not been fully evaluated in subjects coinfected with hepatitis B and/or C virus.

Race

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

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

Tenofovir Disoproxil Fumarate: There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations following the administration of VIREAD.

Gender

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

Pediatric Patients

Emtricitabine has been studied in pediatric subjects from 3 months to 17 years of age. Tenofovir DF has been studied in pediatric subjects from 2 years to less than 18 years of age. The pharmacokinetics of elvitegravir or cobicistat in pediatric subjects have not been established *[See Use in Specific Populations (8.4)]*.

Geriatric Patients

The pharmacokinetics of elvitegravir, cobicistat, emtricitabine, and tenofovir have not been fully evaluated in elderly (65 years of age and older) patients *[See Use in Specific Populations (8.5)]*.

Assessment of Drug Interactions

[See also Contraindications (4) and Drug Interactions (7)]

The drug-drug interaction studies described in Tables 9 and 10 were conducted with STRIBILD, elvitegravir (coadministered with cobicistat or RTV), or cobicistat administered alone.

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 antiretroviral agents is not provided *[See Warnings and Precautions (5.4)]*.

The effects of coadministered drugs on the exposure of elvitegravir are shown in Table 9. The effects of elvitegravir or cobicistat on the exposure of coadministered drugs are shown in Table 10. For information regarding clinical recommendations, *See Drug Interactions (7)*.

Table 9 Drug Interactions: Changes in Pharmacokinetic Parameters for Elvitegravir in the Presence of the Coadministered Drug*

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose (mg)	Cobicistat or RTV Booster Dose (mg)	N	Mean Ratio of Elvitegravir Pharmacokinetic Parameters (90% CI); No Effect=1.00		
					C_{max}	AUC	C_{min}
	20 mL single dose given 4 hours before elvitegravir			8	0.95 (0.84,1.07)	0.96 (0.88,1.04)	1.04 (0.93,1.17)
	20 mL single dose given 4 hours after elvitegravir	50 single	RTV	10	0.98 (0.88,1.10)	0.98 (0.91,1.06)	1.00 (0.90,1.11)

Antacids	elvitegravir	50 single dose	100 single dose				
	20 mL single dose given 2 hours before elvitegravir			11	0.82 (0.74,0.91)	0.85 (0.79,0.91)	0.90 (0.82,0.99)
	20 mL single dose given 2 hours after elvitegravir			10	0.79 (0.71,0.88)	0.80 (0.75,0.86)	0.80 (0.73,0.89)
Carbamazepine	200 twice daily	150 once daily	Cobicistat 150 once daily	12	0.55 (0.49,0.61)	0.31 (0.28,0.33)	0.03 (0.02,0.04)
Famotidine	40 once daily given 12 hours after elvitegravir	150 once daily	Cobicistat 150 once daily	10	1.02 (0.89,1.17)	1.03 (0.95,1.13)	1.18 (1.05,1.32)
	40 once daily given simultaneously with elvitegravir			16	1.00 (0.92,1.10)	1.03 (0.98,1.08)	1.07 (0.98,1.17)
Ketoconazole	200 twice daily	150 once daily	RTV 100 once daily	18	1.17 (1.04,1.33)	1.48 (1.36,1.62)	1.67 (1.48,1.88)
Ledipasvir/ Sofosbuvir	90/400 once daily	150 once daily	Cobicistat 150 once daily†	29	0.88 (0.82,0.95)	1.02 (0.95,1.09)	1.36 (1.23,1.49)
Omeprazole	40 once daily given 2 hours before elvitegravir	50 once daily	RTV 100 once daily	9	0.93 (0.83,1.04)	0.99 (0.91,1.07)	0.94 (0.85,1.04)
	20 once daily given 2 hours before elvitegravir	150 once daily	Cobicistat 150 once daily	11	1.16 (1.04,1.30)	1.10 (1.02,1.19)	1.13 (0.96,1.34)
	20 once daily given 12 hours after elvitegravir			11	1.03 (0.92,1.15)	1.05 (0.93,1.18)	1.10 (0.92,1.32)
Rifabutin	150 once every other day	150 once daily	Cobicistat 150 once daily	12	0.91 (0.84,0.99)	0.79 (0.74,0.85)	0.33 (0.27,0.40)
Rosuvastatin	10 single dose	150 once daily	Cobicistat 150 once daily	10	0.94 (0.83,1.07)	1.02 (0.91,1.14)	0.98 (0.83,1.16)

* All interaction studies conducted in healthy volunteers.

† Percent change of cobicistat PK parameters (90% CI) was 1.25 (1.18 to 1.32) for C_{max}, 1.59 (1.49 to 1.70) for AUC, and 4.25 (3.47 to 5.22) for C_{min}.

Table 10 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Elvitegravir plus Cobicistat, Cobicistat, or STRIBILD*

	Dose of	Elvitegravir	Cobicistat		Mean Ratio of Coadministered Drug Pharmacokinetic Parameters‡ (90% CI);

Coadministered Drug	Coadministered Drug (mg)	Dose† (mg)	Booster Dose (mg)	N	No Effect=1.00		
					C_{max}	AUC	C_{min}
Buprenorphine	16–24 once daily	150 once daily	150 once daily	17	1.12 (0.98,1.27)	1.35 (1.18,1.55)	1.66 (1.43,1.93)
Norbuprenorphine					1.24 (1.03,1.49)	1.42 (1.22,1.67)	1.57 (1.31,1.88)
Carbamazepine	200 twice daily	150 once daily	150 once daily	12	1.40 (1.32,1.49)	1.43 (1.36,1.52)	1.51 (1.41,1.62)
Carbamazepine-10,11-epoxide					0.73 (0.70,0.78)	0.65 (0.63,0.66)	0.59 (0.57,0.61)
Desipramine	50 single dose	NA	150 once daily	8	1.24 (1.08,1.44)	1.65 (1.36,2.02)	NC
Digoxin	0.5 single dose	NA	150 once daily	22	1.41 (1.29,1.55)	1.08 (1.00,1.17)	NC
Ledipasvir	90/400 once daily	150 once daily	Cobicistat 150 once daily	29	1.63 (1.51,1.75)	1.78 (1.64,1.94)	1.91 (1.76,2.08)
Sofosbuvir					1.33 (1.14,1.56)	1.36 (1.21,1.52)	NA
GS-331007§					1.33 (1.22,1.44)	1.44 (1.41,1.48)	1.53 (1.47,1.59)
Naloxone	4–6 once daily	150 once daily	150 once daily	17	0.72 (0.61,0.85)	0.72 (0.59,0.87)	NA
Norgestimate/ ethinyl estradiol	0.180/0.215/ 0.250 norgestimate once daily	150 once daily¶	150 once daily¶	13	2.08 (2.00,2.17)	2.26 (2.15,2.37)	2.67 (2.43,2.92)
	0.025 ethinyl estradiol once daily				0.94 (0.86,1.04)	0.75 (0.69,0.81)	0.56 (0.52,0.61)
R-Methadone	80–120 daily	150 once daily	150 once daily	11	1.01 (0.91,1.13)	1.07 (0.96,1.19	1.10 (0.95,1.28)
S-Methadone					0.96 (0.87,1.06)	1.00 (0.89,1.12)	1.02 (0.89,1.17)
Rifabutin	150 once every other day	150 once daily	150 once daily	12	1.09 (0.98,1.20)#	0.92 (0.83,1.03)#	0.94 (0.85,1.04)#
25-O-desacetyl-rifabutin				12	4.84 (4.09,5.74)#	6.25 (5.08,7.69)#	4.94 (4.04,6.04)#
Rosuvastatin	10 single dose	150 single dose	150 single dose	10	1.89 (1.48,2.42)	1.38 (1.14,1.67)	NC

* All interaction studies conducted in healthy volunteers.

† NA=Not Applicable

‡ NC=Not Calculated

§ The predominant circulating nucleoside metabolite of sofosbuvir.

¶ Study conducted with STRIBILD.

Comparison based on rifabutin 300 mg once daily.

12.4 Microbiology

Mechanism of Action

Elvitegravir: Elvitegravir inhibits the strand transfer activity of HIV-1 integrase (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. 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 Disoproxil Fumarate: 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 in Cell Culture

Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir Disoproxil Fumarate: 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 T lymphoblastoid cell lines, monocyte/macrophage cells, and primary peripheral blood lymphocytes. The 50% effective concentrations (EC_{50}) ranged from 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} value of 0.53 nM). Elvitegravir did not show inhibition of replication of HBV or HCV in cell culture.

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

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

Tenofovir Disoproxil Fumarate: The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in T 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 micromolar. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values ranged from 0.5–2.2 micromolar) and showed strain-specific activity against HIV-2 (EC_{50} values ranged from 1.6–5.5 micromolar).

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 Disoproxil Fumarate: 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 RT. HIV-1 isolates selected by tenofovir expressed a K65R substitution in HIV-1 RT and showed a 2–4 fold reduction in susceptibility to tenofovir.

In Clinical Studies

Elvitegravir: Development of substitutions T66A/I/K, E92G/Q, T97A, S147G, Q148H/K/R, and N155H in the HIV-1 integrase protein was primarily associated with resistance to elvitegravir. In addition to these primary elvitegravir resistance-associated substitutions, E92A, F121C/Y, P145S, Q146I/L/R, and N155S were also occasionally observed and were shown to confer reduced susceptibility to elvitegravir. In virus isolates harboring the observed primary elvitegravir resistance-associated substitutions, additional substitutions in integrase were detected including H51Y, L68I/V, G70R, V72A/N, I73V, Q95K/R, S119R, E138A/K, G140A/C/S, E157Q, K160N, E170A, S230R, and D232N.

Emtricitabine and Tenofovir Disoproxil Fumarate: HIV-1 isolates with reduced susceptibility to emtricitabine or tenofovir have been selected in subjects experiencing virologic failure in clinical trials. Genotypic analysis of these isolates identified the M184V/I and K65R amino acid substitutions in the viral RT, respectively.

Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir Disoproxil Fumarate: In clinical trials of HIV-1-infected subjects with no antiretroviral treatment history *[studies 102 and 103, See Clinical Studies (14)]*, by Week 144, the development of one or more primary substitutions associated with resistance to elvitegravir, emtricitabine, and/or tenofovir was observed in viruses from 51% (18/35) of the STRIBILD-treatment failure subjects with evaluable genotypic resistance data who received at least 8 weeks of STRIBILD and had HIV-1 RNA greater than or equal to 400 copies per mL at confirmed virologic failure, the end of each study year, or the time of early study drug discontinuation. The most common substitutions that emerged were M184V/I (N=17) in HIV-1 RT and the primary elvitegravir resistance-associated substitutions, E92Q (N=9), N155H (N=5), Q148R (N=3), T66I (N=2), and T97A (N=1) in integrase; K65R in RT was also detected (N=5). In virus isolates harboring the observed primary elvitegravir resistance substitutions, additional substitutions in integrase were detected including H51Y, L68I/V, G70R, I73V, G140C, S153A, E157Q, and G163R. The virus in all subjects with evaluable data for RT and IN and whose virus developed integrase substitutions associated with elvitegravir resistance (N=14) also developed the M184I/V RT substitutions, and had reduced susceptibility to both elvitegravir and emtricitabine. In phenotypic analyses, HIV-1 isolates expressing M184V/I RT substitutions showed reduced susceptibility to emtricitabine (42- to greater than 152-fold); those expressing the primary elvitegravir resistance-associated integrase substitutions showed reduced susceptibility to elvitegravir (4- to greater than 198-fold); and those expressing the K65R RT substitution showed reduced susceptibility to tenofovir (0.8- to 1.6-fold), compared to wild-type reference HIV-1.

There was an insufficient number of virologic failures with evaluable data (N=1) in clinical trials of virologically suppressed HIV-1-infected subjects with no history of virologic failure *[studies 115 and 121, See Clinical Studies (14)]* to draw conclusions about the development of resistance.

Cross-Resistance

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.

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. Of the primary elvitegravir resistance-associated substitutions tested

(T66A/I/K, E92G/Q, T97A, S147G, Q148H/K/R, and N155H), all but three (T66I, E92G, and S147G) conferred greater than 1.5-fold reduced susceptibility to raltegravir (above the biological cutoff for raltegravir) when introduced individually into a wild-type virus by site-directed mutagenesis. Of the primary raltegravir resistance-associated substitutions (Y143C/H/R, Q148H/K/R, and N155H), all but Y143C/H conferred greater than 2.5-fold reductions in susceptibility to elvitegravir (above the biological cutoff for elvitegravir).

Emtricitabine: Cross-resistance has been observed among NRTIs. Emtricitabine-resistant isolates harboring an M184V/I substitution in HIV-1 RT were cross-resistant to lamivudine. HIV-1 isolates containing the K65R RT substitution, selected in vivo by abacavir, didanosine, and tenofovir, demonstrated reduced susceptibility to inhibition by emtricitabine.

Tenofovir Disoproxil Fumarate: Cross-resistance has been observed among NRTIs. The K65R substitution in HIV-1 RT selected by tenofovir is also selected in some HIV-1-infected patients treated with abacavir or didanosine. HIV-1 isolates with the K65R substitution also showed reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these NRTIs may occur in patients whose virus harbors the K65R substitution. The K70E substitution selected clinically by tenofovir DF results in reduced susceptibility to abacavir, didanosine, emtricitabine, lamivudine, and tenofovir. 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. Subjects whose virus expressed an L74V RT substitution without zidovudine resistance-associated substitutions (N=8) had reduced response to tenofovir DF. Limited data are available for patients whose virus expressed a Y115F substitution (N=3), Q151M substitution (N=2), or T69 insertion (N=4) in HIV-1 RT, all of whom had a reduced response in clinical trials.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Elvitegravir: Long-term carcinogenicity studies of elvitegravir were carried out in mice (104 weeks) and in rats for up to 88 weeks (males) and 90 weeks (females). No drug-related increases in tumor incidence were found in mice at doses up to 2000 mg per kg per day alone or in combination with 25 mg per kg per day RTV at exposures 3- and 14-fold, respectively, the human systemic exposure at the recommended daily dose of 150 mg. No drug-related increases in tumor incidence were found in rats at doses up to 2000 mg per kg per day at exposures 12- to 27-fold, respectively in male and female, the human systemic exposure.

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.

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: 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 7 (male) and 16 (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 times the human systemic exposure at the therapeutic daily dose.

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

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

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

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 Disoproxil Fumarate: Long-term oral carcinogenicity studies of tenofovir DF in mice and rats were carried out at exposures up to approximately 10 times (mice) and 4 times (rats) those observed in humans at the therapeutic dose for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures 10 times of that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 4 times that observed in humans at the therapeutic dose.

Tenofovir DF was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus assay, tenofovir DF was negative when administered to male mice.

There were no effects on fertility, mating performance or early embryonic development when tenofovir DF was administered to male rats at a dose equivalent to 10 times the human dose based on body-surface-area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats.

14 CLINICAL STUDIES

The efficacy of STRIBILD in HIV-1-infected patients with no antiretroviral treatment history is based on the analyses of 144-week data from two randomized, double-blind, active-controlled trials, Study 102 and Study 103 (N=1408, randomized and dosed). The efficacy of STRIBILD in virologically suppressed HIV-1-infected patients without a history of virologic failure is based on the analyses of 48-week data from two randomized, open-label, controlled studies, Study 115 and Study 121 (N=867, randomized and dosed). Patients in all four studies had estimated creatinine clearance greater than or equal to 70 mL/min at screening.

<u>In HIV-1-Infected Subjects with No Antiretroviral Treatment History</u>

In Study 102, subjects were randomized in a 1:1 ratio to receive either STRIBILD (N=348) once daily or ATRIPLA (N=352) once daily. The mean age was 38 years (range, 18−67), 89% were male, 63% were White, 28% were Black, and 2% were Asian. Twenty-four percent of subjects identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.8 $\log_{10}$ copies per mL (range, 2.6–6.5).

The mean baseline CD4+ cell count was 386 cells per mm^3 (range, 3−1348), and 13% had CD4+ cell counts less than 200 cells per mm^3. Thirty-three percent of subjects had baseline viral loads greater than 100,000 copies per mL.

In Study 103, subjects were randomized in a 1:1 ratio to receive either STRIBILD (N=353) once daily or ATV 300 mg + RTV 100 mg + TRUVADA (N=355) once daily. The mean age was 38 years (range, 19−72), 90% were male, 74% were White, 17% were Black, and 5% were Asian. Sixteen percent of subjects identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.8 $\log_{10}$ copies per mL (range, 1.7−6.6). The mean baseline CD4+ cell count was 370 cells per mm^3 (range, 5−1132), and 13% had CD4+ cell count less than 200 cells per mm^3. Forty-one percent of subjects had baseline viral loads greater than 100,000 copies per mL.

In both studies, subjects were stratified by baseline HIV-1 RNA (less than or equal to 100,000 copies per mL or greater than 100,000 copies per mL).

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

Table 11 Virologic Outcome of Randomized Treatment of Study 102 and Study 103 at Week 144*

	Study 102		**Study 103**	
	STRIBILD N=348	**ATRIPLA N=352**	**STRIBILD N=353**	**ATV+RTV+ TRUVADA N=355**
Virologic Success HIV-1 RNA <50 copies/mL	80%	75%	78%	75%
Treatment Difference	4.9% (95% CI = −1.3%, 11.1%)		3.1% (95% CI = −3.2%, 9.4%)	
Virologic Failure†	7%	10%	8%	7%
No Virologic Data in Week 144 Window				
Discontinued Study Drug Due to AE or Death‡	6%	8%	6%	8%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA <50 copies/mL§	5%	7%	8%	9%
Missing Data During Window but on Study Drug	1%	0%	1%	1%

* Week-144 window is between Day 967 and 1050 (inclusive).

† Includes subjects who had ≥50 copies/mL in the Week-144 window, subjects who discontinued early due to lack or loss of efficacy, subjects who discontinued for reasons other than an adverse event, death, or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥50 copies/mL.

‡ Includes patients who discontinued due to an 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.

§ Includes subjects who discontinued for reasons other than an adverse event, death, or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

In Study 102, the mean increase from baseline in CD4+ cell count at Week 144 was 298 cells per mm^3 in the STRIBILD-treated subjects and 272 cells per mm^3 in the ATRIPLA -treated subjects. In Study 103, the mean increase from baseline in CD4+ cell count at Week 144 was 261 cells per mm^3 in the STRIBILD-treated subjects and 269 cells per mm^3 in the ATV+RTV+TRUVADA-treated subjects.

In Virologically Suppressed HIV-1-Infected Subjects with No History of Virologic Failure

In Study 115, subjects had to be on either their first or second antiretroviral regimen with no history of virologic failure, with 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. Subjects 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). Subjects had a mean age of 41 years (range, 21–76), 86% were male, 80% were White, and 15% were Black. The mean baseline CD4+ cell count was 610 cells per mm^3 (range, 74–1919). At screening subjects were receiving atazanavir (40%), darunavir (40%), lopinavir (17%), fosamprenavir (3%), or saquinavir (<1%) as the PI in their regimen.

In Study 121, subjects had to be on either their first or second antiretroviral regimen with no history of virologic failure, with 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. Subjects 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). Subjects had a mean age of 41 years (range, 20–72), 93% were male, 78% were White, and 17% were Black. The mean baseline CD4+ cell count was 588 cells per mm^3 (range, 100–1614). Randomization was stratified by use of efavirenz in the baseline regimen. At screening subjects were receiving efavirenz (78%) (predominantly as ATRIPLA [74%]), nevirapine (17%), rilpivirine (4%) (as COMPLERA [4%]), or etravirine (1%) as the NNRTI in their regimen.

Virologic outcomes of Study 115 and Study 121 are presented in Table 12. Five treated subjects were excluded from the efficacy analysis: in Study 115, three STRIBILD subjects had protocol-prohibited documented resistance and one PI+RTV+TRUVADA subject was not on a protease inhibitor-based regimen at screening; in Study 121, one STRIBILD subject had protocol-prohibited documented resistance.

Table 12 Virologic Outcomes of Randomized Treatment in Study 115 and Study 121 at Week 48

	Study GS-US-236-0115*		**Study GS-US-236-0121***	
	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%
Virologic Failure†	1%	1%	1%	1%
No Virologic Data in Week 48 Window	6%	12%	6%	11%
Discontinued Study Drug Due to AE or Death‡	2%	1%	2%	1%
Discontinued Study Drug Due to Other				

Reasons and Last Available HIV-1 RNA <50 copies/mL§	4%	10%	4%	9%
Missing Data During Window but on Study Drug	0%	0%	0%	1%

* Week-48 window is between Day 295 and 378 (inclusive).

† Includes subjects who had ≥50 copies/mL in the Week-48 window, subjects who discontinued early due to lack or loss of efficacy, subjects who discontinued for reasons other than an adverse event, death, or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥50 copies/mL.

‡ Includes subjects who discontinued due to an 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.

§ Includes subjects who discontinued for reasons other than an adverse event, death, or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

16 HOW SUPPLIED/STORAGE AND HANDLING

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 (NDC 61958-1201-1) and a silica gel desiccant, and is closed with a child-resistant closure.

Store at 25 °C (77 °F), excursions permitted to 15–30 °C (59–86 °F) (See USP Controlled Room Temperature).

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

A statement to patients and healthcare providers is included on the product's bottle label: **ALERT: Find out about medicines that should NOT be taken with STRIBILD.**

Advise patients that STRIBILD may interact with many drugs; therefore, patients should report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John's wort.

Information for Patients

Advise patients to remain under the care of a healthcare provider when using STRIBILD.

Inform patients that STRIBILD is not a cure for HIV-1 infection. Patients should stay on continuous HIV therapy to control HIV-1 infection and decrease HIV-related illnesses. Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death.

Advise patients to avoid doing things that can spread HIV-1 infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes**

and razor blades.

- **Do not have any kind of sex without protection.** Always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** At least two of the drugs contained in STRIBILD can be passed to the baby in breast milk. It is not known whether this could harm the baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in breast milk.

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Inform patients that lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Advise patients that treatment with STRIBILD should be suspended if they develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity (including nausea, vomiting, unusual or unexpected stomach discomfort, and weakness) *[See Warnings and Precautions (5.1)]*.

HIV-1 and HBV Coinfection

Inform patients that hepatitis B testing is recommended prior to initiating antiretroviral therapy. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued EMTRIVA or VIREAD *[See Warnings and Precautions (5.2)]*.

New Onset or Worsening Renal Impairment

Inform patients that renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported in association with the use of STRIBILD. Advise patients to avoid STRIBILD with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple NSAIDs) *[See Warnings and Precautions (5.3)]*.

Use with Other Antiretroviral Products

Advise patients not to coadminister STRIBILD with other antiretroviral products because STRIBILD provides a complete treatment regimen and because of potential drug interactions *[See Warnings and Precautions (5.4) and Drug Interactions (7)]*.

Advise patients that STRIBILD should not be administered in combination with:

- ATRIPLA, COMPLERA, DESCOVY, EMTRIVA, GENVOYA, ODEFSEY, TRUVADA, TYBOST, VIREAD, or VITEKTA
- With drugs containing lamivudine, including Combivir, Epivir or Epivir-HBV, Epzicom, Triumeq, or Trizivir
- With drugs containing RTV or regimens containing RTV
- With HEPSERA *[See Warnings and Precautions (5.4)]*.

Bone Effects of Tenofovir DF

Inform patients that decreases in bone mineral density have been observed with the use of STRIBILD. Assessment of bone mineral density (BMD) should be considered in patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss *[See Warnings and Precautions (5.6)]*.

Fat Redistribution

Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, and that the cause and long-term health effects of these conditions are not known *[See Warnings and Precautions (5.7)]*.

Immune Reconstitution Syndrome

Inform patients that, in some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed

that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. Advise patients to inform their healthcare provider immediately of any symptoms of infection *[See Warnings and Precautions (5.8)]*.

Dosing Instructions

Advise patients not to discontinue STRIBILD without first informing their healthcare provider.

Inform patients that:

- It is important to take STRIBILD on a regular dosing schedule with food and to avoid missing doses.
- It is important to not miss a dose of STRIBILD. If a patient misses a dose of STRIBILD, the patient should take the missed dose as soon as they remember. If it is almost time for the next dose of STRIBILD, the patient should not take the missed dose but resume the usual dosing schedule.
- They should not take more or less than the prescribed dose of STRIBILD at any one time.

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Patient Information

STRIBILD® (STRY-bild)
(elvitegravir, cobicistat, emtricitabine,
and tenofovir disoproxil fumarate)
Tablets

Important: Ask your healthcare provider or pharmacist about medicines that should not be taken with STRIBILD. For more information, see the section "What should I tell my healthcare provider before taking STRIBILD?"

Read this Patient Information before you start taking STRIBILD and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about STRIBILD?

STRIBILD can cause serious side effects, including:

1. **Build-up of lactic acid in your blood (lactic acidosis).** Lactic acidosis can happen in some people who take STRIBILD or similar (nucleoside analogs) medicines. Lactic acidosis is a serious medical emergency that can lead to death.
   Lactic acidosis can be hard to identify early, because the symptoms could seem like symptoms of other health problems. **Call your healthcare provider right away if you get any of the following symptoms which could be signs of lactic acidosis:**
   - feel very weak or tired
   - have unusual (not normal) muscle pain
   - have trouble breathing
   - have stomach pain with
     - nausea
     - vomiting
   - feel cold, especially in your arms and legs
   - feel dizzy or lightheaded
   - have a fast or irregular heartbeat

2. **Severe liver problems.** Severe liver problems can happen in people who take STRIBILD. In some cases, these liver problems can lead to death. Your liver may become large (hepatomegaly) and you may develop fat in your liver (steatosis).
   Call your healthcare provider right away if you get any of the following symptoms of liver problems:
   - your skin or the white part of your eyes turns yellow (jaundice)
   - dark "tea-colored" urine
   - light-colored bowel movements (stools)
   - loss of appetite for several days or longer
   - nausea
   - stomach pain

   You may be more likely to get lactic acidosis or severe liver problems if you are female, very overweight (obese), or have been taking STRIBILD for a long time.
3. **Worsening of Hepatitis B infection. If you have hepatitis B virus (HBV) infection and take STRIBILD, your HBV may get worse (flare-up) if you stop taking STRIBILD. A "flare-up" is when your HBV infection suddenly returns in a worse way than before.**
   - Do not run out of STRIBILD. Refill your prescription or talk to your healthcare provider before your STRIBILD is all gone.
   - Do not stop taking STRIBILD without first talking to your healthcare provider.
   - If you stop taking STRIBILD, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your HBV infection. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking STRIBILD.

For more information about side effects, see the section **"What are the possible side effects of STRIBILD?"**

What is STRIBILD?

STRIBILD is a prescription medicine that is used without other antiretroviral medicines to treat Human Immunodeficiency Virus-1 (HIV-1) in adults:
- who have not received anti-HIV-1 medicines in the past, **or**
- to replace their current anti-HIV-1 medicines:
  - in people who have been on the same anti-HIV-1 medicine regimen for at least 6 months, **and**
  - who have an amount of HIV-1 in their blood (this is called 'viral load') that is less than 50 copies/mL, **and**
  - have never failed past HIV-1 treatment.

HIV-1 is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

STRIBILD contains the prescription medicines elvitegravir (VITEKTA), cobicistat (TYBOST), emtricitabine (EMTRIVA®) and tenofovir disoproxil fumarate (VIREAD®).

It is not known if STRIBILD is safe and effective in children under 18 years of age.

When used to treat HIV-1 infection, STRIBILD may:
- Reduce the amount of HIV-1 in your blood.
- Increase the number of CD4+ (T) cells in your blood that help fight off other infections.

Reducing the amount of HIV-1 and increasing the CD4+ (T) cells in your blood may help improve your immune system. This may reduce your risk of death or getting infections that can happen when your immune system is weak (opportunistic infections).

STRIBILD does not cure HIV-1 infections or AIDS. You must stay on continuous HIV-1 therapy to

control HIV-1 infection and decrease HIV-related illnesses.

Avoid doing things that can spread HIV-1 infection to others.

- Do not share or re-use needles or other injection equipment.
- Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.
- Do not have any kind of sex without protection. Always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

Ask your healthcare provider if you have any questions about how to prevent passing HIV-1 to other people.

Who should not take STRIBILD?

Do not take STRIBILD if you also take a medicine that contains:

- alfuzosin hydrochloride (UROXATRAL®)
- cisapride (PROPULSID®, PROPULSID QUICKSOLV®)
- carbamazepine (CARBATROL®, EPITOL®, EQUETRO®, TEGRETOL®, TEGRETOL-XR®, TERIL®)
- ergot-containing medicines, including:
  - dihydroergotamine mesylate (D.H.E. 45®, MIGRANAL®)
  - ergotamine tartrate (CAFERGOT®, MIGERGOT®,ERGOSTAT®, MEDIHALER ERGOTAMINE®, WIGRAINE®, WIGRETTES®)
  - methylergonovine maleate (ERGOTRATE®, METHERGINE®)
- lovastatin (ADVICOR®, ALTOPREV®, MEVACOR®)
- lurasidone (LATUDA®)
- midazolam, when taken by mouth
- phenobarbital (LUMINAL®)
- phenytoin (DILANTIN®, PHENYTEK®)
- pimozide (ORAP®)
- rifampin (RIFADIN®, RIFAMATE®, RIFATER®, RIMACTANE®)
- sildenafil (REVATIO®), when used for treating the lung problem, pulmonary arterial hypertension (PAH)
- simvastatin (SIMCOR®, VYTORIN®, ZOCOR®)
- triazolam (HALCION®)
- St. John's wort (Hypericum perforatum) or a product that contains St. John's wort

What should I tell my healthcare provider before taking STRIBILD?

Before taking STRIBILD, tell your healthcare provider if you:

- have liver problems including hepatitis B infection
- have kidney problems
- have bone problems
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if STRIBILD can harm your unborn baby. Tell your healthcare provider if you become pregnant while taking STRIBILD.
  Pregnancy Registry. There is a pregnancy registry for women who take antiviral medicines during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk with your healthcare provider about how you can take part in this registry.
- are breastfeeding or plan to breastfeed. Do not breastfeed if you take STRIBILD.
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  - At least two of the medicines in STRIBILD can pass to your baby in your breast milk. It is not known if the other medicines in STRIBILD can pass into your breast milk.

Talk with your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some medicines may interact with STRIBILD. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with STRIBILD.
- **Do not start a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take STRIBILD with other medicines.

How should I take STRIBILD?

- Take STRIBILD exactly as your healthcare provider tells you to take it. **STRIBILD is taken by itself (not with other anti-HIV medicines) to treat HIV-1 infection.**
- STRIBILD is usually taken 1 time each day.
- Take STRIBILD with food.
- Do not change your dose or stop taking STRIBILD without first talking with your healthcare provider. Stay under a healthcare provider's care when taking STRIBILD.
- If you need to take a medicine for indigestion (antacid) that contains aluminum and magnesium hydroxide or calcium carbonate during treatment with STRIBILD, take it at least 2 hours before or after you take STRIBILD.
- Do not miss a dose of STRIBILD. If you miss a dose of STRIBILD, take the missed dose as soon as you remember. If it is almost time for your next dose of STRIBILD, do not take the missed dose. Take the next dose of STRIBILD at your regular time. Do not take 2 doses at the same time to make up for a missed dose.
- If you take too much STRIBILD, call your healthcare provider or go to the nearest hospital emergency room right away.
- When your STRIBILD supply starts to run low, get more from your healthcare provider or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to STRIBILD and become harder to treat.

What are the possible side effects of STRIBILD?

STRIBILD may cause the following serious side effects, including:

- **See "What is the most important information I should know about STRIBILD?"**
- **New or worse kidney problems, including kidney failure.** Your healthcare provider should do blood and urine tests to check your kidneys before you start and while you are taking STRIBILD. Your healthcare provider may tell you to stop taking STRIBILD if you develop new or worse kidney problems.
- **Bone problems** can happen in some people who take STRIBILD. Bone problems include bone pain, softening, or thinning (which may lead to fractures). Your healthcare provider may need to do tests to check your bones.
- **Changes in body fat can happen in people who take HIV-1 medicine**. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the middle of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term health effects of these conditions are not known.
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having any new symptoms after starting your HIV-1 medicine.

The most common side effects of STRIBILD include:

- nausea
- diarrhea

Tell your healthcare provider 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 provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store STRIBILD?

- Store STRIBILD at room temperature between 68 °F to 77 °F (20 °C to 25 °C).
- Keep STRIBILD in its original container.
- Keep the container tightly closed.
- Do not use STRIBILD if the seal over the bottle opening is broken or missing.

Keep STRIBILD and all medicines out of reach of children.

General information about STRIBILD.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use STRIBILD for a condition for which it was not prescribed. Do not give STRIBILD to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about STRIBILD. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about STRIBILD that is written for health professionals.

For more information, call 1-800-445-3235 or go to www.STRIBILD.com.

What are the ingredients in STRIBILD?

Active ingredients: elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate

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.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured and distributed by:
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203100-GS-007

PRINCIPAL DISPLAY PANEL - 30 Tablet Bottle Label

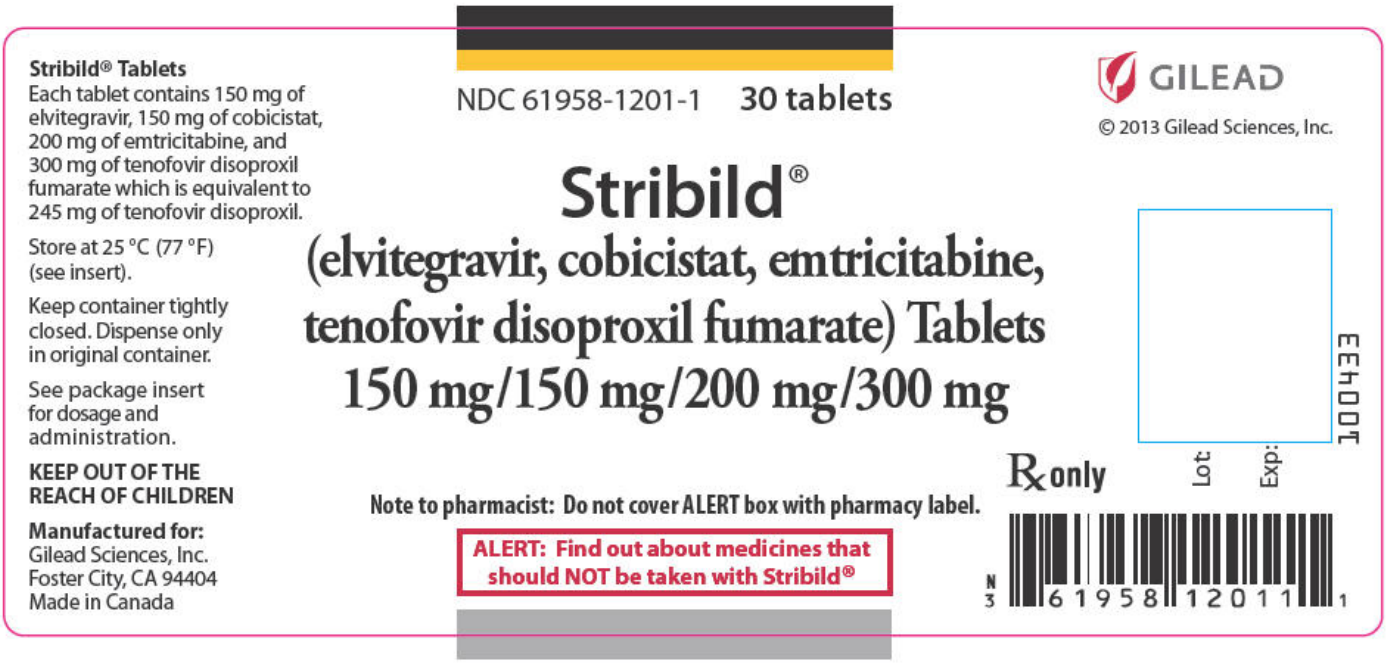
NDC 61958-1201-1
30 tablets

Stribild®
(elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate) Tablets
150 mg/150 mg/200 mg/300 mg

R_x only

Note to pharmacist: Do not cover ALERT box with pharmacy label.

ALERT: Find out about medicines that should NOT be taken with Stribild®



STRIBILD

elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:61958-1201
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
elvitegravir (UNII: 4GDQ854U53) (elvitegravir - UNII:4GDQ854U53)	elvitegravir	150 mg
cobicistat (UNII: LW2E03M5PG) (cobicistat - UNII:LW2E03M5PG)	cobicistat	150 mg
emtricitabine (UNII: G70B4ETF4S) (emtricitabine - UNII:G70B4ETF4S)	emtricitabine	200 mg
tenofovir disoproxil fumarate (UNII: OTT9J7900I) (tenofovir anhydrous - UNII:W4HFE001U5)	tenofovir disoproxil fumarate	300 mg

Inactive Ingredients

Ingredient Name	Strength

MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
HYDROXYPROPYL CELLULOSE (1200000 MW) (UNII: RFW2ET671P)	
POLYVINYL ALCOHOL, UNSPECIFIED (UNII: 532B59J990)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
TALC (UNII: 7SEV7J4R1U)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
ALUMINUM OXIDE (UNII: LMI26O6933)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	

Product Characteristics

Color	GREEN	**Score**	no score
Shape	OVAL (Capsule shape)	**Size**	20mm
Flavor		**Imprint Code**	GSI;1
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:61958-1201-1	30 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	08/27/2012	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA203100	08/27/2012	

Labeler - Gilead Sciences, Inc. (185049848)

Revised: 9/2016 Gilead Sciences, Inc.