Brand Name	Genvoya
Active Ingredient(s)	elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide
Strength	150-150-200-10 mg
Dosage Form	tablet
Inactive Ingredients	croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, silicon dioxide, and sodium lauryl sulfate. Film coating contains polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, indigo carmine aluminum lake, and iron oxide yellow.
NDC	61958-1901-1
DIN	02449498
Canadian Distributor	Gilead Sciences Canada Inc. 600 6711 Mississauga Road, Mississauga, Ontario, Canada L5N 2W3
NDA Number	NDA207561
US Distributor (NDA Holder)	Gilead Sciences, Inc 333 Lakeside Drive, Foster City, CA 94404 USA
Manufacturer (Final Packager)	Not available
API Manufacturer	Not available
Relationship to Sponsor	The Sponsor may have or have had agreements with the U.S. manufacturer for rebates. The Sponsor has no relationship with the foreign manufacturer.

Current FDA-approved Package Insert

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

GENVOYA® (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets, for oral use
Initial U.S. Approval: 2015

WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B
See full prescribing information for complete boxed warning.

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of GENVOYA. Hepatic function should be monitored closely in these patients. If appropriate, anti-hepatitis B therapy may be warranted. (5.1)

----------RECENT MAJOR CHANGES----------
Warnings and Precautions, New Onset or Worsening Renal Impairment (5.4) 03/2021

----------INDICATIONS AND USAGE----------
GENVOYA is a four-drug combination of elvitegravir (EVG), an HIV-1 integrase strand transfer inhibitor (INSTI), cobicistat (COBI), a CYP3A inhibitor, and emtricitabine (FTC) and tenofovir alafenamide (TAF), both HIV-1 nucleoside analog reverse transcriptase inhibitors (NRTIs), and is indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 25 kg 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 per 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 GENVOYA. (1)

----------DOSAGE AND ADMINISTRATION----------
- Testing: Prior to or when initiating GENVOYA test for hepatitis B virus infection. Prior to or when initiating GENVOYA, and during treatment on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. (2.1)
- Recommended dosage in adult and pediatric patients weighing at least 25 kg: One tablet taken orally once daily with food in patients with body weight at least 25 kg and a creatinine clearance greater than or equal to 30 mL per minute, or in adult patients with creatinine clearance less than 15 mL per minute who are receiving chronic hemodialysis. On days of hemodialysis, administer GENVOYA after hemodialysis. (2.2)
- Renal impairment: GENVOYA is not recommended in patients with estimated creatinine clearance of 15 to below 30 mL per minute, or below 15 mL per minute who are not receiving chronic hemodialysis. (2.3)
- Hepatic impairment: GENVOYA is not recommended in patients with severe hepatic impairment. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide. (3)

----------CONTRAINDICATIONS----------
Coadministration of GENVOYA 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 GENVOYA and possible resistance. (4)

----------WARNINGS AND PRECAUTIONS----------
- Risk of adverse reactions or loss of virologic response due to drug interactions: The concomitant use of GENVOYA and other drugs may result in known or potentially significant drug interactions, some of which may lead to loss of therapeutic effect of GENVOYA and possible development of resistance; clinically significant adverse reactions from greater exposures of concomitant drugs; or loss of therapeutic effect of concomitant drugs. (5.2)
- Immune reconstitution syndrome: May necessitate further evaluation and treatment. (5.3)
- New onset or worsening renal impairment: Assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein when initiating GENVOYA and during therapy on a clinically appropriate schedule in all patients. Also assess serum phosphorus in patients with chronic kidney disease. (5.4)
- Lactic acidosis/severe hepatomegaly with steatosis: Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.5)

----------ADVERSE REACTIONS----------
Most common adverse reaction (incidence greater than or equal to 10%, all grades) is nausea. (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----------
- GENVOYA should not be administered with other antiretroviral medications for treatment of HIV-1 infection. (7.1)
- GENVOYA 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 GENVOYA. 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: Not recommended for use during pregnancy because of substantially lower exposures of cobicistat and elvitegravir during pregnancy. GENVOYA should not be initiated in pregnant individuals. (2.5, 8.1)
- Lactation: Breastfeeding is not recommended due to the potential for HIV transmission. (8.2)
- Pediatrics: Not recommended for patients weighing less than 25 kg. (8.4)

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

Revised: 01/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of GENVOYA. 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 GENVOYA. If appropriate, anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

GENVOYA is indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 25 kg 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 per 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 GENVOYA *[see Clinical Studies (14)].*

2 DOSAGE AND ADMINISTRATION

2.1 Testing When Initiating and During Treatment with GENVOYA

Prior to or when initiating GENVOYA, test patients for hepatitis B virus infection *[see Warnings and Precautions (5.1)]*.

Prior to or when initiating GENVOYA, and during treatment with GENVOYA on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus *[see Warnings and Precautions (5.4)]*.

2.2 Recommended Dosage in Adults and Pediatric Patients Weighing at Least 25 kg

GENVOYA is a four-drug fixed dose combination product containing elvitegravir (EVG), cobicistat (COBI), emtricitabine (FTC), and tenofovir alafenamide (TAF). The recommended dosage of GENVOYA is one tablet containing 150 mg EVG,150 mg COBI, 200 mg FTC, and 10 mg TAF taken orally once daily with food in:

- adults and pediatric patients with body weight at least 25 kg and creatinine clearance greater than or equal to 30 mL per minute; or

- adults with creatinine clearance below 15 mL per minute who are receiving chronic hemodialysis. On days of hemodialysis, administer GENVOYA after completion of hemodialysis treatment *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

2.3 Not Recommended in Patients with Severe Renal Impairment

GENVOYA is not recommended in patients with:

- severe renal impairment (estimated creatinine clearance of 15 to below 30 mL per minute); or
- end stage renal disease (ESRD; estimated creatinine clearance below 15 mL per minute) who are not receiving chronic hemodialysis *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)]*.

2.4 Not Recommended in Patients with Severe Hepatic Impairment

GENVOYA is not recommended in patients with severe hepatic impairment (Child-Pugh Class C) *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

2.5 Not Recommended During Pregnancy

GENVOYA is not recommended for use during pregnancy because of substantially lower exposures of cobicistat and elvitegravir during the second and third trimesters *[see Use in Specific Populations (8.1)]*.

GENVOYA should not be initiated in pregnant individuals. An alternative regimen is recommended for individuals who become pregnant during therapy with GENVOYA *[see Use in Specific Populations (8.1)]*.

3 DOSAGE FORMS AND STRENGTHS

Each GENVOYA tablet contains 150 mg of elvitegravir (EVG), 150 mg of cobicistat (COBI), 200 mg of emtricitabine (FTC), and 10 mg of tenofovir alafenamide (TAF) (equivalent to 11.2 mg of tenofovir alafenamide fumarate).

The tablets are green, capsule-shaped, film-coated tablets, debossed with “GSI” on one side of the tablet and the number “510” on the other side of the tablet.

4 CONTRAINDICATIONS

Coadministration of GENVOYA 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 GENVOYA and possible resistance) are listed below *[see Drug Interactions (7.5) and Clinical Pharmacology (12.3)]*.

- Alpha 1-adrenoreceptor antagonist: alfuzosin
- Anticonvulsants: carbamazepine, phenobarbital, phenytoin
- Antimycobacterial: rifampin
- Antipsychotics: lurasidone, pimozide
- Ergot Derivatives: dihydroergotamine, ergotamine, methylergonovine
- Herbal Products: St. John's wort (*Hypericum perforatum*)
- Lipid-modifying Agents: lomitapide, lovastatin, simvastatin
- Phosphodiesterase-5 (PDE-5) Inhibitor: sildenafil when administered as REVATIO® for the treatment of pulmonary arterial hypertension
- Sedative/hypnotics: triazolam, orally administered midazolam

5 WARNINGS AND PRECAUTIONS

5.1 Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV

Patients with HIV-1 should be tested for the presence of hepatitis B virus (HBV) before or when initiating antiretroviral therapy *[see Dosage and Administration (2.1)]*.

Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of GENVOYA. Patients coinfected with HIV-1 and HBV who discontinue GENVOYA should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis, since post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

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

The concomitant use of GENVOYA 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 of therapeutic effect of GENVOYA and possible development of resistance
- Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events, from greater exposures of concomitant drugs metabolized by CYP3A.
- Loss of therapeutic effect of concomitant drugs that utilize CYP3A to form active metabolites.

See Table 5 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations *[see Drug Interactions (7)]*. Consider the potential for drug interactions prior to and during GENVOYA therapy; review concomitant medications during GENVOYA therapy; and monitor for the adverse reactions associated with the concomitant drugs.

5.3 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including emtricitabine, a component of GENVOYA. 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, Guillain-Barré syndrome, and autoimmune hepatitis) 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.

5.4 New Onset or Worsening Renal Impairment

Postmarketing cases of renal impairment, including acute renal failure, proximal renal tubulopathy (PRT), and Fanconi syndrome have been reported with TAF-containing products; while most of these cases were characterized by potential confounders that may have contributed to the reported renal events, it is also possible these factors may have predisposed patients to tenofovir-related adverse events *[see Adverse Reactions (6.1, 6.2)]*. GENVOYA is not recommended in patients with estimated creatinine clearance of 15 to below 30 mL per minute, or in patients with estimated creatinine clearance below 15 mL per minute who are not receiving chronic hemodialysis.

Patients taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents including non-steroidal anti-inflammatory drugs are at increased risk of developing renal-related adverse reactions.

Prior to or when initiating GENVOYA, and during treatment with GENVOYA on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. Discontinue GENVOYA in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

Cobicistat, a component of GENVOYA, produces elevations of serum creatinine due to inhibition of tubular secretion of creatinine without affecting glomerular filtration *[see Adverse Reactions (6.1)]*. The elevation is typically seen within 2 weeks of starting therapy and is reversible after discontinuation. 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.

5.5 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 emtricitabine, a component of GENVOYA, and tenofovir DF, another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with GENVOYA 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).

6 ADVERSE REACTIONS

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

- Severe Acute Exacerbations of Hepatitis B *[see Warnings and Precautions (5.1)]*
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.3)]*
- New Onset or Worsening Renal Impairment *[see Warnings and Precautions (5.4)]*
- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[see Warnings and Precautions (5.5)]*

6.1 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.

Clinical Trials in Treatment-Naïve Adults

The primary safety assessment of GENVOYA was based on Week 144 pooled data from 1,733 subjects in two randomized, double-blind, active-controlled trials, Study 104 and Study 111, in antiretroviral treatment-naïve HIV-1 infected adult subjects. A total of 866 subjects received one tablet of GENVOYA once daily *[see Clinical Studies (14.2)]*.

The most common adverse reaction (all Grades) reported in at least 10% of subjects in the GENVOYA group was nausea. The proportion of subjects who discontinued treatment with GENVOYA or STRIBILD® due to adverse events, regardless of severity, was 1% and 2%, respectively. Table 1 displays the frequency of adverse reactions (all Grades) greater than or equal to 5% in the GENVOYA group.

Table 1 Adverse Reactions[a] (All Grades) Reported in ≥ 5% of HIV-1 Infected Treatment-Naïve Adults Receiving GENVOYA in Studies 104 and 111 (Week 144 analysis)

	GENVOYA N=866	**STRIBILD** N=867
Nausea	11%	13%
Diarrhea	7%	9%
Headache	6%	5%
Fatigue	5%	4%

a. Frequencies of adverse reactions are based on all adverse events attributed to study drugs by the investigator.

The majority of events presented in Table 1 occurred at severity Grade 1.

Clinical Trials in Virologically Suppressed Adults

The safety of GENVOYA in virologically-suppressed adults was based on Week 96 data from 959 subjects in a randomized, open-label, active-controlled trial (Study 109) in which virologically-suppressed subjects were switched from a TDF-containing combination regimen to GENVOYA. Overall, the safety profile of GENVOYA in subjects in this study was similar to that of treatment-naïve subjects *[see Clinical Studies (14.3)]*. Additional adverse reactions observed with GENVOYA in Study 109 included suicidal ideation, suicidal behavior, and suicide attempt (<1% combined); all of these events were serious and all occurred in subjects with a preexisting history of depression or psychiatric illness.

Clinical Trials in Adult Subjects with Renal Impairment

In an open-label trial (Study 112), 248 HIV-1 infected subjects with estimated creatinine clearance between 30 and 69 mL per minute (by Cockcroft-Gault method) were treated with GENVOYA for a median duration of 144 weeks. Of these subjects, 65% had previously been on a stable TDF-containing regimen. A total of 5 subjects permanently discontinued GENVOYA due to the development of renal adverse events through Week 96. Three of these five were among the 80 subjects with baseline estimated creatinine clearance of less than 50 mL/min and two subjects were among the 162 subjects with baseline estimated creatinine clearance of greater than or equal to 50 mL/min. There were no further renal discontinuations between Weeks 96 and 144. Overall, renally impaired subjects receiving GENVOYA in this study had a mean serum creatinine of 1.5 mg/dL at baseline and 1.4 mg/dL at Week 144. Otherwise, the safety profile of GENVOYA in subjects in this study was similar to that of subjects with normal renal function.

Virologically-Suppressed Adults with End Stage Renal Disease (ESRD) Receiving Chronic Hemodialysis

The safety of GENVOYA in subjects with end stage renal disease (ESRD) (estimated creatinine clearance of less than 15 mL/min) on chronic hemodialysis was assessed in

55 subjects (Study 1825) *[see Clinical Studies (14.4)].* The most commonly reported adverse reaction (adverse event assessed as causally related by investigator and all grades) was nausea (7%). Serious adverse events were reported in 53% of subjects and the most common serious adverse events were pneumonia (13%), fluid overload (7%), hyperkalemia (7%) and osteomyelitis (7%). Overall 5% of subjects permanently discontinued treatment due to an adverse event.

Renal Laboratory Tests and Renal Safety

Treatment-Naïve Adults:

Cobicistat (a component of GENVOYA) has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting glomerular filtration *[see Clinical Pharmacology (12.2)]*. Increases in serum creatinine occurred by Week 2 of treatment and remained stable through 144 weeks.

In two 144-week randomized, controlled trials in a total of 1,733 treatment-naïve adults with a median baseline estimated creatinine clearance of 115 mL per minute, mean serum creatinine increased by less than 0.1 mg per dL in the GENVOYA group and by 0.1 mg per dL in the STRIBILD group from baseline to Week 144.

Virologically Suppressed Adults:

In a study of 1,436 virologically-suppressed TDF-treated adults with a mean baseline estimated creatinine clearance of 112 mL per minute who were randomized to continue their treatment regimen or switch to GENVOYA, at Week 96 mean serum creatinine was similar to baseline for both those continuing baseline treatment and those switching to GENVOYA.

Across these trials, renal serious adverse events or discontinuations due to renal adverse reactions were encountered in less than 1% of participants treated with GENVOYA.

Bone Mineral Density Effects

Treatment-Naïve Adults:

In a pooled analysis of Studies 104 and 111, the effects of GENVOYA compared to STRIBILD on bone mineral density (BMD) change from baseline to Week 144 were assessed by dual-energy X-ray absorptiometry (DXA). The mean percentage change in BMD from baseline to Week 144 was −0.92% with GENVOYA compared to −2.95% with STRIBILD at the lumbar spine and −0.75% compared to −3.36% at the total hip. BMD declines of 5% or greater at the lumbar spine were experienced by 15% of GENVOYA subjects and 29% of STRIBILD subjects. BMD declines of 7% or greater at the femoral neck were experienced by 15% of GENVOYA subjects and 29% of STRIBILD subjects. The long-term clinical significance of these BMD changes is not known.

Virologically Suppressed Adults:

In Study 109, TDF-treated subjects were randomized to continue their TDF-based regimen or switch to GENVOYA; changes in BMD from baseline to Week 96 were assessed by DXA. Mean BMD increased in subjects who switched to GENVOYA (2.12% lumbar spine, 2.44% total hip) and decreased slightly in subjects who continued their baseline regimen (−0.09% lumbar spine, −0.46% total hip). BMD declines of 5% or greater at the lumbar spine were experienced by 2% of GENVOYA subjects and 6% of subjects who continued their TDF-based regimen. BMD declines of 7% or greater at the femoral neck were experienced by 2% of GENVOYA subjects and 7% of subjects who continued their TDF-based regimen. The long-term clinical significance of these BMD changes is not known.

Laboratory Abnormalities:

The frequency of laboratory abnormalities (Grades 3–4) occurring in at least 2% of subjects receiving GENVOYA in Studies 104 and 111 are presented in Table 2.

Table 2 Laboratory Abnormalities (Grades 3–4) Reported in ≥ 2% of Subjects Receiving GENVOYA in Studies 104 and 111 (Week 144 analysis)

Laboratory Parameter Abnormality[a]	GENVOYA N=866	STRIBILD N=867
Creatine Kinase (≥10.0 x ULN)	11%	10%
LDL-cholesterol (fasted) (>190 mg/dL)	11%	5%
Total cholesterol (fasted) (>300mg/dL)	4%	3%
Amylase	3%	5%
ALT	3%	3%
AST	3%	4%
Urine RBC (Hematuria) (>75 RBC/HPF)	3%	3%

a. Frequencies are based on treatment-emergent laboratory abnormalities.

Serum Lipids:

Subjects receiving GENVOYA experienced greater increases in serum lipids compared to those receiving STRIBILD.

Changes from baseline in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and total cholesterol to HDL ratio are presented in Table 3.

Table 3 Lipid Values, Mean Change from Baseline, Reported in Subjects Receiving GENVOYA or STRIBILD in Trials 104 and 111[a]

	GENVOYA N=866		STRIBILD N=867	
	Baseline	**Week 144**	**Baseline**	**Week 144**
	mg/dL	Change[b]	mg/dL	Change[b]
Total Cholesterol (fasted)	162 [N=647]	+31 [N=647]	165 [N=627]	+14 [N=627]
Triglycerides (fasted)	111 [N=647]	+29 [N=647]	115 [N=627]	+17 [N=627]
LDL-cholesterol (fasted)	103 [N=647]	+20 [N=643]	107 [N=628]	+8 [N=628]
HDL-cholesterol (fasted)	47 [N=647]	+7 [N=647]	46 [N=627]	+3 [N=627]
Total Cholesterol to HDL ratio	3.7 [N=647]	0.2 [N=647]	3.8 [N=627]	0.1 [N=627]

a. Excludes subjects who received lipid lowering agents during the treatment period.

b. The change from baseline is the mean of within-subject changes from baseline for subjects with both baseline and Week 144 values.

Clinical Trials in Pediatric Subjects:

Safety in Pediatric Patients

The safety of GENVOYA in HIV-1 infected pediatric subjects was evaluated in treatment-naïve subjects between the ages of 12 to less than 18 years and weighing at least 35 kg (N=50) through Week 48 (cohort 1), and in virologically-suppressed subjects between the ages of 6 to less than 12 years and weighing at least 25 kg (N=52) through Week 48 (cohort 2) in an open-label clinical trial (Study 106) *[see Clinical Studies (14.5)]*. With the exception of a decrease in the mean CD4+ cell count observed in cohort 2 of Study 106, the safety profile in pediatric subjects who received treatment with GENVOYA was similar to that in adults. One 13-year-old female subject developed unexplained uveitis while receiving GENVOYA that resolved and did not require discontinuation of GENVOYA.

Bone Mineral Density Effects

Cohort 1: Treatment-naïve adolescents (12 to less than 18 years; at least 35 kg)

Among the subjects in cohort 1 receiving GENVOYA, mean BMD increased from baseline to Week 48, + 4.2% at the lumbar spine and + 1.3% for the total body less head (TBLH). Mean changes from baseline BMD Z-scores were −0.07 for lumbar spine and −0.20 for TBLH at Week 48. One GENVOYA subject had significant (at least 4%) lumbar spine BMD loss at Week 48.

Cohort 2: Virologically-suppressed children (6 to less than 12 years; at least 25 kg)

Among the subjects in cohort 2 receiving GENVOYA, mean BMD increased from baseline to Week 48, +3.9% at the lumbar spine and +4.2% for TBLH. Mean changes from baseline BMD Z-scores were -0.24 for lumbar spine and -0.19 for TBLH at Week 48. Six GENVOYA subjects had significant (at least 4%) lumbar spine BMD loss at Week 48; 2 subjects also had at least 4% TBLH BMD loss at Week 48.

Change from Baseline in CD4+ cell counts

Cohort 2: Virologically-suppressed children (6 to less than 12 years; at least 25 kg)

Cohort 2 of Study 106 evaluated pediatric subjects (N=52) who were virologically-suppressed and who switched from their antiretroviral regimen to GENVOYA. Although all subjects had HIV-1 RNA < 50 copies/mL, there was a decrease from baseline in CD4+ cell count at Weeks 24 and 48. The mean baseline and mean change from baseline in CD4+ cell count and in CD4% from Week 2 to Week 48 are presented in Table 4. All subjects maintained their CD4+ cell counts above 400 cells/mm^3 *[see Pediatric Use (8.4) and Clinical Studies (14.5)].*

Table 4 Mean Change in CD4+ Count and CD4 Percentage from Baseline to Week 48 in Virologically-Suppressed Pediatric Patients from 6 to <12 Years Who Switched to GENVOYA

		Mean Change from Baseline					
	Baseline	**Week 2**	**Week 4**	**Week 12**	**Week 24**	**Week 32**	**Week 48**
CD4+ Cell Count (cells/mm^3)	961 (275.5)[a]	-117	-114	-112	-118	-62	-66
CD4%	38 (6.4)[a]	+0.3%	-0.1%	-0.8%	-0.8%	-1.0%	-0.6%

a. Mean (SD)

6.2 Postmarketing Experience

The following events have been identified during post approval use of products containing TAF, including GENVOYA. Because these events 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.

Skin and Subcutaneous Tissue Disorders

Angioedema, urticaria, and rash

Renal and Urinary Disorders

Acute renal failure, acute tubular necrosis, proximal renal tubulopathy, and Fanconi syndrome

7 DRUG INTERACTIONS

7.1 Not Recommended with Other Antiretroviral Medications

GENVOYA is a complete regimen for the treatment of HIV-1 infection; therefore, coadministration of GENVOYA with other antiretroviral medications for treatment of HIV-1 infection should be avoided. Complete information regarding potential drug-drug interactions with other antiretroviral medications is not provided *[see Contraindications (4), Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.

7.2 Potential for GENVOYA to Affect Other Drugs

Cobicistat, a component of GENVOYA, 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 GENVOYA 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 . Coadministration of GENVOYA with drugs that have active metabolite(s) formed by CYP3A may result in reduced plasma concentration of these active metabolite(s) (see Table 5). Elvitegravir is a modest inducer of CYP2C9 and may decrease the plasma concentrations of CYP2C9 substrates. TAF is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or UGT1A1. TAF is a weak inhibitor of CYP3A *in vitro*. TAF is not an inhibitor or inducer of CYP3A *in vivo*.

7.3 Potential for Other Drugs to Affect One or More Components of GENVOYA

Elvitegravir and cobicistat, components of GENVOYA, 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, elvitegravir, and TAF, which may lead to loss of therapeutic effect of GENVOYA and development of resistance (see Table 5).

Coadministration of GENVOYA with other drugs that inhibit CYP3A may decrease the clearance and increase the plasma concentration of cobicistat. (see Table 5). TAF, a component of GENVOYA, is a substrate of P-gp, BCRP, OATP1B1 and OATP1B3. Drugs that inhibit P-gp and/or BCRP, such as cobicistat, may increase the absorption of TAF (see Table 13). However, when TAF is administered as a component of GENVOYA, its availability is increased by cobicistat and a further increase of TAF concentrations is not expected upon coadministration of an additional P-gp and/or BCRP inhibitor. Drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentration of TAF.

7.4 Drugs Affecting Renal Function

Because emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of

GENVOYA 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 (5.4)]*.

7.5 Established and Other Potentially Significant Interactions

Table 5 provides a listing of established or potentially clinically significant drug interactions *[see Contraindications (4)]*. The drug interactions described are based on studies conducted with either GENVOYA, the components of GENVOYA (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) as individual agents and/or in combination, or are predicted drug interactions that may occur with GENVOYA *[for magnitude of interaction, see Clinical Pharmacology (12.3)]*. The table includes potentially significant interactions but is not all inclusive.

Table 5 Established and Other Potentially Significant[a] 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[b]	Clinical Comment
Alpha 1-adrenoreceptor antagonist: alfuzosin	↑ alfuzosin	Coadministration with alfuzosin is contraindicated due to potential for serious and/or life-threatening reactions such as hypotension.
Antiarrhythmics: e.g., amiodarone bepridil digoxin* disopyramide flecainide systemic lidocaine mexiletine propafenone quinidine	↑ antiarrhythmics ↑ digoxin	Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when coadministered with GENVOYA.
Antibacterials: clarithromycin telithromycin	↑ clarithromycin ↑ telithromycin ↑ cobicistat	Patients with CL_{cr} greater than or equal to 60 mL/minute: No dosage adjustment of clarithromycin is required. Patients with CL_{cr} between 50 mL/minute and 60 mL/minute: The dosage of clarithromycin should be reduced by 50%.

Anticoagulants: Direct Oral Anticoagulants (DOACs) apixaban rivaroxaban betrixaban dabigatran edoxaban	↑ apixaban ↑ rivaroxaban ↑ betrixaban ↑ dabigatran ↑ edoxaban	Due to potentially increased bleeding risk, dosing recommendations for coadministration with GENVOYA depends on the apixaban dose. Refer to apixaban dosing instructions for coadministration with strong CYP3A and P-gp inhibitors in apixaban prescribing information. Coadministration of rivaroxaban with GENVOYA is not recommended because it may lead to an increased bleeding risk. Due to potentially increased bleeding risk, dosing recommendations for coadministration of betrixaban, dabigatran, or edoxaban with a P-gp inhibitor such as GENVOYA depends on DOAC indication and renal function. Refer to DOAC dosing instructions for coadministration with P-gp inhibitors in DOAC prescribing information.
warfarin	Effect on warfarin unknown	Monitor the international normalized ratio (INR) upon coadministration of warfarin with GENVOYA.
Anticonvulsants: carbamazepine* phenobarbital phenytoin oxcarbazepine ethosuximide	↓ elvitegravir ↓ cobicistat ↓ TAF ↑ ethosuximide	Coadministration with carbamazepine, phenobarbital, or phenytoin is contraindicated due to potential for loss of therapeutic effect and development of resistance. Alternative anticonvulsants should be considered when GENVOYA is administered with oxcarbazepine. Clinical monitoring is recommended upon coadministration of ethosuximide with GENVOYA.
Antidepressants: Selective Serotonin Reuptake Inhibitors (SSRIs) e.g., paroxetine Tricyclic Antidepressants (TCAs) e.g., amitriptyline desipramine* imipramine nortriptyline bupropion trazodone	↑ SSRIs (except sertraline) ↑ TCAs ↑ trazodone	Careful dosage titration of the antidepressant and monitoring for antidepressant response are recommended when coadministered with GENVOYA.

Antifungals: itraconazole ketoconazole* voriconazole	↑ elvitegravir ↑ cobicistat ↑ itraconazole ↑ ketoconazole ↑ voriconazole	When administering with GENVOYA, the maximum daily dosage of ketoconazole or itraconazole should not exceed 200 mg per day. An assessment of benefit/risk ratio is recommended to justify use of voriconazole with GENVOYA.
Anti-gout: colchicine	↑ colchicine	GENVOYA 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 GENVOYA:</u> 0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Treatment course to be repeated no earlier than 3 days. <u>Prophylaxis of gout-flares – coadministration of colchicine in patients receiving GENVOYA:</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 GENVOYA:</u> Maximum daily dosage of 0.6 mg (may be given as 0.3 mg twice a day).
Antimycobacterial: rifampin rifabutin* rifapentine	↓ elvitegravir ↓ cobicistat ↓ TAF	Coadministration with rifampin is contraindicated due to potential for loss of therapeutic effect and development of resistance. Coadministration of GENVOYA with rifabutin or rifapentine is not recommended.
Antiplatelets: ticagrelor clopidogrel	↑ ticagrelor ↓ clopidogrel active metabolite	Coadminstration with ticagrelor is not recommended. Coadministration with clopidogrel is not recommended due to protential reduction of the antiplatelet activity of clopidogrel.

Antipsychotics: lurasidone	↑ lurasidone	Coadministration with lurasidone is contraindicated due to potential for serious and/or life-threatening reactions.
pimozide	↑ pimozide	Coadministration with pimozide is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
quetiapine	↑ quetiapine	Initiation of GENVOYA in patients taking quetiapine: 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. Initiation of quetiapine in patients taking GENVOYA: Refer to the quetiapine prescribing information for initial dosing and titration of quetiapine.
Other antipsychotics e.g., perphenazine risperidone thioridazine	↑ antipsychotic	A decrease in dose of the antipsychotics that are metabolized by CYP3A or CYP2D6 may be needed when coadministered with GENVOYA.
Beta-Blockers: e.g., metoprolol timolol	↑ beta-blockers	Clinical monitoring is recommended and a dosage decrease of the beta blocker may be necessary when these agents are coadministered with GENVOYA.
Calcium Channel Blockers: e.g., amlodipine diltiazem felodipine nicardipine nifedipine verapamil	↑ calcium channel blockers	Caution is warranted and clinical monitoring is recommended upon coadministration of calcium channel blockers with GENVOYA.

Corticosteroids: e.g., betamethasone budesonide ciclesonide dexamethasone fluticasone methylprednisolone mometasone prednisone triamcinolone	↓ elvitegravir ↓ cobicistat ↑ corticosteroids	Coadministration with oral dexamethasone or other systemic corticosteroids that induce CYP3A may result in loss of therapeutic effect and development of resistance to elvitegravir. Consider alternative corticosteroids. Coadministration with corticosteroids (all routes of administration) whose exposures are significantly increased by strong CYP3A inhibitors can increase the risk for Cushing's syndrome and adrenal suppression. Alternative corticosteroids including beclomethasone and prednisolone (whose PK and/or PD are less affected by strong CYP3A inhibitors relative to other studied steroids) should be considered, particularly for long-term use.
Endothelin Receptor Antagonists: bosentan	↑ bosentan	<u>Coadministration of bosentan in patients on GENVOYA:</u> In patients who have been receiving GENVOYA for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability. <u>Coadministration of GENVOYA in patients on bosentan:</u> Discontinue use of bosentan at least 36 hours prior to initiation of GENVOYA. After at least 10 days following the initiation of GENVOYA, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability.
Ergot Derivatives: dihydroergotamine ergotamine methylergonovine	↑ ergot derivatives	Coadministration is contraindicated due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues *[see Contraindications (4)]*.
Herbal Products: St. John's wort *(Hypericum perforatum)*	↓ elvitegravir ↓ cobicistat ↓ TAF	Coadministration is contraindicated due to potential for loss of therapeutic effect and development of resistance.
Hormonal Contraceptives: drospirenone/ethinyl estradiol* levonorgestrel norgestimate/ethinyl estradiol	↑ drospirenone ↑ norgestimate ↑ levonorgestrel ↓ ethinyl estradiol	Additional or alternative non-hormonal forms of contraception should be considered when estrogen based contraceptives are coadministered with GENVOYA. Plasma concentrations of drospirenone may be increased when coadministered with cobicistat-containing products. Clinical monitoring is recommended due to the potential for hyperkalemia. The effects of increases in the 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 GENVOYA should be considered, particularly in patients who have risk factors for these events. The effect of GENVOYA on other hormonal contraceptives (e.g., contraceptive patch, contraceptive vaginal ring, or injectable contraceptives) or oral contraceptives containing progestogens other than drospirenone, levonorgestrel, or norgestimate has not been studied; therefore, alternative (non-hormonal) methods of contraception can be considered.
Immuno-suppressants: e.g., cyclosporine (CsA) sirolimus tacrolimus	↑ immuno-suppressants ↑ elvitegravir (with CsA) ↑ cobicistat (with CsA)	Therapeutic monitoring of the immunosuppressive agents is recommended upon coadministration with GENVOYA. Monitor for adverse events associated with GENVOYA when coadministered with cyclosporine.
Lipid-modifying Agents: **HMG-CoA Reductase Inhibitors:** lovastatin simvastatin atorvastatin **Other Lipid-modifying Agents:** lomitapide	↑ lovastatin ↑ simvastatin ↑ atorvastatin ↑ lomitapide	Coadministration with lovastatin or simvastatin is contraindicated due to potential for serious reactions such as myopathy including rhabdomyolysis. Initiate atorvastatin with the lowest starting dose of atorvastatin and titrate carefully while monitoring for safety (e.g., myopathy). Do not exceed a dosage of atorvastatin 20 mg daily. Coadministration with lomitapide is contraindicated due to potential for markedly increased transaminases.
Narcotic Analgesics: buprenorphine/ naloxone* fentanyl tramadol	↑ buprenorphine ↑ norbuprenorphine ↓ naloxone ↑ fentanyl ↑ tramadol	No dosage adjustment of buprenorphine/naloxone is required upon coadministration with GENVOYA. Patients should be closely monitored for sedation and cognitive effects. Careful monitoring of therapeutic and adverse effects of fentanyl (including potentially fatal respiratory depression) is recommended with coadministration. A dose decrease may be needed for tramadol with concomitant use.
Inhaled Beta Agonist: salmeterol	↑ salmeterol	Coadministration of salmeterol and GENVOYA is not recommended. Coadministration of salmeterol with GENVOYA may result in increased risk of cardiovascular adverse events associated with

		salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Medications or Oral Supplements Containing Polyvalent Cations (e.g., Mg, Al, Ca, Fe, Zn): calcium or iron supplements, including multivitamins cation-containing antacids* or laxatives sucralfate buffered medications	↓ elvitegravir	Separate GENVOYA and administration of medications, antacids, or oral supplements containing polyvalent cations by at least 2 hours.
Phosphodiesterase-5 (PDE5) Inhibitors: sildenafil tadalafil vardenafil	↑ PDE5 inhibitors	<u>Use of PDE-5 inhibitors for pulmonary arterial hypertension (PAH):</u> Coadministration of sildenafil with GENVOYA is contraindicated when used for treatment of PAH, due to potential for PDE-5 inhibitor associated adverse reactions, including hypotension, syncope, visual disturbances, and priapism. The following dose adjustments are recommended for the use of tadalafil with GENVOYA: *Coadministration of tadalafil in patients on GENVOYA:* In patients receiving GENVOYA for at least 1 week, start tadalafil at 20 mg once daily. Increase tadalafil dose to 40 mg once daily based upon individual tolerability. *Coadministration of GENVOYA in patients on tadalafil:* Avoid use of tadalafil during the initiation of GENVOYA. Stop tadalafil at least 24 hours prior to starting GENVOYA. After at least one week following initiation of GENVOYA, 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> Sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg in 72 hours, or tadalafil at a single dose not exceeding 10 mg in 72 hours can be used with increased monitoring for PDE-5 inhibitor associated with adverse events.

Sedative/hypnotic: midazolam (oral) triazolam Other benzodiazepines: e.g., parenterally administered midazolam clorazepate diazepam estazolam flurazepam buspirone zolpidem	↑ midazolam ↑ triazolam ↑sedatives/hypnotics	Coadministration with triazolam or orally administered midazolam is contraindicated due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression. Triazolam and orally administered midazolam are extensively metabolized by CYP3A. Coadministration of triazolam or orally administered midazolam with GENVOYA may cause large increases in the concentrations of these benzodiazepines. Coadministration of parenteral midazolam with GENVOYA 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.

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

a. This table is not all inclusive.

b. ↑ = Increase, ↓ = Decrease

7.6 Drugs without Clinically Significant Interactions with GENVOYA

Based on drug interaction studies conducted with the components of GENVOYA, no clinically significant drug interactions have been observed or are expected when GENVOYA is combined with the following drugs: famciclovir, famotidine, ledipasvir, methadone, omeprazole, prasugrel (active metabolite), sertraline, sofosbuvir, velpatasvir, and voxilaprevir.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to GENVOYA during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

GENVOYA is not recommended during pregnancy *[see Dosage and Administration (2.5)]*. A literature report evaluating the pharmacokinetics of antiretrovirals during pregnancy demonstrated substantially lower exposures of elvitegravir and cobicistat in the second and third trimesters *(see Data)*.

Prospective pregnancy data from the APR are not sufficient to adequately assess the risk of birth defects or miscarriage. However, elvitegravir (EVG), cobicistat (COBI), emtricitabine (FTC), and tenofovir alafenamide (TAF) use during pregnancy have been evaluated in a limited number of individuals as reported to the APR. Available data from the APR show no statistically significant difference in the overall risk of major birth defects for EVG, COBI, FTC or TAF compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) *(see Data)*. The rate of miscarriage is not reported in the APR. In the U.S. general population, the estimated background risk of miscarriage in clinically recognized pregnancies is 15-20%.

In animal studies, no adverse developmental effects were observed when the components of GENVOYA were administered separately during the period of organogenesis at exposures up to 23 and 0.2 times (rat and rabbits, respectively: elvitegravir), 1.6 and 3.8 times (rats and rabbits, respectively: cobicistat), 60 and 108 times (mice and rabbits, respectively; emtricitabine) and equal to and 53 times (rats and rabbits, respectively; TAF) the exposure at the recommended daily dosage of these components in GENVOYA *(see Data)*. Likewise, no adverse developmental effects were seen when elvitegravir or cobicistat was administered to rats through lactation at exposures up to 18 times or 1.2 times, respectively, the human exposure at the recommended therapeutic dose, and when emtricitabine was administered to mice through lactation at exposures up to approximately 60 times the exposure at the recommended daily dose. No adverse effects were observed in the offspring when TDF was administered through lactation at tenofovir exposures of approximately 14 times the exposure at the recommended daily dosage of GENVOYA.

Data

Human Data

A prospective study, reported in the literature, enrolled 30 pregnant women living with HIV who were receiving elvitegravir and cobicistat-based regimens in the second or third trimesters of pregnancy and through 6 to 12 weeks postpartum to evaluate the pharmacokinetics (PK) of antiretrovirals during pregnancy. Twenty-eight women completed the study through the postpartum period. Paired pregnancy/postpartum PK data were available from 14 and 24 women for the second and third trimesters, respectively. Exposures of elvitegravir and cobicistat were substantially lower during the second and third trimesters compared to postpartum. The proportion of pregnant women who were virologically suppressed was 77% in the second trimester, 92% in the third trimester, and 76% postpartum. No correlation was observed between viral suppression and elvitegravir exposure. HIV status was also assessed for infants: 25 were uninfected, 2 had indeterminate status, and no information was available for 3 infants.

Prospective reports from the APR of overall major birth defects in pregnancies exposed to the components of GENVOYA are compared with a U.S. background major birth defect rate. Methodological limitations of the APR include the use of MACDP as the external comparator group. Limitations of using an external

comparator include differences in methodology and populations, as well as confounding due to the underlying disease.

Elvitegravir (EVG):

Based on prospective reports to the APR of over 440 exposures to EVG-containing regimens during pregnancy resulting in live births (including over 350 exposed in the first trimester and 70 exposed in the second/third trimester), the prevalence of birth defects in live births was 3.0% (95% CI: 1.5% to 5.2%) and 1.4% (95% CI: 0.0% to 7.7%) following first and second/third trimester exposure, respectively, to EVG-containing regimens.

Cobicistat (COBI):

Based on prospective reports to the APR of over 560 exposures to COBI-containing regimens during pregnancy resulting in live births (including over 470 exposed in the first trimester and over 80 exposed in the second/third trimester), the prevalence of birth defects in live births was 3.6% (95% CI: 2.1% to 5.7%) and 1.1% (95% CI: 0.0% to 6.2%) following first and second/third trimester, respectively, to COBI-containing regimens.

Emtricitabine (FTC):

Based on prospective reports to the APR of over 5,400 exposures to FTC-containing regimens during pregnancy resulting in live births (including over 3,900 exposed in the first trimester and over 1,500 exposed in the second/third trimester), the prevalence of birth defects in live births was 2.6% (95% CI: 2.2% to 3.2%) and 2.7% (95% CI: 1.9% to 3.7%) following first and second/third trimester exposure, respectively, to FTC-containing regimens.

Tenofovir Alafenamide (TAF):

Based on prospective reports to the APR of over 660 exposures to TAF-containing regimens during pregnancy resulting in live births (including over 520 exposed in the first trimester and over 130 exposed in the second/third trimester), the prevalence of birth defects in live births was 4.2% (95% CI: 2.6% to 6.3%) and 3.0% (95% CI: 0.8% to 7.5%) following first and second/third trimester exposure, respectively, to TAF-containing regimens.

Animal Data

Elvitegravir:

Elvitegravir was administered orally to pregnant rats (0, 300, 1000, and 2000 mg/kg/day) and rabbits (0, 50, 150, and 450 mg/kg/day) through organogenesis (on gestation days 7 through 17 and days 7 through 19, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with elvitegravir in rats at exposures (AUC) approximately 23 times and in rabbits at approximately 0.2 times the human exposures at the recommended daily dose. In a pre/postnatal developmental study, elvitegravir was administered orally to rats at

doses of 0, 300, 1000, and 2000 mg/kg from gestation day 7 to day 20 of lactation. At doses of 2000 mg/kg/day of elvitegravir, neither maternal nor developmental toxicity was noted. Systemic exposures (AUC) at this dose were 18 times the human exposures at the recommended daily dose.

Cobicistat:

Cobicistat was administered orally to pregnant rats at doses of 0, 25, 50, 125 mg/kg/day on gestation day 6 to 17. Increases in post-implantation loss and decreased fetal weights were observed at a maternal toxic dose of 125 mg/kg/day. No malformations were noted at doses up to 125 mg/kg/day. Systemic exposures (AUC) at 50 mg/kg/day in pregnant females were 1.6 times higher than human exposures at the recommended daily dose.

In pregnant rabbits, cobicistat was administered orally at doses of 0, 20, 50, and 100 mg/kg/day during gestation days 7 to 20. No maternal or embryo/fetal effects were noted at the highest dose of 100 mg/kg/day. Systemic exposures (AUC) at 100 mg/kg/day were 3.8 times higher than human exposures at the recommended daily dose.

In a pre/postnatal developmental study in rats, cobicistat was administered orally at doses of 0, 10, 30, and 75 mg/kg from gestation day 6 to postnatal day 20, 21, or 22. At doses of 75 mg/kg/day of cobicistat, neither maternal nor developmental toxicity was noted. Systemic exposures (AUC) at this dose were 1.2 times the human exposures at the recommended daily dose.

Emtricitabine:

Emtricitabine was administered orally to pregnant mice (250, 500, or 1000 mg/kg/day) and rabbits (100, 300, or 1000 mg/kg/day) through organogenesis (on gestation days 6 through 15, and 7 through 19, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with emtricitabine in mice at exposures (AUC) approximately 60 times higher and in rabbits at approximately 108 times higher than human exposures at the recommended daily dose.

In a pre/postnatal development study with emtricitabine, mice were administered doses up to 1000 mg/kg/day; no significant adverse effects directly related to drug were observed in the offspring exposed daily from before birth (*in utero*) through sexual maturity at daily exposures (AUC) of approximately 60 times higher than human exposures at the recommended daily dose.

Tenofovir Alafenamide (TAF):

TAF was administered orally to pregnant rats (25, 100, or 250 mg/kg/day) and rabbits (10, 30, or 100 mg/kg/day) through organogenesis (on gestation days 6 through 17, and 7 through 20, respectively). No adverse embryo-fetal effects were observed in rats and rabbits at TAF exposures similar to (rats) and approximately 53 (rabbits) times higher than the exposure in humans at the recommended daily dose of GENVOYA. TAF is rapidly converted to tenofovir; the observed tenofovir exposure

in rats and rabbits were 59 (rats) and 93 (rabbits) times higher than human tenofovir exposures at the recommended daily doses. Since TAF is rapidly converted to tenofovir and lower tenofovir exposures in rats and mice were observed after TAF administration compared to TDF administration, a pre/postnatal development study in rats was conducted only with TDF. Doses up to 600 mg/kg/day were administered through lactation; no adverse effects were observed in the offspring on gestation day 7 [and lactation day 20] at tenofovir exposures of approximately 14 [21] times higher than the exposures in humans at the recommended daily dose of GENVOYA.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV.

Based on published data, emtricitabine has been shown to be present in human breast milk; it is unknown if elvitegravir, cobicistat, and TAF are present in human breast milk. Elvitegravir and cobicistat are present in rat milk, and tenofovir has been shown to be present in the milk of lactating rats and rhesus monkeys after administration of TDF *[see Data]*. It is unknown if TAF is present in animal milk.

It is not known if GENVOYA affects milk production or has effects on the breastfed child. Because of the potential for 1) HIV transmission (in HIV-negative infants); 2) developing viral resistance (in HIV-positive infants); and 3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving GENVOYA.

Data

Animal Data

Elvitegravir: During the pre/postnatal developmental toxicology study at doses up to 2000 mg/kg/day, a mean elvitegravir milk to plasma ratio of 0.1 was measured 30 minutes after administration to rats on lactation day 14.

Cobicistat: During the pre/postnatal developmental toxicology study at doses up to 75 mg/kg/day, mean cobicistat milk to plasma ratio of up to 1.9 was measured 2 hours after administration to rats on lactation day 10.

Tenofovir Alafenamide: Studies in rats and monkeys have demonstrated that tenofovir is secreted in milk. During the pre/postnatal developmental toxicology study, tenofovir was excreted into the milk of lactating rats following oral administration of TDF (up to 600 mg/kg/day) at up to approximately 24% of the median plasma concentration in the highest dosed animals at lactation day 11. Tenofovir was excreted into the milk of lactating rhesus monkeys, following a single subcutaneous (30 mg/kg) dose of tenofovir, at concentrations up to approximately

4% of plasma concentration resulting in exposure (AUC) of approximately 20% of plasma exposure.

8.4 Pediatric Use

The safety and effectiveness of GENVOYA for the treatment of HIV-1 infection was established in pediatric patients with body weight greater than or equal to 25 kg *[see Indications and Usage (1) and Dosage and Administration (2.2)]*.

Use of GENVOYA in pediatric patients less than 18 years of age and weighing at least 25 kg is supported by studies in adults and by an open-label study in antiretroviral treatment-naïve HIV-1 infected pediatric subjects aged 12 to less than 18 years and weighing at least 35 kg (cohort 1 of Study 106, N=50) and in virologically-suppressed pediatric subjects aged 6 to less than 12 years and weighing at least 25 kg (cohort 2 of Study 106, N=52). The safety and efficacy of GENVOYA in adolescent subjects was similar to that in adults *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.5)].* The safety and efficacy of GENVOYA in subjects 6 to 12 years of age weighing at least 25 kg was similar to that in antiretroviral treatment-naïve adults and adolescents with the exception of a decrease from baseline CD4+ cell count *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.5)]*.

A pharmacokinetic evaluation of a reduced strength GENVOYA formulation containing 90 mg of EVG, 90 mg of COBI, 120 mg of FTC, and 6 mg TAF was performed in 27 virologically-suppressed pediatric patients at least 2 years of age and weighing at least 14 to less than 25 kg (cohort 3 of Study 106). Virologic, immunologic, and safety outcomes were similar to those observed in cohort 2 of Study 106. No clinically meaningful differences in drug exposures except EVG were identified between pediatric patients in cohort 3 receiving the reduced strength formulation and adults receiving the GENVOYA tablet containing 150 mg of EVG,150 mg of COBI, 200 mg of FTC, and 10 mg TAF. The median observed EVG C_{trough} values in subjects in cohort 3 were significantly lower than the values correlated with efficacy in adults. Therefore, efficacy cannot be extrapolated from adults to pediatric patients weighing 14 to 25 kg.

Safety and effectiveness of GENVOYA in pediatric patients weighing less than 25 kg have not been established.

8.5 Geriatric Use

Clinical trials of GENVOYA included 97 subjects (80 receiving GENVOYA) aged 65 years and over. No differences in safety or efficacy have been observed between elderly subjects and adults between 18 and less than 65 years of age.

8.6 Renal Impairment

The pharmacokinetics, safety, and virologic and immunologic responses of GENVOYA in HIV-1 infected adult subjects with renal impairment (estimated creatinine clearance between 30 and 69 mL per minute by Cockcroft-Gault method) were evaluated in 248 subjects in an open-label trial, Study 112.

The pharmacokinetics, safety, virologic and immunologic responses of GENVOYA in HIV-1 infected adult subjects with ESRD (estimated creatinine clearance of less than 15 mL per minute by Cockcroft-Gault method) receiving chronic hemodialysis were evaluated in 55 subjects in an open-label trial, Study 1825 *[see Adverse Reactions (6.1) and Clinical Studies (14.4)]*.

No dosage adjustment of GENVOYA is recommended in patients with estimated creatinine clearance greater than or equal to 30 mL per minute, or in adult patients with ESRD (estimated creatinine clearance below 15 mL per minute) who are receiving chronic hemodialysis. On days of hemodialysis, administer GENVOYA after completion of hemodialysis treatment *[see Dosage and Administration (2.2)]*.

GENVOYA is not recommended in patients with severe renal impairment (estimated creatinine clearance of 15 to below 30 mL per minute), or in patients with ESRD who are not receiving chronic hemodialysis, as the safety of GENVOYA has not been established in these populations *[see Dosage and Administration (2.3), Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dosage adjustment of GENVOYA is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. GENVOYA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, GENVOYA is not recommended for use in patients with severe hepatic impairment *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

No data are available on overdose of GENVOYA in patients. If overdose occurs, monitor the patient for evidence of toxicity. Treatment of overdose with GENVOYA 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 recommended dose of elvitegravir in GENVOYA. In one study, elvitegravir (administered with the CYP3A inhibitor cobicistat) 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 recommended dose of cobicistat in GENVOYA. In two studies, a single dose of cobicistat 400 mg (2.7 times the dose in GENVOYA) 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 recommended dose of emtricitabine in GENVOYA. In one clinical pharmacology study, single doses of emtricitabine 1200 mg (6 times the dose in GENVOYA) 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 alafenamide (TAF): Limited clinical experience is available at doses higher than the recommended dose of TAF in GENVOYA. A single dose of 125 mg TAF (12.5 times the dose in GENVOYA) was administered to 48 healthy subjects; no serious adverse reactions were reported. The effects of higher doses are unknown. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%.

11 DESCRIPTION

GENVOYA (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) is a fixed-dose combination tablet containing elvitegravir (EVG), cobicistat (COBI), emtricitabine (FTC), and tenofovir alafenamide (TAF) for oral administration.

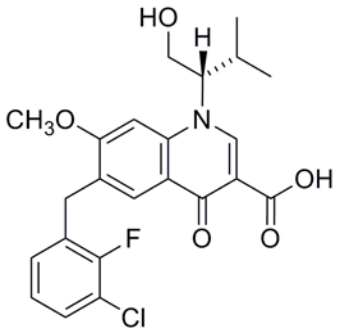
- EVG is an HIV-1 integrase strand transfer inhibitor.
- COBI is a mechanism-based inhibitor of cytochrome P450 (CYP) enzymes of the CYP3A family.
- FTC, a synthetic nucleoside analog of cytidine, is an HIV nucleoside analog reverse transcriptase inhibitor (HIV NRTI).
- TAF, an HIV NRTI, is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate.

Each tablet contains 150 mg of EVG, 150 mg of COBI, 200 mg of FTC, and 10 mg of TAF (equivalent to 11.2 mg of tenofovir alafenamide fumarate).

The tablets include the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, silicon dioxide, and sodium lauryl sulfate. The tablets are film-coated with a coating material containing FD&C Blue No. 2/indigo carmine aluminum lake, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

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.

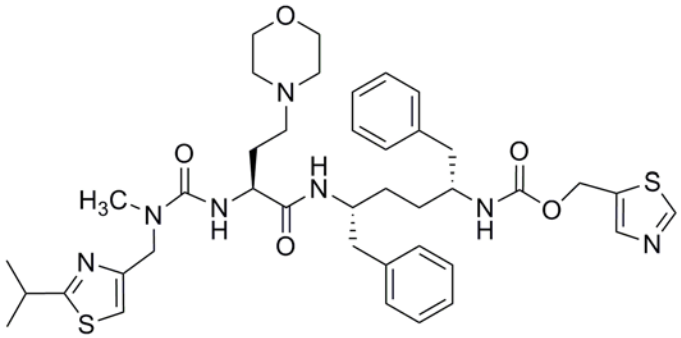
It has a molecular formula of $C_{23}H_{23}ClFNO_5$ and a molecular weight of 447.88. It has the following structural formula:



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 2,7,10,12-tetraazatridecanoic acid, 12-methyl-13-[2-(1-methylethyl)-4-thiazolyl]-9-[2-(4-morpholinyl)ethyl]-8,11-dioxo-3,6-bis(phenylmethyl)-, 5-thiazolylmethyl ester, (3*R*,6*R*,9*S*)-.

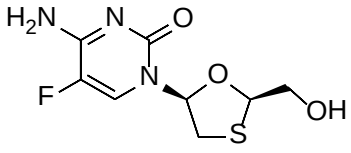
It has a molecular formula of $C_{40}H_{53}N_7O_5S_2$ and a molecular weight of 776.02. It has the following structural formula:



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

Emtricitabine: The chemical name of emtricitabine is 4-amino-5-fluoro-1-(2*R*-hydroxymethyl-1,3-oxathiolan-5*S*-yl)-(1*H*)-pyrimidin-2-one. 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.

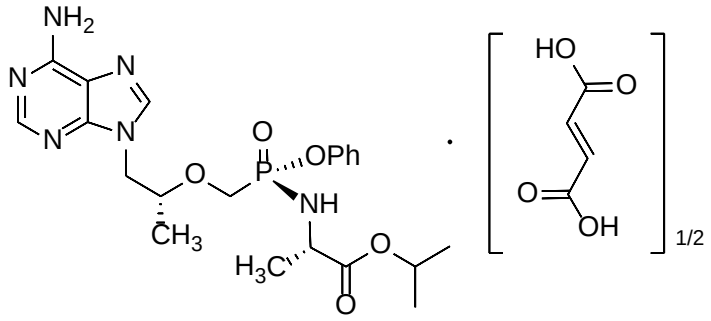
It has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24. It has the following structural formula:



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

Tenofovir alafenamide (TAF): The chemical name of tenofovir alafenamide fumarate drug substance is L-alanine, *N*-[(*S*)-[[(1*R*)-2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester, (2*E*)-2-butenedioate (2:1).

It has an empirical formula of $C_{21}H_{29}O_5N_6P \bullet ½(C_4H_4O_4)$ and a formula weight of 534.5. It has the following structural formula:



Tenofovir alafenamide fumarate is a white to off-white or tan powder with a solubility of 4.7 mg per mL in water at 20 °C.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

GENVOYA is a fixed-dose combination of antiretroviral drugs elvitegravir (plus the CYP3A inhibitor cobicistat), emtricitabine, and tenofovir alafenamide *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Cardiac Electrophysiology

Thorough QT studies have been conducted for elvitegravir, cobicistat, and TAF. The effect of emtricitabine or the combination regimen GENVOYA 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 GENVOYA) 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 GENVOYA) 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 GENVOYA fixed-dose combination tablet is lower than the lowest dose

studied in the thorough QT study, it is unlikely that treatment with GENVOYA will result in clinically relevant PR prolongation.

Tenofovir Alafenamide (TAF): In a thorough QT/QTc study in 48 healthy subjects, TAF at the therapeutic dose or at a supratherapeutic dose approximately 5 times the recommended therapeutic dose did not affect the QT/QTc interval and did not prolong the PR interval.

Effects on Serum Creatinine

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

12.3 Pharmacokinetics

Absorption, Distribution, Metabolism, and Excretion

The pharmacokinetic (PK) properties of the components of GENVOYA are provided in Table 6. The multiple dose PK parameters of elvitegravir, cobicistat, emtricitabine, TAF and its metabolite tenofovir are provided in Table 7.

Table 6 Pharmacokinetic Properties of the Components of GENVOYA

	Elvitegravir	Cobicistat	Emtricitabine	TAF
Absorption				
T_{max} (h)	4	3	3	1
Effect of light meal (relative to fasting): AUC Ratio[a]	1.34 (1.19, 1.51)	1.03 (0.90, 1.17)	0.95 (0.91, 1.00)	1.15 (1.07, 1.24)
Effect of high fat meal (relative to fasting): AUC Ratio[a]	1.87 (1.66, 2.10)	0.83 (0.73, 0.95)	0.96 (0.92, 1.00)	1.18 (1.09, 1.26)
Distribution				
% Bound to human plasma proteins	~99	~98	<4	~80
Source of protein binding data	*Ex vivo*	*In vitro*	*In vitro*	*Ex vivo*
Blood-to-plasma ratio	0.73	0.5	0.6	1.0
Metabolism				
Metabolism	CYP3A (major) UGT1A1/3 (minor)	CYP3A (major) CYP2D6 (minor)	Not significantly metabolized	Cathepsin A[b] (PBMCs) CES1 (hepatocytes) CYP3A (minimal)
Elimination				
Major route of elimination	Metabolism	Metabolism	Glomerular filtration and active tubular secretion	Metabolism (>80% of oral dose)
$t_{1/2}$ (h)[c]	12.9	3.5	10	0.51
% Of dose excreted in urine[d]	6.7	8.2	70	<1%
% Of dose excreted in feces[d]	94.8	86.2	13.7	31.7

PBMCs = peripheral blood mononuclear cells; CES1 = carboxylesterase 1.

a. Values refer to geometric mean ratio in AUC [fed / fasted] and (90% confidence interval). Elvitegravir light meal=~373 kcal, 20% fat; GENVOYA light meal=~400 kcal, 20% fat; elvitegravir and GENVOYA high fat meal=~800 kcal, 50% fat. Based on the effect of food on elvitegravir, GENVOYA should be taken with food.

b. *In vivo,* TAF is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. *In vitro* studies have shown that TAF is metabolized to tenofovir by cathepsin A in PBMCs and macrophages; and by CES1 in hepatocytes. Upon coadministration with the moderate CYP3A inducer probe efavirenz, TAF exposure was not significantly affected.

c. $t_{1/2}$ values refer to median terminal plasma half-life. Note that the pharmacologically active metabolite, tenofovir diphosphate, has a half-life of 150–180 hours within PBMCs.

d. Dosing in mass balance studies: elvitegravir (single dose administration of [^{14}C] elvitegravir coadministered with 100 mg ritonavir); 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); TAF (single dose administration of [^{14}C] TAF).

Table 7 Multiple Dose Pharmacokinetic Parameters of Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Alafenamide (TAF) and its Metabolite Tenofovir Following Oral Administration of GENVOYA with Food in HIV-Infected Adults

Parameter Mean (CV%)	Elvitegravir[a]	Cobicistat[a]	Emtricitabine[a]	TAF[b]	Tenofovir[c]
C_{max} (microgram per mL)	2.1 (33.7)	1.5 (28.4)	2.1 (20.2)	0.16 (51.1)	0.02 (26.1)
AUC_{tau} (microgram•hour per mL)	22.8 (34.7)	9.5 (33.9)	11.7 (16.6)	0.21 (71.8)	0.29 (27.4)
C_{trough} (microgram per mL)	0.29 (61.7)	0.02 (85.2)	0.10 (46.7)	NA	0.01 (28.5)

CV = Coefficient of Variation; NA = Not Applicable

a. From Intensive PK analysis in a Phase 2 trial in HIV infected adults, Study 102 (N=19).

b. From Population PK analysis in two trials of treatment-naïve adults with HIV-1 infection, Studies 104 and 111 (N=539).

c. From Population PK analysis in two trials of treatment-naïve adults with HIV-1 infection, Studies 104 and 111 (N=841).

Special Populations

Geriatric Patients

Pharmacokinetics of elvitegravir, cobicistat, emtricitabine and tenofovir have not been fully evaluated in the elderly (65 years of age and older). Age does not have a clinically relevant effect on exposures of TAF up to 75 years of age *[see Use in Specific Populations (8.5)]*.

Pediatric Patients

Mean exposures of elvitegravir, cobicistat, and TAF achieved in 24 pediatric subjects aged 12 to less than 18 years who received thedose of GENVOYA containing 150 mg EVG, 150 mg COBI, 200 mg FTC, and 10 mg TAF in Study 106 were decreased compared to exposures achieved in treatment-naïve adults receiving the same dose of GENVOYA, but were overall deemed acceptable based on exposure-response relationships; emtricitabine exposure in adolescents was similar to that in treatment-naïve adults (Table 8).

Table 8 Multiple Dose Pharmacokinetic Parameters of Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Alafenamide (TAF) and its Metabolite Tenofovir Following Oral Administration of GENVOYA in HIV-Infected Pediatric Subjects Aged 12 to less than 18 Years[a]

Parameter Mean (CV%)	Elvitegravir	Cobicistat	Emtricitabine	TAF	Tenofovir
C_{max} (microgram per mL)	2.2 (19.2)	1.2 (35.0)	2.3 (22.5)	0.17 (64.4)	0.02 (23.7)
AUC_{tau} (microgram•hour per mL)	23.8 (25.5)	8.2[b] (36.1)	14.4 (23.9)	0.20[b] (50.0)	0.29[b] (18.8)
C_{trough} (microgram per mL)	0.30 (81.0)	0.03[c] (180.0)	0.10[b] (38.9)	NA	0.01 (21.4)

CV = Coefficient of Variation; NA = Not Applicable

a. From Intensive PK analysis in a trial in treatment-naïve pediatric subjects with HIV-1 infection, cohort 1 of Study 106 (N=24).

b. N=23

c. N=15

Exposures of the components of GENVOYA achieved in 23 pediatric subjects between the ages of 6 to less than 12 years who received the dose of GENVOYA containing 150 mg EVG, 150 mg COBI, 200 mg FTC, and 10 mg TAF in Study 106 were higher (20 to 80% for AUC) than exposures achieved in adults receiving the same dose of GENVOYA; the increase was not considered clinically significant as the safety profiles were similar in adult and pediatric patients (Table 9) *[see Use in Specific Populations (8.4)]*.

Table 9 Multiple Dose Pharmacokinetic Parameters of Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Alafenamide (TAF) and its Metabolite Tenofovir Following Oral Administration of GENVOYA in HIV-Infected Pediatric Subjects Aged 6 to less than 12 Years[a]

Parameter Mean (CV%)	Elvitegravir	Cobicistat	Emtricitabine	TAF	Tenofovir
C_{max} (microgram per mL)	3.1 (38.7)	2.1 (46.7)	3.4 (27.0)	0.31 (61.2)	0.03 (20.8)
AUC_{tau} (microgram•hour per mL)	33.8[b] (57.8)	15.9[c] (51.7)	20.6[b] (18.9)	0.33 (44.8)	0.44 (20.9)
C_{trough} (microgram per mL)	0.37 (118.5)	0.1 (168.7)	0.11 (24.1)	NA	0.02 (24.9)

CV = Coefficient of Variation; NA = Not Applicable

a. From Intensive PK analysis in a trial in virologically-suppressed pediatric subjects with HIV-1 infection, cohort 2 of Study 106 (N=23).

b. N=22

c. N=20

Race, Gender

No clinically significant differences in pharmacokinetics of GENVOYA have been identified based on race or gender.

Patients with Renal Impairment

The pharmacokinetics of GENVOYA in HIV-1 infected subjects with mild or moderate renal impairment (estimated creatinine clearance between 30 and 69 mL per minute by Cockcroft-Gault method), and in HIV-1 infected subjects with ESRD (estimated creatinine clearance of less than 15 mL per minute by Cockcroft-Gault method) receiving chronic hemodialysis were evaluated in subsets of virologically suppressed subjects in respective open-label trials, Study 112 and Study 1825. The pharmacokinetics of elvitegravir, cobicistat, and tenofovir alafenamide were similar among healthy subjects, subjects with mild or moderate renal impairment, and subjects with ESRD receiving chronic hemodialysis; increases in emtricitabine and tenofovir exposures in subjects with renal impairment were not considered clinically relevant (Table 10).

Table 10 Pharmacokinetics of GENVOYA in HIV-Infected Adults with Renal Impairment as Compared to Subjects with Normal Renal Function

	AUC_{tau} (microgram•hour per mL) Mean (CV%)			
Estimated Creatinine Clearance[a]	**≥90 mL per minute (N=18)[b]**	**60–89 mL per minute (N=11)[c]**	**30–59 mL per minute (N=18)[d]**	**<15 mL per minute (N=12)[e]**
Emtricitabine	11.4 (11.9)	17.6 (18.2)	23.0 (23.6)	62.9 (48.0)[f]
Tenofovir	0.32 (14.9)	0.46 (31.5)	0.61 (28.4)	8.72 (39.4)[g]

a. By Cockcroft-Gault method.
b. From a Phase 2 study in HIV-infected adults with normal renal function.
c. These subjects from Study 112 had an estimated creatinine clearance between 60 and 69 mL per minute.
d. Study 112.
e. Study 1825; PK assessed prior to hemodialysis following 3 consecutive daily doses of GENVOYA.
f. N=11.
g. N=10.

Patients with Hepatic Impairment

Elvitegravir and Cobicistat: A study of the pharmacokinetics of elvitegravir (administered with the CYP3A inhibitor cobicistat) was performed in healthy subjects and subjects with moderate hepatic impairment (Child-Pugh Class B). No clinically relevant differences in elvitegravir or cobicistat pharmacokinetics were observed between subjects with moderate hepatic impairment and healthy subjects *[see Use in Specific Populations (8.7)]*.

Emtricitabine: The pharmacokinetics of emtricitabine has 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 Alafenamide (TAF): Clinically relevant changes in TAF and tenofovir pharmacokinetics were not observed in subjects with mild to moderate (Child-Pugh Class A and B) hepatic impairment *[see Use in Specific Populations (8.7)]*.

Hepatitis B and/or Hepatitis C Virus Co-infection

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 elvitegravir (administered with the CYP3A inhibitor cobicistat).

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 Alafenamide (TAF): Pharmacokinetics of emtricitabine and TAF have not been fully evaluated in subjects coinfected with hepatitis B and/or C virus.

Drug Interaction Studies

[see also Contraindications (4) and *Drug Interactions (7)]*

The drug-drug interaction studies described in Tables 11–14 were conducted with GENVOYA, elvitegravir (coadministered with cobicistat or ritonavir), cobicistat administered alone, or TAF (administered alone or coadministered with emtricitabine).

As GENVOYA should not be administered with other antiretroviral medications, information regarding drug-drug interactions with other antiretrovirals agents is not provided.

The effects of coadministered drugs on the exposure of elvitegravir, emtricitabine, and TAF are shown in Table 11, Table 12, and Table 13 respectively. The effects of GENVOYA or its components on the exposure of coadministered drugs are shown in Table 14. For information regarding clinical recommendations, see Drug Interactions (7).

Table 11 Drug Interactions: Changes in Pharmacokinetic Parameters for Elvitegravir in the Presence of the Coadministered Drug[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose (mg)	CYP3A Inhibitor Cobicistat or Ritonavir Dose (mg)	N	Mean Ratio of Elvitegravir Pharmacokinetic Parameters (90% CI); No effect = 1.00		
					C_{max}	AUC	C_{min}
Maximum strength antacid[b]	20 mL single dose given 4 hours before elvitegravir	50 single dose	Ritonavir 100 single dose	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			10	0.98 (0.88,1.10)	0.98 (0.91,1.06)	1.00 (0.90,1.11)
	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)
Atorvastatin	10 single dose	150 once daily[c]	Cobicistat 150 once daily[c]	16	0.91 (0.85,0.98)	0.92 (0.87,0.98)	0.88 (0.81,0.96)
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 (0.02,0.40)
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	Ritonavir 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[c]	Cobicistat 150 once daily[c]	30	0.98 (0.90,1.07)	1.11 (1.02,1.20)	1.46 (1.28,1.66)

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose (mg)	CYP3A Inhibitor Cobicistat or Ritonavir Dose (mg)	N	Mean Ratio of Elvitegravir Pharmacokinetic Parameters (90% CI); No effect = 1.00		
					C_{max}	AUC	C_{min}
Omeprazole	40 once daily given 2 hours before elvitegravir	50 once daily	Ritonavir 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)
Sertraline	50 single dose	150 once daily[c]	Cobicistat 150 once daily[c]	19	0.88 (0.82,0.93)	0.94 (0.89,0.98)	0.99 (0.93,1.05)
Sofosbuvir/ Velpatasvir	400/100 once daily	150 once daily[c]	Cobicistat 150 once daily[c]	24	0.87 (0.80,0.94)	0.94 (0.88,1.00)	1.08 (0.97,1.20)
Sofosbuvir/ Velpatasvir/ Voxilaprevir	400/100/100 + 100 Voxilaprevir[d] once daily	150 once daily[c]	Cobicistat 150 once daily[c]	29	0.79 (0.75,0.85)	0.94 (0.88,1.00)	1.32 (1.17,1.49)

a. All interaction studies conducted in healthy volunteers.

b. Maximum strength antacid contained 80 mg aluminum hydroxide, 80 mg magnesium hydroxide, and 8 mg simethicone, per mL.

c. Study conducted with GENVOYA.

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

Table 12 Drug Interactions: Changes in Pharmacokinetic Parameters for Emtricitabine in the Presence of the Coadministered Drug[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Emtricitabine Dose (mg)	N	Mean Ratio of Emtricitabine Pharmacokinetic Parameters (90% CI); No effect = 1.00		
				C_{max}	AUC	C_{min}
Famciclovir	500 single dose	200 single dose	12	0.90 (0.80,1.01)	0.93 (0.87,0.99)	NC

a. All interaction studies conducted in healthy volunteers.

Table 13 Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir Alafenamide (TAF) in the Presence of the Coadministered Drug[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	TAF Dose (mg)	N	Mean Ratio of TAF Pharmacokinetic Parameters (90% CI); No effect = 1.00		
				C_{max}	AUC	C_{min}
Cobicistat	150 once daily	8 once daily	12	2.83 (2.20,3.65)	2.65 (2.29,3.07)	NC
Ledipasvir/ Sofosbuvir	90/400 once daily	10 once daily[b]	30	0.90 (0.73,1.11)	0.86 (0.78,0.95)	NC
Sertraline	50 single dose	10 once daily[b]	19	1.00 (0.86,1.16)	0.96 (0.89,1.03)	NC
Sofosbuvir/ Velpatasvir	400/100 once daily	10 once daily[b]	24	0.80 (0.68,0.94)	0.87 (0.81,0.94)	NC
Sofosbuvir/ Velpatasvir/ Voxilaprevir	400/100/100 + 100 Voxilaprevir[c] once daily	10 once daily[b]	29	0.79 (0.68,0.92)	0.93 (0.85,1.01)	NC

NC = Not Calculated

a. All interaction studies conducted in healthy volunteers.

b. Study conducted with GENVOYA.

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

Table 14 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of GENVOYA or the Individual Components[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose (mg)	CYP3A Inhibitor Cobicistat Dose (mg)	FTC Dose (mg)	TAF Dose (mg)	N	Mean Ratio of Coadministered Drug Pharmacokinetic Parameters (90% CI); No effect = 1.00		
							C_{max}	AUC	C_{min}
Atorvastatin	10 single dose	150 once daily[c]	150 once daily[c]	200 once daily[c]	10 once daily[c]	16	2.32 (1.91,2.82)	2.60 (2.31,2.93)	NC
Buprenorphine	16 - 24 once daily	150 once daily	150 once daily	N/A	N/A	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	N/A	N/A	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)

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose (mg)	CYP3A Inhibitor Cobicistat Dose (mg)	FTC Dose (mg)	TAF Dose (mg)	N	Mean Ratio of Coadministered Drug Pharmacokinetic Parameters (90% CI); No effect = 1.00		
							C_{max}	AUC	C_{min}
Desipramine	50 single dose	N/A	150 once daily	N/A	N/A	8	1.24 (1.08,1.44)	1.65 (1.36,2.02)	NC
Digoxin	0.5 single dose	N/A	150 once daily	N/A	N/A	22	1.41 (1.29,1.55)	1.08 (1.00,1.17)	NC
Famciclovir	500 single dose	N/A	N/A	200 single dose	N/A	12	0.93 (0.78,1.11)	0.91 (0.84,0.99)	N/A
Ledipasvir	90 once daily	150 once daily[c]	150 once daily[c]	200 once daily[c]	10 once daily[c]	30	1.65 (1.53,1.78)	1.79 (1.64,1.96)	1.93 (1.74,2.15)
Sofosbuvir	400 once daily						1.28 (1.13,1.47)	1.47 (1.35,1.59)	N/A
GS-331007[b]							1.29 (1.24,1.35)	1.48 (1.44,1.53)	1.66 (1.60,1.73)
Naloxone	4–6 once daily	150 once daily	150 once daily	N/A	N/A	17	0.72 (0.61,0.85)	0.72 (0.59,0.87)	N/A
Norgestimate/ ethinyl estradiol[d]	0.180/0.215/ 0.250 norgestimate once daily	150 once daily[d]	150 once daily[d]	200 once daily[d]	N/A	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)
Norgestromin	0.180/0.215/ 0.250 norgestimate once daily / 0.025 ethinyl estradiol once daily	N/A	N/A	200 once daily[e]	25 once daily[e]	15	1.17 (1.07,1.26)	1.12 (1.07,1.17)	1.16 (1.08,1.24)
Norgestrel							1.10 (1.02,1.18)	1.09 (1.01,1.18)	1.11 (1.03,1.20)
Ethinyl estradiol							1.22 (1.15,1.29)	1.11 (1.07,1.16)	1.02 (0.92,1.12)
R-Methadone	80–120 daily	150 once daily	150 once daily	N/A	N/A	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)
Sertraline	50 single dose	150 once daily[c]	150 once daily[c]	200 once daily[c]	10 once daily[c]	19	1.14 (0.94,1.38)	0.93 (0.77,1.13)	N/A
Rifabutin	150 once every other day	150 once daily	150 once daily	N/A	N/A	12	1.09 (0.98,1.20)[f]	0.92 (0.83,1.03)[f]	0.94 (0.85,1.04)[f]
25-O-desacetyl-rifabutin						12	4.84 (4.09,5.74)[f]	6.25 (5.08,7.69)[f]	4.94 (4.04,6.04)[f]
Rosuvastatin	10 single dose	150 once daily	150 once daily	N/A	N/A	10	1.89 (1.48,2.42)	1.38 (1.14,1.67)	NC

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose (mg)	CYP3A Inhibitor Cobicistat Dose (mg)	FTC Dose (mg)	TAF Dose (mg)	N	Mean Ratio of Coadministered Drug Pharmacokinetic Parameters (90% CI); No effect = 1.00		
							C_{max}	AUC	C_{min}
Sofosbuvir	400 once daily	150 once daily[c]	150 once daily[c]	200 once daily[c]	10 once daily[c]	24	1.23 (1.07,1.42)	1.37 (1.24,1.52)	N/A
GS-331007[b]							1.29 (1.25,1.33)	1.48 (1.43,1.53)	1.58 (1.52,1.65)
Velpatasvir	100 once daily						1.30 (1.17,1.45)	1.50 (1.35,1.66)	1.60 (1.44,1.78)
Sofosbuvir	400 once daily	150 once daily[c]	150 once daily[c]	200 once daily[c]	10 once daily[c]	29	1.27 (1.09,1.48)	1.22 (1.12,1.32)	NC
GS-331007[b]							1.28 (1.25,1.32)	1.43 (1.39,1.47)	NC
Velpatasvir	100 once daily						0.96 (0.89,1.04)	1.16 (1.06,1.27)	1.46 (1.30,1.64)
Voxilaprevir	100 + 100[g] once daily						1.92 (1.63,2.26)	2.71 (2.30,3.19)	4.50 (3.68,5.50)

FTC = emtricitabine; TAF = tenofovir alafenamide

N/A = Not Applicable; NC = Not Calculated

a. All interaction studies conducted in healthy volunteers.

b. The predominant circulating inactive metabolite of sofosbuvir.

c. Study conducted with GENVOYA.

d. Study conducted with STRIBILD.

e. Study conducted with DESCOVY.

f. Comparison based on rifabutin 300 mg once daily.

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

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 reverse transcriptase 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, Ɛ, and mitochondrial DNA polymerase γ.

Tenofovir Alafenamide (TAF): TAF is a phosphonamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analog). Plasma exposure to TAF allows for permeation into cells and then TAF is intracellularly converted to tenofovir through hydrolysis by cathepsin A. Tenofovir is subsequently phosphorylated by cellular kinases to the active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV-1 replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination.

Tenofovir has activity that is specific to human immunodeficiency virus and hepatitis B virus. Cell culture studies have shown that both emtricitabine and tenofovir can be fully phosphorylated when combined in cells. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of mitochondrial toxicity in cell culture based on several assays including mitochondrial DNA analyses.

Antiviral Activity in Cell Culture

Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir Alafenamide (TAF): The combination of elvitegravir, emtricitabine, and TAF was not antagonistic in cell culture combination antiviral activity assays and was not affected by the addition of cobicistat. In addition, elvitegravir, cobicistat, emtricitabine, and TAF were not antagonistic with a panel of representatives from the major classes of approved anti-HIV-1 agents (INSTIs, NNRTIs, NRTIs, and PIs).

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 1.3 – 640 nM. Emtricitabine displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 7–75 nM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 7–1500 nM).

Tenofovir Alafenamide (TAF): The antiviral activity of TAF against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells and CD4-T lymphocytes. The EC_{50} values for TAF ranged from 2.0 to 14.7 nM.

TAF displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including sub-types A, B, C, D, E, F, and G (EC_{50} values ranged from 0.10 to 12.0 nM) and strain specific activity against HIV-2 (EC_{50} values ranged from 0.91 to 2.63 nM).

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: HIV-1 isolates with reduced susceptibility to emtricitabine have been selected in cell culture. Reduced susceptibility to emtricitabine was associated with M184V or I substitutions in HIV-1 RT.

Tenofovir Alafenamide (TAF): HIV-1 isolates with reduced susceptibility to TAF have been selected in cell culture. HIV-1 isolates selected by TAF expressed a K65R substitution in HIV-1 RT, sometimes in the presence of S68N or L429I substitutions; in addition, a K70E substitution in HIV-1 RT was observed.

In Clinical Trials

In Treatment-Naïve Subjects:

In a pooled analysis of antiretroviral-naïve subjects receiving GENVOYA in Studies 104 and 111, genotyping was performed on plasma HIV-1 isolates from all subjects with HIV-1 RNA greater than 400 copies per mL at confirmed virologic failure, at Week 144, or at time of early study drug discontinuation. As of Week 144, the development of genotypic resistance to elvitegravir, emtricitabine, or TAF was observed in 12 of 22 subjects with evaluable resistance data from paired baseline and GENVOYA treatment-failure isolates (12 of 866 subjects [1.4%]) compared with 13 of 20 treatment-failure isolates from subjects with evaluable resistance data in the STRIBILD treatment group (13 of 867 subjects [1.5%]). Of the 12 subjects with resistance development in the GENVOYA group, the resistance-associated substitutions that emerged were M184V/I (N=11) and K65R/N (N=2) in reverse transcriptase and T66T/A/I/V (N=2), E92Q (N=4), E138K (N=1), Q148Q/R (N=1) and N155H (N=2) in integrase. Of the 13 subjects with resistance development in the STRIBILD group, the resistance-associated substitutions that emerged were M184V/I (N=9), K65R/N (N=4), and L210W (N=1) in reverse transcriptase and E92Q/V (N=4), E138K (N=3), Q148R (N=2), and N155H/S (N=3) in integrase. In both treatment groups, most subjects who

developed substitutions associated with resistance to elvitegravir also developed emtricitabine resistance-associated substitutions. These genotypic resistance results were confirmed by phenotypic analyses.

In Virologically Suppressed Subjects:

Three virologic failure subjects were identified with emergent genotypic and phenotypic resistance to GENVOYA (all three with M184I or V and one with K219Q in reverse transcriptase; two with E92Q or G in integrase) out of 8 virologic failure subjects with resistance data in a clinical study of virologically-suppressed subjects who switched from a regimen containing emtricitabine/TDF and a third agent to GENVOYA (Study 109, N=959).

Cross-Resistance

No cross-resistance has been demonstrated for elvitegravir-resistant HIV-1 isolates and emtricitabine or tenofovir, or for emtricitabine- or tenofovir-resistant isolates and elvitegravir.

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 amino acid 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). Some viruses expressing elvitegravir or raltegravir resistance amino acid substitutions maintain susceptibility to dolutegravir.

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 Alafenamide (TAF): Tenofovir resistance substitutions, K65R and K70E, result in reduced susceptibility to abacavir, didanosine, emtricitabine, lamivudine, and tenofovir.

HIV-1 with multiple TAMs (M41L, D67N, K70R, L210W, T215F/Y, K219Q/E/N/R), or multinucleoside resistant HIV-1 with a T69S double insertion mutation or with a Q151M mutation complex including K65R, showed reduced susceptibility to TAF in cell culture.

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 times, 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 times, 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 times higher exposures (AUC), respectively, than in humans 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 18 times 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 recommended daily dose.

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

Cobicistat did not affect fertility in male or female rats at daily exposures (AUC) approximately 4 times 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 times 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 recommended dose).

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

Emtricitabine did not affect fertility in male rats at approximately 140 times or in male and female mice at approximately 60 times 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 times higher than human exposures at the recommended 200 mg daily dose.

Tenofovir Alafenamide (TAF)

Since TAF is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice is observed after TAF administration compared to TDF administration, carcinogenicity studies were conducted only with TDF. Long-term oral carcinogenicity studies of TDF 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 300 mg therapeutic dose of TDF for HIV-1 infection. The tenofovir exposure in these studies was approximately 167 times (mice) and 55 times (rat) those observed in humans after administration of GENVOYA treatment. At the high dose in female mice, liver adenomas were increased at tenofovir exposures 10 times (300 mg TDF) and 167 times (10 mg TAF in GENVOYA) that in humans. In rats, the study was negative for carcinogenic findings.

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

There were no effects on fertility, mating performance or early embryonic development when TAF was administered to male rats at a dose equivalent to 155 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 14 days prior to mating through Day 7 of gestation.

13.2 Animal Toxicology and/or Pharmacology

Minimal to slight infiltration of mononuclear cells in the posterior uvea was observed in dogs with similar severity after three and nine month administration of TAF; reversibility was seen after a three month recovery period. At the NOAEL for eye toxicity, the

systemic exposure in dogs was 5 (TAF) and 15 (tenofovir) times the exposure seen in humans at the recommended daily GENVOYA dosage.

14 CLINICAL STUDIES

14.1 Description of Clinical Trials

The efficacy and safety of GENVOYA were evaluated in the studies summarized in Table 15.

Table 15 Trials Conducted with GENVOYA in Subjects with HIV-1 Infection

Trial	Population	Study Arms (N)	Timepoint (Week)
Study 104[a] Study 111[a]	Treatment-naïve adults	GENVOYA (866) STRIBILD (867)	144
Study 109[b]	Virologically-suppressed[d] adults	GENVOYA (959) ATRIPLA® or TRUVADA®+atazanavir+cobicistat or ritonavir or STRIBILD (477)	96
Study 112[c]	Virologically-suppressed[d] adults with renal impairment[e]	GENVOYA (242)	144
Study 1825[c]	Virologically-suppressed[d] adults with ESRD[f] receiving chronic hemodialysis	GENVOYA (55)	48
Study 106 (cohort 1)[c]	Treatment-naïve adolescents between the ages of 12 to less than 18 years (at least 35 kg)	GENVOYA (50)	48
Study 106 (cohort 2)[c]	Virologically-suppressed[d] children between the ages of 6 to less than 12 years (at least 25 kg)	GENVOYA (52)	48

a. Randomized, double blind, active controlled trial.

b. Randomized, open label, active controlled trial.

c. Open label trial.

d. HIV-1 RNA less than 50 copies per mL.

e. Estimated creatinine clearance between 30 and 69 mL per minute by Cockcroft-Gault method.

f. End stage renal disease (estimated creatinine clearance of less than 15 mL per minute by Cockcroft-Gault method).

14.2 Clinical Trial Results in HIV-1 Treatment-Naïve Subjects

In both Study 104 and Study 111, subjects were randomized in a 1:1 ratio to receive either GENVOYA (N=866) once daily or STRIBILD (elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, TDF 300 mg) (N=867) once daily. The mean age was 36 years (range 18–76), 85% were male, 57% were White, 25% were Black, and 10% were Asian. Nineteen percent of subjects identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.5 $\log_{10}$ copies per mL (range 1.3–7.0) and 23% of subjects had baseline viral loads greater than 100,000 copies per mL. The mean baseline CD4+ cell count was 427 cells per mm^3 (range 0–1360) and 13% had CD4+ cell counts less than 200 cells per mm^3.

Pooled treatment outcomes of Studies 104 and 111 through Week 144 are presented in Table 16.

Table 16 Pooled Virologic Outcomes of Randomized Treatment in Studies 104 and 111 at Week 144[a] in Treatment-Naïve Subjects

	GENVOYA (N=866)	STRIBILD (N=867)
HIV-1 RNA < 50 copies/mL[b]	84%	80%
HIV-1 RNA ≥ 50 copies/mL[c]	5%	4%
No Virologic Data at Week 144 Window	11%	16%
Discontinued Study Drug Due to AE or Death[d]	2%	3%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[e]	9%	11%
Missing Data During Window but on Study Drug	1%	1%

a. Week 144 window was between Day 966 and 1049 (inclusive).

b. The primary endpoint was assessed at Week 48 and the virologic success rate was 92% in the GENVOYA group and 90% in the STRIBILD group, with a treatment difference of 2.0% (95% CI: -0.7% to 4.7%). The difference at Week 144 was primarily driven by discontinuations due to other reasons with last available HIV-1 RNA <50 copies/mL.

c. Included 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 (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.

d. Includes subjects who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

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

Treatment outcomes were similar across subgroups by age, sex, race, baseline viral load, and baseline CD4+ cell count.

In Studies 104 and 111, the mean increase from baseline in CD4+ cell count at Week 144 was 326 cells per mm^3 in GENVOYA-treated subjects and 305 cells per mm^3 in STRIBILD-treated subjects.

14.3 Clinical Trial Results in HIV-1 Virologically-Suppressed Adults Who Switched to GENVOYA

In Study 109, the efficacy and safety of switching from ATRIPLA, TRUVADA plus atazanavir (given with either cobicistat or ritonavir), or STRIBILD to GENVOYA once daily were evaluated in a randomized, open-label trial of virologically-suppressed (HIV-1 RNA less than 50 copies per mL) HIV-1 infected adults (N=1436). Subjects must have been suppressed (HIV-1 RNA less than 50 copies per mL) on their baseline regimen for at least 6 months and had no known resistance-associated substitutions to any of the components of GENVOYA prior to study entry. Subjects were randomized in a 2:1 ratio to either switch to GENVOYA at baseline (N=959), or stay on their baseline antiretroviral regimen (N=477). Subjects had a mean age of 41 years (range 21–77), 89% were male, 67% were White, and 19% were Black. The mean baseline CD4+ cell count was 697 cells per mm^3 (range 79–1951).

Subjects were stratified by prior treatment regimen. At screening, 42% of subjects were receiving TRUVADA plus atazanavir (given with either cobicistat or ritonavir), 32% were receiving STRIBILD, and 26% were receiving ATRIPLA.

Treatment outcomes of Study 109 through 96 weeks are presented in Table 17.

Table 17 Virologic Outcomes of Study 109 at Week 96[a] in Virologically-Suppressed Adults who Switched to GENVOYA

	GENVOYA (N=959)	ATRIPLA or TRUVADA+atazanavir +cobicistat or ritonavir or STRIBILD (N=477)
HIV-1 RNA < 50 copies/mL	93%	89%
HIV-1 RNA ≥ 50 copies/mL[b]	2%	2%
No Virologic Data at Week 48 Window	5%	9%
Discontinued Study Drug Due to AE or Death[c]	1%	3%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[d]	3%	6%
Missing Data During Window but on Study Drug	1%	<1%

a. Week 96 window was between Day 630 and 713 (inclusive).

b. Included subjects who had ≥50 copies/mL in the Week 96 window; subjects who discontinued early due to lack or loss of efficacy; subjects who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥50 copies/mL.

c. Includes subjects who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

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

Treatment outcomes were similar across subgroups receiving ATRIPLA, TRUVADA plus atazanavir (given with either cobicistat or ritonavir), or STRIBILD prior to

randomization. In Study 109, the mean increase from baseline in CD4+ cell count at Week 96 was 60 cells per mm^3 in GENVOYA-treated subjects and 42 cells per mm^3 in subjects who stayed on their baseline regimen.

14.4 Clinical Trial Results in HIV-1 Infected Subjects with Renal Impairment

Study 112: Virologically-suppressed adults with renal impairment

In Study 112, the efficacy and safety of GENVOYA once daily were evaluated in an open-label clinical trial of 248 HIV-1 infected subjects with renal impairment (estimated creatinine clearance between 30 and 69 mL per minute by Cockcroft-Gault method). Of the 248 enrolled, 6 were treatment-naïve and 242 were virologically suppressed (HIV-1 RNA less than 50 copies per mL) for at least 6 months before switching to GENVOYA *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

The mean age was 58 years (range 24–82), with 63 subjects (26%) who were 65 years of age or older. Seventy-nine percent were male, 63% were White, 18% were Black, and 14% were Asian. Thirteen percent of subjects identified as Hispanic/Latino. The mean baseline CD4+ cell count was 664 cells per mm^3 (range 126–1813). At Week 144, 81% (197/242 virologically suppressed subjects) maintained HIV-1 RNA less than 50 copies per mL after switching to GENVOYA. All six treatment-naïve subjects were virologically suppressed at Week 144. Five subjects among the entire study population had virologic failure at Week 144.

Study 1825: Virologically-suppressed adults with end stage renal disease (ESRD) receiving chronic hemodialysis

In Study 1825, the efficacy and safety of GENVOYA once daily were evaluated in an open-label clinical trial of 55 virologically-suppressed (HIV-1 RNA less than 50 copies per mL for at least 6 months before switching to GENVOYA) HIV-1 infected subjects with ESRD (estimated creatinine clearance of less than 15 mL per minute by Cockcroft-Gault method) receiving chronic hemodialysis for at least 6 months *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

Subjects had a mean age of 48 years (range 23–64), 76% were male, 82% were Black, 18% were White, and 15% identified as Hispanic/Latino. The mean baseline CD4+ cell count was 545 cell per mm^3 (range 205–1473). At Week 48, 82% (45/55) maintained HIV-1 RNA less than 50 copies per mL after switching to GENVOYA. Two subjects had HIV-1 RNA ≥ 50 copies per mL by Week 48. Seven subjects discontinued the study drug due to AE or other reasons while suppressed. One subject did not have an HIV-1 RNA measurement at Week 48.

14.5 Clinical Trial Results in HIV-1 Infected Pediatric Subjects Between the Ages of 6 to Less than 18 Years

In Study 106, an open-label, single arm trial the efficacy, safety, and pharmacokinetics of GENVOYA in HIV-1 infected pediatric subjects were evaluated in treatment-naïve adolescents between the ages of 12 to less than 18 years weighing at least 35 kg (N=50) and in virologically-suppressed children between the ages of 6 to less than 12 years weighing at least 25 kg (N=52).

Cohort 1: Treatment-naïve adolescents (12 to less than 18 years; at least 35 kg)

Subjects in cohort 1 treated with GENVOYA once daily had a mean age of 15 years (range 12-17); 44% were male, 12% were Asian, and 88% were Black. At baseline, mean plasma HIV-1 RNA was 4.6 $\log_{10}$ copies per mL (22% had baseline plasma HIV-1 RNA greater than 100,000 copies per mL), mean (SD) CD4+ cell count was 471 (212.2) cells per mm^3, and mean (SD) CD4+ percentage was 23.6% (8.8%).

In subjects in cohort 1 treated with GENVOYA, 92% (46/50) achieved HIV-1 RNA less than 50 copies per mL at Week 48. The mean increase from baseline in CD4+ cell count at Week 48 was 224 cells per mm^3. Three of 50 subjects had virologic failure at Week 48; no emergent resistance to GENVOYA was detected through Week 48.

Cohort 2: Virologically-suppressed children (6 to less than 12 years; at least 25 kg)

Subjects in cohort 2 treated with GENVOYA once daily had a mean age of 10 years (range: 7-11), a mean baseline weight of 31.7 kg, 42% were male, 25% were Asian, and 71% were Black. At baseline, the mean (SD) CD4+ cell count was 961 (275.5) cells per mm^3 and the mean (SD) CD4 percentage was 38.2% (6.4%). After switching to GENVOYA, 98% (51/52) of subjects in cohort 2 remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 48. No subject qualified for resistance analysis through Week 48. The mean change from baseline in CD4+ cell count was -66 (203.6) cells per mm^3 and the mean (SD) change in CD4 percentage was -0.6% (4.4%) at Week 48. All subjects maintained CD4+ cell counts above 400 cells/mm^3 *[see Adverse Reactions (6.1) and Pediatric Use (8.4)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

GENVOYA tablets are available in bottles containing 30 tablets with a silica gel desiccant, polyester coil, and child-resistant closure as follows:

- GENVOYA tablets each contain 150 mg of elvitegravir (EVG), 150 mg of cobicistat (COBI), 200 mg of emtricitabine (FTC), and 10 mg of tenofovir alafenamide (TAF). These tablets are green, capsule-shaped, film-coated, debossed with “GSI” on one side of the tablet and the number “510” on the other side (NDC 61958-1901-1).

Store below 30 °C (86 °F).

- Keep container tightly closed.
- Dispense only in original container.

17 PATIENT COUNSELING INFORMATION

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

Drug Interactions

GENVOYA may interact with many drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or non-prescription medication or herbal products including St. John's wort *[see Contraindications (4) and Drug Interactions (7)]*.

Post-treatment Acute Exacerbation of Hepatitis B in Patients with HBV Co-Infection

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued products containing emtricitabine and/or TDF, and may likewise occur with discontinuation of GENVOYA *[see Warnings and Precautions (5.1)]*. Advise the patient to not discontinue GENVOYA without first informing their healthcare provider.

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any symptoms of infection, as 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 *[see Warnings and Precautions (5.3)]*.

Renal Impairment

Advise patients to avoid taking GENVOYA with concurrent or recent use of nephrotoxic agents. Postmarketing cases of renal impairment, including acute renal failure, have been reported *[see Warnings and Precautions (5.4)].*

Lactic Acidosis and Severe Hepatomegaly

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with use of drugs similar to GENVOYA. Advise patients that they should stop GENVOYA if they develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity *[see Warnings and Precautions (5.5)]*.

Missed Dosage

Inform patients that it is important to take GENVOYA on a regular dosing schedule with food and to avoid missing doses as it can result in development of resistance *[see Dosage and Administration (2.2)]*.

Pregnancy

Advise patients that GENVOYA is not recommended during pregnancy and to alert their healthcare provider if they become pregnant while taking GENVOYA *[see Dosage and Administration (2.5) and Use in Specific Populations (8.1)].* Inform

patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant individuals exposed to GENVOYA *[see Use in Specific Populations (8.1)]*.

Lactation

Instruct patients with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in breast milk *[see Use in Specific Populations (8.2)].*

Manufactured and distributed by: Gilead Sciences, Inc. Foster City, CA 94404

Patient Information
GENVOYA® (jen-VOY-uh)
(elvitegravir, cobicistat, emtricitabine,
and tenofovir alafenamide)
tablets

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

What is the most important information I should know about GENVOYA?
GENVOYA can cause serious side effects, including:

- **Worsening of hepatitis B virus (HBV) infection. Your healthcare provider will test you for HBV infection before or when you start treatment with GENVOYA. If you have HBV infection and take GENVOYA, your HBV may get worse (flare-up) if you stop taking GENVOYA. A "flare-up" is when your HBV infection suddenly returns in a worse way than before.**
  - Do not run out of GENVOYA. Refill your prescription or talk to your healthcare provider before your GENVOYA is all gone.
  - Do not stop taking GENVOYA without first talking to your healthcare provider.
  - If you stop taking GENVOYA, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your liver, and may give you a medicine to treat hepatitis B. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking GENVOYA.

For more information about side effects, see "What are the possible side effects of GENVOYA?"

What is GENVOYA?

GENVOYA is a prescription medicine that is used without other human immunodeficiency virus-1 (HIV-1) medicines to treat HIV-1 infection in adults and children who weigh at least 55 pounds (25 kg):

- who have not received HIV-1 medicines in the past, **or**
- to replace their current HIV-1 medicines for people whose healthcare provider determines that they meet certain requirements.

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

GENVOYA contains the prescription medicines elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide.

It is not known if GENVOYA is safe and effective in children who weigh less than 55 pounds (25 kg).

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

- alfuzosin hydrochloride
- carbamazepine
- ergot-containing medicines, including:
  - dihydroergotamine mesylate
  - ergotamine tartrate
  - methylergonovine maleate
- lomitapide
- lovastatin
- lurasidone
- midazolam, when taken by mouth
- phenobarbital
- phenytoin
- pimozide
- rifampin
- sildenafil, when used for treating the lung problem, pulmonary arterial hypertension
- simvastatin
- triazolam
- St. John's wort (*Hypericum perforatum)* or a product that contains St. John's wort.

What should I tell my healthcare provider before taking GENVOYA?

Before taking GENVOYA, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems, including HBV infection
- have kidney problems
- are pregnant or plan to become pregnant.
  - It is not known if GENVOYA can harm your unborn baby.
  - GENVOYA should not be used during pregnancy because you may not have enough GENVOYA in your body during pregnancy.
  - Tell your healthcare provider if you become pregnant during treatment with GENVOYA. Your healthcare provider may prescribe different medicines if you become pregnant while taking GENVOYA.

Pregnancy Registry: There is a pregnancy registry for women who take antiretroviral 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 GENVOYA.
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  - At least one of the medicines in GENVOYA can pass to your baby in your breast milk. It is not known if the other medicines in GENVOYA can pass into your breast milk.

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

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 GENVOYA. 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 GENVOYA.
- Do not start a new medicine without telling your healthcare provider. Your healthcare provider can tell you if it is safe to take GENVOYA with other medicines.

How should I take GENVOYA?

- Take GENVOYA exactly as your healthcare provider tells you to take it. GENVOYA is taken by itself (not with other HIV-1 medicines) to treat HIV-1 infection.
- Take GENVOYA 1 time each day with food.
- If you are on dialysis, take your daily dose of GENVOYA following dialysis.
- Do not change your dose or stop taking GENVOYA without first talking with your healthcare provider. Stay under a healthcare provider's care during treatment with GENVOYA.
- If you need to take a medicine for indigestion (antacid) that contains aluminum hydroxide, magnesium hydroxide, or calcium carbonate during treatment with GENVOYA, take it at least 2 hours before or after you take GENVOYA.
- Do not miss a dose of GENVOYA.
- When your GENVOYA 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 GENVOYA and become harder to treat.
- If you take too much GENVOYA, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of GENVOYA?
GENVOYA may cause serious side effects, including:

- **See "What is the most important information I should know about GENVOYA?"**
- **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.
- **New or worse kidney problems, including kidney failure.** Your healthcare provider should do blood and urine tests to check your kidneys when starting and during treatment with GENVOYA. Your healthcare provider may tell you to stop taking GENVOYA if you develop new or worse kidney problems.
- **Too much lactic acid in your blood (lactic acidosis).** Too much lactic acid is a serious but rare medical emergency that can lead to death. Tell your healthcare provider right away if you get these symptoms: weakness or being more tired than usual, unusual muscle pain, being short of breath or fast breathing, stomach pain with nausea and vomiting, cold or blue hands and feet, feel dizzy or lightheaded, or a fast or abnormal heartbeat.
- **Severe liver problems.** In rare cases, severe liver problems can happen that can lead to death. Tell your healthcare provider right away if you get these symptoms: skin or the white part of your eyes turns yellow, dark "tea-colored" urine, light-colored stools, loss of appetite for several days or longer, nausea, or stomach-area pain.

The most common side effect of GENVOYA is nausea.

These are not all the possible side effects of GENVOYA.

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 GENVOYA?

- Store GENVOYA below 86°F (30°C).
- Keep GENVOYA in its original container.
- Keep the container tightly closed.

Keep GENVOYA and all medicines out of reach of children.

General information about the safe and effective use of GENVOYA.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use GENVOYA for a condition for which it was not prescribed. Do not give GENVOYA to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about GENVOYA that is written for health professionals.

What are the ingredients in GENVOYA?
Active ingredients: elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide
Inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, silicon dioxide, and sodium lauryl sulfate. The tablets are film-coated with a coating material containing FD&C Blue No. 2/indigo carmine aluminum lake, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Manufactured and distributed by: Gilead Sciences, Inc. Foster City, CA 94404

For more information, call 1-800-445-3235 or go to www.GENVOYA.com.
This Patient Information has been approved by the U.S. Food and Drug Administration Revised: 01/2022

Proposed Package Insert

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

GENVOYA® (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets, for oral use
Initial U.S. Approval: 2015

WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B
See full prescribing information for complete boxed warning.

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of GENVOYA. Hepatic function should be monitored closely in these patients. If appropriate, anti-hepatitis B therapy may be warranted. (5.1)

----------RECENT MAJOR CHANGES ----------
Warnings and Precautions, New Onset or Worsening Renal Impairment (5.4) 03/2021

----------INDICATIONS AND USAGE ----------
GENVOYA is a four-drug combination of elvitegravir (EVG), an HIV-1 integrase strand transfer inhibitor (INSTI), cobicistat (COBI), a CYP3A inhibitor, and emtricitabine (FTC) and tenofovir alafenamide (TAF), both HIV-1 nucleoside analog reverse transcriptase inhibitors (NRTIs), and is indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 25 kg 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 per 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 GENVOYA. (1)

----------DOSAGE AND ADMINISTRATION ----------
- Testing: Prior to or when initiating GENVOYA test for hepatitis B virus infection. Prior to or when initiating GENVOYA, and during treatment on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. (2.1)
- Recommended dosage in adult and pediatric patients weighing at least 25 kg: One tablet taken orally once daily with food in patients with body weight at least 25 kg and a creatinine clearance greater than or equal to 30 mL per minute, or in adult patients with creatinine clearance less than 15 mL per minute who are receiving chronic hemodialysis. On days of hemodialysis, administer GENVOYA after hemodialysis. (2.2)
- Renal impairment: GENVOYA is not recommended in patients with estimated creatinine clearance of 15 to below 30 mL per minute, or below 15 mL per minute who are not receiving chronic hemodialysis. (2.3)
- Hepatic impairment: GENVOYA is not recommended in patients with severe hepatic impairment. (2.4)

----------DOSAGE FORMS AND STRENGTHS ----------
Tablets: 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide. (3)

----------CONTRAINDICATIONS----------
Coadministration of GENVOYA 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 GENVOYA and possible resistance. (4)

----------WARNINGS AND PRECAUTIONS----------
- Risk of adverse reactions or loss of virologic response due to drug interactions: The concomitant use of GENVOYA and other drugs may result in known or potentially significant drug interactions, some of which may lead to loss of therapeutic effect of GENVOYA and possible development of resistance; clinically significant adverse reactions from greater exposures of concomitant drugs; or loss of therapeutic effect of concomitant drugs. (5.2)
- Immune reconstitution syndrome: May necessitate further evaluation and treatment. (5.3)
- New onset or worsening renal impairment: Assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein when initiating GENVOYA and during therapy on a clinically appropriate schedule in all patients. Also assess serum phosphorus in patients with chronic kidney disease. (5.4)
- Lactic acidosis/severe hepatomegaly with steatosis: Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.5)

----------ADVERSE REACTIONS ----------
Most common adverse reaction (incidence greater than or equal to 10%, all grades) is nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact LifeScience Logistics at 1-855-738-6171 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS ----------
- GENVOYA should not be administered with other antiretroviral medications for treatment of HIV-1 infection. (7.1)
- GENVOYA 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 GENVOYA. 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: Not recommended for use during pregnancy because of substantially lower exposures of cobicistat and elvitegravir during pregnancy. GENVOYA should not be initiated in pregnant individuals. (2.5, 8.1)
- Lactation: Breastfeeding is not recommended due to the potential for HIV transmission. (8.2)
- Pediatrics: Not recommended for patients weighing less than 25 kg. (8.4)

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

Revised: 01/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of GENVOYA. 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 GENVOYA. If appropriate, anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

GENVOYA is indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 25 kg 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 per 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 GENVOYA *[see Clinical Studies (14)].*

2 DOSAGE AND ADMINISTRATION

2.1 Testing When Initiating and During Treatment with GENVOYA

Prior to or when initiating GENVOYA, test patients for hepatitis B virus infection *[see Warnings and Precautions (5.1)]*.

Prior to or when initiating GENVOYA, and during treatment with GENVOYA on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus *[see Warnings and Precautions (5.4)]*.

2.2 Recommended Dosage in Adults and Pediatric Patients Weighing at Least 25 kg

GENVOYA is a four-drug fixed dose combination product containing elvitegravir (EVG), cobicistat (COBI), emtricitabine (FTC), and tenofovir alafenamide (TAF). The recommended dosage of GENVOYA is one tablet containing 150 mg EVG,150 mg COBI, 200 mg FTC, and 10 mg TAF taken orally once daily with food in:

- adults and pediatric patients with body weight at least 25 kg and creatinine clearance greater than or equal to 30 mL per minute; or

- adults with creatinine clearance below 15 mL per minute who are receiving chronic hemodialysis. On days of hemodialysis, administer GENVOYA after completion of hemodialysis treatment *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

2.3 Not Recommended in Patients with Severe Renal Impairment

GENVOYA is not recommended in patients with:

- severe renal impairment (estimated creatinine clearance of 15 to below 30 mL per minute); or
- end stage renal disease (ESRD; estimated creatinine clearance below 15 mL per minute) who are not receiving chronic hemodialysis *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)]*.

2.4 Not Recommended in Patients with Severe Hepatic Impairment

GENVOYA is not recommended in patients with severe hepatic impairment (Child-Pugh Class C) *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

2.5 Not Recommended During Pregnancy

GENVOYA is not recommended for use during pregnancy because of substantially lower exposures of cobicistat and elvitegravir during the second and third trimesters *[see Use in Specific Populations (8.1)]*.

GENVOYA should not be initiated in pregnant individuals. An alternative regimen is recommended for individuals who become pregnant during therapy with GENVOYA *[see Use in Specific Populations (8.1)]*.

3 DOSAGE FORMS AND STRENGTHS

Each GENVOYA tablet contains 150 mg of elvitegravir (EVG), 150 mg of cobicistat (COBI), 200 mg of emtricitabine (FTC), and 10 mg of tenofovir alafenamide (TAF) (equivalent to 11.2 mg of tenofovir alafenamide fumarate).

The tablets are green, capsule-shaped, film-coated tablets, debossed with “GSI” on one side of the tablet and the number “510” on the other side of the tablet.

4 CONTRAINDICATIONS

Coadministration of GENVOYA 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 GENVOYA and possible resistance) are listed below *[see Drug Interactions (7.5) and Clinical Pharmacology (12.3)]*.

- Alpha 1-adrenoreceptor antagonist: alfuzosin
- Anticonvulsants: carbamazepine, phenobarbital, phenytoin
- Antimycobacterial: rifampin
- Antipsychotics: lurasidone, pimozide
- Ergot Derivatives: dihydroergotamine, ergotamine, methylergonovine
- Herbal Products: St. John's wort (*Hypericum perforatum*)
- Lipid-modifying Agents: lomitapide, lovastatin, simvastatin
- Phosphodiesterase-5 (PDE-5) Inhibitor: sildenafil when administered as REVATIO® for the treatment of pulmonary arterial hypertension
- Sedative/hypnotics: triazolam, orally administered midazolam

5 WARNINGS AND PRECAUTIONS

5.1 Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV

Patients with HIV-1 should be tested for the presence of hepatitis B virus (HBV) before or when initiating antiretroviral therapy *[see Dosage and Administration (2.1)]*.

Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of GENVOYA. Patients coinfected with HIV-1 and HBV who discontinue GENVOYA should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis, since post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

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

The concomitant use of GENVOYA 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 of therapeutic effect of GENVOYA and possible development of resistance
- Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events, from greater exposures of concomitant drugs metabolized by CYP3A.
- Loss of therapeutic effect of concomitant drugs that utilize CYP3A to form active metabolites.

See Table 5 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations *[see Drug Interactions (7)]*. Consider the potential for drug interactions prior to and during GENVOYA therapy; review concomitant medications during GENVOYA therapy; and monitor for the adverse reactions associated with the concomitant drugs.

5.3 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including emtricitabine, a component of GENVOYA. 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, Guillain-Barré syndrome, and autoimmune hepatitis) 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.

5.4 New Onset or Worsening Renal Impairment

Postmarketing cases of renal impairment, including acute renal failure, proximal renal tubulopathy (PRT), and Fanconi syndrome have been reported with TAF-containing products; while most of these cases were characterized by potential confounders that may have contributed to the reported renal events, it is also possible these factors may have predisposed patients to tenofovir-related adverse events *[see Adverse Reactions (6.1, 6.2)]*. GENVOYA is not recommended in patients with estimated creatinine clearance of 15 to below 30 mL per minute, or in patients with estimated creatinine clearance below 15 mL per minute who are not receiving chronic hemodialysis.

Patients taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents including non-steroidal anti-inflammatory drugs are at increased risk of developing renal-related adverse reactions.

Prior to or when initiating GENVOYA, and during treatment with GENVOYA on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. Discontinue GENVOYA in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

Cobicistat, a component of GENVOYA, produces elevations of serum creatinine due to inhibition of tubular secretion of creatinine without affecting glomerular filtration *[see Adverse Reactions (6.1)]*. The elevation is typically seen within 2 weeks of starting therapy and is reversible after discontinuation. 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.

5.5 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 emtricitabine, a component of GENVOYA, and tenofovir DF, another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with GENVOYA 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).

6 ADVERSE REACTIONS

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

- Severe Acute Exacerbations of Hepatitis B *[see Warnings and Precautions (5.1)]*
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.3)]*
- New Onset or Worsening Renal Impairment *[see Warnings and Precautions (5.4)]*
- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[see Warnings and Precautions (5.5)]*

6.1 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.

Clinical Trials in Treatment-Naïve Adults

The primary safety assessment of GENVOYA was based on Week 144 pooled data from 1,733 subjects in two randomized, double-blind, active-controlled trials, Study 104 and Study 111, in antiretroviral treatment-naïve HIV-1 infected adult subjects. A total of 866 subjects received one tablet of GENVOYA once daily *[see Clinical Studies (14.2)]*.

The most common adverse reaction (all Grades) reported in at least 10% of subjects in the GENVOYA group was nausea. The proportion of subjects who discontinued treatment with GENVOYA or STRIBILD® due to adverse events, regardless of severity, was 1% and 2%, respectively. Table 1 displays the frequency of adverse reactions (all Grades) greater than or equal to 5% in the GENVOYA group.

Table 1 Adverse Reactions[a] (All Grades) Reported in ≥ 5% of HIV-1 Infected Treatment-Naïve Adults Receiving GENVOYA in Studies 104 and 111 (Week 144 analysis)

	GENVOYA N=866	**STRIBILD** N=867
Nausea	11%	13%
Diarrhea	7%	9%
Headache	6%	5%
Fatigue	5%	4%

a. Frequencies of adverse reactions are based on all adverse events attributed to study drugs by the investigator.

The majority of events presented in Table 1 occurred at severity Grade 1.

Clinical Trials in Virologically Suppressed Adults

The safety of GENVOYA in virologically-suppressed adults was based on Week 96 data from 959 subjects in a randomized, open-label, active-controlled trial (Study 109) in which virologically-suppressed subjects were switched from a TDF-containing combination regimen to GENVOYA. Overall, the safety profile of GENVOYA in subjects in this study was similar to that of treatment-naïve subjects *[see Clinical Studies (14.3)]*. Additional adverse reactions observed with GENVOYA in Study 109 included suicidal ideation, suicidal behavior, and suicide attempt (<1% combined); all of these events were serious and all occurred in subjects with a preexisting history of depression or psychiatric illness.

Clinical Trials in Adult Subjects with Renal Impairment

In an open-label trial (Study 112), 248 HIV-1 infected subjects with estimated creatinine clearance between 30 and 69 mL per minute (by Cockcroft-Gault method) were treated with GENVOYA for a median duration of 144 weeks. Of these subjects, 65% had previously been on a stable TDF-containing regimen. A total of 5 subjects permanently discontinued GENVOYA due to the development of renal adverse events through Week 96. Three of these five were among the 80 subjects with baseline estimated creatinine clearance of less than 50 mL/min and two subjects were among the 162 subjects with baseline estimated creatinine clearance of greater than or equal to 50 mL/min. There were no further renal discontinuations between Weeks 96 and 144. Overall, renally impaired subjects receiving GENVOYA in this study had a mean serum creatinine of 1.5 mg/dL at baseline and 1.4 mg/dL at Week 144. Otherwise, the safety profile of GENVOYA in subjects in this study was similar to that of subjects with normal renal function.

Virologically-Suppressed Adults with End Stage Renal Disease (ESRD) Receiving Chronic Hemodialysis

The safety of GENVOYA in subjects with end stage renal disease (ESRD) (estimated creatinine clearance of less than 15 mL/min) on chronic hemodialysis was assessed in

55 subjects (Study 1825) *[see Clinical Studies (14.4)].* The most commonly reported adverse reaction (adverse event assessed as causally related by investigator and all grades) was nausea (7%). Serious adverse events were reported in 53% of subjects and the most common serious adverse events were pneumonia (13%), fluid overload (7%), hyperkalemia (7%) and osteomyelitis (7%). Overall 5% of subjects permanently discontinued treatment due to an adverse event.

Renal Laboratory Tests and Renal Safety

Treatment-Naïve Adults:

Cobicistat (a component of GENVOYA) has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting glomerular filtration *[see Clinical Pharmacology (12.2)]*. Increases in serum creatinine occurred by Week 2 of treatment and remained stable through 144 weeks.

In two 144-week randomized, controlled trials in a total of 1,733 treatment-naïve adults with a median baseline estimated creatinine clearance of 115 mL per minute, mean serum creatinine increased by less than 0.1 mg per dL in the GENVOYA group and by 0.1 mg per dL in the STRIBILD group from baseline to Week 144.

Virologically Suppressed Adults:

In a study of 1,436 virologically-suppressed TDF-treated adults with a mean baseline estimated creatinine clearance of 112 mL per minute who were randomized to continue their treatment regimen or switch to GENVOYA, at Week 96 mean serum creatinine was similar to baseline for both those continuing baseline treatment and those switching to GENVOYA.

Across these trials, renal serious adverse events or discontinuations due to renal adverse reactions were encountered in less than 1% of participants treated with GENVOYA.

Bone Mineral Density Effects

Treatment-Naïve Adults:

In a pooled analysis of Studies 104 and 111, the effects of GENVOYA compared to STRIBILD on bone mineral density (BMD) change from baseline to Week 144 were assessed by dual-energy X-ray absorptiometry (DXA). The mean percentage change in BMD from baseline to Week 144 was −0.92% with GENVOYA compared to −2.95% with STRIBILD at the lumbar spine and −0.75% compared to −3.36% at the total hip. BMD declines of 5% or greater at the lumbar spine were experienced by 15% of GENVOYA subjects and 29% of STRIBILD subjects. BMD declines of 7% or greater at the femoral neck were experienced by 15% of GENVOYA subjects and 29% of STRIBILD subjects. The long-term clinical significance of these BMD changes is not known.

Virologically Suppressed Adults:

In Study 109, TDF-treated subjects were randomized to continue their TDF-based regimen or switch to GENVOYA; changes in BMD from baseline to Week 96 were assessed by DXA. Mean BMD increased in subjects who switched to GENVOYA (2.12% lumbar spine, 2.44% total hip) and decreased slightly in subjects who continued their baseline regimen (−0.09% lumbar spine, −0.46% total hip). BMD declines of 5% or greater at the lumbar spine were experienced by 2% of GENVOYA subjects and 6% of subjects who continued their TDF-based regimen. BMD declines of 7% or greater at the femoral neck were experienced by 2% of GENVOYA subjects and 7% of subjects who continued their TDF-based regimen. The long-term clinical significance of these BMD changes is not known.

Laboratory Abnormalities:

The frequency of laboratory abnormalities (Grades 3–4) occurring in at least 2% of subjects receiving GENVOYA in Studies 104 and 111 are presented in Table 2.

Table 2 Laboratory Abnormalities (Grades 3–4) Reported in ≥ 2% of Subjects Receiving GENVOYA in Studies 104 and 111 (Week 144 analysis)

Laboratory Parameter Abnormality[a]	GENVOYA N=866	STRIBILD N=867
Creatine Kinase (≥10.0 x ULN)	11%	10%
LDL-cholesterol (fasted) (>190 mg/dL)	11%	5%
Total cholesterol (fasted) (>300mg/dL)	4%	3%
Amylase	3%	5%
ALT	3%	3%
AST	3%	4%
Urine RBC (Hematuria) (>75 RBC/HPF)	3%	3%

a. Frequencies are based on treatment-emergent laboratory abnormalities.

Serum Lipids:

Subjects receiving GENVOYA experienced greater increases in serum lipids compared to those receiving STRIBILD.

Changes from baseline in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and total cholesterol to HDL ratio are presented in Table 3.

Table 3 Lipid Values, Mean Change from Baseline, Reported in Subjects Receiving GENVOYA or STRIBILD in Trials 104 and 111[a]

	GENVOYA N=866		STRIBILD N=867	
	Baseline	**Week 144**	**Baseline**	**Week 144**
	mg/dL	Change[b]	mg/dL	Change[b]
Total Cholesterol (fasted)	162 [N=647]	+31 [N=647]	165 [N=627]	+14 [N=627]
Triglycerides (fasted)	111 [N=647]	+29 [N=647]	115 [N=627]	+17 [N=627]
LDL-cholesterol (fasted)	103 [N=647]	+20 [N=643]	107 [N=628]	+8 [N=628]
HDL-cholesterol (fasted)	47 [N=647]	+7 [N=647]	46 [N=627]	+3 [N=627]
Total Cholesterol to HDL ratio	3.7 [N=647]	0.2 [N=647]	3.8 [N=627]	0.1 [N=627]

a. Excludes subjects who received lipid lowering agents during the treatment period.

b. The change from baseline is the mean of within-subject changes from baseline for subjects with both baseline and Week 144 values.

Clinical Trials in Pediatric Subjects:

Safety in Pediatric Patients

The safety of GENVOYA in HIV-1 infected pediatric subjects was evaluated in treatment-naïve subjects between the ages of 12 to less than 18 years and weighing at least 35 kg (N=50) through Week 48 (cohort 1), and in virologically-suppressed subjects between the ages of 6 to less than 12 years and weighing at least 25 kg (N=52) through Week 48 (cohort 2) in an open-label clinical trial (Study 106) *[see Clinical Studies (14.5)]*. With the exception of a decrease in the mean CD4+ cell count observed in cohort 2 of Study 106, the safety profile in pediatric subjects who received treatment with GENVOYA was similar to that in adults. One 13-year-old female subject developed unexplained uveitis while receiving GENVOYA that resolved and did not require discontinuation of GENVOYA.

Bone Mineral Density Effects

Cohort 1: Treatment-naïve adolescents (12 to less than 18 years; at least 35 kg)

Among the subjects in cohort 1 receiving GENVOYA, mean BMD increased from baseline to Week 48, + 4.2% at the lumbar spine and + 1.3% for the total body less head (TBLH). Mean changes from baseline BMD Z-scores were −0.07 for lumbar spine and −0.20 for TBLH at Week 48. One GENVOYA subject had significant (at least 4%) lumbar spine BMD loss at Week 48.

Cohort 2: Virologically-suppressed children (6 to less than 12 years; at least 25 kg)

Among the subjects in cohort 2 receiving GENVOYA, mean BMD increased from baseline to Week 48, +3.9% at the lumbar spine and +4.2% for TBLH. Mean changes from baseline BMD Z-scores were -0.24 for lumbar spine and -0.19 for TBLH at Week 48. Six GENVOYA subjects had significant (at least 4%) lumbar spine BMD loss at Week 48; 2 subjects also had at least 4% TBLH BMD loss at Week 48.

Change from Baseline in CD4+ cell counts

Cohort 2: Virologically-suppressed children (6 to less than 12 years; at least 25 kg)

Cohort 2 of Study 106 evaluated pediatric subjects (N=52) who were virologically-suppressed and who switched from their antiretroviral regimen to GENVOYA. Although all subjects had HIV-1 RNA < 50 copies/mL, there was a decrease from baseline in CD4+ cell count at Weeks 24 and 48. The mean baseline and mean change from baseline in CD4+ cell count and in CD4% from Week 2 to Week 48 are presented in Table 4. All subjects maintained their CD4+ cell counts above 400 cells/mm^3 *[see Pediatric Use (8.4) and Clinical Studies (14.5)].*

Table 4 Mean Change in CD4+ Count and CD4 Percentage from Baseline to Week 48 in Virologically-Suppressed Pediatric Patients from 6 to <12 Years Who Switched to GENVOYA

		Mean Change from Baseline					
	Baseline	**Week 2**	**Week 4**	**Week 12**	**Week 24**	**Week 32**	**Week 48**
CD4+ Cell Count (cells/mm^3)	961 (275.5)[a]	-117	-114	-112	-118	-62	-66
CD4%	38 (6.4)[a]	+0.3%	-0.1%	-0.8%	-0.8%	-1.0%	-0.6%

a. Mean (SD)

6.2 Postmarketing Experience

The following events have been identified during post approval use of products containing TAF, including GENVOYA. Because these events 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.

Skin and Subcutaneous Tissue Disorders

Angioedema, urticaria, and rash

Renal and Urinary Disorders

Acute renal failure, acute tubular necrosis, proximal renal tubulopathy, and Fanconi syndrome

7 DRUG INTERACTIONS

7.1 Not Recommended with Other Antiretroviral Medications

GENVOYA is a complete regimen for the treatment of HIV-1 infection; therefore, coadministration of GENVOYA with other antiretroviral medications for treatment of HIV-1 infection should be avoided. Complete information regarding potential drug-drug interactions with other antiretroviral medications is not provided *[see Contraindications (4), Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.

7.2 Potential for GENVOYA to Affect Other Drugs

Cobicistat, a component of GENVOYA, 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 GENVOYA 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 . Coadministration of GENVOYA with drugs that have active metabolite(s) formed by CYP3A may result in reduced plasma concentration of these active metabolite(s) (see Table 5). Elvitegravir is a modest inducer of CYP2C9 and may decrease the plasma concentrations of CYP2C9 substrates. TAF is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or UGT1A1. TAF is a weak inhibitor of CYP3A *in vitro*. TAF is not an inhibitor or inducer of CYP3A *in vivo*.

7.3 Potential for Other Drugs to Affect One or More Components of GENVOYA

Elvitegravir and cobicistat, components of GENVOYA, 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, elvitegravir, and TAF, which may lead to loss of therapeutic effect of GENVOYA and development of resistance (see Table 5).

Coadministration of GENVOYA with other drugs that inhibit CYP3A may decrease the clearance and increase the plasma concentration of cobicistat. (see Table 5). TAF, a component of GENVOYA, is a substrate of P-gp, BCRP, OATP1B1 and OATP1B3. Drugs that inhibit P-gp and/or BCRP, such as cobicistat, may increase the absorption of TAF (see Table 13). However, when TAF is administered as a component of GENVOYA, its availability is increased by cobicistat and a further increase of TAF concentrations is not expected upon coadministration of an additional P-gp and/or BCRP inhibitor. Drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentration of TAF.

7.4 Drugs Affecting Renal Function

Because emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of

GENVOYA 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 (5.4)]*.

7.5 Established and Other Potentially Significant Interactions

Table 5 provides a listing of established or potentially clinically significant drug interactions *[see Contraindications (4)]*. The drug interactions described are based on studies conducted with either GENVOYA, the components of GENVOYA (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) as individual agents and/or in combination, or are predicted drug interactions that may occur with GENVOYA *[for magnitude of interaction, see Clinical Pharmacology (12.3)]*. The table includes potentially significant interactions but is not all inclusive.

Table 5 Established and Other Potentially Significant[a] 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[b]	Clinical Comment
Alpha 1-adrenoreceptor antagonist: alfuzosin	↑ alfuzosin	Coadministration with alfuzosin is contraindicated due to potential for serious and/or life-threatening reactions such as hypotension.
Antiarrhythmics: e.g., amiodarone bepridil digoxin* disopyramide flecainide systemic lidocaine mexiletine propafenone quinidine	↑ antiarrhythmics ↑ digoxin	Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when coadministered with GENVOYA.
Antibacterials: clarithromycin telithromycin	↑ clarithromycin ↑ telithromycin ↑ cobicistat	Patients with CL_{cr} greater than or equal to 60 mL/minute: No dosage adjustment of clarithromycin is required. Patients with CL_{cr} between 50 mL/minute and 60 mL/minute: The dosage of clarithromycin should be reduced by 50%.

Anticoagulants: Direct Oral Anticoagulants (DOACs) apixaban rivaroxaban betrixaban dabigatran edoxaban	↑ apixaban ↑ rivaroxaban ↑ betrixaban ↑ dabigatran ↑ edoxaban	Due to potentially increased bleeding risk, dosing recommendations for coadministration with GENVOYA depends on the apixaban dose. Refer to apixaban dosing instructions for coadministration with strong CYP3A and P-gp inhibitors in apixaban prescribing information. Coadministration of rivaroxaban with GENVOYA is not recommended because it may lead to an increased bleeding risk. Due to potentially increased bleeding risk, dosing recommendations for coadministration of betrixaban, dabigatran, or edoxaban with a P-gp inhibitor such as GENVOYA depends on DOAC indication and renal function. Refer to DOAC dosing instructions for coadministration with P-gp inhibitors in DOAC prescribing information.
warfarin	Effect on warfarin unknown	Monitor the international normalized ratio (INR) upon coadministration of warfarin with GENVOYA.
Anticonvulsants: carbamazepine* phenobarbital phenytoin oxcarbazepine ethosuximide	↓ elvitegravir ↓ cobicistat ↓ TAF ↑ ethosuximide	Coadministration with carbamazepine, phenobarbital, or phenytoin is contraindicated due to potential for loss of therapeutic effect and development of resistance. Alternative anticonvulsants should be considered when GENVOYA is administered with oxcarbazepine. Clinical monitoring is recommended upon coadministration of ethosuximide with GENVOYA.
Antidepressants: Selective Serotonin Reuptake Inhibitors (SSRIs) e.g., paroxetine Tricyclic Antidepressants (TCAs) e.g., amitriptyline desipramine* imipramine nortriptyline bupropion trazodone	↑ SSRIs (except sertraline) ↑ TCAs ↑ trazodone	Careful dosage titration of the antidepressant and monitoring for antidepressant response are recommended when coadministered with GENVOYA.

Antifungals: itraconazole ketoconazole* voriconazole	↑ elvitegravir ↑ cobicistat ↑ itraconazole ↑ ketoconazole ↑ voriconazole	When administering with GENVOYA, the maximum daily dosage of ketoconazole or itraconazole should not exceed 200 mg per day. An assessment of benefit/risk ratio is recommended to justify use of voriconazole with GENVOYA.
Anti-gout: colchicine	↑ colchicine	GENVOYA 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 GENVOYA:</u> 0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Treatment course to be repeated no earlier than 3 days. <u>Prophylaxis of gout-flares – coadministration of colchicine in patients receiving GENVOYA:</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 GENVOYA:</u> Maximum daily dosage of 0.6 mg (may be given as 0.3 mg twice a day).
Antimycobacterial: rifampin	↓ elvitegravir ↓ cobicistat ↓ TAF	Coadministration with rifampin is contraindicated due to potential for loss of therapeutic effect and development of resistance.
rifabutin* rifapentine		Coadministration of GENVOYA with rifabutin or rifapentine is not recommended.
Antiplatelets: ticagrelor	↑ ticagrelor	Coadminstration with ticagrelor is not recommended.
clopidogrel	↓ clopidogrel active metabolite	Coadministration with clopidogrel is not recommended due to protential reduction of the antiplatelet activity of clopidogrel.

Antipsychotics: lurasidone	↑ lurasidone	Coadministration with lurasidone is contraindicated due to potential for serious and/or life-threatening reactions.
pimozide	↑ pimozide	Coadministration with pimozide is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
quetiapine	↑ quetiapine	Initiation of GENVOYA in patients taking quetiapine: 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. Initiation of quetiapine in patients taking GENVOYA: Refer to the quetiapine prescribing information for initial dosing and titration of quetiapine.
Other antipsychotics e.g., perphenazine risperidone thioridazine	↑ antipsychotic	A decrease in dose of the antipsychotics that are metabolized by CYP3A or CYP2D6 may be needed when coadministered with GENVOYA.
Beta-Blockers: e.g., metoprolol timolol	↑ beta-blockers	Clinical monitoring is recommended and a dosage decrease of the beta blocker may be necessary when these agents are coadministered with GENVOYA.
Calcium Channel Blockers: e.g., amlodipine diltiazem felodipine nicardipine nifedipine verapamil	↑ calcium channel blockers	Caution is warranted and clinical monitoring is recommended upon coadministration of calcium channel blockers with GENVOYA.

Corticosteroids: e.g., betamethasone budesonide ciclesonide dexamethasone fluticasone methylprednisolone mometasone prednisone triamcinolone	↓ elvitegravir ↓ cobicistat ↑ corticosteroids	Coadministration with oral dexamethasone or other systemic corticosteroids that induce CYP3A may result in loss of therapeutic effect and development of resistance to elvitegravir. Consider alternative corticosteroids. Coadministration with corticosteroids (all routes of administration) whose exposures are significantly increased by strong CYP3A inhibitors can increase the risk for Cushing's syndrome and adrenal suppression. Alternative corticosteroids including beclomethasone and prednisolone (whose PK and/or PD are less affected by strong CYP3A inhibitors relative to other studied steroids) should be considered, particularly for long-term use.
Endothelin Receptor Antagonists: bosentan	↑ bosentan	<u>Coadministration of bosentan in patients on GENVOYA:</u> In patients who have been receiving GENVOYA for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability. <u>Coadministration of GENVOYA in patients on bosentan:</u> Discontinue use of bosentan at least 36 hours prior to initiation of GENVOYA. After at least 10 days following the initiation of GENVOYA, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability.
Ergot Derivatives: dihydroergotamine ergotamine methylergonovine	↑ ergot derivatives	Coadministration is contraindicated due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues *[see Contraindications (4)]*.
Herbal Products: St. John's wort *(Hypericum perforatum)*	↓ elvitegravir ↓ cobicistat ↓ TAF	Coadministration is contraindicated due to potential for loss of therapeutic effect and development of resistance.
Hormonal Contraceptives: drospirenone/ethinyl estradiol* levonorgestrel norgestimate/ethinyl estradiol	↑ drospirenone ↑ norgestimate ↑ levonorgestrel ↓ ethinyl estradiol	Additional or alternative non-hormonal forms of contraception should be considered when estrogen based contraceptives are coadministered with GENVOYA. Plasma concentrations of drospirenone may be increased when coadministered with cobicistat-containing products. Clinical monitoring is recommended due to the potential for hyperkalemia. The effects of increases in the 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 GENVOYA should be considered, particularly in patients who have risk factors for these events. The effect of GENVOYA on other hormonal contraceptives (e.g., contraceptive patch, contraceptive vaginal ring, or injectable contraceptives) or oral contraceptives containing progestogens other than drospirenone, levonorgestrel, or norgestimate has not been studied; therefore, alternative (non-hormonal) methods of contraception can be considered.
Immuno-suppressants: e.g., cyclosporine (CsA) sirolimus tacrolimus	↑ immuno-suppressants ↑ elvitegravir (with CsA) ↑ cobicistat (with CsA)	Therapeutic monitoring of the immunosuppressive agents is recommended upon coadministration with GENVOYA. Monitor for adverse events associated with GENVOYA when coadministered with cyclosporine.
Lipid-modifying Agents: **HMG-CoA Reductase Inhibitors:** lovastatin simvastatin atorvastatin **Other Lipid-modifying Agents:** lomitapide	↑ lovastatin ↑ simvastatin ↑ atorvastatin ↑ lomitapide	Coadministration with lovastatin or simvastatin is contraindicated due to potential for serious reactions such as myopathy including rhabdomyolysis. Initiate atorvastatin with the lowest starting dose of atorvastatin and titrate carefully while monitoring for safety (e.g., myopathy). Do not exceed a dosage of atorvastatin 20 mg daily. Coadministration with lomitapide is contraindicated due to potential for markedly increased transaminases.
Narcotic Analgesics: buprenorphine/ naloxone* fentanyl tramadol	↑ buprenorphine ↑ norbuprenorphine ↓ naloxone ↑ fentanyl ↑ tramadol	No dosage adjustment of buprenorphine/naloxone is required upon coadministration with GENVOYA. Patients should be closely monitored for sedation and cognitive effects. Careful monitoring of therapeutic and adverse effects of fentanyl (including potentially fatal respiratory depression) is recommended with coadministration. A dose decrease may be needed for tramadol with concomitant use.
Inhaled Beta Agonist: salmeterol	↑ salmeterol	Coadministration of salmeterol and GENVOYA is not recommended. Coadministration of salmeterol with GENVOYA may result in increased risk of cardiovascular adverse events associated with

		salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Medications or Oral Supplements Containing Polyvalent Cations (e.g., Mg, Al, Ca, Fe, Zn): calcium or iron supplements, including multivitamins cation-containing antacids* or laxatives sucralfate buffered medications	↓ elvitegravir	Separate GENVOYA and administration of medications, antacids, or oral supplements containing polyvalent cations by at least 2 hours.
Phosphodiesterase-5 (PDE5) Inhibitors: sildenafil tadalafil vardenafil	↑ PDE5 inhibitors	<u>Use of PDE-5 inhibitors for pulmonary arterial hypertension (PAH):</u> Coadministration of sildenafil with GENVOYA is contraindicated when used for treatment of PAH, due to potential for PDE-5 inhibitor associated adverse reactions, including hypotension, syncope, visual disturbances, and priapism. The following dose adjustments are recommended for the use of tadalafil with GENVOYA: *Coadministration of tadalafil in patients on GENVOYA:* In patients receiving GENVOYA for at least 1 week, start tadalafil at 20 mg once daily. Increase tadalafil dose to 40 mg once daily based upon individual tolerability. *Coadministration of GENVOYA in patients on tadalafil:* Avoid use of tadalafil during the initiation of GENVOYA. Stop tadalafil at least 24 hours prior to starting GENVOYA. After at least one week following initiation of GENVOYA, 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> Sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg in 72 hours, or tadalafil at a single dose not exceeding 10 mg in 72 hours can be used with increased monitoring for PDE-5 inhibitor associated with adverse events.

Sedative/hypnotic: midazolam (oral) triazolam Other benzodiazepines: e.g., parenterally administered midazolam clorazepate diazepam estazolam flurazepam buspirone zolpidem	↑ midazolam ↑ triazolam ↑sedatives/hypnotics	Coadministration with triazolam or orally administered midazolam is contraindicated due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression. Triazolam and orally administered midazolam are extensively metabolized by CYP3A. Coadministration of triazolam or orally administered midazolam with GENVOYA may cause large increases in the concentrations of these benzodiazepines. Coadministration of parenteral midazolam with GENVOYA 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.

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

a. This table is not all inclusive.

b. ↑ = Increase, ↓ = Decrease

7.6 Drugs without Clinically Significant Interactions with GENVOYA

Based on drug interaction studies conducted with the components of GENVOYA, no clinically significant drug interactions have been observed or are expected when GENVOYA is combined with the following drugs: famciclovir, famotidine, ledipasvir, methadone, omeprazole, prasugrel (active metabolite), sertraline, sofosbuvir, velpatasvir, and voxilaprevir.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to GENVOYA during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

GENVOYA is not recommended during pregnancy *[see Dosage and Administration (2.5)]*. A literature report evaluating the pharmacokinetics of antiretrovirals during pregnancy demonstrated substantially lower exposures of elvitegravir and cobicistat in the second and third trimesters *(see Data)*.

Prospective pregnancy data from the APR are not sufficient to adequately assess the risk of birth defects or miscarriage. However, elvitegravir (EVG), cobicistat (COBI), emtricitabine (FTC), and tenofovir alafenamide (TAF) use during pregnancy have been evaluated in a limited number of individuals as reported to the APR. Available data from the APR show no statistically significant difference in the overall risk of major birth defects for EVG, COBI, FTC or TAF compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) *(see Data)*. The rate of miscarriage is not reported in the APR. In the U.S. general population, the estimated background risk of miscarriage in clinically recognized pregnancies is 15-20%.

In animal studies, no adverse developmental effects were observed when the components of GENVOYA were administered separately during the period of organogenesis at exposures up to 23 and 0.2 times (rat and rabbits, respectively: elvitegravir), 1.6 and 3.8 times (rats and rabbits, respectively: cobicistat), 60 and 108 times (mice and rabbits, respectively; emtricitabine) and equal to and 53 times (rats and rabbits, respectively; TAF) the exposure at the recommended daily dosage of these components in GENVOYA *(see Data)*. Likewise, no adverse developmental effects were seen when elvitegravir or cobicistat was administered to rats through lactation at exposures up to 18 times or 1.2 times, respectively, the human exposure at the recommended therapeutic dose, and when emtricitabine was administered to mice through lactation at exposures up to approximately 60 times the exposure at the recommended daily dose. No adverse effects were observed in the offspring when TDF was administered through lactation at tenofovir exposures of approximately 14 times the exposure at the recommended daily dosage of GENVOYA.

Data

Human Data

A prospective study, reported in the literature, enrolled 30 pregnant women living with HIV who were receiving elvitegravir and cobicistat-based regimens in the second or third trimesters of pregnancy and through 6 to 12 weeks postpartum to evaluate the pharmacokinetics (PK) of antiretrovirals during pregnancy. Twenty-eight women completed the study through the postpartum period. Paired pregnancy/postpartum PK data were available from 14 and 24 women for the second and third trimesters, respectively. Exposures of elvitegravir and cobicistat were substantially lower during the second and third trimesters compared to postpartum. The proportion of pregnant women who were virologically suppressed was 77% in the second trimester, 92% in the third trimester, and 76% postpartum. No correlation was observed between viral suppression and elvitegravir exposure. HIV status was also assessed for infants: 25 were uninfected, 2 had indeterminate status, and no information was available for 3 infants.

Prospective reports from the APR of overall major birth defects in pregnancies exposed to the components of GENVOYA are compared with a U.S. background major birth defect rate. Methodological limitations of the APR include the use of MACDP as the external comparator group. Limitations of using an external

comparator include differences in methodology and populations, as well as confounding due to the underlying disease.

Elvitegravir (EVG):

Based on prospective reports to the APR of over 440 exposures to EVG-containing regimens during pregnancy resulting in live births (including over 350 exposed in the first trimester and 70 exposed in the second/third trimester), the prevalence of birth defects in live births was 3.0% (95% CI: 1.5% to 5.2%) and 1.4% (95% CI: 0.0% to 7.7%) following first and second/third trimester exposure, respectively, to EVG-containing regimens.

Cobicistat (COBI):

Based on prospective reports to the APR of over 560 exposures to COBI-containing regimens during pregnancy resulting in live births (including over 470 exposed in the first trimester and over 80 exposed in the second/third trimester), the prevalence of birth defects in live births was 3.6% (95% CI: 2.1% to 5.7%) and 1.1% (95% CI: 0.0% to 6.2%) following first and second/third trimester, respectively, to COBI-containing regimens.

Emtricitabine (FTC):

Based on prospective reports to the APR of over 5,400 exposures to FTC-containing regimens during pregnancy resulting in live births (including over 3,900 exposed in the first trimester and over 1,500 exposed in the second/third trimester), the prevalence of birth defects in live births was 2.6% (95% CI: 2.2% to 3.2%) and 2.7% (95% CI: 1.9% to 3.7%) following first and second/third trimester exposure, respectively, to FTC-containing regimens.

Tenofovir Alafenamide (TAF):

Based on prospective reports to the APR of over 660 exposures to TAF-containing regimens during pregnancy resulting in live births (including over 520 exposed in the first trimester and over 130 exposed in the second/third trimester), the prevalence of birth defects in live births was 4.2% (95% CI: 2.6% to 6.3%) and 3.0% (95% CI: 0.8% to 7.5%) following first and second/third trimester exposure, respectively, to TAF-containing regimens.

Animal Data

Elvitegravir:

Elvitegravir was administered orally to pregnant rats (0, 300, 1000, and 2000 mg/kg/day) and rabbits (0, 50, 150, and 450 mg/kg/day) through organogenesis (on gestation days 7 through 17 and days 7 through 19, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with elvitegravir in rats at exposures (AUC) approximately 23 times and in rabbits at approximately 0.2 times the human exposures at the recommended daily dose. In a pre/postnatal developmental study, elvitegravir was administered orally to rats at

doses of 0, 300, 1000, and 2000 mg/kg from gestation day 7 to day 20 of lactation. At doses of 2000 mg/kg/day of elvitegravir, neither maternal nor developmental toxicity was noted. Systemic exposures (AUC) at this dose were 18 times the human exposures at the recommended daily dose.

Cobicistat:

Cobicistat was administered orally to pregnant rats at doses of 0, 25, 50, 125 mg/kg/day on gestation day 6 to 17. Increases in post-implantation loss and decreased fetal weights were observed at a maternal toxic dose of 125 mg/kg/day. No malformations were noted at doses up to 125 mg/kg/day. Systemic exposures (AUC) at 50 mg/kg/day in pregnant females were 1.6 times higher than human exposures at the recommended daily dose.

In pregnant rabbits, cobicistat was administered orally at doses of 0, 20, 50, and 100 mg/kg/day during gestation days 7 to 20. No maternal or embryo/fetal effects were noted at the highest dose of 100 mg/kg/day. Systemic exposures (AUC) at 100 mg/kg/day were 3.8 times higher than human exposures at the recommended daily dose.

In a pre/postnatal developmental study in rats, cobicistat was administered orally at doses of 0, 10, 30, and 75 mg/kg from gestation day 6 to postnatal day 20, 21, or 22. At doses of 75 mg/kg/day of cobicistat, neither maternal nor developmental toxicity was noted. Systemic exposures (AUC) at this dose were 1.2 times the human exposures at the recommended daily dose.

Emtricitabine:

Emtricitabine was administered orally to pregnant mice (250, 500, or 1000 mg/kg/day) and rabbits (100, 300, or 1000 mg/kg/day) through organogenesis (on gestation days 6 through 15, and 7 through 19, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with emtricitabine in mice at exposures (AUC) approximately 60 times higher and in rabbits at approximately 108 times higher than human exposures at the recommended daily dose.

In a pre/postnatal development study with emtricitabine, mice were administered doses up to 1000 mg/kg/day; no significant adverse effects directly related to drug were observed in the offspring exposed daily from before birth (*in utero*) through sexual maturity at daily exposures (AUC) of approximately 60 times higher than human exposures at the recommended daily dose.

Tenofovir Alafenamide (TAF):

TAF was administered orally to pregnant rats (25, 100, or 250 mg/kg/day) and rabbits (10, 30, or 100 mg/kg/day) through organogenesis (on gestation days 6 through 17, and 7 through 20, respectively). No adverse embryo-fetal effects were observed in rats and rabbits at TAF exposures similar to (rats) and approximately 53 (rabbits) times higher than the exposure in humans at the recommended daily dose of GENVOYA. TAF is rapidly converted to tenofovir; the observed tenofovir exposure

in rats and rabbits were 59 (rats) and 93 (rabbits) times higher than human tenofovir exposures at the recommended daily doses. Since TAF is rapidly converted to tenofovir and lower tenofovir exposures in rats and mice were observed after TAF administration compared to TDF administration, a pre/postnatal development study in rats was conducted only with TDF. Doses up to 600 mg/kg/day were administered through lactation; no adverse effects were observed in the offspring on gestation day 7 [and lactation day 20] at tenofovir exposures of approximately 14 [21] times higher than the exposures in humans at the recommended daily dose of GENVOYA.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV.

Based on published data, emtricitabine has been shown to be present in human breast milk; it is unknown if elvitegravir, cobicistat, and TAF are present in human breast milk. Elvitegravir and cobicistat are present in rat milk, and tenofovir has been shown to be present in the milk of lactating rats and rhesus monkeys after administration of TDF *[see Data]*. It is unknown if TAF is present in animal milk.

It is not known if GENVOYA affects milk production or has effects on the breastfed child. Because of the potential for 1) HIV transmission (in HIV-negative infants); 2) developing viral resistance (in HIV-positive infants); and 3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving GENVOYA.

Data

Animal Data

Elvitegravir: During the pre/postnatal developmental toxicology study at doses up to 2000 mg/kg/day, a mean elvitegravir milk to plasma ratio of 0.1 was measured 30 minutes after administration to rats on lactation day 14.

Cobicistat: During the pre/postnatal developmental toxicology study at doses up to 75 mg/kg/day, mean cobicistat milk to plasma ratio of up to 1.9 was measured 2 hours after administration to rats on lactation day 10.

Tenofovir Alafenamide: Studies in rats and monkeys have demonstrated that tenofovir is secreted in milk. During the pre/postnatal developmental toxicology study, tenofovir was excreted into the milk of lactating rats following oral administration of TDF (up to 600 mg/kg/day) at up to approximately 24% of the median plasma concentration in the highest dosed animals at lactation day 11. Tenofovir was excreted into the milk of lactating rhesus monkeys, following a single subcutaneous (30 mg/kg) dose of tenofovir, at concentrations up to approximately

4% of plasma concentration resulting in exposure (AUC) of approximately 20% of plasma exposure.

8.4 Pediatric Use

The safety and effectiveness of GENVOYA for the treatment of HIV-1 infection was established in pediatric patients with body weight greater than or equal to 25 kg *[see Indications and Usage (1) and Dosage and Administration (2.2)]*.

Use of GENVOYA in pediatric patients less than 18 years of age and weighing at least 25 kg is supported by studies in adults and by an open-label study in antiretroviral treatment-naïve HIV-1 infected pediatric subjects aged 12 to less than 18 years and weighing at least 35 kg (cohort 1 of Study 106, N=50) and in virologically-suppressed pediatric subjects aged 6 to less than 12 years and weighing at least 25 kg (cohort 2 of Study 106, N=52). The safety and efficacy of GENVOYA in adolescent subjects was similar to that in adults *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.5)].* The safety and efficacy of GENVOYA in subjects 6 to 12 years of age weighing at least 25 kg was similar to that in antiretroviral treatment-naïve adults and adolescents with the exception of a decrease from baseline CD4+ cell count *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.5)]*.

A pharmacokinetic evaluation of a reduced strength GENVOYA formulation containing 90 mg of EVG, 90 mg of COBI, 120 mg of FTC, and 6 mg TAF was performed in 27 virologically-suppressed pediatric patients at least 2 years of age and weighing at least 14 to less than 25 kg (cohort 3 of Study 106). Virologic, immunologic, and safety outcomes were similar to those observed in cohort 2 of Study 106. No clinically meaningful differences in drug exposures except EVG were identified between pediatric patients in cohort 3 receiving the reduced strength formulation and adults receiving the GENVOYA tablet containing 150 mg of EVG,150 mg of COBI, 200 mg of FTC, and 10 mg TAF. The median observed EVG C_{trough} values in subjects in cohort 3 were significantly lower than the values correlated with efficacy in adults. Therefore, efficacy cannot be extrapolated from adults to pediatric patients weighing 14 to 25 kg.

Safety and effectiveness of GENVOYA in pediatric patients weighing less than 25 kg have not been established.

8.5 Geriatric Use

Clinical trials of GENVOYA included 97 subjects (80 receiving GENVOYA) aged 65 years and over. No differences in safety or efficacy have been observed between elderly subjects and adults between 18 and less than 65 years of age.

8.6 Renal Impairment

The pharmacokinetics, safety, and virologic and immunologic responses of GENVOYA in HIV-1 infected adult subjects with renal impairment (estimated creatinine clearance between 30 and 69 mL per minute by Cockcroft-Gault method) were evaluated in 248 subjects in an open-label trial, Study 112.

The pharmacokinetics, safety, virologic and immunologic responses of GENVOYA in HIV-1 infected adult subjects with ESRD (estimated creatinine clearance of less than 15 mL per minute by Cockcroft-Gault method) receiving chronic hemodialysis were evaluated in 55 subjects in an open-label trial, Study 1825 *[see Adverse Reactions (6.1) and Clinical Studies (14.4)]*.

No dosage adjustment of GENVOYA is recommended in patients with estimated creatinine clearance greater than or equal to 30 mL per minute, or in adult patients with ESRD (estimated creatinine clearance below 15 mL per minute) who are receiving chronic hemodialysis. On days of hemodialysis, administer GENVOYA after completion of hemodialysis treatment *[see Dosage and Administration (2.2)]*.

GENVOYA is not recommended in patients with severe renal impairment (estimated creatinine clearance of 15 to below 30 mL per minute), or in patients with ESRD who are not receiving chronic hemodialysis, as the safety of GENVOYA has not been established in these populations *[see Dosage and Administration (2.3), Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dosage adjustment of GENVOYA is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. GENVOYA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, GENVOYA is not recommended for use in patients with severe hepatic impairment *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

No data are available on overdose of GENVOYA in patients. If overdose occurs, monitor the patient for evidence of toxicity. Treatment of overdose with GENVOYA 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 recommended dose of elvitegravir in GENVOYA. In one study, elvitegravir (administered with the CYP3A inhibitor cobicistat) 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 recommended dose of cobicistat in GENVOYA. In two studies, a single dose of cobicistat 400 mg (2.7 times the dose in GENVOYA) 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 recommended dose of emtricitabine in GENVOYA. In one clinical pharmacology study, single doses of emtricitabine 1200 mg (6 times the dose in GENVOYA) 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 alafenamide (TAF): Limited clinical experience is available at doses higher than the recommended dose of TAF in GENVOYA. A single dose of 125 mg TAF (12.5 times the dose in GENVOYA) was administered to 48 healthy subjects; no serious adverse reactions were reported. The effects of higher doses are unknown. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%.

11 DESCRIPTION

GENVOYA (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) is a fixed-dose combination tablet containing elvitegravir (EVG), cobicistat (COBI), emtricitabine (FTC), and tenofovir alafenamide (TAF) for oral administration.

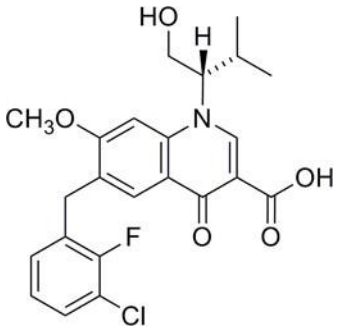
- EVG is an HIV-1 integrase strand transfer inhibitor.
- COBI is a mechanism-based inhibitor of cytochrome P450 (CYP) enzymes of the CYP3A family.
- FTC, a synthetic nucleoside analog of cytidine, is an HIV nucleoside analog reverse transcriptase inhibitor (HIV NRTI).
- TAF, an HIV NRTI, is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate.

Each tablet contains 150 mg of EVG, 150 mg of COBI, 200 mg of FTC, and 10 mg of TAF (equivalent to 11.2 mg of tenofovir alafenamide fumarate).

The tablets include the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, silicon dioxide, and sodium lauryl sulfate. The tablets are film-coated with a coating material containing FD&C Blue No. 2/indigo carmine aluminum lake, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

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.

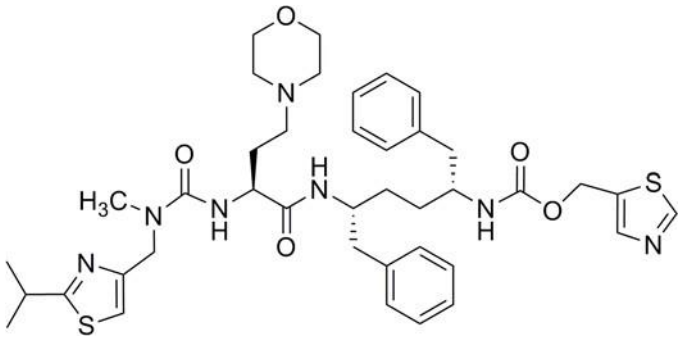
It has a molecular formula of $C_{23}H_{23}ClFNO_5$ and a molecular weight of 447.88. It has the following structural formula:



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 2,7,10,12-tetraazatridecanoic acid, 12-methyl-13-[2-(1-methylethyl)-4-thiazolyl]-9-[2-(4-morpholinyl)ethyl]-8,11-dioxo-3,6-bis(phenylmethyl)-, 5-thiazolylmethyl ester, (3*R*,6*R*,9*S*)-.

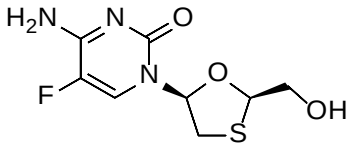
It has a molecular formula of $C_{40}H_{53}N_7O_5S_2$ and a molecular weight of 776.02. It has the following structural formula:



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

Emtricitabine: The chemical name of emtricitabine is 4-amino-5-fluoro-1-(2*R*-hydroxymethyl-1,3-oxathiolan-5*S*-yl)-(1*H*)-pyrimidin-2-one. 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.

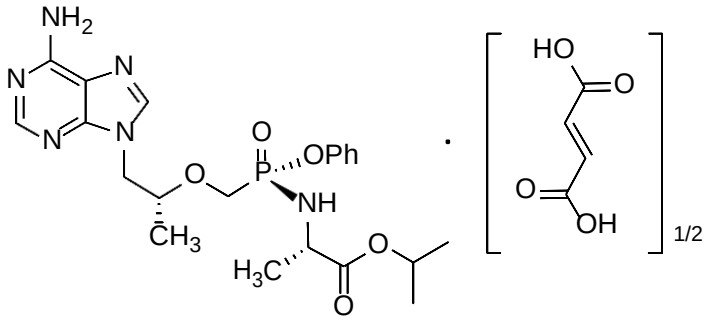
It has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24. It has the following structural formula:



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

Tenofovir alafenamide (TAF): The chemical name of tenofovir alafenamide fumarate drug substance is L-alanine, *N*-[(*S*)-[[(1*R*)-2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester, (2*E*)-2-butenedioate (2:1).

It has an empirical formula of $C_{21}H_{29}O_5N_6P \bullet ½(C_4H_4O_4)$ and a formula weight of 534.5. It has the following structural formula:



Tenofovir alafenamide fumarate is a white to off-white or tan powder with a solubility of 4.7 mg per mL in water at 20 °C.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

GENVOYA is a fixed-dose combination of antiretroviral drugs elvitegravir (plus the CYP3A inhibitor cobicistat), emtricitabine, and tenofovir alafenamide *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Cardiac Electrophysiology

Thorough QT studies have been conducted for elvitegravir, cobicistat, and TAF. The effect of emtricitabine or the combination regimen GENVOYA 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 GENVOYA) 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 GENVOYA) 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 GENVOYA fixed-dose combination tablet is lower than the lowest dose

studied in the thorough QT study, it is unlikely that treatment with GENVOYA will result in clinically relevant PR prolongation.

Tenofovir Alafenamide (TAF): In a thorough QT/QTc study in 48 healthy subjects, TAF at the therapeutic dose or at a supratherapeutic dose approximately 5 times the recommended therapeutic dose did not affect the QT/QTc interval and did not prolong the PR interval.

Effects on Serum Creatinine

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

12.3 Pharmacokinetics

Absorption, Distribution, Metabolism, and Excretion

The pharmacokinetic (PK) properties of the components of GENVOYA are provided in Table 6. The multiple dose PK parameters of elvitegravir, cobicistat, emtricitabine, TAF and its metabolite tenofovir are provided in Table 7.

Table 6 Pharmacokinetic Properties of the Components of GENVOYA

	Elvitegravir	Cobicistat	Emtricitabine	TAF
Absorption				
T_{max} (h)	4	3	3	1
Effect of light meal (relative to fasting): AUC Ratio[a]	1.34 (1.19, 1.51)	1.03 (0.90, 1.17)	0.95 (0.91, 1.00)	1.15 (1.07, 1.24)
Effect of high fat meal (relative to fasting): AUC Ratio[a]	1.87 (1.66, 2.10)	0.83 (0.73, 0.95)	0.96 (0.92, 1.00)	1.18 (1.09, 1.26)
Distribution				
% Bound to human plasma proteins	~99	~98	<4	~80
Source of protein binding data	*Ex vivo*	*In vitro*	*In vitro*	*Ex vivo*
Blood-to-plasma ratio	0.73	0.5	0.6	1.0
Metabolism				
Metabolism	CYP3A (major) UGT1A1/3 (minor)	CYP3A (major) CYP2D6 (minor)	Not significantly metabolized	Cathepsin A[b] (PBMCs) CES1 (hepatocytes) CYP3A (minimal)
Elimination				
Major route of elimination	Metabolism	Metabolism	Glomerular filtration and active tubular secretion	Metabolism (>80% of oral dose)
$t_{1/2}$ (h)[c]	12.9	3.5	10	0.51
% Of dose excreted in urine[d]	6.7	8.2	70	<1%
% Of dose excreted in feces[d]	94.8	86.2	13.7	31.7

PBMCs = peripheral blood mononuclear cells; CES1 = carboxylesterase 1.

a. Values refer to geometric mean ratio in AUC [fed / fasted] and (90% confidence interval). Elvitegravir light meal=~373 kcal, 20% fat; GENVOYA light meal=~400 kcal, 20% fat; elvitegravir and GENVOYA high fat meal=~800 kcal, 50% fat. Based on the effect of food on elvitegravir, GENVOYA should be taken with food.

b. *In vivo,* TAF is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. *In vitro* studies have shown that TAF is metabolized to tenofovir by cathepsin A in PBMCs and macrophages; and by CES1 in hepatocytes. Upon coadministration with the moderate CYP3A inducer probe efavirenz, TAF exposure was not significantly affected.

c. $t_{1/2}$ values refer to median terminal plasma half-life. Note that the pharmacologically active metabolite, tenofovir diphosphate, has a half-life of 150–180 hours within PBMCs.

d. Dosing in mass balance studies: elvitegravir (single dose administration of [^{14}C] elvitegravir coadministered with 100 mg ritonavir); 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); TAF (single dose administration of [^{14}C] TAF).

Table 7 Multiple Dose Pharmacokinetic Parameters of Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Alafenamide (TAF) and its Metabolite Tenofovir Following Oral Administration of GENVOYA with Food in HIV-Infected Adults

Parameter Mean (CV%)	Elvitegravir[a]	Cobicistat[a]	Emtricitabine[a]	TAF[b]	Tenofovir[c]
C_{max} (microgram per mL)	2.1 (33.7)	1.5 (28.4)	2.1 (20.2)	0.16 (51.1)	0.02 (26.1)
AUC_{tau} (microgram•hour per mL)	22.8 (34.7)	9.5 (33.9)	11.7 (16.6)	0.21 (71.8)	0.29 (27.4)
C_{trough} (microgram per mL)	0.29 (61.7)	0.02 (85.2)	0.10 (46.7)	NA	0.01 (28.5)

CV = Coefficient of Variation; NA = Not Applicable

a. From Intensive PK analysis in a Phase 2 trial in HIV infected adults, Study 102 (N=19).

b. From Population PK analysis in two trials of treatment-naïve adults with HIV-1 infection, Studies 104 and 111 (N=539).

c. From Population PK analysis in two trials of treatment-naïve adults with HIV-1 infection, Studies 104 and 111 (N=841).

Special Populations

Geriatric Patients

Pharmacokinetics of elvitegravir, cobicistat, emtricitabine and tenofovir have not been fully evaluated in the elderly (65 years of age and older). Age does not have a clinically relevant effect on exposures of TAF up to 75 years of age *[see Use in Specific Populations (8.5)]*.

Pediatric Patients

Mean exposures of elvitegravir, cobicistat, and TAF achieved in 24 pediatric subjects aged 12 to less than 18 years who received thedose of GENVOYA containing 150 mg EVG, 150 mg COBI, 200 mg FTC, and 10 mg TAF in Study 106 were decreased compared to exposures achieved in treatment-naïve adults receiving the same dose of GENVOYA, but were overall deemed acceptable based on exposure-response relationships; emtricitabine exposure in adolescents was similar to that in treatment-naïve adults (Table 8).

Table 8 Multiple Dose Pharmacokinetic Parameters of Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Alafenamide (TAF) and its Metabolite Tenofovir Following Oral Administration of GENVOYA in HIV-Infected Pediatric Subjects Aged 12 to less than 18 Years[a]

Parameter Mean (CV%)	Elvitegravir	Cobicistat	Emtricitabine	TAF	Tenofovir
C_{max} (microgram per mL)	2.2 (19.2)	1.2 (35.0)	2.3 (22.5)	0.17 (64.4)	0.02 (23.7)
AUC_{tau} (microgram•hour per mL)	23.8 (25.5)	8.2[b] (36.1)	14.4 (23.9)	0.20[b] (50.0)	0.29[b] (18.8)
C_{trough} (microgram per mL)	0.30 (81.0)	0.03[c] (180.0)	0.10[b] (38.9)	NA	0.01 (21.4)

CV = Coefficient of Variation; NA = Not Applicable

a. From Intensive PK analysis in a trial in treatment-naïve pediatric subjects with HIV-1 infection, cohort 1 of Study 106 (N=24).

b. N=23

c. N=15

Exposures of the components of GENVOYA achieved in 23 pediatric subjects between the ages of 6 to less than 12 years who received the dose of GENVOYA containing 150 mg EVG, 150 mg COBI, 200 mg FTC, and 10 mg TAF in Study 106 were higher (20 to 80% for AUC) than exposures achieved in adults receiving the same dose of GENVOYA; the increase was not considered clinically significant as the safety profiles were similar in adult and pediatric patients (Table 9) *[see Use in Specific Populations (8.4)]*.

Table 9 Multiple Dose Pharmacokinetic Parameters of Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Alafenamide (TAF) and its Metabolite Tenofovir Following Oral Administration of GENVOYA in HIV-Infected Pediatric Subjects Aged 6 to less than 12 Years[a]

Parameter Mean (CV%)	Elvitegravir	Cobicistat	Emtricitabine	TAF	Tenofovir
C_{max} (microgram per mL)	3.1 (38.7)	2.1 (46.7)	3.4 (27.0)	0.31 (61.2)	0.03 (20.8)
AUC_{tau} (microgram•hour per mL)	33.8[b] (57.8)	15.9[c] (51.7)	20.6[b] (18.9)	0.33 (44.8)	0.44 (20.9)
C_{trough} (microgram per mL)	0.37 (118.5)	0.1 (168.7)	0.11 (24.1)	NA	0.02 (24.9)

CV = Coefficient of Variation; NA = Not Applicable

a. From Intensive PK analysis in a trial in virologically-suppressed pediatric subjects with HIV-1 infection, cohort 2 of Study 106 (N=23).

b. N=22

c. N=20

Race, Gender

No clinically significant differences in pharmacokinetics of GENVOYA have been identified based on race or gender.

Patients with Renal Impairment

The pharmacokinetics of GENVOYA in HIV-1 infected subjects with mild or moderate renal impairment (estimated creatinine clearance between 30 and 69 mL per minute by Cockcroft-Gault method), and in HIV-1 infected subjects with ESRD (estimated creatinine clearance of less than 15 mL per minute by Cockcroft-Gault method) receiving chronic hemodialysis were evaluated in subsets of virologically suppressed subjects in respective open-label trials, Study 112 and Study 1825. The pharmacokinetics of elvitegravir, cobicistat, and tenofovir alafenamide were similar among healthy subjects, subjects with mild or moderate renal impairment, and subjects with ESRD receiving chronic hemodialysis; increases in emtricitabine and tenofovir exposures in subjects with renal impairment were not considered clinically relevant (Table 10).

Table 10 Pharmacokinetics of GENVOYA in HIV-Infected Adults with Renal Impairment as Compared to Subjects with Normal Renal Function

	AUC_{tau} (microgram•hour per mL) Mean (CV%)			
Estimated Creatinine Clearance[a]	**≥90 mL per minute (N=18)[b]**	**60–89 mL per minute (N=11)[c]**	**30–59 mL per minute (N=18)[d]**	**<15 mL per minute (N=12)[e]**
Emtricitabine	11.4 (11.9)	17.6 (18.2)	23.0 (23.6)	62.9 (48.0)[f]
Tenofovir	0.32 (14.9)	0.46 (31.5)	0.61 (28.4)	8.72 (39.4)[g]

a. By Cockcroft-Gault method.
b. From a Phase 2 study in HIV-infected adults with normal renal function.
c. These subjects from Study 112 had an estimated creatinine clearance between 60 and 69 mL per minute.
d. Study 112.
e. Study 1825; PK assessed prior to hemodialysis following 3 consecutive daily doses of GENVOYA.
f. N=11.
g. N=10.

Patients with Hepatic Impairment

Elvitegravir and Cobicistat: A study of the pharmacokinetics of elvitegravir (administered with the CYP3A inhibitor cobicistat) was performed in healthy subjects and subjects with moderate hepatic impairment (Child-Pugh Class B). No clinically relevant differences in elvitegravir or cobicistat pharmacokinetics were observed between subjects with moderate hepatic impairment and healthy subjects *[see Use in Specific Populations (8.7)]*.

Emtricitabine: The pharmacokinetics of emtricitabine has 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 Alafenamide (TAF): Clinically relevant changes in TAF and tenofovir pharmacokinetics were not observed in subjects with mild to moderate (Child-Pugh Class A and B) hepatic impairment *[see Use in Specific Populations (8.7)]*.

Hepatitis B and/or Hepatitis C Virus Co-infection

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 elvitegravir (administered with the CYP3A inhibitor cobicistat).

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 Alafenamide (TAF): Pharmacokinetics of emtricitabine and TAF have not been fully evaluated in subjects coinfected with hepatitis B and/or C virus.

Drug Interaction Studies

[see also Contraindications (4) and *Drug Interactions (7)]*

The drug-drug interaction studies described in Tables 11–14 were conducted with GENVOYA, elvitegravir (coadministered with cobicistat or ritonavir), cobicistat administered alone, or TAF (administered alone or coadministered with emtricitabine).

As GENVOYA should not be administered with other antiretroviral medications, information regarding drug-drug interactions with other antiretrovirals agents is not provided.

The effects of coadministered drugs on the exposure of elvitegravir, emtricitabine, and TAF are shown in Table 11, Table 12, and Table 13 respectively. The effects of GENVOYA or its components on the exposure of coadministered drugs are shown in Table 14. For information regarding clinical recommendations, see Drug Interactions (7).

Table 11 Drug Interactions: Changes in Pharmacokinetic Parameters for Elvitegravir in the Presence of the Coadministered Drug[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose (mg)	CYP3A Inhibitor Cobicistat or Ritonavir Dose (mg)	N	Mean Ratio of Elvitegravir Pharmacokinetic Parameters (90% CI); No effect = 1.00		
					C_{max}	AUC	C_{min}
Maximum strength antacid[b]	20 mL single dose given 4 hours before elvitegravir	50 single dose	Ritonavir 100 single dose	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			10	0.98 (0.88,1.10)	0.98 (0.91,1.06)	1.00 (0.90,1.11)
	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)
Atorvastatin	10 single dose	150 once daily[c]	Cobicistat 150 once daily[c]	16	0.91 (0.85,0.98)	0.92 (0.87,0.98)	0.88 (0.81,0.96)
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 (0.02,0.40)
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	Ritonavir 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[c]	Cobicistat 150 once daily[c]	30	0.98 (0.90,1.07)	1.11 (1.02,1.20)	1.46 (1.28,1.66)

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose (mg)	CYP3A Inhibitor Cobicistat or Ritonavir Dose (mg)	N	Mean Ratio of Elvitegravir Pharmacokinetic Parameters (90% CI); No effect = 1.00		
					C_{max}	AUC	C_{min}
Omeprazole	40 once daily given 2 hours before elvitegravir	50 once daily	Ritonavir 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)
Sertraline	50 single dose	150 once daily[c]	Cobicistat 150 once daily[c]	19	0.88 (0.82,0.93)	0.94 (0.89,0.98)	0.99 (0.93,1.05)
Sofosbuvir/ Velpatasvir	400/100 once daily	150 once daily[c]	Cobicistat 150 once daily[c]	24	0.87 (0.80,0.94)	0.94 (0.88,1.00)	1.08 (0.97,1.20)
Sofosbuvir/ Velpatasvir/ Voxilaprevir	400/100/100 + 100 Voxilaprevir[d] once daily	150 once daily[c]	Cobicistat 150 once daily[c]	29	0.79 (0.75,0.85)	0.94 (0.88,1.00)	1.32 (1.17,1.49)

a. All interaction studies conducted in healthy volunteers.

b. Maximum strength antacid contained 80 mg aluminum hydroxide, 80 mg magnesium hydroxide, and 8 mg simethicone, per mL.

c. Study conducted with GENVOYA.

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

Table 12 Drug Interactions: Changes in Pharmacokinetic Parameters for Emtricitabine in the Presence of the Coadministered Drug[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Emtricitabine Dose (mg)	N	Mean Ratio of Emtricitabine Pharmacokinetic Parameters (90% CI); No effect = 1.00		
				C_{max}	AUC	C_{min}
Famciclovir	500 single dose	200 single dose	12	0.90 (0.80,1.01)	0.93 (0.87,0.99)	NC

a. All interaction studies conducted in healthy volunteers.

Table 13 Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir Alafenamide (TAF) in the Presence of the Coadministered Drug[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	TAF Dose (mg)	N	Mean Ratio of TAF Pharmacokinetic Parameters (90% CI); No effect = 1.00		
				C_{max}	AUC	C_{min}
Cobicistat	150 once daily	8 once daily	12	2.83 (2.20,3.65)	2.65 (2.29,3.07)	NC
Ledipasvir/ Sofosbuvir	90/400 once daily	10 once daily[b]	30	0.90 (0.73,1.11)	0.86 (0.78,0.95)	NC
Sertraline	50 single dose	10 once daily[b]	19	1.00 (0.86,1.16)	0.96 (0.89,1.03)	NC
Sofosbuvir/ Velpatasvir	400/100 once daily	10 once daily[b]	24	0.80 (0.68,0.94)	0.87 (0.81,0.94)	NC
Sofosbuvir/ Velpatasvir/ Voxilaprevir	400/100/100 + 100 Voxilaprevir[c] once daily	10 once daily[b]	29	0.79 (0.68,0.92)	0.93 (0.85,1.01)	NC

NC = Not Calculated

a. All interaction studies conducted in healthy volunteers.

b. Study conducted with GENVOYA.

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

Table 14 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of GENVOYA or the Individual Components[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose (mg)	CYP3A Inhibitor Cobicistat Dose (mg)	FTC Dose (mg)	TAF Dose (mg)	N	Mean Ratio of Coadministered Drug Pharmacokinetic Parameters (90% CI); No effect = 1.00		
							C_{max}	AUC	C_{min}
Atorvastatin	10 single dose	150 once daily[c]	150 once daily[c]	200 once daily[c]	10 once daily[c]	16	2.32 (1.91,2.82)	2.60 (2.31,2.93)	NC
Buprenorphine	16 - 24 once daily	150 once daily	150 once daily	N/A	N/A	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	N/A	N/A	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)

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose (mg)	CYP3A Inhibitor Cobicistat Dose (mg)	FTC Dose (mg)	TAF Dose (mg)	N	Mean Ratio of Coadministered Drug Pharmacokinetic Parameters (90% CI); No effect = 1.00		
							C_{max}	AUC	C_{min}
Desipramine	50 single dose	N/A	150 once daily	N/A	N/A	8	1.24 (1.08,1.44)	1.65 (1.36,2.02)	NC
Digoxin	0.5 single dose	N/A	150 once daily	N/A	N/A	22	1.41 (1.29,1.55)	1.08 (1.00,1.17)	NC
Famciclovir	500 single dose	N/A	N/A	200 single dose	N/A	12	0.93 (0.78,1.11)	0.91 (0.84,0.99)	N/A
Ledipasvir	90 once daily	150 once daily[c]	150 once daily[c]	200 once daily[c]	10 once daily[c]	30	1.65 (1.53,1.78)	1.79 (1.64,1.96)	1.93 (1.74,2.15)
Sofosbuvir	400 once daily						1.28 (1.13,1.47)	1.47 (1.35,1.59)	N/A
GS-331007[b]							1.29 (1.24,1.35)	1.48 (1.44,1.53)	1.66 (1.60,1.73)
Naloxone	4–6 once daily	150 once daily	150 once daily	N/A	N/A	17	0.72 (0.61,0.85)	0.72 (0.59,0.87)	N/A
Norgestimate/ ethinyl estradiol[d]	0.180/0.215/ 0.250 norgestimate once daily	150 once daily[d]	150 once daily[d]	200 once daily[d]	N/A	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)
Norgestromin	0.180/0.215/ 0.250 norgestimate once daily / 0.025 ethinyl estradiol once daily	N/A	N/A	200 once daily[e]	25 once daily[e]	15	1.17 (1.07,1.26)	1.12 (1.07,1.17)	1.16 (1.08,1.24)
Norgestrel							1.10 (1.02,1.18)	1.09 (1.01,1.18)	1.11 (1.03,1.20)
Ethinyl estradiol							1.22 (1.15,1.29)	1.11 (1.07,1.16)	1.02 (0.92,1.12)
R-Methadone	80–120 daily	150 once daily	150 once daily	N/A	N/A	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)
Sertraline	50 single dose	150 once daily[c]	150 once daily[c]	200 once daily[c]	10 once daily[c]	19	1.14 (0.94,1.38)	0.93 (0.77,1.13)	N/A
Rifabutin	150 once every other day	150 once daily	150 once daily	N/A	N/A	12	1.09 (0.98,1.20)[f]	0.92 (0.83,1.03)[f]	0.94 (0.85,1.04)[f]
25-O-desacetyl-rifabutin						12	4.84 (4.09,5.74)[f]	6.25 (5.08,7.69)[f]	4.94 (4.04,6.04)[f]
Rosuvastatin	10 single dose	150 once daily	150 once daily	N/A	N/A	10	1.89 (1.48,2.42)	1.38 (1.14,1.67)	NC

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose (mg)	CYP3A Inhibitor Cobicistat Dose (mg)	FTC Dose (mg)	TAF Dose (mg)	N	Mean Ratio of Coadministered Drug Pharmacokinetic Parameters (90% CI); No effect = 1.00		
							C_{max}	AUC	C_{min}
Sofosbuvir	400 once daily	150 once daily[c]	150 once daily[c]	200 once daily[c]	10 once daily[c]	24	1.23 (1.07,1.42)	1.37 (1.24,1.52)	N/A
GS-331007[b]							1.29 (1.25,1.33)	1.48 (1.43,1.53)	1.58 (1.52,1.65)
Velpatasvir	100 once daily						1.30 (1.17,1.45)	1.50 (1.35,1.66)	1.60 (1.44,1.78)
Sofosbuvir	400 once daily	150 once daily[c]	150 once daily[c]	200 once daily[c]	10 once daily[c]	29	1.27 (1.09,1.48)	1.22 (1.12,1.32)	NC
GS-331007[b]							1.28 (1.25,1.32)	1.43 (1.39,1.47)	NC
Velpatasvir	100 once daily						0.96 (0.89,1.04)	1.16 (1.06,1.27)	1.46 (1.30,1.64)
Voxilaprevir	100 + 100[g] once daily						1.92 (1.63,2.26)	2.71 (2.30,3.19)	4.50 (3.68,5.50)

FTC = emtricitabine; TAF = tenofovir alafenamide

N/A = Not Applicable; NC = Not Calculated

a. All interaction studies conducted in healthy volunteers.

b. The predominant circulating inactive metabolite of sofosbuvir.

c. Study conducted with GENVOYA.

d. Study conducted with STRIBILD.

e. Study conducted with DESCOVY.

f. Comparison based on rifabutin 300 mg once daily.

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

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 reverse transcriptase 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, Ɛ, and mitochondrial DNA polymerase γ.

Tenofovir Alafenamide (TAF): TAF is a phosphonamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analog). Plasma exposure to TAF allows for permeation into cells and then TAF is intracellularly converted to tenofovir through hydrolysis by cathepsin A. Tenofovir is subsequently phosphorylated by cellular kinases to the active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV-1 replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination.

Tenofovir has activity that is specific to human immunodeficiency virus and hepatitis B virus. Cell culture studies have shown that both emtricitabine and tenofovir can be fully phosphorylated when combined in cells. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of mitochondrial toxicity in cell culture based on several assays including mitochondrial DNA analyses.

Antiviral Activity in Cell Culture

Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir Alafenamide (TAF): The combination of elvitegravir, emtricitabine, and TAF was not antagonistic in cell culture combination antiviral activity assays and was not affected by the addition of cobicistat. In addition, elvitegravir, cobicistat, emtricitabine, and TAF were not antagonistic with a panel of representatives from the major classes of approved anti-HIV-1 agents (INSTIs, NNRTIs, NRTIs, and PIs).

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 1.3 – 640 nM. Emtricitabine displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 7–75 nM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 7–1500 nM).

Tenofovir Alafenamide (TAF): The antiviral activity of TAF against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells and CD4-T lymphocytes. The EC_{50} values for TAF ranged from 2.0 to 14.7 nM.

TAF displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including sub-types A, B, C, D, E, F, and G (EC_{50} values ranged from 0.10 to 12.0 nM) and strain specific activity against HIV-2 (EC_{50} values ranged from 0.91 to 2.63 nM).

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: HIV-1 isolates with reduced susceptibility to emtricitabine have been selected in cell culture. Reduced susceptibility to emtricitabine was associated with M184V or I substitutions in HIV-1 RT.

Tenofovir Alafenamide (TAF): HIV-1 isolates with reduced susceptibility to TAF have been selected in cell culture. HIV-1 isolates selected by TAF expressed a K65R substitution in HIV-1 RT, sometimes in the presence of S68N or L429I substitutions; in addition, a K70E substitution in HIV-1 RT was observed.

In Clinical Trials

In Treatment-Naïve Subjects:

In a pooled analysis of antiretroviral-naïve subjects receiving GENVOYA in Studies 104 and 111, genotyping was performed on plasma HIV-1 isolates from all subjects with HIV-1 RNA greater than 400 copies per mL at confirmed virologic failure, at Week 144, or at time of early study drug discontinuation. As of Week 144, the development of genotypic resistance to elvitegravir, emtricitabine, or TAF was observed in 12 of 22 subjects with evaluable resistance data from paired baseline and GENVOYA treatment-failure isolates (12 of 866 subjects [1.4%]) compared with 13 of 20 treatment-failure isolates from subjects with evaluable resistance data in the STRIBILD treatment group (13 of 867 subjects [1.5%]). Of the 12 subjects with resistance development in the GENVOYA group, the resistance-associated substitutions that emerged were M184V/I (N=11) and K65R/N (N=2) in reverse transcriptase and T66T/A/I/V (N=2), E92Q (N=4), E138K (N=1), Q148Q/R (N=1) and N155H (N=2) in integrase. Of the 13 subjects with resistance development in the STRIBILD group, the resistance-associated substitutions that emerged were M184V/I (N=9), K65R/N (N=4), and L210W (N=1) in reverse transcriptase and E92Q/V (N=4), E138K (N=3), Q148R (N=2), and N155H/S (N=3) in integrase. In both treatment groups, most subjects who

developed substitutions associated with resistance to elvitegravir also developed emtricitabine resistance-associated substitutions. These genotypic resistance results were confirmed by phenotypic analyses.

In Virologically Suppressed Subjects:

Three virologic failure subjects were identified with emergent genotypic and phenotypic resistance to GENVOYA (all three with M184I or V and one with K219Q in reverse transcriptase; two with E92Q or G in integrase) out of 8 virologic failure subjects with resistance data in a clinical study of virologically-suppressed subjects who switched from a regimen containing emtricitabine/TDF and a third agent to GENVOYA (Study 109, N=959).

Cross-Resistance

No cross-resistance has been demonstrated for elvitegravir-resistant HIV-1 isolates and emtricitabine or tenofovir, or for emtricitabine- or tenofovir-resistant isolates and elvitegravir.

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 amino acid 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). Some viruses expressing elvitegravir or raltegravir resistance amino acid substitutions maintain susceptibility to dolutegravir.

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 Alafenamide (TAF): Tenofovir resistance substitutions, K65R and K70E, result in reduced susceptibility to abacavir, didanosine, emtricitabine, lamivudine, and tenofovir.

HIV-1 with multiple TAMs (M41L, D67N, K70R, L210W, T215F/Y, K219Q/E/N/R), or multinucleoside resistant HIV-1 with a T69S double insertion mutation or with a Q151M mutation complex including K65R, showed reduced susceptibility to TAF in cell culture.

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 times, 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 times, 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 times higher exposures (AUC), respectively, than in humans 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 18 times 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 recommended daily dose.

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

Cobicistat did not affect fertility in male or female rats at daily exposures (AUC) approximately 4 times 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 times 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 recommended dose).

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

Emtricitabine did not affect fertility in male rats at approximately 140 times or in male and female mice at approximately 60 times 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 times higher than human exposures at the recommended 200 mg daily dose.

Tenofovir Alafenamide (TAF)

Since TAF is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice is observed after TAF administration compared to TDF administration, carcinogenicity studies were conducted only with TDF. Long-term oral carcinogenicity studies of TDF 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 300 mg therapeutic dose of TDF for HIV-1 infection. The tenofovir exposure in these studies was approximately 167 times (mice) and 55 times (rat) those observed in humans after administration of GENVOYA treatment. At the high dose in female mice, liver adenomas were increased at tenofovir exposures 10 times (300 mg TDF) and 167 times (10 mg TAF in GENVOYA) that in humans. In rats, the study was negative for carcinogenic findings.

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

There were no effects on fertility, mating performance or early embryonic development when TAF was administered to male rats at a dose equivalent to 155 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 14 days prior to mating through Day 7 of gestation.

13.2 Animal Toxicology and/or Pharmacology

Minimal to slight infiltration of mononuclear cells in the posterior uvea was observed in dogs with similar severity after three and nine month administration of TAF; reversibility was seen after a three month recovery period. At the NOAEL for eye toxicity, the

systemic exposure in dogs was 5 (TAF) and 15 (tenofovir) times the exposure seen in humans at the recommended daily GENVOYA dosage.

14 CLINICAL STUDIES

14.1 Description of Clinical Trials

The efficacy and safety of GENVOYA were evaluated in the studies summarized in Table 15.

Table 15 Trials Conducted with GENVOYA in Subjects with HIV-1 Infection

Trial	Population	Study Arms (N)	Timepoint (Week)
Study 104[a] Study 111[a]	Treatment-naïve adults	GENVOYA (866) STRIBILD (867)	144
Study 109[b]	Virologically-suppressed[d] adults	GENVOYA (959) ATRIPLA® or TRUVADA®+atazanavir+cobicistat or ritonavir or STRIBILD (477)	96
Study 112[c]	Virologically-suppressed[d] adults with renal impairment[e]	GENVOYA (242)	144
Study 1825[c]	Virologically-suppressed[d] adults with ESRD[f] receiving chronic hemodialysis	GENVOYA (55)	48
Study 106 (cohort 1)[c]	Treatment-naïve adolescents between the ages of 12 to less than 18 years (at least 35 kg)	GENVOYA (50)	48
Study 106 (cohort 2)[c]	Virologically-suppressed[d] children between the ages of 6 to less than 12 years (at least 25 kg)	GENVOYA (52)	48

a. Randomized, double blind, active controlled trial.

b. Randomized, open label, active controlled trial.

c. Open label trial.

d. HIV-1 RNA less than 50 copies per mL.

e. Estimated creatinine clearance between 30 and 69 mL per minute by Cockcroft-Gault method.

f. End stage renal disease (estimated creatinine clearance of less than 15 mL per minute by Cockcroft-Gault method).

14.2 Clinical Trial Results in HIV-1 Treatment-Naïve Subjects

In both Study 104 and Study 111, subjects were randomized in a 1:1 ratio to receive either GENVOYA (N=866) once daily or STRIBILD (elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, TDF 300 mg) (N=867) once daily. The mean age was 36 years (range 18–76), 85% were male, 57% were White, 25% were Black, and 10% were Asian. Nineteen percent of subjects identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.5 $\log_{10}$ copies per mL (range 1.3–7.0) and 23% of subjects had baseline viral loads greater than 100,000 copies per mL. The mean baseline CD4+ cell count was 427 cells per mm^3 (range 0–1360) and 13% had CD4+ cell counts less than 200 cells per mm^3.

Pooled treatment outcomes of Studies 104 and 111 through Week 144 are presented in Table 16.

Table 16 Pooled Virologic Outcomes of Randomized Treatment in Studies 104 and 111 at Week 144[a] in Treatment-Naïve Subjects

	GENVOYA (N=866)	STRIBILD (N=867)
HIV-1 RNA < 50 copies/mL[b]	84%	80%
HIV-1 RNA ≥ 50 copies/mL[c]	5%	4%
No Virologic Data at Week 144 Window	11%	16%
Discontinued Study Drug Due to AE or Death[d]	2%	3%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[e]	9%	11%
Missing Data During Window but on Study Drug	1%	1%

a. Week 144 window was between Day 966 and 1049 (inclusive).

b. The primary endpoint was assessed at Week 48 and the virologic success rate was 92% in the GENVOYA group and 90% in the STRIBILD group, with a treatment difference of 2.0% (95% CI: -0.7% to 4.7%). The difference at Week 144 was primarily driven by discontinuations due to other reasons with last available HIV-1 RNA <50 copies/mL.

c. Included 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 (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.

d. Includes subjects who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

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

Treatment outcomes were similar across subgroups by age, sex, race, baseline viral load, and baseline CD4+ cell count.

In Studies 104 and 111, the mean increase from baseline in CD4+ cell count at Week 144 was 326 cells per mm^3 in GENVOYA-treated subjects and 305 cells per mm^3 in STRIBILD-treated subjects.

14.3 Clinical Trial Results in HIV-1 Virologically-Suppressed Adults Who Switched to GENVOYA

In Study 109, the efficacy and safety of switching from ATRIPLA, TRUVADA plus atazanavir (given with either cobicistat or ritonavir), or STRIBILD to GENVOYA once daily were evaluated in a randomized, open-label trial of virologically-suppressed (HIV-1 RNA less than 50 copies per mL) HIV-1 infected adults (N=1436). Subjects must have been suppressed (HIV-1 RNA less than 50 copies per mL) on their baseline regimen for at least 6 months and had no known resistance-associated substitutions to any of the components of GENVOYA prior to study entry. Subjects were randomized in a 2:1 ratio to either switch to GENVOYA at baseline (N=959), or stay on their baseline antiretroviral regimen (N=477). Subjects had a mean age of 41 years (range 21–77), 89% were male, 67% were White, and 19% were Black. The mean baseline CD4+ cell count was 697 cells per mm^3 (range 79–1951).

Subjects were stratified by prior treatment regimen. At screening, 42% of subjects were receiving TRUVADA plus atazanavir (given with either cobicistat or ritonavir), 32% were receiving STRIBILD, and 26% were receiving ATRIPLA.

Treatment outcomes of Study 109 through 96 weeks are presented in Table 17.

Table 17 Virologic Outcomes of Study 109 at Week 96[a] in Virologically-Suppressed Adults who Switched to GENVOYA

	GENVOYA (N=959)	ATRIPLA or TRUVADA+atazanavir +cobicistat or ritonavir or STRIBILD (N=477)
HIV-1 RNA < 50 copies/mL	93%	89%
HIV-1 RNA ≥ 50 copies/mL[b]	2%	2%
No Virologic Data at Week 48 Window	5%	9%
Discontinued Study Drug Due to AE or Death[c]	1%	3%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[d]	3%	6%
Missing Data During Window but on Study Drug	1%	<1%

a. Week 96 window was between Day 630 and 713 (inclusive).

b. Included subjects who had ≥50 copies/mL in the Week 96 window; subjects who discontinued early due to lack or loss of efficacy; subjects who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥50 copies/mL.

c. Includes subjects who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

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

Treatment outcomes were similar across subgroups receiving ATRIPLA, TRUVADA plus atazanavir (given with either cobicistat or ritonavir), or STRIBILD prior to

randomization. In Study 109, the mean increase from baseline in CD4+ cell count at Week 96 was 60 cells per mm^3 in GENVOYA-treated subjects and 42 cells per mm^3 in subjects who stayed on their baseline regimen.

14.4 Clinical Trial Results in HIV-1 Infected Subjects with Renal Impairment

Study 112: Virologically-suppressed adults with renal impairment

In Study 112, the efficacy and safety of GENVOYA once daily were evaluated in an open-label clinical trial of 248 HIV-1 infected subjects with renal impairment (estimated creatinine clearance between 30 and 69 mL per minute by Cockcroft-Gault method). Of the 248 enrolled, 6 were treatment-naïve and 242 were virologically suppressed (HIV-1 RNA less than 50 copies per mL) for at least 6 months before switching to GENVOYA *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

The mean age was 58 years (range 24–82), with 63 subjects (26%) who were 65 years of age or older. Seventy-nine percent were male, 63% were White, 18% were Black, and 14% were Asian. Thirteen percent of subjects identified as Hispanic/Latino. The mean baseline CD4+ cell count was 664 cells per mm^3 (range 126–1813). At Week 144, 81% (197/242 virologically suppressed subjects) maintained HIV-1 RNA less than 50 copies per mL after switching to GENVOYA. All six treatment-naïve subjects were virologically suppressed at Week 144. Five subjects among the entire study population had virologic failure at Week 144.

Study 1825: Virologically-suppressed adults with end stage renal disease (ESRD) receiving chronic hemodialysis

In Study 1825, the efficacy and safety of GENVOYA once daily were evaluated in an open-label clinical trial of 55 virologically-suppressed (HIV-1 RNA less than 50 copies per mL for at least 6 months before switching to GENVOYA) HIV-1 infected subjects with ESRD (estimated creatinine clearance of less than 15 mL per minute by Cockcroft-Gault method) receiving chronic hemodialysis for at least 6 months *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

Subjects had a mean age of 48 years (range 23–64), 76% were male, 82% were Black, 18% were White, and 15% identified as Hispanic/Latino. The mean baseline CD4+ cell count was 545 cell per mm^3 (range 205–1473). At Week 48, 82% (45/55) maintained HIV-1 RNA less than 50 copies per mL after switching to GENVOYA. Two subjects had HIV-1 RNA ≥ 50 copies per mL by Week 48. Seven subjects discontinued the study drug due to AE or other reasons while suppressed. One subject did not have an HIV-1 RNA measurement at Week 48.

14.5 Clinical Trial Results in HIV-1 Infected Pediatric Subjects Between the Ages of 6 to Less than 18 Years

In Study 106, an open-label, single arm trial the efficacy, safety, and pharmacokinetics of GENVOYA in HIV-1 infected pediatric subjects were evaluated in treatment-naïve adolescents between the ages of 12 to less than 18 years weighing at least 35 kg (N=50) and in virologically-suppressed children between the ages of 6 to less than 12 years weighing at least 25 kg (N=52).

Cohort 1: Treatment-naïve adolescents (12 to less than 18 years; at least 35 kg)

Subjects in cohort 1 treated with GENVOYA once daily had a mean age of 15 years (range 12-17); 44% were male, 12% were Asian, and 88% were Black. At baseline, mean plasma HIV-1 RNA was 4.6 $\log_{10}$ copies per mL (22% had baseline plasma HIV-1 RNA greater than 100,000 copies per mL), mean (SD) CD4+ cell count was 471 (212.2) cells per mm^3, and mean (SD) CD4+ percentage was 23.6% (8.8%).

In subjects in cohort 1 treated with GENVOYA, 92% (46/50) achieved HIV-1 RNA less than 50 copies per mL at Week 48. The mean increase from baseline in CD4+ cell count at Week 48 was 224 cells per mm^3. Three of 50 subjects had virologic failure at Week 48; no emergent resistance to GENVOYA was detected through Week 48.

Cohort 2: Virologically-suppressed children (6 to less than 12 years; at least 25 kg)

Subjects in cohort 2 treated with GENVOYA once daily had a mean age of 10 years (range: 7-11), a mean baseline weight of 31.7 kg, 42% were male, 25% were Asian, and 71% were Black. At baseline, the mean (SD) CD4+ cell count was 961 (275.5) cells per mm^3 and the mean (SD) CD4 percentage was 38.2% (6.4%). After switching to GENVOYA, 98% (51/52) of subjects in cohort 2 remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 48. No subject qualified for resistance analysis through Week 48. The mean change from baseline in CD4+ cell count was -66 (203.6) cells per mm^3 and the mean (SD) change in CD4 percentage was -0.6% (4.4%) at Week 48. All subjects maintained CD4+ cell counts above 400 cells/mm^3 *[see Adverse Reactions (6.1) and Pediatric Use (8.4)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

GENVOYA tablets are available in bottles containing 30 tablets with a silica gel desiccant, polyester coil, and child-resistant closure as follows:

- GENVOYA tablets each contain 150 mg of elvitegravir (EVG), 150 mg of cobicistat (COBI), 200 mg of emtricitabine (FTC), and 10 mg of tenofovir alafenamide (TAF). These tablets are green, capsule-shaped, film-coated, debossed with “GSI” on one side of the tablet and the number “510” on the other side (NDC 42067-125-01).

Store below 30 °C (86 °F).

- Keep container tightly closed.
- Dispense only in original container.

This drug was imported from Canada without the authorization of Gilead Sciences, Inc. under the State of Florida Section 804 Importation Program.

Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

17 PATIENT COUNSELING INFORMATION

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

Drug Interactions

GENVOYA may interact with many drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or non-prescription medication or herbal products including St. John's wort *[see Contraindications (4) and Drug Interactions (7)]*.

Post-treatment Acute Exacerbation of Hepatitis B in Patients with HBV Co-Infection

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued products containing emtricitabine and/or TDF, and may likewise occur with discontinuation of GENVOYA *[see Warnings and Precautions (5.1)]*. Advise the patient to not discontinue GENVOYA without first informing their healthcare provider.

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any symptoms of infection, as 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 *[see Warnings and Precautions (5.3)]*.

Renal Impairment

Advise patients to avoid taking GENVOYA with concurrent or recent use of nephrotoxic agents. Postmarketing cases of renal impairment, including acute renal failure, have been reported *[see Warnings and Precautions (5.4)].*

Lactic Acidosis and Severe Hepatomegaly

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with use of drugs similar to GENVOYA. Advise patients that they should stop GENVOYA if they develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity *[see Warnings and Precautions (5.5)]*.

Missed Dosage

Inform patients that it is important to take GENVOYA on a regular dosing schedule with food and to avoid missing doses as it can result in development of resistance *[see Dosage and Administration (2.2)]*.

Pregnancy

Advise patients that GENVOYA is not recommended during pregnancy and to alert their healthcare provider if they become pregnant while taking GENVOYA *[see*

Dosage and Administration (2.5) and Use in Specific Populations (8.1)]. Inform

patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant individuals exposed to GENVOYA *[see Use in Specific Populations (8.1)]*.

Lactation

Instruct patients with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in breast milk *[see Use in Specific Populations (8.2)].*

Manufactured and distributed by: Gilead Sciences, Inc. Foster City, CA 94404

Patient Information

GENVOYA® (jen-VOY-uh)
(elvitegravir, cobicistat, emtricitabine,
and tenofovir alafenamide)
tablets

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

What is the most important information I should know about GENVOYA?
GENVOYA can cause serious side effects, including:

- **Worsening of hepatitis B virus (HBV) infection. Your healthcare provider will test you for HBV infection before or when you start treatment with GENVOYA. If you have HBV infection and take GENVOYA, your HBV may get worse (flare-up) if you stop taking GENVOYA. A "flare-up" is when your HBV infection suddenly returns in a worse way than before.**
  - Do not run out of GENVOYA. Refill your prescription or talk to your healthcare provider before your GENVOYA is all gone.
  - Do not stop taking GENVOYA without first talking to your healthcare provider.
  - If you stop taking GENVOYA, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your liver, and may give you a medicine to treat hepatitis B. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking GENVOYA.

For more information about side effects, see "What are the possible side effects of GENVOYA?"

What is GENVOYA?

GENVOYA is a prescription medicine that is used without other human immunodeficiency virus-1 (HIV-1) medicines to treat HIV-1 infection in adults and children who weigh at least 55 pounds (25 kg):

- who have not received HIV-1 medicines in the past, **or**
- to replace their current HIV-1 medicines for people whose healthcare provider determines that they meet certain requirements.

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

GENVOYA contains the prescription medicines elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide.

It is not known if GENVOYA is safe and effective in children who weigh less than 55 pounds (25 kg).

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

- alfuzosin hydrochloride
- carbamazepine
- ergot-containing medicines, including:
  - dihydroergotamine mesylate
  - ergotamine tartrate
  - methylergonovine maleate
- lomitapide
- lovastatin
- lurasidone
- midazolam, when taken by mouth
- phenobarbital
- phenytoin
- pimozide
- rifampin
- sildenafil, when used for treating the lung problem, pulmonary arterial hypertension
- simvastatin
- triazolam
- St. John's wort (*Hypericum perforatum)* or a product that contains St. John's wort.

What should I tell my healthcare provider before taking GENVOYA?

Before taking GENVOYA, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems, including HBV infection
- have kidney problems
- are pregnant or plan to become pregnant.
  - It is not known if GENVOYA can harm your unborn baby.
  - GENVOYA should not be used during pregnancy because you may not have enough GENVOYA in your body during pregnancy.
  - Tell your healthcare provider if you become pregnant during treatment with GENVOYA. Your healthcare provider may prescribe different medicines if you become pregnant while taking GENVOYA.

Pregnancy Registry: There is a pregnancy registry for women who take antiretroviral 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 GENVOYA.
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  - At least one of the medicines in GENVOYA can pass to your baby in your breast milk. It is not known if the other medicines in GENVOYA can pass into your breast milk.

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

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 GENVOYA. 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 GENVOYA.
- Do not start a new medicine without telling your healthcare provider. Your healthcare provider can tell you if it is safe to take GENVOYA with other medicines.

How should I take GENVOYA?

- Take GENVOYA exactly as your healthcare provider tells you to take it. GENVOYA is taken by itself (not with other HIV-1 medicines) to treat HIV-1 infection.
- Take GENVOYA 1 time each day with food.
- If you are on dialysis, take your daily dose of GENVOYA following dialysis.
- Do not change your dose or stop taking GENVOYA without first talking with your healthcare provider. Stay under a healthcare provider's care during treatment with GENVOYA.
- If you need to take a medicine for indigestion (antacid) that contains aluminum hydroxide, magnesium hydroxide, or calcium carbonate during treatment with GENVOYA, take it at least 2 hours before or after you take GENVOYA.
- Do not miss a dose of GENVOYA.
- When your GENVOYA 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 GENVOYA and become harder to treat.
- If you take too much GENVOYA, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of GENVOYA?
GENVOYA may cause serious side effects, including:

- **See "What is the most important information I should know about GENVOYA?"**
- **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.
- **New or worse kidney problems, including kidney failure.** Your healthcare provider should do blood and urine tests to check your kidneys when starting and during treatment with GENVOYA. Your healthcare provider may tell you to stop taking GENVOYA if you develop new or worse kidney problems.
- **Too much lactic acid in your blood (lactic acidosis).** Too much lactic acid is a serious but rare medical emergency that can lead to death. Tell your healthcare provider right away if you get these symptoms: weakness or being more tired than usual, unusual muscle pain, being short of breath or fast breathing, stomach pain with nausea and vomiting, cold or blue hands and feet, feel dizzy or lightheaded, or a fast or abnormal heartbeat.
- **Severe liver problems.** In rare cases, severe liver problems can happen that can lead to death. Tell your healthcare provider right away if you get these symptoms: skin or the white part of your eyes turns yellow, dark "tea-colored" urine, light-colored stools, loss of appetite for several days or longer, nausea, or stomach-area pain.

The most common side effect of GENVOYA is nausea.

These are not all the possible side effects of GENVOYA.

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 GENVOYA?

- Store GENVOYA below 86°F (30°C).
- Keep GENVOYA in its original container.
- Keep the container tightly closed.

Keep GENVOYA and all medicines out of reach of children.

General information about the safe and effective use of GENVOYA.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use GENVOYA for a condition for which it was not prescribed. Do not give GENVOYA to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about GENVOYA that is written for health professionals.

What are the ingredients in GENVOYA?
Active ingredients: elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide
Inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, silicon dioxide, and sodium lauryl sulfate. The tablets are film-coated with a coating material containing FD&C Blue No. 2/indigo carmine aluminum lake, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Manufactured and distributed by: Gilead Sciences, Inc. Foster City, CA 94404

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

This Patient Information has been approved by the U.S. Food and Drug Administration Revised: 01/2022

This drug was imported from Canada without the authorization of Gilead Sciences, Inc. under the State of Florida Section 804 Importation Program. Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

Annotated Label Comparisons

PI Comparisons FDA VS. FLCPDIP
Differences
Updated information Adverse Reactions Contact
How Supplied/Storage and Handling added SIP804 language
Patient Information added SIP804 language
Listed new NDC #
Added Importation language & Importer name & address
Listed only drug strength purchased for program

FDA

----------ADVERSE REACTIONS ----------

Most common adverse reaction (incidence greater than or equal to 10%, all grades) is nausea. (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.

16 HOW SUPPLIED/STORAGE AND HANDLING

GENVOYA tablets are available in bottles containing 30 tablets with a silica gel desiccant, polyester coil, and child-resistant closure as follows:

- GENVOYA tablets each contain 150 mg of elvitegravir (EVG), 150 mg of cobicistat (COBI), 200 mg of emtricitabine (FTC), and 10 mg of tenofovir alafenamide (TAF). These tablets are green, capsule-shaped, film-coated, debossed with "GSI" on one side of the tablet and the number "510" on the other side (NDC 61958-1901-1).

Store below 30 °C (86 °F).

- Keep container tightly closed.
- Dispense only in original container.

What are the ingredients in GENVOYA?
Active ingredients: elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide
Inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, silicon dioxide, and sodium lauryl sulfate. The tablets are film-coated with a coating material containing FD&C Blue No. 2/indigo carmine aluminum lake, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.
Manufactured and distributed by: Gilead Sciences, Inc. Foster City, CA 94404
GENVOYA is a trademark of Gilead Sciences, Inc., or its related companies.
 207561-GS--017
For more information, call 1-800-445-3235 or go to www.GENVOYA.com.
This Patient Information has been approved by the U.S. Food and Drug Administration Revised: 01/2022

FLSIP

----------ADVERSE REACTIONS ----------

Most common adverse reaction (incidence greater than or equal to 10%, all grades) is nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact LifeScience Logistics at 1-855-738-6171 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

16 HOW SUPPLIED/STORAGE AND HANDLING

GENVOYA tablets are available in bottles containing 30 tablets with a silica gel desiccant, polyester coil, and child-resistant closure as follows:

- GENVOYA tablets each contain 150 mg of elvitegravir (EVG), 150 mg of cobicistat (COBI), 200 mg of emtricitabine (FTC), and 10 mg of tenofovir alafenamide (TAF). These tablets are green, capsule-shaped, film-coated, debossed with "GSI" on one side of the tablet and the number "510" on the other side (NDC 42067-125-01).

Store below 30 °C (86 °F).

- Keep container tightly closed.
- Dispense only in original container.

This drug was imported from Canada without the authorization of Gilead Sciences, Inc. under the State of Florida Section 804 Importation Program.

Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

What are the ingredients in GENVOYA?
Active ingredients: elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide
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Manufactured and distributed by: Gilead Sciences, Inc. Foster City, CA 94404
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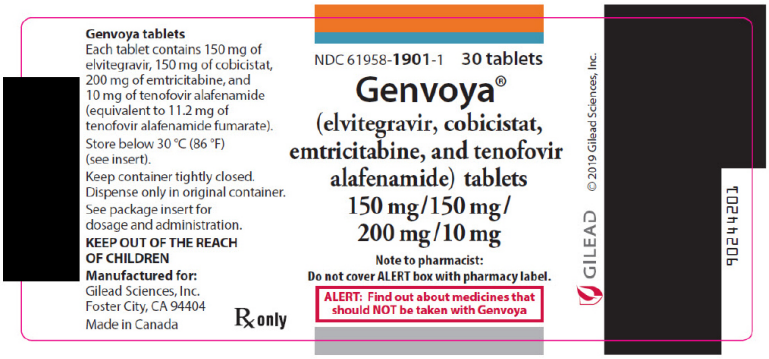
For more information, call 1-800-445-3235 or go to www.GENVOYA.com.
This Patient Information has been approved by the U.S. Food and Drug Administration Revised: 01/2022

This drug was imported from Canada without the authorization of Gilead Sciences, Inc. under the State of Florida Section 804 Importation Program. Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

Proposed Package Label



Label Comparisons FDA VS. FLCPDIP
Differences
NDC
GTN
Bar Codes FPO with Associated NDCs
SIP804 Importation Language
Label SIZE due to production process & adding SIP804 language
Importer Name & Address
Brand logos FPO low resolution. Native art files requested upon SIP804 approval.

Comparisons
FDA to FLSIP

Recent FDA Approved Label	US Proprietary Name	US Generic Name	US Strength	NDC	NDA or ANDA	Applicant Holder Name	Applicant Holder Address	US Active Ingredients	Date Labeling Prepared for FLSIP	LSL Proprietary Name	LSL Generic Name	FLSIP Strength	LSL NDC	LSL Relabeler Name	Applicant Holder Name	Applicant Holder Address	FLSIP Active Ingredients	FDA Comments
1/31/2022	Genvoya	Elvitegravir-cobicistat-emtricitabine-tenofovir alafenamide	150-150-200-10 mg	61958-1901-1	207561	Gilead Sciences, Inc.	Foster City, CA 94404	Elvitegravir-cobicistat-emtricitabine-tenofovir alafenamide	Mar-23	Genvoya	Elvitegravir-cobicistat-emtricitabine-tenofovir alafenamide	150-150-200-10 mg	42067-115-01	LifeScience Logistics, LLC	Gilead Sciences, Inc.	Foster City, CA 94404	Elvitegravir-cobicistat-emtricitabine-tenofovir alafenamide	n/a

Canadian and FDA Comparison

Comparisons
Canada to FDA

Active Ingredient	Canadian Submission Number	Canadian Proprietary Name	Canadian Generic Name	DIN	Date Labeling Approved	Company Name	Address	Canadian Strength	Dosage Form	# of active Ingred.	Canadian Ingredients	US Proprietary Name	US Generic Name	US Strength	NDC	NDA or ANDA	Applicant Holder Name	US Ingredients	Comments for FDA
COBICISTAT,EMTRICITABINE,TENOFOVIR ALAFENAMIDE (TENOFOVIR ALAFENAMIDE HEMIFUMARATE), EMTRICITABINE	250387	Genvoya	Elviteg-cob-emtri-tenof alafen	2449498	Revision: August 6, 2021	GILEAD SCIENCES CANADA INC	600 6711 Mississauga Road Mississauga Ontario Canada L5N 2W3	150-150-200-10 mg	Oral Tablet, Once daily	4	Elviteg-cob-emtri-tenof alafen	Genvoya	Elviteg-cob-emtri-tenof alafen	150-150-200-10 mg	61958-1901-1	NDA207561	Gilead Sciences, Inc. Foster City, CA 94404	Elviteg-cob-emtri-tenof alafen	n/a

Canadian Monograph

PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrGENVOYA®

elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide tablets

150 mg/150 mg/200 mg/10 mg*, Oral

*as 11.2 mg tenofovir alafenamide hemifumarate

Antiretroviral Agent

Gilead Sciences Canada, Inc.
Mississauga, ON L5N 2W3

www.gilead.ca

Date of Initial Authorization:
November 27, 2015

Date of Revision:
August 6, 2021

Submission Control Number: 250387

RECENT MAJOR LABEL CHANGES

2 Contraindications	11/2020
7 Warnings and Precautions, General	05/2020

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

GENVOYA (150 mg elvitegravir/150 mg cobicistat/200 mg emtricitabine/10 mg tenofovir alafenamide) is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients weighing ≥ 25 kg and with no known mutations associated with resistance to the individual components of GENVOYA.

1.1 Pediatrics

Pediatrics (weighing ≥ 25 kg): The safety and efficacy in children weighing ≥ 25 kg are based on data from an open-label clinical study (see **8 ADVERSE REACTIONS** and **14 CLINICAL TRIALS**).

Pediatrics (weighing < 25 kg): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for use in pediatrics weighing < 25 kg.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): No differences in safety or efficacy have been observed between elderly patients and adult patients < 65 years of age (see **10 CLINICAL PHARMACOLOGY**).

2 CONTRAINDICATIONS

GENVOYA is contraindicated in patients with known hypersensitivity to any of the components of the product. For a complete listing, see the **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING** section of the Product Monograph.

Coadministration with the following drugs listed in Table 1 is contraindicated due to the potential for serious and/or life-threatening events or loss of virologic response and possible resistance to GENVOYA. See also **9.4 Drug-Drug Interactions**.

Table 1. Drugs That Are Contraindicated with GENVOYA

Drug Class	Drugs within class that are contraindicated with GENVOYA	Clinical Comment
Alpha 1-adrenoreceptor antagonists	alfuzosin	Potential for increased alfuzosin concentrations, which can result in hypotension.
Anticonvulsants	carbamazepine, phenobarbital, phenytoin	Carbamazepine, phenobarbital, and phenytoin are potent inducers of CYP450 metabolism and may cause significant decrease in the plasma concentration of elvitegravir, cobicistat and tenofovir alafenamide. This may result in loss of therapeutic effect to GENVOYA.

Drug Class	Drugs within class that are contraindicated with GENVOYA	Clinical Comment
Antihistamines	astemizole*, terfenadine*	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimycobacterials	rifampin	Rifampin is a potent inducer of CYP450 metabolism and may cause significant decrease in the plasma concentration of elvitegravir, cobicistat and tenofovir alafenamide. This may result in loss of therapeutic effect to GENVOYA.
Benzodiazepines	orally administered midazolam*, triazolam	Triazolam and orally administered midazolam are extensively metabolized by CYP3A4. Coadministration of triazolam or orally administered midazolam with GENVOYA may cause large increases in the concentration of these benzodiazepines. The potential exists for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression.
Beta 2-adrenoceptor agonist	salmeterol	Coadministration of salmeterol with GENVOYA may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Direct oral anticoagulants	apixaban, rivaroxaban	Apixaban and rivaroxaban are primarily metabolized by CYP3A4 and transported by P-gp. Coadministration with GENVOYA may result in increased plasma concentrations of apixaban or rivaroxaban, which may lead to an increased bleeding risk.
Ergot derivatives	dihydroergotamine, ergonovine, ergotamine, methylergonovine*	Potential for serious and/or life-threatening events such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI motility agents	cisapride*	Potential for serious and/or life-threatening events such as cardiac arrhythmias.
Herbal products	St. John's Wort (*Hypericum perforatum*)	Coadministration of products containing St. John's Wort and GENVOYA may result in reduced plasma concentrations of elvitegravir, cobicistat and tenofovir alafenamide. 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.
Microsomal triglyceride transfer protein inhibitor	lomitapide	Potential for increased lomitapide concentrations which may result in markedly increased transaminases.

Drug Class	Drugs within class that are contraindicated with GENVOYA	Clinical Comment
Neuroleptics	lurasidone pimozide	Potential for serious and/or life-threatening reactions. Potential for serious and/or life-threatening events such as cardiac arrhythmias.
PDE-5 inhibitors	sildenafil†	A safe and effective dose in combination with GENVOYA has not been established for sildenafil (REVATIO®) when used for the treatment of pulmonary arterial hypertension. There is increased potential for sildenafil-associated adverse events (which include visual disturbances, hypotension, priapism, and syncope).

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

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Post-treatment Exacerbation of Hepatitis B**

GENVOYA is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of GENVOYA have not been established in patients coinfected with HIV-1 and HBV. Discontinuation of GENVOYA therapy in patients coinfected with HIV-1 and HBV may be associated with severe acute exacerbations of hepatitis due to the emtricitabine or tenofovir alafenamide components of GENVOYA. 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 GENVOYA. If appropriate, initiation of anti-hepatitis B therapy may be warranted (see **7.1 Special Populations**).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

GENVOYA is one tablet (containing 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine and 10 mg of tenofovir alafenamide) taken orally once daily with food.

Testing Prior to Initiation and During Treatment with GENVOYA

Prior to or when initiating GENVOYA, test patients for hepatitis B virus infection.

Prior to or when initiating GENVOYA, and during treatment with GENVOYA, assess serum creatinine, estimated creatinine clearance (CrCl), urine glucose and urine protein in all patients on a clinically appropriate schedule. In patients with chronic kidney disease, also assess serum phosphorus (see **7 WARNINGS AND PRECAUTIONS**, **Renal**).

4.2 Recommended Dose and Dosage Adjustment

Adults and Pediatric Patients weighing ≥ 25 kg

The recommended dose of GENVOYA is one tablet daily.

Pediatrics (weighing < 25 kg)

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for use in pediatrics weighing < 25 kg.

Geriatrics (≥ 65 years of age)

No dose adjustment is required for elderly patients. No differences in safety or efficacy have been observed between elderly patients and adult patients < 65 years of age.

Renal Impairment

No dose adjustment of GENVOYA is required in adult patients with estimated CrCl ≥ 30 mL/minute or in adult patients with end stage renal disease (estimated CrCl < 15 mL/minute) on chronic hemodialysis. On days of hemodialysis, administer GENVOYA after completion of hemodialysis treatment.

GENVOYA is not recommended in patients with estimated CrCl ≥ 15 and < 30 mL/minute, or < 15 mL/minute who are not on chronic hemodialysis, as the safety of GENVOYA has not been established in these populations.

No data are available to make dose recommendations in pediatric patients with renal impairment.

Hepatic Impairment

No dose adjustment of GENVOYA is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. GENVOYA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C); therefore, GENVOYA is not recommended for use in patients with severe hepatic impairment (see **10 CLINICAL PHARMACOLOGY**).

4.4 Administration

GENVOYA is one tablet (containing 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine and 10 mg of tenofovir alafenamide) taken orally once daily with food.

4.5 Missed Dose

If a patient misses a dose of GENVOYA within 18 hours of the time it is usually taken, the patient should take GENVOYA with food as soon as possible, and then take the next dose of GENVOYA at the regularly scheduled time.

If a patient misses a dose of GENVOYA by more than 18 hours, the patient should not take the missed dose, but resume the usual dosing schedule.

5 OVERDOSAGE

If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with GENVOYA 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 GENVOYA. 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 GENVOYA. In two studies, a single dose of cobicistat 400 mg (2.7 times the dose in GENVOYA) 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 emtricitabine in GENVOYA. In one clinical pharmacology study, single doses of emtricitabine 1200 mg (6 times the dose in GENVOYA) were administered to 11 subjects. No severe adverse reactions were reported. The effects of higher doses are not known.

Emtricitabine can be removed by hemodialysis, which removes approximately 30% of the emtricitabine dose over a 3 hour dialysis period starting within 1.5 hours of emtricitabine dosing.

It is not known whether emtricitabine can be removed by peritoneal dialysis.

Tenofovir alafenamide

Limited clinical experience is available at doses higher than the therapeutic dose of tenofovir alafenamide in GENVOYA. A single supratherapeutic dose of 125 mg tenofovir alafenamide was administered to 48 healthy subjects. No serious adverse reactions were reported. The effects of higher doses are unknown. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2. Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/ Strength/Composition	Non-medicinal Ingredients
Oral	Tablet 150 mg elvitegravir/150 mg cobicistat/200 mg emtricitabine/10 mg tenofovir alafenamide (as 11.2 mg tenofovir alafenamide hemifumarate)	Croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, silicon dioxide, and sodium lauryl sulfate. The tablets are coated with a coating material containing polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, indigo carmine aluminum lake, and iron oxide yellow.

GENVOYA is available as green capsule-shaped, film-coated tablets, debossed with 'GSI' on one side of the tablet and '510' on the other side of the tablet. Each bottle contains 30 tablets and a silica gel desiccant and closed with a child-resistant closure.

7 WARNINGS AND PRECAUTIONS

Please see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**.

General

GENVOYA is a fixed dose combination of elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide.

It should not be coadministered with any other antiretroviral products including products which contain elvitegravir, cobicistat, emtricitabine, or tenofovir alafenamide (ATRIPLA®, BIKTARVY®, COMPLERA®, DESCOVY®, EMTRIVA®, ODEFSEY®, Prezcobix®, STRIBILD®, Symtuza®, TRUVADA®, TYBOST®, VEMLIDY®); or with products containing lamivudine or tenofovir disoproxil fumarate (3TC®, ATRIPLA, Combivir®, COMPLERA, Delstrigo®, Dovato®, Kivexa®, STRIBILD, Triumeq®, Trizivir®, TRUVADA, VIREAD®). GENVOYA should not be administered concurrently with ritonavir or ritonavir-containing products (Kaletra®, Norvir®) or regimens due to similar effects of cobicistat and ritonavir on cytochrome P450 (CYP3A). GENVOYA should not be administered with adefovir dipivoxil (HEPSERA®).

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

Coadministration of GENVOYA with drugs that are primarily metabolized by CYP3A may result in increased plasma concentrations of such drugs, which may lead to serious and/or life-threatening events. Coadministration of GENVOYA with drugs that have active metabolite(s) formed by CYP3A may result in reduced plasma concentrations of these active metabolite(s), potentially leading to loss of therapeutic effect of the coadministered drug. Drugs that induce CYP3A activity may decrease plasma concentrations of cobicistat and elvitegravir, which may

lead to loss of therapeutic effect of GENVOYA and development of resistance (see **2 CONTRAINDICATIONS** and **9 DRUG INTERACTIONS**).

Driving and Operating Machinery

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

Endocrine and Metabolism

Serum Lipids and Blood Glucose

Serum lipid and blood glucose levels may increase during antiretroviral therapy (ART). Disease control and lifestyle changes may also be contributing factors. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders and blood glucose elevations should be managed as clinically appropriate.

Hepatic/Biliary/Pancreatic

Hepatic Impairment

No pharmacokinetic or safety data are available regarding the use of GENVOYA in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, GENVOYA is not recommended for use in patients with severe hepatic impairment.

The safety and efficacy of GENVOYA have not been established in patients with underlying liver disorders. Patients with chronic hepatitis B or C who are treated with ART are at increased risk for severe and potentially fatal hepatic adverse events (see **7.1 Special Populations**).

Pancreatitis

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

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 emtricitabine, a component of GENVOYA, and tenofovir disoproxil fumarate, another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with GENVOYA 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).

Immune

Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome has been reported in patients treated with combination ART, including emtricitabine, a component of GENVOYA. 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* complex (MAC) infection, cytomegalovirus (CMV) infection, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis (TB)), which may necessitate further evaluation and treatment.

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

Musculoskeletal

Bone Effects

Tenofovir alafenamide and tenofovir have been shown to be associated with decreases in bone mineral density (BMD) in animal toxicology studies and in human clinical trials. In a pooled analysis of two Phase 3 clinical studies in HIV-1 infected ART treatment-naïve adults, the percentage of patients treated with GENVOYA who had more than a 3% decrease from baseline in hip and spine BMD at Week 48 was 17% and 27%, respectively, at Week 96 was 23% and 26%, respectively, and at Week 144 was 28% and 30%, respectively (see **14 CLINICAL TRIALS**).

The effects of tenofovir alafenamide-associated changes in BMD on long-term bone health and future fracture risk are unknown.

Renal

Although cobicistat may cause modest increases in serum creatinine and modest declines in estimated CrCl without affecting renal glomerular function (see **8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data**) patients who experience a confirmed increase in serum creatinine of greater than 0.4 mg per dL (35.36 µmol/L) from baseline should be closely monitored for renal safety, including measuring serum phosphorus, urine glucose and urine protein (see **4.1 Dosing Considerations**).

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 prodrugs in both animal toxicology studies and human trials. In clinical trials with GENVOYA, there have been no cases of Fanconi syndrome or proximal renal tubulopathy.

Patients taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents including non-steroidal anti-inflammatory drugs are at increased risk of developing renal-related adverse reactions.

GENVOYA is not recommended in patients with estimated CrCl of 15 to below 30 mL/min, or in patients with estimated CrCl below 15 mL/min who are not receiving chronic hemodialysis.

7.1 Special Populations

7.1.1 Pregnant Women

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

In the embryo-fetal development study in rats, administration of tenofovir alafenamide was associated with reduced fetal body weight and delayed ossification rate at ≥ 100 mg/kg. The no-observed-adverse-effect-level (NOAEL) for embryo-fetal development was 25 mg/kg (approximately 10 times the clinical tenofovir exposure based on AUC).

In the embryo-fetal toxicity study in pregnant rabbits, administration of tenofovir alafenamide resulted in significantly increased number of litters with minor external and visceral anomalies at 100 mg/kg (approximately 90 times the clinical tenofovir exposure based on AUC). The NOAEL for embryo-fetal development was 30 mg/kg/day (approximately 17 times the clinical tenofovir exposure based on AUC).

In the peri- and postnatal development study, administration of tenofovir disoproxil fumarate, another prodrug of tenofovir, to pregnant rats resulted in increased peri/postparturn pup mortality, reduced pup survival, reduced pup body weights, reduced survival of F1 generation, reduced body weight/food consumption of F1 generation and delayed sexual maturation of F1 generation at ≥ 400 mg/kg (approximately 90 times the clinical tenofovir exposure based on AUC). The NOAEL for these effects was 150 mg/kg (approximately 25 times the clinical tenofovir exposure based on AUC). These results are considered relevant to tenofovir alafenamide.

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

7.1.2 Breast-feeding

HIV-1 infected mothers should 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, cobicistat, or tenofovir alafenamide is excreted in human milk.

In humans, samples of breast milk obtained from five HIV-1 infected mothers show that emtricitabine is secreted in human milk at estimated neonatal concentrations 3 to 12 times higher than the emtricitabine IC_{50} but 3 to 12 times lower than the C_{min} achieved from oral

administration of emtricitabine. Breastfeeding infants whose mothers are being treated with emtricitabine may be at risk for developing viral resistance to emtricitabine. Other emtricitabine-associated risks in infants breastfed by mothers being treated with emtricitabine are unknown.

Tenofovir-associated risks, including the risk of developing viral resistance to tenofovir, in infants breastfed by mothers being treated with tenofovir alafenamide 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 GENVOYA.**

7.1.3 Pediatrics

Pediatrics (weighing < 25 kg): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for use in pediatrics weighing < 25 kg.

7.1.5 Others

Patients Coinfected with HIV and HBV

The safety and efficacy of GENVOYA have not been established in patients coinfected with HIV-1 and HBV. It is recommended that all patients with HIV-1 be tested for HBV before or when initiating ART.

Severe acute exacerbations of hepatitis B (and association with liver decompensation and liver failure in some patients) may occur in patients coinfected with HBV and HIV-1 after discontinuation of emtricitabine and tenofovir alafenamide, two of the components of GENVOYA.

Hepatic function should be closely monitored with both clinical and laboratory follow-up for at least several months in patients who discontinue GENVOYA and are coinfected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure. Therefore, in these patients, discontinuation of treatment without initiation of alternative anti-hepatitis B therapy is not recommended.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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

- Severe Acute Exacerbations of Hepatitis B [See **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**]
- Immune Reconstitution Inflammatory Syndrome [See **7 WARNINGS AND PRECAUTIONS**]
- Lactic Acidosis/Severe Hepatomegaly with Steatosis [See **7 WARNINGS AND PRECAUTIONS**]

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Clinical Trials in Treatment-Naïve Adults

The safety assessment of GENVOYA is based on Weeks 48, 96, and 144 pooled data from 1733 patients in two comparative clinical trials, Study GS-US-292-0104 (Study 104) and Study GS-US-292-0111 (Study 111), in antiretroviral treatment-naive HIV-1 infected adult patients. A total of 866 patients received GENVOYA once daily.

The proportion of patients who discontinued treatment with GENVOYA or STRIBILD due to adverse events, regardless of severity, was 0.9% and 1.5% at Week 48, and 1.3% and 3.3% at Week 144, respectively. Table 3 displays the frequency of adverse reactions (Grades 2-4) greater than or equal to 1% observed in patients receiving GENVOYA.

Table 3. Adverse Reactions[a] (Grades 2-4) Reported in ≥ 1% of HIV-1 Infected Treatment-Naïve Adults Receiving GENVOYA in Studies 104 and 111 (Week 48 and 144 Analysis)

	Week 48 and 144[b]	
	GENVOYA (N=866)	**STRIBILD (N=867)**
GASTROINTESTINAL DISORDERS		
Nausea	1%	1%
Diarrhea	1%	< 1%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue	1%	1%
NERVOUS SYSTEM DISORDERS		
Headache	1%	1%

a. Frequencies of adverse reactions are based on Grades 2-4 adverse events attributed to study drugs by the investigator.
b. The frequency of adverse reactions are the same for Week 48 through Week 144.

Clinical Trials in Virologically Suppressed Patients

No new adverse reactions to GENVOYA were identified through Weeks 48 and 96 in an open-label clinical trial GS-US-292-0109 (Study 109) of virologically suppressed patients who switched from a tenofovir disoproxil fumarate-containing combination regimen to GENVOYA (N=959).

Clinical Trials in Adult Patients with Renal Impairment

The safety of GENVOYA was evaluated through Weeks 24, 96, and 144 in an open-label clinical trial GS-US-292-0112 (Study 112) in 248 HIV-1 infected patients who were either treatment-naïve (N=6) or virologically suppressed (N=242) with mild to moderate renal impairment (estimated CrCl by Cockcroft-Gault method 30 - 69 mL/min). The safety profile of GENVOYA in patients with mild to moderate renal impairment was similar to that in patients with normal renal function (estimated CrCl ≥ 80 mL/min) (see **14 CLINICAL TRIALS**).

The safety of GENVOYA in 55 virologically suppressed HIV-1 infected patients with end stage renal disease (estimated CrCl by Cockcroft-Gault method < 15 mL/min) on chronic hemodialysis was evaluated through Week 48 in a single arm, open-label clinical study (GS-US-292-1825). The safety profile of GENVOYA in patients with end stage renal disease on chronic hemodialysis was similar to that in patients with normal renal function.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Pediatrics (6 to < 18 years of age)

The safety of GENVOYA was evaluated in 50 HIV-1 infected, treatment-naïve pediatric patients between the ages of 12 to < 18 years (≥ 35 kg) through Week 48 in Cohort 1 of an open-label clinical trial GS-US-292-0106 (Study 106) and in 23 virologically suppressed pediatric patients between the ages of 6 to < 12 years (≥ 25 kg) through Week 24 in Cohort 2 of Study 106 (see **14 CLINICAL TRIALS**). The safety profile in pediatric patients who received treatment with GENVOYA was similar to that in adults.

One 13 year old female patient in Cohort 1 developed unexplained uveitis while receiving GENVOYA that resolved and did not require discontinuation of GENVOYA.

In Cohort 1 of Study 106, 4 patients experienced treatment-emergent worsening in the spine (N = 39) and/or TBLH (N = 37) height-age-adjusted BMD Z-score clinical status from baseline at Week 24, where a relationship to GENVOYA could not be excluded. However, two of these patients subsequently showed improvements in BMD at Week 48. In Cohort 2 of Study 106, 2 patients had significant (at least 4%) lumbar spine BMD loss at Week 24 (see **7 WARNINGS AND PRECAUTIONS**).

Also within Cohort 2 of Study 106, although all subjects had HIV-1 RNA < 50 copies/mL, there was a decrease from baseline in mean CD4+ cell count at Week 24. All subjects maintained their CD4+ cell counts above 400 cells/mm^3 (see **14.1 Clinical Trials by Indication**, **HIV-1 With No Known Mutations in Pediatrics**).

The mean baseline and mean change from baseline in CD4+ cell count and in CD4% from Week 2 to Week 24 are presented in Table 4.

Table 4. Mean Change in CD4+ Count and Percentage from Baseline to Week 24 in Virologically-Suppressed Pediatric Patients from 6 to < 12 Years Who Switched to GENVOYA

	Baseline	Mean Change from Baseline			
		Week 2	Week 4	Week 12	Week 24
CD4+ Cell Count (cells/mm^3)	966 (201.7)[a]	-162	-125	-162	-150
CD4%	40 (5.3)[a]	+ 0.5%	-0.1%	-0.8%	-1.5%

a. Mean (SD)

8.3 Less Common Clinical Trial Adverse Reactions (< 1%)

In addition to the adverse reactions presented in Table 3, abdominal pain, dyspepsia, flatulence, rash, and vomiting occurred at a frequency of < 1% and/or at severity of Grade 1 in the GENVOYA group.

Adverse Reactions from Clinical Trials of the Components of GENVOYA

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

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

The frequency of laboratory abnormalities (Grades 3-4) occurring in at least 2% of patients receiving GENVOYA in Studies 104 and 111 are presented in Table 5.

Table 5. Laboratory Abnormalities (Grades 3-4) Reported in ≥ 2% of Patients Receiving GENVOYA in Studies 104 and 111 (Week 48, and Week 144 Analyses)

	Week 48		Week 144	
	GENVOYA (N=866)	**STRIBILD (N=867)**	**GENVOYA (N=866)**	**STRIBILD (N=867)**
Laboratory Parameter Abnormality[a]				
Amylase (> 2.0 x ULN)	< 2%	3%	3%	5%
ALT (> 5.0 x ULN)	< 2%	< 2%	3%	3%
AST (> 5.0 x ULN)	< 2%	< 2%	3%	4%
Creatine Kinase (≥ 10.0 x ULN)	7%	6%	11%	10%
Urine RBC (Hematuria) (> 75 RBC/HPF)	< 2%	2%	3%	3%
LDL-cholesterol (fasted) (> 4.92 mmol/L)	5%	2%	11%	5%
Total Cholesterol (fasted) (> 7.77 mmol/L)	< 2%	1%	4%	3%
Lipase[b] (≥ 3.0 x ULN)	4%	8%	5%	8%

a. Frequencies are based on treatment-emergent laboratory abnormalities.

b. Lipase test was performed only for patients with serum amylase > 1.5 x ULN (N=90 for GENVOYA arm, N=113 for STRIBILD arm at Week 48; N=127 for GENVOYA arm, N=154 for STRIBILD arm at Week 144).

Cobicistat (a component of GENVOYA) has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function. Increases in serum creatinine occurred by Week 2 of treatment and remained stable through 144 weeks. In treatment-naïve patients, a mean change from baseline of 7.07 ± 10.96 µmol/L, 3.54 ± 10.08 µmol/L, and 3.54 ± 10.61 µmol/L was observed after 48, 96, and 144 weeks of treatment, respectively.

Serum Lipids

Patients receiving GENVOYA experienced higher increases in serum lipids than those receiving STRIBILD. In the clinical trials of GENVOYA, a similar percentage of patients receiving GENVOYA and STRIBILD were on lipid lowering agents at baseline (2% and 3%, respectively). Similar percentages of subjects in each treatment group initiated lipid-modifying medications through Week 144, 5.5% and 5.8% in subjects receiving GENVOYA and STRIBILD, respectively.

Changes from baseline in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, and total cholesterol to HDL ratio at Weeks 48 and 144 are presented in Table 6.

Table 6. Lipid Values, Mean Change from Baseline, Reported in Patients Receiving GENVOYA or STRIBILD in Studies 104 and 111[a] (Week 48 and Week 144 Analyses)

	Week 48				Week 144			
	GENVOYA (N=866)		STRIBILD (N=867)		GENVOYA (N=866)		STRIBILD (N=867)	
	Baseline	Change[b] at Week 48	Baseline	Change[b] at Week 48	Baseline	Change[c] at Week 144	Baseline	Change[c] at Week 144
Total Cholesterol (fasted), mmol/L	4.19 [N=757]	+ 0.78 [N=757]	4.29 [N=742]	+ 0.34 [N=742]	4.19 [N=647]	+ 0.80 [N=647]	4.27 [N=627]	+ 0.36 [N=627]
HDL-cholesterol (fasted), mmol/L	1.19 [N=757]	+ 0.18 [N=757]	1.16 [N=742]	+ 0.10 [N=742]	1.21 [N=647]	+ 0.18 [N=647]	1.19 [N=627]	+ 0.08 [N=627]
LDL-cholesterol (fasted), mmol/L	2.69 [N=753]	+ 0.39 [N=753]	2.77 [N=744]	+ 0.08 [N=744]	2.66 [N=643]	+ 0.52 [N=643]	2.77 [N=628]	+ 0.21 [N=628]
Triglycerides (fasted), mmol/L	1.28 [N=757]	+ 0.33 [N=757]	1.34 [N=742]	+ 0.11 [N=742]	1.25 [N=647]	+ 0.33 [N=647]	1.30 [N=627]	+ 0.19 [N=627]
Total Cholesterol to HDL ratio	3.7 [N=757]	0.2 [N=757]	3.9 [N=742]	0 [N=742]	3.7 [N=647]	0.2 [N=647]	3.8 [N=627]	0.1 [N=627]

a. Excludes patients who received lipid lowering agents during the treatment period.
b. The change from baseline is the mean of within patient changes from baseline for patients with both baseline and Week 48 values.
c. The change from baseline is the mean of within patient changes from baseline for patients with both baseline and Week 144 value.

8.5 Post-Market Adverse Reactions

In addition to the adverse reaction reports from clinical trials, the following possible adverse reactions have been identified during post-approval use of products containing emtricitabine or tenofovir alafenamide. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been considered possible adverse reactions due to a combination of their seriousness, frequency of reporting or potential causal relationship with treatment. No additional adverse reactions have been identified during post-approval use of other components of GENVOYA.

Emtricitabine

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

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

Tenofovir Alafenamide

Skin and subcutaneous tissue disorders:	Angioedema, urticaria

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

Cobicistat, a component of GENVOYA, is a strong inhibitor of cytochrome P450 (CYP3A) and a CYP3A substrate. Coadministration of GENVOYA with drugs that are primarily metabolized by CYP3A may result in increased plasma concentrations of such drugs, which may lead to serious and/or life-threatening events. Coadministration of GENVOYA with drugs that have active metabolite(s) formed by CYP3A may result in reduced plasma concentrations of these active metabolite(s). Elvitegravir, a component of GENVOYA, is metabolized by CYP3A. Drugs that induce CYP3A activity may decrease plasma concentrations of cobicistat, elvitegravir and tenofovir alafenamide, which may lead to loss of therapeutic effect of GENVOYA and development of resistance (see **2 CONTRAINDICATIONS**, **7 WARNINGS AND PRECAUTIONS** and **9 DRUG INTERACTIONS**, **Table 7 – Established and Other Potentially Significant Drug Interactions**).

9.2 Drug Interactions Overview

Potential of GENVOYA to Affect Other Drugs

Cobicistat, a component of GENVOYA, is a strong inhibitor of CYP3A and a weak inhibitor of CYP2D6. The transporters that cobicistat inhibits include p-glycoprotein (P-gp), BCRP, OATP1B1, and OATP1B3. Thus, coadministration of GENVOYA 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. Coadministration of GENVOYA with drugs that have active metabolite(s) formed by CYP3A may result in reduced plasma concentrations of these active metabolite(s). Elvitegravir is a modest inducer of CYP2C9 and may decrease the plasma concentrations of CYP2C9 substrates.

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

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

Coadministration of GENVOYA with other drugs that inhibit CYP3A may decrease the clearance and increase the plasma concentration of cobicistat (see **9 DRUG INTERACTIONS**, **Table 7**).

Coadministration of GENVOYA with drugs that inhibit the lysosomal carboxypeptidase cathepsin A (CatA) may decrease metabolism of tenofovir alafenamide to tenofovir in target cells, which may lead to reduced therapeutic effect of GENVOYA and development of resistance (see **9 DRUG INTERACTIONS, Table 7**).

Tenofovir alafenamide is also a substrate of P-gp and CYP3A4. Drugs that potently induce CYP3A4 activity may decrease the exposure to tenofovir alafenamide, which may result in reduced antiviral activity of GENVOYA and development of resistance (see **9 DRUG INTERACTIONS, Table 7**).

9.3 Drug-Behavioural Interactions

Interactions of GENVOYA with individual behavioural risks have not been established.

9.4 Drug-Drug Interactions

GENVOYA is indicated as a complete regimen for the treatment of HIV-1 infection; therefore, GENVOYA should not be coadministered with other antiretroviral medications for treatment of HIV-1 infection. Complete information regarding potential drug-drug interactions with other antiretrovirals products is not provided (see **7 WARNINGS AND PRECAUTIONS, General**).

Established and Other Potentially Significant Interactions

The drug interactions described in Table 7 are based on studies conducted with GENVOYA, or the components of GENVOYA (elvitegravir, cobicistat, emtricitabine or tenofovir alafenamide) as individual components and/or in combination, or are potential drug interactions that may occur

with GENVOYA. The table is not comprehensive and not all-inclusive (see also **2 CONTRAINDICATIONS**).

Table 7. Established and Other Potentially Significant[a] Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Alpha 1-Adrenoreceptor Antagonist: alfuzosin	↑ alfuzosin	Alfuzosin is primarily metabolized by CYP3A. Coadministration with GENVOYA may result in increased plasma concentrations of alfuzosin, which is associated with the potential for serious and/or life-threatening reactions. Coadministration of GENVOYA and alfuzosin is contraindicated.
Antiarrhythmics: amiodarone bepridil* digoxin disopyramide flecainide systemic lidocaine mexiletine propafenone quinidine	↑ antiarrhythmics	Concentrations of these antiarrhythmic drugs may be increased when coadministered with cobicistat. Caution is warranted and clinical monitoring is recommended upon coadministration of these agents with GENVOYA.
Antibacterials: clarithromycin telithromycin*	↑ clarithromycin ↑ telithromycin ↑ cobicistat	Concentrations of clarithromycin and/or cobicistat may be altered when clarithromycin is coadministered with GENVOYA. <u>Patients with CLcr ≥ 60 mL/min:</u> No dose adjustment of clarithromycin is required. <u>Patients with CLcr between 30 mL/min and 60 mL/min:</u> The dose of clarithromycin should be reduced by 50%. Concentrations of telithromycin and/or cobicistat may be increased when telithromycin is coadministered with GENVOYA. Clinical monitoring is recommended upon coadministration with GENVOYA.
Anticoagulants:	↓ or ↑ warfarin	Concentrations of warfarin may be affected upon coadministration with GENVOYA. It is

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
warfarin		recommended that the international normalized ratio (INR) be monitored upon coadministration with GENVOYA.
Direct Oral Anticoagulants (DOACs): apixaban rivaroxaban dabigatran edoxaban	↑ DOACs	DOACs are primarily metabolized by CYP3A4 and/or transported by P-gp. Coadministration with GENVOYA may result in increased plasma concentrations of the DOAC, which may lead to an increased bleeding risk. Coadministration of a DOAC affected by both P-gp and CYP3A4, including apixaban and rivaroxaban, is contraindicated with GENVOYA. Clinical monitoring and/or dose adjustment is recommended when a DOAC transported by P-gp, including dabigatran or edoxaban, is coadministered with GENVOYA. Refer to the Product Monograph of the coadministered DOAC.
Anticonvulsants: carbamazepine ethosuximide oxcarbazepine phenobarbital phenytoin	↑ ethosuximide ↓ elvitegravir ↓ cobicistat ↓ tenofovir alafenamide	Carbamazepine, a potent CYP3A inducer, decreases cobicistat, elvitegravir and tenofovir alafenamide plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Coadministration of GENVOYA with carbamazepine, phenobarbital, or phenytoin is contraindicated. Coadministration of oxcarbazepine, a CYP3A inducer, may decrease cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Alternative anticonvulsants should be considered. Concentrations of ethosuximide may be increased when coadministered with cobicistat. Clinical monitoring is recommended upon coadministration with GENVOYA.
Antidepressants: Selective Serotonin Reuptake Inhibitors (SSRIs): sertraline TCAs trazodone	↑ SSRIs ↔ sertraline ↑ TCAs ↑ trazodone	Concentrations of sertraline are not affected upon coadministration with GENVOYA. No dose adjustment is required upon coadministration. Concentrations of other antidepressant agents may be increased when coadministered with cobicistat. Dose titration may be required for most drugs of the SSRI class. Concentrations of trazodone may increase upon coadministration with cobicistat. Dose reduction should be considered when trazodone is coadministered with GENVOYA.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Antifungals: itraconazole ketoconazole voriconazole	↑ antifungals ↑ cobicistat	Concentrations of ketoconazole, itraconazole and/or cobicistat may increase with coadministration of GENVOYA. When administering with GENVOYA, the maximum daily dose of ketoconazole and itraconazole should not exceed 200 mg per day. Concentrations of voriconazole may be increased when coadministered with cobicistat. Clinical monitoring may be needed upon coadministration with GENVOYA.
Anti-gout: colchicine	↑ colchicine	Dose reductions of colchicine may be required. GENVOYA should not be coadministered with colchicine in patients with renal or hepatic impairment.
Antihistamines: astemizole terfenadine	↑ astemizole ↑ terfenadine	Concentrations of astemizole and terfenadine may be increased when coadministered with cobicistat. Clinical monitoring is recommended when these agents are coadministered with GENVOYA.
Antimycobacterial: rifabutin rifampin rifapentine	↓ elvitegravir ↓ cobicistat ↓ tenofovir alafenamide	Coadministration of rifampin, rifabutin, and rifapentine, potent CYP3A inducers, may significantly decrease cobicistat, elvitegravir and tenofovir alafenamide plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Coadministration of GENVOYA with rifampin is contraindicated. Coadministration of GENVOYA with rifabutin or rifapentine is not recommended.
Antiplatelets: clopidogrel prasugrel	↓ clopidogrel active metabolite ↔ prasugrel active metabolite	Coadministration of clopidogrel with cobicistat is expected to decrease clopidogrel active metabolite plasma concentrations, which may reduce the antiplatelet activity of clopidogrel. Coadministration of clopidogrel with GENVOYA is not recommended. GENVOYA is not expected to have a clinically relevant effect on plasma concentrations of the active metabolite of prasugrel.
Antipsychotics: Quetiapine	↑ quetiapine	GENVOYA should not be used in combination with quetiapine. Due to CYP3A4 inhibition by cobicistat, concentrations of quetiapine are expected to increase, which can result in serious and/or life-threatening adverse reactions. If coadministration is necessary, monitoring and

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
		quetiapine dose reduction may be required.
Benzodiazepines: diazepam lorazepam midazolam triazolam	↑ diazepam ↔ lorazepam ↑ midazolam ↑ triazolam	Midazolam and triazolam are primarily metabolized by CYP3A. Coadministration with GENVOYA may result in increased plasma concentrations of these drugs, which are associated with the potential for serious and/or life-threatening reactions. Coadministration of GENVOYA and orally administered midazolam and triazolam are contraindicated. Concentrations of other benzodiazepines, including diazepam and parenterally administered midazolam, may be increased when administered with GENVOYA. Coadministration should be done in a setting that ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dose reduction may be necessary. Based on non-CYP-mediated elimination pathways for lorazepam, no effect on plasma concentrations is expected upon coadministration with GENVOYA.
Beta-Blockers: metoprolol timolol	↑ beta-blockers	Concentrations of beta-blockers may be increased when coadministered with cobicistat. Clinical monitoring is recommended and a dose decrease may be necessary when these agents are coadministered with GENVOYA.
Calcium Channel Blockers: amlodipine diltiazem felodipine nicardipine* nifedipine verapamil	↑ calcium channel blockers	Concentrations of calcium channel blockers may be increased when coadministered with cobicistat. Caution is warranted and clinical monitoring is recommended upon coadministration with GENVOYA.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Systemic Corticosteroids: dexamethasone	↓ elvitegravir ↓ cobicistat	Coadministration of dexamethasone, a CYP3A inducer, may significantly decrease cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Alternative corticosteroids should be considered.
Corticosteroids: betamethasone budesonide dexamethasone fluticasone mometasone triamcinolone	↑ corticosteroids	Coadministration of GENVOYA with corticosteroids that are sensitive to CYP3A inhibition can increase the risk for Cushing's syndrome and adrenal suppression, which have been reported during postmarketing use of cobicistat-containing products. Coadministration of corticosteroids sensitive to CYP3A inhibition and GENVOYA is not recommended unless the potential benefit to the patient outweighs the risks. Alternative corticosteroids which are less dependent on CYP3A metabolism should be considered, particularly for long-term use.
Endothelin Receptor Antagonists: bosentan	↓ elvitegravir ↓ cobicistat	Coadministration with GENVOYA may lead to decreased elvitegravir and/or cobicistat exposures and loss of therapeutic effect and development of resistance. Alternative endothelin receptor antagonists may be considered.
Ergot Derivatives: dihydroergotamine ergonovine* ergotamine methylergonovine	↑ ergot derivatives	Ergot derivatives are primarily metabolized by CYP3A. Coadministration with GENVOYA may result in increased plasma concentrations of these drugs, which is associated with the potential for serious and/or life-threatening reactions. Coadministration of GENVOYA and dihydroergotamine, ergonovine, ergotamine, and methylergonovine are contraindicated.
GI Motility Agents: cisapride*	↑ cisapride	Cisapride is primarily metabolized by CYP3A. Coadministration with GENVOYA may result in increased plasma concentrations of cisapride, which is associated with the potential for serious and/or life-threatening reactions. Coadministration of GENVOYA and cisapride is contraindicated.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Hepatitis C Virus Antiviral Agents: elbasvir/grazoprevir	↑ elbasvir ↑ grazoprevir	Coadministration with GENVOYA may result in increased plasma concentrations of elbasvir and grazoprevir. Coadministration of GENVOYA with elbasvir/grazoprevir is not recommended.
HMG-CoA Reductase Inhibitors: atorvastatin lovastatin rosuvastatin simvastatin	↑ HMG-CoA reductase inhibitors	HMG CoA reductase inhibitors are primarily metabolized by CYP3A. Coadministration with GENVOYA may result in increased plasma concentrations of lovastatin or simvastatin, which are associated with the potential for serious and/or life-threatening reactions. Coadministration of GENVOYA with lovastatin and simvastatin are contraindicated. Concentrations of atorvastatin are increased when coadministered with elvitegravir and cobicistat. Start with the lowest dose of atorvastatin and titrate carefully while monitoring for safety (eg, myopathy). Do not exceed a dosage of atorvastatin 20 mg daily. Concentrations of rosuvastatin are transiently increased when coadministered with elvitegravir and cobicistat. Dose modifications are not necessary when rosuvastatin is administered in combination with GENVOYA.
Hormonal Contraceptives: drospirenone/ethinyl estradiol norgestimate/ethinyl estradiol	↑ drospirenone ↑ norgestimate ↓ ethinyl estradiol	Plasma concentrations of drospirenone may be increased when coadministered with cobicistat-containing products. Clinical monitoring is recommended due to the potential for hyperkalemia. Coadministration of GENVOYA and a norgestimate/ethinyl estradiol-containing hormonal oral contraceptive is expected to decrease plasma concentrations of ethinyl estradiol and increase norgestimate. Use caution when coadministering GENVOYA and a hormonal contraceptive. The hormonal contraceptive should contain at least 30 mcg of ethinyl estradiol. The effects of increases in the concentration of the progestational component norgestimate are not fully known and can include increased risk of insulin resistance, dyslipidemia, acne and venous

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
		thrombosis. The potential unknown risks and benefits associated with coadministration of norgestimate/ethinyl estradiol with GENVOYA should be considered, particularly in women who have risk factors for these events. Coadministration of GENVOYA, or its components, with oral contraceptives containing progestogens other than drospirenone or norgestimate or with other hormonal contraceptives (eg, contraceptive patch, contraceptive vaginal ring) has not been studied; therefore alternative non-hormonal methods of contraception should be considered.
Immunosuppressants: cyclosporine rapamycin* sirolimus tacrolimus	↑ immuno-suppressants ↑ tenofovir alafenamide	Concentrations of these immunosuppressant agents may be increased when coadministered with cobicistat. Coadministration with cyclosporine may result in increased plasma concentration of tenofovir alafenamide. Therapeutic monitoring is recommended upon coadministration with GENVOYA.
Narcotic Analgesics: buprenorphine/ naloxone	↑ buprenorphine ↑ norbuprenorphine ↓ naloxone	Concentrations of buprenorphine and norbuprenorphine are increased when coadministered with GENVOYA. No dose adjustment of buprenorphine/naloxone is required upon coadministration with GENVOYA. Patients should be closely monitored for sedation and cognitive effects.
Inhaled Beta Agonist: salmeterol	↑ salmeterol	Coadministration with GENVOYA may result in increased plasma concentrations of salmeterol, which is associated with the potential for serious and/or life-threatening reactions. Coadministration of salmeterol and GENVOYA is not recommended.
Medications or Oral Supplements Containing Polyvalent Cations (eg, Mg, Al, Ca, Fe, Zn): calcium or iron supplements, including multivitamins cation-containing antacids or laxatives sucralfate buffered medications	↓ elvitegravir	Elvitegravir plasma concentrations are expected to be lower with medications or oral supplements containing polyvalent cations, including antacids, due to local complexation in the GI tract and not to changes in gastric pH. It is recommended to separate GENVOYA and administration of medications, antacids, or oral supplements containing polyvalent cations by at least 2 hours. For information on other acid reducing agents (eg, H_2-receptor antagonists and proton pump inhibitors), see **9 DRUG INTERACTIONS**, **Drugs**

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
		without Clinically Significant Interactions with GENVOYA.
Microsomal triglyceride transfer protein inhibitor: lomitapide	↑ lomitapide	Coadministration with GENVOYA is contraindicated due to potential for markedly increased transaminases.
Neuroleptics: perphenazine pimozide risperidone thioridazine*	↑ neuroleptics	Pimozide is primarily metabolized by CYP3A. Coadministration with GENVOYA may result in increased plasma concentrations of pimozide, which is associated with the potential for serious and/or life-threatening reactions. Coadministration of GENVOYA with pimozide is contraindicated. For other neuroleptics, consider reducing the dose of the neuroleptic upon coadministration with GENVOYA.
Phosphodiesterase-5 (PDE-5) Inhibitors: sildenafil tadalafil vardenafil	↑ PDE-5 inhibitors	PDE-5 inhibitors are primarily metabolized by CYP3A. Coadministration with GENVOYA may result in increased plasma concentrations of sildenafil and tadalafil, which may result in PDE-5 inhibitor-associated adverse reactions. Coadministration of GENVOYA with sildenafil for the treatment of pulmonary arterial hypertension is contraindicated. Caution should be exercised, including consideration of dose reduction, when coadministering GENVOYA with tadalafil for the treatment of pulmonary arterial hypertension. For the treatment of erectile dysfunction, it is recommended that a single dose of sildenafil no more than 25 mg in 48 hours, vardenafil no more than 2.5 mg in 72 hours, or tadalafil no more than 10 mg in 72 hours be coadministered with GENVOYA.
Sedative/hypnotics: buspirone orally-administered zolpidem*	↑sedatives /hypnotics	With sedative/hypnotics, dose reduction may be necessary upon coadministration with GENVOYA and clinical monitoring is recommended.

*Not marketed in Canada.
CLcr = creatinine clearance; HMG-CoA = 3-hydroxy-3-methyl-glutaryl-CoA
a. This table is not all inclusive.
b. ↑ = increase, ↓ = decrease, ↔ = no effect

Drugs without Clinically Significant Interactions with GENVOYA

Based on drug interaction studies conducted with GENVOYA or the components of GENVOYA, no clinically significant drug interactions have been observed or are expected with entecavir, famciclovir, famotidine, ledipasvir/sofosbuvir, omeprazole, ribavirin, sertraline, sofosbuvir, sofosbuvir/velpatasvir, and sofosbuvir/velpatasvir/voxilaprevir.

Methadone exposures are unaffected upon coadministration with elvitegravir and cobicistat. No dose adjustment of methadone is required upon coadministration with GENVOYA.

Assessment of Drug Interactions

Emtricitabine

In vitro and clinical pharmacokinetic drug-drug interaction studies have shown that the potential for CYP-mediated interactions involving emtricitabine with other medicinal products is low.

Emtricitabine is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No drug-drug interactions due to competition for renal excretion have been observed; however, coadministration of emtricitabine with drugs that are eliminated by active tubular secretion may increase concentrations of emtricitabine, and/or the coadministered drug.

Drugs that decrease renal function may increase concentrations of emtricitabine.

Tenofovir Alafenamide

Tenofovir alafenamide is a substrate of P-gp and BCRP transporters. Drugs that strongly affect P-gp and BCRP activity may lead to changes in tenofovir alafenamide absorption. However, upon coadministration with cobicistat in GENVOYA, near maximal inhibition of P-gp by cobicistat is achieved leading to increased availability of tenofovir alafenamide with resulting exposures comparable to tenofovir alafenamide 25 mg single agent. As such, tenofovir alafenamide exposures following administration of GENVOYA are not expected to be further increased when used in combination with another P-gp and/or BCRP inhibitor.

In vitro and clinical pharmacokinetic drug-drug interactions studies have shown that the potential for CYP-mediated interactions involving tenofovir alafenamide with other medicinal products is low.

Tenofovir alafenamide is not an inhibitor or inducer of CYP3A *in vivo*.

Drug Interaction Studies

Drug-drug interaction studies were conducted with GENVOYA or various combinations of GENVOYA components including elvitegravir (coadministered with cobicistat or ritonavir), cobicistat administered alone, or tenofovir alafenamide (administered alone or coadministered with emtricitabine).

As GENVOYA should not be administered with other antiretroviral medications, information regarding drug-drug interactions with other antiretroviral agents is not provided (see **7 WARNINGS AND PRECAUTIONS**).

The effects of coadministered drugs on the exposure of elvitegravir are shown in Table 8. The effects of coadministered drugs on the exposure of tenofovir alafenamide are shown in Table 9. The effects of GENVOYA or its components on the exposure of coadministered drugs are shown in Table 10.

Table 8. Drug Interactions: Changes in Pharmacokinetic Parameters for Elvitegravir in the Presence of the Coadministered Drug[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose (mg)	Cobicistat or Ritonavir Booster Dose (mg)	N	% Change of Elvitegravir Pharmacokinetic Parameters (90% CI)[b]		
					C_{max}	AUC	C_{min}
Antacids	20 mL single dose given 4 hours before elvitegravir	50 single dose	Ritonavir 100 single dose	8	⇔	⇔	⇔
	20 mL single dose given 4 hours after elvitegravir			10	⇔	⇔	⇔
	20 mL single dose given 2 hours before elvitegravir			11	⇔	⇔	⇔
	20 mL single dose given 2 hours after elvitegravir			10	⇔	⇔	⇔
	20 mL single dose simultaneously administered with elvitegravir	50 single dose	Ritonavir 100 single dose	13	↓47 (↓53 to ↓40)	↓45 (↓50 to ↓40)	↓41 (↓48 to ↓33)
Atorvastatin	10 single dose	150 once daily[e]	Cobicistat 150 once daily[e]	16	⇔	⇔	⇔
Carbamazepine	200 twice daily	150 once daily	Cobicistat 150 once daily	12	↓45 (↓51 to ↓39)	↓69 (↓72 to ↓67)	↓97 (↓98 to ↓60)
Famotidine[c]	40 once daily given 12 hours after elvitegravir	150 once daily	Cobicistat 150 once	10	⇔	⇔	⇔

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose (mg)	Cobicistat or Ritonavir Booster Dose (mg)	N	% Change of Elvitegravir Pharmacokinetic Parameters (90% CI)[b]		
					C_{max}	AUC	C_{min}
	40 once daily given simultaneously with elvitegravir		daily	16	⇔	⇔	⇔
Ketoconazole	200 twice daily	150 once daily	Ritonavir 100 once daily	18	⇔	↑48 (↑36 to ↑62)	↑67 (↑48 to ↑88)
Ledipasvir/ Sofosbuvir	90/400 once daily	150 once daily[d]	Cobicistat 150 once daily[d]	30	⇔	⇔	↑46 (↑28 to ↑66)
Omeprazole[c]	40 once daily given 2 hours before elvitegravir	50 once daily	Ritonavir 100 once daily	9	⇔	⇔	⇔
	20 once daily given 2 hours before elvitegravir	150 once daily	Cobicistat 150 once daily	11	⇔	⇔	⇔
	20 once daily given 12 hours after elvitegravir			11	⇔	⇔	⇔
Rifabutin	150 once every other day	150 once daily	Cobicistat 150 once daily	12	⇔	↓21 (↓26 to ↓15)	↓67 (↓73 to ↓60)
Rosuvastatin	10 single dose	150 once daily	Cobicistat 150 once daily	10	⇔	⇔	⇔
Sertraline	50 single dose	150 once daily[e]	Cobicistat 150 once daily[e]	19	⇔	⇔	⇔
Sofosbuvir/Velpatasvir	400/100 once daily	150 once daily[e]	Cobicistat 150 once daily[e]	24	⇔	⇔	⇔
Sofosbuvir/ Velpatasvir/ Voxilaprevir	400/100/100 + 100 Voxilaprevir[g] once daily	150 once daily[e]	Cobicistat 150 once daily[e]	29	⇔	⇔	↑32 (↑17 to ↑49)

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

a. All interaction studies conducted in healthy volunteers.

b. All No Effect Boundaries are 70% -143% unless otherwise specified.

c. No Effect Boundary 70% - no upper bound.

d. % change of Cobicistat PK parameters (90% CI) was unchanged for C_{max}, ↑59% (↑49%, ↑70%) for AUC, and ↑325% (↑247%, ↑422%) for C_{min}.
e. Study conducted with GENVOYA.
f. Study conducted with STRIBILD.
g. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Table 9. Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir Alafenamide in the Presence of the Coadministered Drug[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Tenofovir Alafenamide (mg)	N	% Change of Tenofovir Alafenamide Pharmacokinetic Parameters (90% CI)[b]		
				C_{max}	AUC	C_{min}
Cobicistat	150 once daily	8 once daily	12	↑183 (↑120 to ↑265)	↑165 (↑129 to ↑207)	NA
Ledipasvir/Sofosbuvir	90/400 once daily	10 once daily[d]	30	⇔	⇔	NA
Efavirenz	600 once daily	40 once daily[c]	11	↓22 (↓42 to ↑5)	⇔	NA
Sertraline	50 single dose	10 once daily[d]	19	⇔	⇔	NA
Sofosbuvir/Velpatasvir	400/100 once daily	10 once daily[d]	24	↓20 (↓32 to ↓6)	⇔	NA
Sofosbuvir/ Velpatasvir/Voxilaprevir	400/100/100 + 100 Voxilaprevir[e] once daily	10 once daily[d]	29	↓21 (↓32 to ↓8)	⇔	NA

NA = Not Available/Not Applicable
a. All interaction studies conducted in healthy volunteers.
b. All No Effect Boundaries are 70% -143% unless otherwise specified.
c. Study conducted with DESCOVY.
d. Study conducted with GENVOYA.
e. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Table 10. Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of GENVOYA or the Individual Components[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose[b] (mg)	Cobicistat Booster Dose (mg)	Tenofovir Alafenamide (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters (90% CI)[b]		
						C_{max}	AUC	C_{min}
Atorvastatin	10 single dose	150 once daily[f]	150 once daily[f]	10 once daily[f]	16	↑132 (↑91 to ↑182)	↑160 (↑131 to ↑193)	NC
Buprenorphine	16 - 24 once daily	150 once daily	150 once daily	NA	17	⇔	↑35 (↑18 to ↑55)	↑66 (↑43 to ↑93)
Norbuprenorphine						↑24 (↑3 to ↑49)	↑42 (↑22 to ↑67)	↑57 (↑31 to ↑88)
Carbamazepine	200 twice daily	150 once daily	150 once daily	NA	12	↑40 (↑32 to ↑49)	↑43 (↑36 to ↑52)	↑51 (↑41 to ↑62)
Carbamazepine-10,11-epoxide						⇔	↓35 (↓37 to ↓34)	↓41 (↓43 to ↓39)
Desipramine[c]	50 single dose	NA	150 once daily	NA	8	↑24 (↑8 to ↑44)	↑65 (↑36 to ↑102)	NA

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose[b] (mg)	Cobicistat Booster Dose (mg)	Tenofovir Alafenamide (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters (90% CI)[b]		
						C_{max}	AUC	C_{min}
Digoxin[c]	0.5 single dose	NA	150 once daily	NA	22	↑41 (↑29 to ↑55)	⇔	NA
Ledipasvir	90 once daily	150 once daily[f]	150 once daily[f]	10 once daily[f]	30	↑65 (↑53 to ↑78)	↑79 (↑64 to ↑96)	↑93 (↑74 to ↑115)
Sofosbuvir	400 once daily					↑28 (↑13 to ↑47)	↑47 (↑35 to ↑59)	NA
GS-331007[i]						↑29 (↑24 to ↑35)	↑48 (↑44 to ↑53)	↑66 (↑60 to ↑73)
Naloxone	4 - 6 once daily	150 once daily	150 once daily	NA	17	↓28 (↓39 to ↓15)	↓28 ↓41 to ↓13)	NA
Norgestimate[c]/ ethinyl estradiol[c]	0.180/0.215/ 0.250 norgestimate once daily	150 once daily[d]	150 once daily[d]	NA	13	↑108 (↑100 to ↑117)	↑126 (↑115 to ↑137)	↑167 (↑143 to ↑192)
	0.025 ethinyl estradiol once daily					⇔	↓25 (↓31 to ↓19)	↓44 (↓48 to ↓39)

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose[b] (mg)	Cobicistat Booster Dose (mg)	Tenofovir Alafenamide (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters (90% CI)[b]		
						C_{max}	AUC	C_{min}
Norelgestromin	0.180/0.215/ 0.250 norgestimate once daily / 0.025 ethinyl estradiol once daily	NA	NA	25 once daily[e]	15	⇔	⇔	⇔
Norgestrel						⇔	⇔	⇔
Ethinyl estradiol						⇔	⇔	⇔
R-Methadone	80-120 daily	150 once daily	150 once daily	NA	11	⇔	⇔	⇔
S-Methadone						⇔	⇔	⇔
Sertraline	50 single dose	150 once daily[f]	150 once daily[f]	10 once daily[f]	19	⇔	⇔	NA
Rifabutin	150 once every other day	150 once daily	150 once daily	NA	12	⇔[g]	⇔[g]	⇔[g]
25-O-desacetyl-rifabutin					12	↑384 (↑309 to ↑474)[g]	↑525 (↑408 to ↑669)[g]	↑394 (↑304 to ↑504)[g]
Rosuvastatin	10 single dose	150 once daily	150 once daily	NA	10	↑89 (↑48 to ↑142)[h]	↑38 (↑13 to ↑67)	NA

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose[b] (mg)	Cobicistat Booster Dose (mg)	Tenofovir Alafenamide (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters (90% CI)[b]		
						C_{max}	AUC	C_{min}
Sofosbuvir	400/100 once daily	150 once daily[f]	150 once daily[f]	10 once daily[f]	24	↑23 (↑7 to ↑42)	↑37 (↑24 to ↑52)	NA
GS-331007[i]						↑29 (↑25 to ↑33)	↑48 (↑43 to ↑53)	↑58 (↑52 to ↑65)
Velpatasvir						↑30 (↑17 to ↑45)	↑50 (↑35 to ↑66)	↑60 (↑44 to ↑78)
Sofosbuvir	400 once daily	150 once daily[f]	150 once daily[f]	10 once daily[f]	29	↑27 (↑9 to ↑48)	⇔	NC
GS-331007[i]						⇔	↑43 (↑39 to ↑47)	NC
Velpatasvir	100 once daily					⇔	⇔	↑46 (↑30 to ↑64)
Voxilaprevir	100 + 100[j] once daily					↑92 (↑63 to ↑126)	↑171 (↑130 to ↑219)	↑350 (↑268 to ↑450)

NA = Not Available/Not Applicable
a. All interaction studies conducted in healthy volunteers.
b. All No Effect Boundaries are 70% -143% unless otherwise specified.
c. No Effect Boundary 80%-125%.
d. Study conducted with STRIBILD.
e. Study conducted with DESCOVY (emtricitabine/tenofovir alafenamide).

f. Study conducted with GENVOYA.
g. Comparison based on rifabutin 300 mg once daily.
h. No Effect Boundary 70%-175% for rosuvastatin C_{max}.
i. The predominant circulating metabolite of sofosbuvir.
j Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

9.5 Drug-Food Interactions

Relative to fasting conditions, administration with a light meal (~373 kcal, 20% fat) increased the mean systemic exposure of elvitegravir by 34%. The alterations in mean systemic exposures of cobicistat and emtricitabine were not clinically significant.

Relative to fasting conditions, administration with a high fat meal (~800 kcal, 50% fat) increased the mean systemic exposure of elvitegravir by 87%. The alterations in mean systemic exposures of cobicistat and emtricitabine were not clinically significant.

Relative to fasting conditions, administration of GENVOYA with a light meal (~400 kcal, 20% fat) or high-fat meal (~800 kcal, 50% fat) increased the mean systemic exposures of tenofovir alafenamide by approximately 15% and 18%, respectively. The alterations in mean systemic exposures of tenofovir alafenamide were not clinically significant.

GENVOYA should be taken with food.

9.6 Drug-Herb Interactions

Coadministration of St. John's wort, a potent CYP3A inducer, may significantly decrease cobicistat, elvitegravir and tenofovir alafenamide plasma concentrations, which may result in loss of therapeutic effect and development of resistance.

Coadministration of GENVOYA with St. John's wort is contraindicated.

9.7 Drug-Laboratory Test Interactions

Interactions of GENVOYA with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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

Elvitegravir

Elvitegravir is an HIV-1 integrase strand transfer inhibitor (INSTI). Integrase is an HIV-1 encoded enzyme that is required for viral replication. Inhibition of integrase prevents the integration of HIV-1 DNA into host genomic DNA, blocking the formation of the HIV-1 provirus and propagation of the viral infection. Elvitegravir does not inhibit human topoisomerases I or II.

Cobicistat

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

Emtricitabine

Emtricitabine is a nucleoside analogue of 2'-deoxycytidine. Emtricitabine is phosphorylated by cellular enzymes to form emtricitabine triphosphate. Emtricitabine triphosphate inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination.

Emtricitabine has activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2) and hepatitis B virus.

Emtricitabine triphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there was no evidence of toxicity to mitochondria *in vitro* and *in vivo*.

Tenofovir Alafenamide

Tenofovir alafenamide is a phosphonamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue) and differs from tenofovir disoproxil fumarate which is another prodrug of tenofovir. Tenofovir alafenamide is permeable into cells and due to increased plasma stability, and intracellular activation through hydrolysis by cathepsin A, tenofovir alafenamide is efficient in loading tenofovir into peripheral blood mononuclear cells (PBMCs) (including lymphocytes and other HIV target cells) and macrophages. Intracellular tenofovir is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination.

Tenofovir has activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2). Tenofovir alafenamide displayed antiviral activity in cell culture against all HIV-1 groups. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ. In the *in vitro* study, tenofovir alafenamide did not significantly affect mitochondrial DNA in HepG2 cells.

10.2 Pharmacodynamics

Effects on Electrocardiogram

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

The electrocardiographic effects of cobicistat were determined in a study of 48 healthy adult patients. Cobicistat did not prolong the QTcF interval at exposures 2- and 4-fold above the recommended therapeutic dose. A modest increase in PR interval (+9.6 msec) occurred around C_{max}, 3 to 5 hours after dosing with 250 mg of cobicistat. This finding was not considered to be clinically significant.

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

In a thorough QT/QTc study in 48 healthy patients, tenofovir alafenamide at the therapeutic dose or at a supratherapeutic dose approximately 5 times the recommended therapeutic dose did not affect the QT/QTc interval and did not prolong the PR interval.

Effects on Serum Creatinine

The effect of cobicistat on serum creatinine was investigated in a Phase 1 study in patients with normal renal function (estimated CrCl ≥ 80 mL/min; N = 18) and mild to moderate renal impairment (estimated CrCl: 50-79 mL/min; N = 12). A statistically significant change of estimated CrCl by Cockcroft-Gault method from baseline was observed after 7 days of treatment with cobicistat 150 mg among patients with normal renal function (-9.9 ± 13.1 mL/min) and mild to moderate renal impairment (-11.9 ± 7.0 mL/min). These decreases in estimated CrCl by Cockcroft-Gault method were reversible after cobicistat was discontinued. The actual glomerular filtration rate, as determined by the clearance of probe drug iohexol, was not altered from baseline following treatment of cobicistat among patients with normal renal function and mild to moderate renal impairment, indicating cobicistat inhibits tubular secretion of creatinine, reflected as a reduction in estimated CrCl by Cockcroft-Gault method, without affecting the actual glomerular filtration rate.

10.3 Pharmacokinetics

Absorption:

GENVOYA: Following oral administration with food in HIV-1 infected adult patients, peak plasma concentrations were observed 4 hours post-dose for elvitegravir, 3 hours post-dose for cobicistat, 3 hours post-dose for emtricitabine, and 1 hour post-dose for tenofovir alafenamide (see Table 11 for additional pharmacokinetic parameters).

Table 11. Pharmacokinetic Parameters of Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Alafenamide, and its Metabolite Tenofovir Exposure Following Oral Administration of GENVOYA with Food in HIV-Infected Adults

Parameter Mean (CV%)	Elvitegravir[a]	Cobicistat[b]	Emtricitabine[b]	Tenofovir Alafenamide[c]	Tenofovir[d]
C_{max} (microgram per mL)	1.7 (22.5)	1.1 (35.6)	1.9 (27.1)	0.16 (51.1)	0.02 (26.1)
AUC_{tau} (microgram•hour per mL)	23.0 (32.5)	8.3 (46.1)	12.7 (35.3)	0.21 (71.8)	0.29 (27.4)
C_{trough} (microgram per mL)	0.45 (57.7)	0.05 (262.8)	0.14 (174.2)	NA	0.01 (28.5)

CV = Coefficient of Variation; NA = Not Applicable
a. From Population Pharmacokinetic analysis, N=419.
b. From Intensive Pharmacokinetic analysis, N=61-62, except cobicistat C_{trough} N=53.
c. From Population Pharmacokinetic analysis, N=539.
d. From Population Pharmacokinetic analysis in Studies 104 and 111, N=841.

Distribution:

Elvitegravir

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

Cobicistat

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

Emtricitabine

In vitro binding of emtricitabine to human plasma proteins is < 4% and is independent of concentration over the range of 0.02 to 200 µg/mL. At peak plasma concentration, the mean plasma to blood drug concentration ratio was ~ 1.0 and the mean semen to plasma drug concentration ratio was ~ 4.0.

Tenofovir Alafenamide

The binding of tenofovir to human plasma proteins is < 0.7% and is independent of concentration over the range of 0.01–25 µg/mL. The binding of tenofovir alafenamide to human plasma proteins in samples collected during clinical studies was approximately 80%.

Metabolism:

Elvitegravir

The majority of elvitegravir metabolism is mediated by CYP3A enzymes. Elvitegravir also undergoes glucuronidation via UGT1A1/3 enzymes.

Cobicistat

Cobicistat is metabolized by CYP3A and to a minor extent by CYP2D6 enzymes and does not undergo glucuronidation.

Emtricitabine

Emtricitabine is not significantly metabolized.

Tenofovir Alafenamide

Metabolism is a major elimination pathway for tenofovir alafenamide in humans, accounting for > 80% of an oral dose. *In vitro* studies have shown that tenofovir alafenamide is metabolized to tenofovir (major metabolite) by cathepsin A in peripheral blood mononuclear cells (PBMCs) (including lymphocytes and other HIV target cells) and macrophages; and by carboxylesterase-1 in hepatocytes. Tenofovir alafenamide is a substrate of P-gp and BCRP transporters, and is

minimally metabolized by CYP3A4. Upon coadministration with the moderate CYP3A inducer probe efavirenz, tenofovir alafenamide exposure was unaffected.

In vivo, tenofovir alafenamide is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. In human clinical studies, a 10 mg oral dose of tenofovir alafenamide in GENVOYA resulted in tenofovir diphosphate concentrations > 4-fold higher in PBMCs and > 90% lower concentrations of tenofovir in plasma as compared to a 300 mg oral dose of tenofovir disoproxil fumarate in STRIBILD.

In vitro, tenofovir alafenamide is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or UGT1A1. Tenofovir alafenamide is not an inhibitor or inducer of CYP3A *in vivo*.

Elimination:

Elvitegravir

The median terminal plasma half-life of elvitegravir is approximately 12.9 hours. After single dose administration of [^{14}C] elvitegravir (coadministered with 100 mg ritonavir), 94.8% and 6.7% of the administered dose was excreted in feces and urine, respectively.

Cobicistat

The median terminal plasma half-life of cobicistat is approximately 3.5 hours. With single dose administration of [^{14}C] cobicistat after multiple dosing of cobicistat for six days, 86.2% and 8.2% of the administered dose was excreted in feces and urine, respectively.

Emtricitabine

Emtricitabine is primarily excreted in the urine by a combination of glomerular filtration and active tubular secretion.

Tenofovir Alafenamide

Tenofovir alafenamide is eliminated following metabolism to tenofovir. Tenofovir is eliminated from the body in the feces and urine by both glomerular filtration and active tubular secretion. Tenofovir alafenamide and tenofovir have a median plasma half-life of 0.51 and 32.37 hours, respectively. Renal excretion of intact tenofovir alafenamide is a minor pathway with less than 1% of the dose eliminated in urine. The pharmacologically active metabolite, tenofovir diphosphate, has a half-life of 150-180 hours within PBMCs.

Special Populations and Conditions

- **Pediatrics (≥ 6 to < 18 years of age)**

  Exposures of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide achieved in 24 pediatric patients aged 12 to < 18 years who received GENVOYA in Study 106 (Table 12) were similar to exposures achieved in treatment-naïve adults (Table 11) following administration of GENVOYA.

Table 12. Multiple Dose Pharmacokinetic Parameters of Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Alafenamide (TAF) and its Metabolite Tenofovir Following Oral Administration of GENVOYA in HIV-Infected Pediatric Patients Aged 12 to less than 18 Years[a]

Parameter Mean (CV%)	Elvitegravir	Cobicistat	Emtricitabine	Tenofovir Alafenamide	Tenofovir
C_{max} (microgram per mL)	2.2 (19.2)	1.2 (35.0)	2.3 (22.5)	0.17 (64.4)	0.02 (23.7)
AUC_{tau} (microgram•hour per mL)	23.8 (25.5)	8.2[b] (36.1)	14.4 (23.9)	0.20[b] (50.0)	0.29[b] (18.8)
C_{trough} (microgram per mL)	0.30 (81.0)	0.03[c] (180.0)	0.10[b] (38.9)	NA	0.01 (21.4)

CV = Coefficient of Variation; NA = Not Applicable
a. From Intensive PK analysis in a trial in treatment-naïve pediatric patients with HIV-1 infection, cohort 1 of Study 106 (N=24).
b. N=23
c. N=15

Exposures of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide achieved in 23 pediatric patients between the ages of 6 to < 12 years (≥ 25 kg) who received GENVOYA in Study 106 (Table 13) were generally higher (20-80%) than exposures achieved in adults (Table 11); however, the increase was not considered clinically relevant as the safety profiles were similar in adult and pediatric patients.

Table 13. Multiple Dose Pharmacokinetic Parameters of Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Alafenamide (TAF) and its Metabolite Tenofovir Following Oral Administration of GENVOYA in HIV-Infected Pediatric Patients Aged 6 to less than 12 Years[a]

Parameter Mean (CV%)	Elvitegravir	Cobicistat	Emtricitabine	Tenofovir Alafenamide	Tenofovir
C_{max} (microgram per mL)	3.1 (38.7)	2.1 (46.7)	3.4 (27.0)	0.31 (61.2)	0.03 (20.8)
AUC_{tau} (microgram•hour per mL)	33.8[b] (57.8)	15.9[c] (51.7)	20.6[b] (18.9)	0.33 (44.8)	0.44 (20.9)
C_{trough} (microgram per mL)	0.37 (118.5)	0.1 (168.7)	0.11 (24.1)	NA	0.02 (24.9)

CV = Coefficient of Variation; NA = Not Applicable
a. From Intensive PK analysis in a trial in virologically-suppressed pediatric patients with HIV-1 infection, cohort 2 of Study 106 (N=23).
b. N=22
c. N=20

- **Geriatrics (≥ 65 years of age)**

  Pharmacokinetic-pharmacodynamic analysis of HIV-infected patients in Phase 2 and Phase 3 trials of GENVOYA showed that within the age range studied (8 to 82 years), age did not have a clinically relevant effect on exposures of tenofovir alafenamide.

- **Sex**

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

- **Ethnic Origin**

  ***Elvitegravir, Cobicistat and Tenofovir Alafenamide*:** Population pharmacokinetic analysis in HIV-1 infected patients indicated that race had no clinically relevant effect on the exposure of cobicistat-boosted elvitegravir, cobicistat or tenofovir alafenamide.

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

- **Hepatic Insufficiency**

  ***Elvitegravir and Cobicistat*:** A study of the pharmacokinetics of cobicistat-boosted elvitegravir was performed in healthy patients and patients with moderate hepatic impairment. No clinically relevant differences in elvitegravir or cobicistat pharmacokinetics were observed between patients with moderate hepatic impairment (Child-Pugh Class B) and healthy patients. No dosage adjustment of elvitegravir or cobicistat is necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of elvitegravir or cobicistat has not been studied.

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

  ***Tenofovir Alafenamide*:** Clinically relevant changes in the pharmacokinetics of tenofovir alafenamide or its metabolite tenofovir were not observed in patients with mild, moderate, or severe hepatic impairment; no tenofovir alafenamide dose adjustment is required in patients with hepatic impairment.

- **Renal Insufficiency**

  <u>Mild to Moderate Renal Impairment (estimated CrCl ≥ 30 and < 70 mL/min)</u>

  The safety, virologic, and immunologic responses of GENVOYA in HIV-1 infected patients with mild to moderate renal impairment (estimated CrCl by Cockcroft-Gault method 30 - 69 mL/min) were evaluated in 242 virologically suppressed patients and 6 treatment-naïve patients in an open-label trial, Study 112. The safety profile of GENVOYA in patients with mild to moderate renal impairment was similar to that in patients with normal renal function.

Severe Renal Impairment (estimated CrCl ≥ 15 and < 30 mL/minute)

No clinically relevant differences in elvitegravir, cobicistat, tenofovir alafenamide, or tenofovir pharmacokinetics were observed between healthy patients and patients with severe renal impairment (estimated CrCl ≥ 15 and < 30 mL/min) in Phase 1 studies of cobicistat-boosted elvitegravir or of tenofovir alafenamide, respectively. In a separate Phase 1 study of emtricitabine alone, emtricitabine exposures were increased in subjects with severe renal impairment. The safety of GENVOYA has not been established in subjects with estimated CrCl ≥ 15 mL/min and < 30 mL/min.

End Stage Renal Disease (estimated CrCl < 15 mL/minute)

Exposures of emtricitabine and tenofovir in 12 subjects with end stage renal disease (estimated CrCl < 15 mL/minute) on chronic hemodialysis who received GENVOYA in Study 1825 were significantly higher than in subjects with normal renal function. However, the safety profile of GENVOYA in subjects with end stage renal disease on chronic hemodialysis was similar to that in subjects with normal renal function. No clinically relevant differences in elvitegravir, cobicistat, or tenofovir alafenamide pharmacokinetics were observed in patients with end stage renal disease as compared to those with normal renal function.

There are no pharmacokinetic data on elvitegravir, cobicistat, or tenofovir alafenamide in patients with estimated CrCl < 15 mL/min not on chronic hemodialysis.

- **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 Alafenamide*:** Pharmacokinetics of emtricitabine and tenofovir alafenamide have not been fully evaluated in patients coinfected with hepatitis B and/or C virus.

11 STORAGE, STABILITY AND DISPOSAL

Store below 30°C (86°F).

- Keep container tightly closed.
- Dispense only in original container.
- Do not use if seal over bottle opening is broken or missing.
- Keep out of reach and sight of children

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

GENVOYA is a fixed-dose combination, single tablet regimen containing elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide hemifumarate. Elvitegravir is an HIV-1 integrase strand transfer inhibitor (INSTI). Cobicistat is a mechanism-based inhibitor of cytochrome P450 (CYP) enzymes of the CYP3A family. Emtricitabine is a synthetic nucleoside analog of cytidine. Tenofovir alafenamide, a nucleoside reverse transcriptase inhibitor (NRTI), is a prodrug of tenofovir converted *in vivo* to tenofovir, and acyclic nucleoside phosphanate (nucleotide) analog of adenosine 5'-monophosphate.

Elvitegravir

Drug Substance

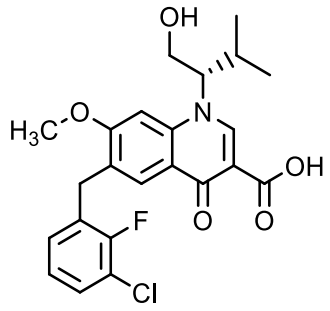
Common Name: elvitegravir (USAN)

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

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

Molecular Weight: 447.9

Structural Formula:



Physicochemical Properties:

Description: Elvitegravir is a white to pale yellow powder.

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

Cobicistat

Drug Substance

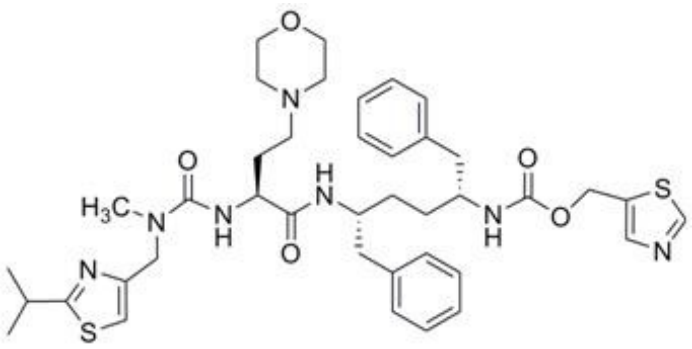
Common Name: cobicistat (USAN)

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

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

Molecular Weight: 776.0

Structural Formula:



Physicochemical Properties:

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

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

Emtricitabine

Drug Substance

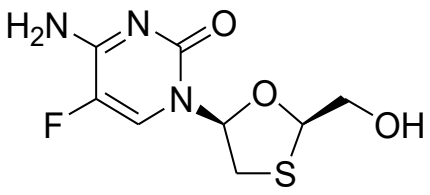
Common Name: emtricitabine (USAN)

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

Empirical Formula: $C_8H_{10}FN_3O_3S$

Molecular Weight: 247.24

Structural Formula:



Physicochemical Properties:

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

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

Tenofovir alafenamide

Drug Substance

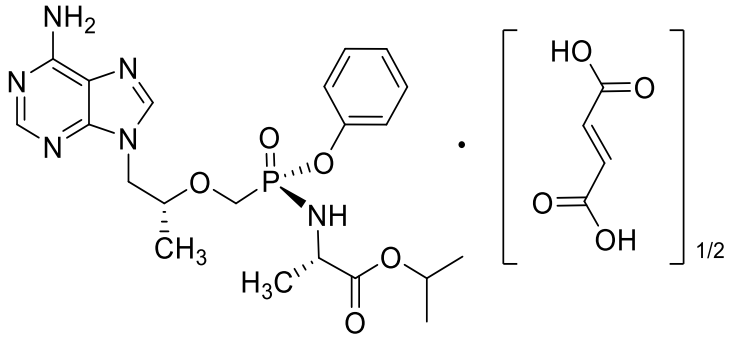
Common Name: Tenofovir alafenamide hemifumarate
Tenofovir alafenamide fumarate (USAN)

Chemical Name: Propan-2-yl N-[(S)-({[(2R)-1-(6-amino-9H-purin-9-yl)propan-2-yl]-oxy}methyl)(phenoxy)phosphoryl]-l-alaninate, (2E)-but-2-enedioate (2:1)

Empirical Formula: $C_{21}H_{29}O_5N_6P \cdot 1/2(C_4H_4O_4)$

Molecular Weight: 534.5

Structural Formula:



Physicochemical Properties:

Description: TAF hemifumarate is a white to off-white or tan powder.

Solubility: The solubility of TAF hemifumarate in water, pH 8.0 (50 mM phosphate buffer) at 20°C is 4.86 mg/mL. The partition coefficient (log P) is 1.6 and the pKa is 3.96.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

HIV-1 With No Known Mutations to the Individual Components of GENVOYA

Description of Clinical Studies

The efficacy and safety of GENVOYA in HIV-1 infected, treatment-naïve adults are based on 48-week data from two randomized, double-blind, active-controlled studies, Study 104 and Study 111 (N=1733). The efficacy and safety of GENVOYA in virologically suppressed HIV-1 infected adults are based on 48-week data from a randomized, open-label, active-controlled study, Study 109 (N=1436).

The efficacy and safety of GENVOYA in HIV-1 infected, virologically suppressed patients with mild to moderate renal impairment is based on 24-week data from an open-label study, Study 112 (N=242).

The efficacy and safety of GENVOYA in HIV-1 infected, virologically suppressed patients with end stage renal disease on chronic hemodialysis is based on 48-week data from a single arm, open-label study, Study 1825 (N=55).

The efficacy and safety of GENVOYA in HIV-1 infected, treatment-naïve pediatric patients between the ages of 12 to < 18 years (≥ 35 kg) is based on 24-week data from Cohort 1 of an open-label study, Study 106 (N=50).

The efficacy and safety of GENVOYA in virologically suppressed HIV-1 pediatric patients between the ages of 6 to < 12 years (≥ 25 kg) is based on 24-week from Cohort 2 of an open-label study, Study 106 (N=23).

Treatment Naïve HIV-1 Infected Patients

In both Study 104 and Study 111, patients were randomized in a 1:1 ratio to receive either GENVOYA (N = 866) once daily or STRIBILD (elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg; N = 867) once daily.

In Studies 104 and 111, the mean age was 36 years (range 18-76), 85% were male, 57% were White, 25% were Black, and 10% were Asian. Nineteen percent of patients identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.5 log10 copies per mL (range 1.3–7.0). The mean baseline CD4+ cell count was 427 cells /mm^3 (range 0-1360) and 13% had CD4+ cell counts < 200 cells /mm^3. Twenty-three percent of patients had baseline viral loads > 100,000 copies per mL.

For demographic and baseline characteristics for Study 104 and 111, see

Table 14.

Table 14. Pooled Demographic and Baseline Characteristics of Antiretroviral Treatment-naïve HIV-1 Infected Adult Patients in Studies 104 and 111

	GENVOYA (N=866)	STRIBILD (N=867)
Demographic characteristics		
Median age, years (range)	33 (18-74)	35 (18-76)
Sex		
Male	733	740
Female	133	127
Race		
American Indian/ Alaska Native	5	8
White	485	498
Black	223	213
Native Hawaiian/ Pacific Islander	5	4
Asian	91	89
Other	57	55
Baseline disease characteristics		
Median baseline plasma HIV-1 RNA log_{10} copies/mL (range)	4.58 (2.57-6.89)	4.58 (1.28-6.98)
Percentage of patients with viral load ≤ 100,000 copies/mL	77.4	77.5
Percentage of patients with viral load > 100,000 to ≤ 400,000 copies/mL	17.0	17.8
Percentage of patients with viral load > 400,000 copies/mL	5.7	4.7
Median baseline CD4+ cell count /µL (range)	404 (0-1311)	406 (1-1360)
Percentage of patients with CD4+ cell counts < 200 cells/mm^3	13.0	13.5
HIV disease status		
Asymptomatic	779	800
Symptomatic HIV infection	53	34
AIDS	31	29

Unknown	3	4
Estimated CrCl by Cockcroft-Gault method (mL/min), median (Q1, Q3)	117.0 (99.6, 135.6)	113.9 (99.0, 133.6)
Proteinuria by urinalysis (dipstick)		
Grade 0	778	780
Grade 1	80	67
Grade 2	8	18
Grade 3	0	1
-Missing-	0	1

In both studies, patients were stratified by baseline HIV-1 RNA (≤ 100,000 copies per mL, > 100,000 copies per mL to ≤ 400,000 copies per mL, or > 400,000 copies per mL), by CD4 count (< 50 cells per µL, 50-199 cells per µL, or ≥ 200 cells per µL), and by region (US or ex-US).

Treatment outcomes of Studies 104 and 111 through 48 and 144 weeks are presented in Table 15.

Table 15. Pooled Virologic Outcomes of Studies 104 and 111 at Weeks 48[a] and 144[b]

	Week 48		Week 144	
	GENVOYA (N=866)	**STRIBILD (N=867)**	**GENVOYA (N=866)**	**STRIBILD (N=867)**
Virologic Success HIV-1 RNA < 50 copies/mL	92%	90%	84%	80%
Treatment Difference	2.0% (95% CI: -0.7% to 4.7%)		4.2% (95% CI: 0.6% to 7.8%)	
Virologic Failure HIV-1 RNA ≥ 50 copies/mL[c]	4%	4%	5%	4%
No Virologic Data at Week 48 or Week 144 Window	4%	6%	11%	16%
Discontinued Study Drug Due to AE or Death[d]	1%	2%	1%	3%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[e]	2%	4%	9%	11%
Missing Data During Window but on Study Drug	1%	< 1%	1%	1%
Proportion (%) of Patients with HIV-1 RNA < 50 copies/mL by Subgroup				
Age				
< 50 years	716/777 (92%)	680/753 (90%)	647/777 (83%)	602/753 (80%)
≥ 50 years	84/89 (94%)	104/114 (91%)	82/89 (92%)	92/114 (81%)
Sex				
Male	674/733 (92%)	673/740 (91%)	616/733 (84%)	603/740 (81%)
Female	126/133 (95%)	111/127 (87%)	113/133 (85%)	91/127 (72%)

	Week 48		Week 144	
	GENVOYA (N=866)	**STRIBILD (N=867)**	**GENVOYA (N=866)**	**STRIBILD (N=867)**
Race				
Black	197/223 (88%)	177/213 (83%)	168/223 (75%)	152/213 (71%)
Nonblack	603/643 (94%)	607/654 (93%)	561/643 (87%)	542/654 (83%)
Baseline Viral Load				
≤ 100,000 copies/mL	629/670 (94%)	610/672 (91%)	567/670 (85%)	537/672 (80%)
> 100,000 copies/mL	171/196 (87%)	174/195 (89%)	162/196 (83%)	157/195 (81%)
Baseline CD4+ cell count				
< 200 cells /mm^3	96/112 (86%)	104/117 (89%)	93/112 (83%)	94/117 (80%)
≥ 200 cells /mm^3	703/753 (93%)	680/750 (91%)	635/753 (84%)	600/750 (80%)

a. Week 48 window was between Day 294 and 377 (inclusive).
b. Week 144 window was between Day 966 and 1049 (inclusive).
c. Included patients who had ≥ 50 copies/mL in the Week 48 or 144 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.
d. Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
e. Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy; eg, withdrew consent, loss to follow-up, etc.

GENVOYA met the noninferiority criteria in achieving HIV-1 RNA < 50 copies/mL at Week 48 and 96 when compared to STRIBILD. At Week 144, GENVOYA demonstrated statistical superiority (p = 0.021) in achieving HIV-1 RNA < 50 copies/mL when compared to STRIBILD. In Studies 104 and 111, the 95% CIs for differences in virologic success between treatment groups included zero for most subgroups evaluated suggesting no differences between the treatments.

In Studies 104 and 111, the mean increase from baseline in CD4+ cell count at Week 48, Week 96, and Week 144 was 230 cells/mm^3, 280 cells/mm^3, and 326 cells/mm^3, respectively, in GENVOYA-treated patients, and 211 cells/mm^3, 266 cells /mm^3, and 305 cells/mm^3, respectively, in STRIBILD treated patients (p = 0.024, p = 0.14, and p = 0.06 at Week 48, Week 96, and Week 144, respectively).

Bone Mineral Density

In the pooled analysis of Studies 104 and 111, the effects of GENVOYA compared to that of STRIBILD on bone mineral density (BMD) from baseline to Week 48, Week 96, and Week 144 were assessed by dual-energy X-ray absorptiometry (DXA). As shown in Table 16, in patients who had both baseline and Weeks 48, 96, and 144 measurements (Week 48: N = 780 and 784 in the GENVOYA group and N = 767 and 773 in the STRIBILD group, for hip and spine, respectively; Week 96: N = 716 and 722 in the GENVOYA group and N = 711 and 714 in the STRIBILD group for hip and spine, respectively; Week 144: N = 690 and 702 in the GENVOYA group and N = 683 and 686 in the STRIBILD group, for hip and spine, respectively) there were smaller decreases in BMD in the GENVOYA group as compared to STRIBILD.

Table 16. Measures of Bone Mineral Density in Studies 104 and 111 (Week 48, Week 96, and Week 144 Analyses)

	Week 48				Week 96				Week 144			
	GENVOYA	STRIBILD	Treatment Difference		GENVOYA	STRIBILD	Treatment Difference		GENVOYA	STRIBILD	Treatment Difference	
Hip DXA Analysis	**N=780**	**N=767**	**Difference in LSM (95% CI)**	**P-value**	**N=716**	**N=711**	**Difference in LSM (95% CI)**	**P-value**	**N=690**	**N=683**	**Difference in LSM (95% CI)**	**P-value**
Mean (SD) Percent Change in BMD	-0.7% (3.3%)	-3.0% (3.4%)	2.3% (2.0 to 2.6)	p < 0.001	-0.7% (3.9%)	-3.3% (4.0%)	2.6% (2.2 to 3.0)	p < 0.001	-0.8% (4.4%)	-3.4% (4.3%)	2.6% (2.2 to 3.1)	p < 0.001
Patients with Categorical Change:												
> 3% Decrease in BMD	17%	50%	--	--	23%	56%	--	--	28%	55%	--	--
> 3% Increase in BMD	7%	3%			12%	6%			13%	6%		
Patients with No Decrease (≥ zero % change) in BMD	35%	14%	--	--	39%	16%	--	--	40%	19%	--	--
Lumbar Spine DXA Analysis	**N=784**	**N=773**			**N=722**	**N=714**			**N=702**	**N=686**		
Mean (SD) Percent Change in BMD	-1.3% (3.1%)	-2.9% (3.2%)	1.6% (1.2 to 1.9)	p < 0.001	-1.0% (3.7%)	-2.8% (3.9%)	1.8% (1.4 to 2.2)	p < 0.001	-0.9% (4.1%)	-3.0% (4.3%)	2.0% (1.6 to 2.5)	p < 0.001

	Week 48				Week 96				Week 144			
	GENVOYA	STRIBILD	Treatment Difference		GENVOYA	STRIBILD	Treatment Difference		GENVOYA	STRIBILD	Treatment Difference	
Patients with Categorical Change:												
> 3% Decrease in BMD	27%	46%	--	--	26%	48%	--	--	30%	49%	--	--
> 3% Increase in BMD	7%	3%			11%	6%			13%	7%		
Patients with No Decrease (≥ zero % change) in BMD	34%	17%	--	--	37%	21%	--	--	39%	22%	--	--

Changes in Renal Laboratory Tests and Renal Safety

Laboratory tests were performed in Studies 104 and 111 to compare the effect of TAF, administered as a component of GENVOYA, to that of tenofovir DF, administered as a component of STRIBILD, on renal laboratory parameters. As shown in Table 17, there were statistically significantly higher increases in serum creatinine, Urine Protein to Creatinine Ratio (UPCR), Urine Albumin to Creatinine Ratio (UACR), urine retinol binding protein (RBP) to creatinine ratio, and urine beta-2-microglobulin to creatinine ratio in the STRIBILD group as compared to the GENVOYA group. There were zero cases of Fanconi syndrome or Proximal Renal Tubulopathy (PRT) in the GENVOYA group through Week 144.

Table 17. Change from Baseline in Renal Laboratory Tests in Studies 104 and 111 (Week 48, Week 96, and Week 144 Analyses)

	Week 48			Week 96			Week 144		
	GENVOYA (N=866)	STRIBILD (N=867)	Treatment Difference	GENVOYA (N=866)	STRIBILD (N=867)	Treatment Difference	GENVOYA (N=866)	STRIBILD (N=867)	Treatment Difference
Serum Creatinine (µmol/L)[a]	7.07 ± 10.96	9.72 ± 19.18	-3.54 p < 0.001	3.54 ± 10.08	6.19 ± 11.23	-2.65 p < 0.001	3.54 ± 10.61	6.19 ± 11.23	-3.54 p < 0.001
Proteinuria by Urine Dipstick[b]	31%	37%	p = 0.022	36%	41%	p = 0.034	40%	45%	p = 0.027
Urine Protein to Creatinine Ratio [UPCR][c]	-3.4%	19.8%	p < 0.001	-9.1%	16.2%	p < 0.001	-10.5%	25.2%	p < 0.001
Urine Albumin to Creatinine Ratio [UACR][c,d]	-4.7%	7.1%	p < 0.001	-5.2%	4.9%	p < 0.001	-[d]	-[d]	-[d]
Urine RBP to Creatinine Ratio[c]	9.2%	51.2%	p < 0.001	13.8%	74.2%	p < 0.001	34.8%	111%	p < 0.001
Urine Beta-2-Microglobulin to Creatinine Ratio[c]	-31.7%	24.1%	p < 0.001	-32.1%	33.5%	p < 0.001	-25.7%	53.8%	p < 0.001

a. Mean change ± SD.
b. Includes all severity grades (1-3).
c. Median percent change.
d. UACR was assessed up to Week 96.

At Weeks 48, 96, and 144, the proportion of patients with any grade hypophosphatemia in GENVOYA was 3.6%, 5.6%, and 6.8%, respectively, and 4.0%, 5.4%, and 7.6%, respectively, in STRIBILD. The median (Q1, Q3) change from baseline in $FEPO_4$ was 2.0% (-1.2%, 5.6%), 2.1% (-1.3%, 5.5%), and 3.0% (-0.7%, 7.2%) at Weeks 48, 96, and 144, respectively, in patients receiving GENVOYA, and 2.6% (-0.7%, 6.4%), 2.7% (-0.8%, 7.0%), and 4.1% (0.2%, 8.0%) at Weeks 48, 96, and 144, respectively, in patients receiving STRIBILD (p = 0.006, 0.009, and 0.001, at Weeks 48, 96, and 144, respectively).

The median (Q1, Q3) change from baseline in the ratio of the renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate (TmP/GFR) was -0.2 (-0.7 mg/dL, 0.2 mg/dL), -0.3 mg/dL (-0.9 mg/dL, 0.2 mg/dL), and -0.4 mg/dL (-1.0 mg/dL, 0.1 mg/dL) at Weeks 48, 96, and 144, respectively, in patients receiving GENVOYA, and -0.3 (-0.7 mg/dL, 0.2 mg/dL), -0.4 mg/dL (-0.8 mg/dL, 0.1 mg/dL), and -0.5 mg/dL (-1.0 mg/dL, 1.0 mg/dL) at Weeks 48, 96, and 144, respectively, in patients receiving STRIBILD (p = 0.21, 0.35, and 0.011 at Weeks 48, 96, and 144, respectively).

Changes in Lipid Laboratory Tests

Increases from baseline were observed in both treatment groups for the fasting lipid parameters total cholesterol, direct LDL, HDL, and triglycerides at Weeks 48, 96, and 144. The median increase from baseline for these parameters was greater in the GENVOYA group compared with the STRIBILD group (p < 0.001 for the difference between treatment groups for fasting total cholesterol, direct LDL, HDL, and triglycerides). Median (Q1, Q3) change from baseline at Weeks 48, 96, and 144 in total cholesterol to HDL ratio was 0.1 (-0.3, 0.5), 0.1 (-0.3, 0.7), and 0.2 (-0.3, 0.7), respectively, in the GENVOYA group and 0.0 (-0.5, 0.4), 0.0 (-0.4, 0.5), and 0.1 (-0.4, 0.6), respectively, in the STRIBILD group (p < 0.001 for the difference between treatment groups at Weeks 48 and 96; p = 0.006 at Week 144).

Virologically Suppressed HIV-1 Infected Patients

In Study 109, the efficacy and safety of switching from either ATRIPLA (efavirenz/emtricitabine/tenofovir disoproxil fumarate [EFV/FTC/TDF]), TRUVADA (emtricitabine/tenofovir disoproxil fumarate [FTC/TDF]) plus atazanavir (boosted by either cobicistat or ritonavir), or STRIBILD to GENVOYA were evaluated in a randomized, open-label study of virologically suppressed (HIV-1 RNA < 50 copies/mL) HIV-1 infected adults (N = 1436). Patients must have been stably suppressed (HIV-1 RNA < 50 copies/mL) on their baseline regimen for at least 6 months and had no resistance mutations to any of the components of GENVOYA prior to study entry. Patients were randomized in a 2:1 ratio to either switch to GENVOYA at baseline (N = 959), or stay on their baseline antiretroviral regimen (N = 477). Patients had a mean age of 41 years (range 21-77), 89% were male, 67% were White, and 19% were Black. The mean baseline CD4+ cell count was 697 cells/mm^3 (range 79-1951). Demographic and baseline characteristics are presented in Table 18.

Patients were stratified by prior treatment regimen. At screening, 42% of patients were receiving TRUVADA plus atazanavir (boosted by either cobicistat or ritonavir), 32% of patients were receiving STRIBILD, and 26% of patients were receiving ATRIPLA.

Table 18. Demographic and Baseline Characteristics of Virologically Suppressed HIV-1 Infected Adult Patients in Study 109

	Study 109	
	GENVOYA (N= 959)	**Baseline Regimen (N= 477)**
Demographic characteristics		
Median age, years (range)	41 (21-77)	40 (22-69)
Sex		
Male	856	427
Female	103	50
Race		
American Indian/ Alaska Native	5	2
White	651	314
Black	169	102
Native Hawaiian/ Pacific Islander	6	1
Asian	59	35
Other	67	22
Not permitted	2	1
Prior treatment regimen		
STB	306	153
ATR	251	125
ATV/boosted +TVD	402	199
Baseline disease characteristics		
HIV-1 RNA < 50 copies/mL	943	466
CD4 cell count (cells/µL), median (Q1, Q3)	675 (520, 833)	662 (525, 831)
Estimated CrCl by Cockcroft-Gault method (mL/min), median (Q1, Q3)	105.7 (89.4, 126.0)	107.7 (88.7, 128.2)
Proteinuria by urinalysis (dipstick)		
Grade 0	873	430
Grade 1	81	44
Grade 2	4	3
Grade 3	0	0
-Missing-	1	0

STB: STRIBILD; ATR: ATRIPLA; ATV: atazanavir; TVD: TRUVADA

Treatment outcomes of Study 109 through 48 and 96 weeks are presented in Table 19.

Table 19. Virologic Outcomes of Study 109 at Weeks 48[a] and 96[b]

	Week 48		Week 96	
	GENVOYA (N=959)	**Baseline Regimen (N=477)**	**GENVOYA (N=959)**	**Baseline Regimen (N=477)**
Virologic Success HIV-1 RNA < 50 copies/mL	97%	93%	93%	89%
Treatment Difference	4.1% (95% CI: 1.6% to 6.7%)		3.7% (95% CI: 0.4% to 7.0%)	
p-value	p < 0.001		p = 0.017	
Virologic Failure HIV-1 RNA ≥ 50 copies/mL[c]	1%	1%	2%	2%
No Virologic Data at Week 48 Window	2%	6%	5%	9%
Discontinued Study Drug Due to AE or Death[d]	1%	1%	1%	3%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[e]	1%	4%	3%	6%
Missing Data During Window but on Study Drug	0	≤ 1%	1%	< 1%

a. Week 48 window was between Day 294 and 377 (inclusive).
b. Week 96 window was between Day 630 and 713 (inclusive).
c. Included patients who had ≥ 50 copies/mL in the Week 48 or Week 96 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.
d. Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
e. Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy; eg, withdrew consent, loss to follow-up, etc.

Switching to GENVOYA was superior at Week 48 (p < 0.001) and at Week 96 (p = 0.017) in maintaining HIV-1 RNA < 50 copies/mL when compared to patients who stayed on their baseline regimen.

The mean increase from baseline in CD4+ cell count at Week 48 and Week 96 was 35 cells/mm^3 and 60 cells /mm^3 in GENVOYA-treated patients, respectively, and 24 cells/mm^3 and 42 cells /mm^3 in patients who stayed on their baseline regimen, respectively.

Bone Mineral Density: Changes in BMD from baseline to Week 48 were assessed by DXA in patients who had both baseline and Week 48 measurements (N=869 and N=881 in the GENVOYA arm, and N=428 and N=436 in patients who remained on their baseline regimen, for hip and spine, respectively). Changes in BMD from baseline to Week 96 were assessed by DXA in patients who had both baseline and Week 96 measurements (N= 809 and N= 821 in the

GENVOYA arm, and N= 396 and N= 401 in patients who remained on their baseline regimen, for hip and spine, respectively). Results for Weeks 48 and 96 are summarized in Table 20.

At Week 96, the mean (SD) change from baseline was 2.4% (3.6) and 2.1% (3.8) in the GENVOYA group and -0.5% (3.4) and -0.1% (3.5) in the FTC/TDF + 3rd agent baseline regimen group, in hip and spine BMD, respectively ($p < 0.001$ for the differences between groups at Week 96).

Table 20. Measures of Bone Mineral Density in Study 109 (Week 48 and Week 96 Analyses)

	Week 48				Week 96			
	GENVOYA	**Baseline Regimen**	**Treatment Difference**		**GENVOYA**	**Baseline Regimen**	**Treatment Difference**	
Hip DXA Analysis	**N=869**	**N=428**	**Difference in LSM (95% CI)**	**P-value**	**N=809**	**N=396**	**Difference in LSM (95% CI)**	**P-value**
Mean (SD) Percent Change in BMD	1.5% (2.7%)	-0.3% (2.8%)	1.8% (1.5 to 2.1)	p < 0.001	2.4% (3.6%)	-0.5% (3.4%)	2.9% (2.5 to 3.3)	p < 0.001
Patients with Categorical Change: > 3% Decrease in BMD > 3% Increase in BMD	 3% 21%	 13% 7%	--		 2% 35%	 15% 9%	--	
Patients with No Decrease (≥ zero % change) in BMD	78%	46%	--		82%	43%	--	
Lumbar Spine DXA Analysis	**N=881**	**N=436**			**N=821**	**N=401**		
Mean (SD) Percent Change in BMD	1.6% (3.8%)	-0.4% (4.1%)	2.0% (1.5 to 2.4)	p < 0.001	2.1% (3.8%)	-0.1% (3.5%)	2.2% (1.8 to 2.6)	p < 0.001
Patients with Categorical Change: > 3% Decrease in BMD > 3% Increase in BMD	 8% 33%	 19% 13%	--		 6% 37%	 17% 18%	--	
Patients with No Decrease (≥ zero % change) in BMD	74%	47%	--		75%	47%	--	

Changes in Renal Laboratory Tests and Renal Safety

There were decreases from baseline in proteinuria (UPCR), albuminuria (UACR), and tubular proteinuria (urine RBP to creatinine ratio and urine beta-2-microglobulin to creatinine ratio), and also in other measures of proximal renal tubular dysfunction (including fractional excretion of uric acid [FEUA]) in patients receiving GENVOYA, as compared with increases from baseline in patients who stayed on their TDF-containing baseline regimen, collectively indicating a reduced impact of TAF on proximal renal tubular function. At Week 96, the median percentage change in UPCR was −26% vs. 9%; in UACR it was −14% vs. 11%. At Week 48, the median percentage change in urine RBP to creatinine ratio was −33% vs. 18%; and in urine beta-2-microglobulin to creatinine ratio it was −52% vs. 19%. P-value was < 0.001 for all comparisons. There were zero cases of Fanconi syndrome or PRT in patients switching to GENVOYA through Week 96.

HIV-1 Infected Patients with Renal Impairment

Study 112: Virologically-suppressed adults with renal impairment

In Study 112, the efficacy and safety of GENVOYA were evaluated in an open-label clinical study in which 242 HIV-1 infected patients with mild to moderate renal impairment (estimated CrCl by Cockcroft-Gault method between 30 to 69 mL/minute) switched to GENVOYA as shown in Table 21. Patients were virologically suppressed (HIV-1 RNA < 50 copies/mL) for at least 6 months before switching to GENVOYA.

The mean age was 58 years (range 24-82), with 63 patients (26%) who were ≥ 65 years of age. Seventy-nine percent were male, 63% were White, 18% were Black, and 14% were Asian. Thirteen percent of patients identified as Hispanic/Latino. At baseline, median estimated CrCl was 56 mL/minute, and 33% of patients had an estimated CrCl from 30 to 49 mL/minute. The mean baseline CD4+ cell count was 664 cells /mm^3 (range 126-1813).

Table 21. Demographic and Baseline Characteristics of Virologically Suppressed HIV-1 Infected Adult Patients in Study 112

	Study 112	
	Cohort 1: ART-Experienced	
	Baseline estimated CrCl by Cockcroft-Gault method < 50 mL/min (N = 80)	**Baseline estimated CrCl by Cockcroft-Gault method ≥ 50 mL/min (N = 162)**
Demographic characteristics		
Median age, years (range)	59 (31-82)	58 (24-76)
Sex		
Male	59	133
Female	21	29
Race		

American Indian/ Alaska Native	1	0
White	39	113
Black	14	30
Native Hawaiian/ Pacific Islander	0	2
Asian	23	11
Other	3	4
Not permitted	0	2
Baseline disease characteristics		
HIV-1 RNA categories (copies/mL)		
< 50	78	158
≥ 50 to ≤ 100,000	2	4
> 100,000 to ≤ 400,000	0	0
CD4 cell count (cells/uL), median (Q1, Q3)	622 (449, 844)	635 (461, 797)
HIV disease status		
Asymptomatic	46	134
Symptomatic HIV infection	18	10
AIDS	16	18
Estimated CrCl by Cockcroft-Gault method[b] (mL/min), median (Q1, Q3)	42.6 (37.7, 45.7)	60.3 (55.5, 65.0)
Proteinuria by urinalysis (dipstick)		
Grade 0	45	118
Grade 1	23	33
Grade 2	12	11
Grade 3	0	0

In a substudy, patients given GENVOYA (N=32) had no change from baseline in their actual glomerular filtration rate at Week 24, as measured by iohexol clearance.

At Week 24, 95.0% (230/242 patients) maintained HIV-1 RNA < 50 copies/mL after switching to GENVOYA. Three patients had virologic failure at Week 24. At Week 96, 88.4% (214/242) of patients maintained HIV-1 RNA < 50 copies/mL after switching to GENVOYA. At Week 144, 83.1% (197/237) maintained HIV-1 RNA < 50 copies/mL after switching to GENVOYA; 14.8% of patients had no virologic data in the Week 144 window. Five patients among the entire study population had virologic failure at Week 144.

Changes from baseline in renal laboratory tests at Weeks 24, 96, and 144 in patients who switched to GENVOYA are presented in Table 22. The prevalence of clinically significant proteinuria (UPCR > 200 mg/g) was 42% at baseline, and decreased to 21%, 18%, and 16% at Weeks 24, 96, and 144, respectively. The prevalence of clinically significant albuminuria (UACR ≥ 30 mg/g) was 49% at baseline, and decreased to 27%, 27%, and 32% at Weeks 24, 96, and 144, respectively. Other renal assessments, including fractional excretion of uric acid, serum cystatin C, and serum phosphorus showed small changes from baseline at each time point through Weeks 24, 96, and 144. Overall, multiple assessments of renal function indicate that changes in renal function were observed as soon as 1 week after switching to GENVOYA and persisted through 144 weeks.

Table 22. Change from Baseline in Renal Laboratory Tests at Week 24, Week 96, and Week 144 in Virologically Suppressed Patients with Renal Impairment who Switched to GENVOYA in Study 112 (Week 24, Week 96, and Week 144 Analyses)

	Week 24	Week 96	Week 144
	GENVOYA (N=242)		
Serum Creatinine (µmol/L)[a]	1.77 ± 22.19	-2.65 ± 24.66	-4.42 ± 25.38
Improvement in Proteinuria by Urine Dipstick[b]	57/76 (75%)	60/71 (85%)	56/66 (85%)
Urine Protein to Creatinine Ratio [UPCR][c]	-35.3%	-37.7%	-45.7%
Urine Albumin to Creatinine Ratio [UACR][c]	-38.8%	-45.5%	-35.1%
Urine RBP to Creatinine Ratio[c]	-56.2%	-64.1%	-63.8%
Urine Beta-2-Microglobulin to Creatinine Ratio[c]	-70.7%	-83.6%	-81.9%

a. Mean change ± SD.
b. An improvement of at least 1 toxicity grade from baseline.
c. Median percent change.

Bone Mineral Density: In virologically suppressed patients with renal impairment who switched to GENVOYA, mean percentage increases from baseline at Weeks 24, 96, and 144 were observed in hip and spine BMD. At Week 144, assessment of BMD using a threshold of 3% for changes from baseline revealed higher percentages of patients had increases versus decreases from baseline in BMD at both hip (38.4% versus 9.0%) and spine (47.4% versus 10.3%).

At Week 144, the mean (SD) percentage BMD increase from baseline was 3.2% (4.9) at the hip and 3.6% (5.2) at the spine for patients who switched to GENVOYA from a TDF-based regimen.

The median (Q1, Q3) percentage increases from baseline in hip and spine BMD were higher in virologically suppressed patients who switched to GENVOYA from a TDF-based regimen (hip: 2.3% [0.4%, 4.8%], spine: 3.7% [0.7%, 6.0%]) than in those patients who switched to GENVOYA from a non-TDF-based regimen (hip: 1.0% [-1.5%, 3.3%], spine: 0.6% [-1.6%, 4.1%]). The percentage changes (increases) from baseline in hip and spine BMD were statistically significant at each time point through Week 144 for virologically suppressed patients who switched to GENVOYA from a TDF-based regimen ($p < 0.001$).

Study 1825: Virologically-suppressed adults with end stage renal disease (ESRD) receiving chronic hemodialysis

In Study 1825, the efficacy and safety of GENVOYA were evaluated in a single arm, open-label clinical study in which 55 HIV-1 infected adults with end stage renal disease (estimated CrCl by Cockcroft-Gault method < 15 mL/min) receiving chronic hemodialysis for at least 6 months switched to GENVOYA. Patients were virologically suppressed (HIV-1 RNA < 50 copies/mL) for at least 6 months before switching to GENVOYA.

The mean age was 48 years (range 23-64). Seventy-six percent were male, 82% were Black and 18% were White. Fifteen percent of patients identified as Hispanic/Latino. The mean baseline CD4+ cell count was 545 cells/mm^3 (range 205-1473).

At Week 48, 81.8% (45/55 patients) maintained HIV-1 RNA < 50 copies/mL after switching to GENVOYA. Two patients had HIV-1 RNA ≥ 50 copies/mL by Week 48. Seven patients discontinued the study drug due to AE or other reasons while suppressed. One patient did not have an HIV-1 RNA measurement at Week 48. There were no clinically significant changes in fasting lipid laboratory tests in patients who switched to GENVOYA.

HIV-1 With No Known Mutations in Pediatrics

In Study 106, the efficacy, safety, and pharmacokinetics of GENVOYA in HIV-1 infected patients were evaluated in an open-label study in HIV-1-infected treatment-naïve adolescents between the ages of 12 to < 18 years (≥ 35 kg) (N=50) through Week 48 and in virologically suppressed pediatric patients between the ages of 6 to < 12 years (≥ 25 kg) (N=23) through Week 24.

Cohort 1: Treatment-Naïve Adolescents (12 to < 18 Years of Age and Weighing ≥ 35 kg)

Patients in Cohort 1 had a mean age of 15 years (range: 12 to 17), 44% were male, 12% were Asian, and 88% were black. At baseline, mean plasma HIV-1 RNA was 4.6 $\log_{10}$ copies/mL, median CD4+ cell count was 456 cells/mm^3 (range: 95 to 1110), and median CD4+% was 23% (range: 7% to 45%). Twenty-two percent had baseline plasma HIV-1 RNA > 100,000 copies/mL as shown in Table 23.

Table 23. Demographic and Baseline Characteristics of Treatment-naïve HIV-1 Infected Adolescent Patients in Study 106 (Cohort 1)

	Study 106 (Cohort 1)
	GENVOYA (N= 50)
Demographic characteristics	
Median age, years (range)	15 (12-17)
Sex	
Male	22
Female	28
Race	
Asian	6
Black	44
Baseline BMI (kg/m^2), median (Q1, Q3)	20.0 (18.1, 23.1)
Baseline disease characteristics	
HIV-1 RNA (log10 copies/mL), median (Q1, Q3)	4.65 (4.25, 4.94)
HIV-1 RNA > 100,000 copies/mL	11
CD4 cell count (cells/µL), median (Q1, Q3)	456 (332, 574)
Mode of infection (HIV risk factors)	
Heterosexual sex	12
Homosexual sex	8
IV drug use	1
Vertical transmission	32
HIV disease status	
Asymptomatic	42
Symptomatic HIV infection	8
Estimated CrCl by Schwartz formula (mL/min/1.73 m^2), median (Q1, Q3)	156 (129.0, 185.0)
Proteinuria by urinalysis (dipstick), n (%)	
Grade 0	48

	Study 106 (Cohort 1)
	GENVOYA (N= 50)
Grade 1	1
Grade 2	1
Grade 3	0

Cohort 1: Treatment-naïve Adolescents (≥ 12 to < 18 Years of Age and Weighing ≥ 35 kg)

At Week 24, out of 23 patients assessed for efficacy, 91% of patients treated with GENVOYA achieved HIV-1 RNA < 50 copies/mL. At Week 48, 92% (46/50) of patients treated with GENVOYA achieved HIV-1 RNA < 50 copies/mL. The mean increase from baseline in CD4+ cell count at Weeks 24 and 48 was 212 cells/mm^3 and 224 cells /mm^3, respectively. Two patients had virologic failure by snapshot at Week 24 and three of the 50 patients had virologic failure by snapshot at Week 48; no emergent resistance to GENVOYA was detected through Weeks 24 and 48.

Fifty patients in Cohort 1 were assessed for safety at Weeks 24 and 48 (these patients received GENVOYA for 24 and 48 weeks). BMD by DXA was assessed in 47 patients for spine at both Week 24 and Week 48. BMD by DXA was assessed in 45 and 44 patients for total body less head (TBLH) at Week 24 and Week 48, respectively. Mean (SD) BMD increased from baseline to Week 24, +1.6% (3.9%) at the lumbar spine and +0.6 % (2.5%) for TBLH. Mean (SD) BMD increased from baseline to Week 48, +4.2% (5.0%) at the lumbar spine and +1.3% (2.7%) for TBLH.

Cohort 2: Virologically Suppressed Children (6 to < 12 Years of Age and Weighing ≥ 25 kg)

Patients in Cohort 2 had a mean age of 10 years (range: 8 to 11), a mean baseline weight of 31.6 kg (range: 26 to 58), 39% were male, 13% were Asian, and 78% were black. At baseline, median CD4+ cell count was 969 cells/mm^3 (range: 603 to 1421), and median CD4+% was 39% (range: 30% to 51%). All 23 patients had baseline plasma HIV-1 RNA < 50 copies/mL as shown in Table 24.

Table 24. Demographic and Baseline Characteristics of Virologically Suppressed Patients in Study 106 (Cohort 2)

	Study 106 (Cohort 2)
	GENVOYA (N= 23)
Demographic characteristics	
Median age, years (range)	10 (8-11)
Sex	
Male	9
Female	14
Race	
Asian	3
Black	18
White	2
Baseline BMI (kg/m^2), median (Q1, Q3)	15.9 (15.2, 18.1)
Baseline disease characteristics	
HIV-1 RNA < 50 copies/mL	23
CD4 cell count (cells/µL), median (Q1, Q3)	969 (843, 1087)
Mode of infection (HIV risk factors)	
Vertical transmission	23
HIV disease status	
Asymptomatic	23
Estimated CrCl by Schwartz formula (mL/min/1.73 m^2), median (Q1, Q3)	150.0 (134.7, 165.6)
Proteinuria by urinalysis (dipstick), n (%)	
Grade 0	22
Grade 1	1
Grade 2	0
Grade 3	0

Cohort 2: Virologically Suppressed Children (6 to < 12 Years of Age and Weighing ≥ 25 kg)

At Week 24, 100% (23/23) of patients in Cohort 2 remained suppressed (HIV-1 RNA < 50 copies/mL) after switching to GENVOYA. The mean change from baseline in CD4+ cell count at Week 24 was -150 cells/mm^3. No emergent resistance to GENVOYA was detected through Week 24.

Among the patients in Cohort 2 who had both baseline and Week 24 measurements, BMD by DXA was assessed in 21 patients for spine and 23 patients for TBLH. Mean (SD) BMD increased from baseline to Week 24, +2.9% (4.9%) at the lumbar spine and +1.7% (2.5%) for TBLH.

15 MICROBIOLOGY

Antiviral Activity

Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir Alafenamide: When tested, elvitegravir, emtricitabine, and tenofovir alafenamide demonstrated synergistic antiviral activity in cell culture. Antiviral synergy was maintained for elvitegravir, emtricitabine, and tenofovir alafenamide when tested in the presence 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 µM. Emtricitabine displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007–0.075 µM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.007–1.5 µM).

***Tenofovir Alafenamide*:** The antiviral activity of tenofovir alafenamide against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells and CD4-T lymphocytes. The EC_{50} values for tenofovir alafenamide were in the range of 2.0 to 14.7 nM.

Tenofovir alafenamide displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including sub-types A, B, C, D, E, F, and G (EC_{50} values ranged from 0.10 to 12.0 nM) and strain specific activity against HIV-2 (EC_{50} values ranged from 0.91 to 2.63 nM).

In a study of tenofovir alafenamide with a broad panel of representatives from the major classes of approved anti-HIV agents (NRTIs, NNRTIs, INSTIs, and PIs), additive to synergistic effects were observed. No antagonism was observed for these combinations.

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: HIV-1 isolates with reduced susceptibility to emtricitabine have been selected in cell culture. Reduced susceptibility to emtricitabine was associated with M184V/I substitutions in HIV-1 RT.

Tenofovir Alafenamide: HIV-1 isolates with reduced susceptibility to tenofovir alafenamide have been selected in cell culture. HIV-1 isolates selected by tenofovir alafenamide expressed a K65R substitution in HIV-1 RT; in addition, a K70E substitution in HIV-1 RT has been transiently observed. HIV-1 isolates with the K65R substitution have reduced susceptibility to abacavir, emtricitabine, tenofovir alafenamide, tenofovir, and lamivudine. *In vitro* drug resistance selection studies with tenofovir alafenamide have shown no development of resistance increases above 2.5-fold after 6 months in culture.

In Clinical Trials

***In Treatment-Naïve Patients*:** In a pooled analysis of antiretroviral-naive patients receiving GENVOYA in Phase 3 Studies 104 and 111, genotyping was performed on plasma HIV-1 isolates from all patients with HIV-1 RNA ≥ 400 copies/mL at confirmed virologic failure, at Week 144, or at time of early study drug discontinuation. As of Week 144, the development of one or more primary elvitegravir, emtricitabine, or tenofovir alafenamide resistance-associated mutations was observed in 12 of 22 patients with evaluable genotypic data from paired baseline and GENVOYA treatment-failure isolates (12 of 866 patients [1.4%]) compared with 12 of 20 treatment-failure isolates from patients with evaluable genotypic data in the STRIBILD treatment group (12 of 867 patients [1.4%]). Of the 12 patients with resistance development in the GENVOYA group, the mutations that emerged were M184V/I (N = 11) and K65R/N (N = 2) in reverse transcriptase and T66T/A/I/V (N = 2), E92Q (N = 4), Q148Q/R (N = 1) and N155H (N = 2) in integrase. Of the 12 patients with resistance development in the STRIBILD group, the mutations that emerged were M184V/I (N = 9), K65R/N (N = 4), and L210L/W (N = 1) in reverse transcriptase and E92Q/V (N = 4), Q148R (N = 2), and N155H/S (N = 3) in integrase. In both treatment groups, most patients who developed resistance mutations to elvitegravir developed resistance mutations to both emtricitabine and elvitegravir.

In phenotypic analyses of patients in the final resistance analysis population, 7 of 22 patients (32%) had HIV-1 isolates with reduced susceptibility to elvitegravir in the GENVOYA group compared with 7 of 20 patients (35%) in the STRIBILD group, 8 patients (36%) had reduced susceptibility to emtricitabine in the GENVOYA group compared with 7 patients (35%) in the STRIBILD group. One patient in the GENVOYA group (1 of 22 [4.5%]) and 2 patients in the STRIBILD group (2 of 20 [10%]) had reduced susceptibility to tenofovir.

***In Virologically Suppressed Patients*:** Three patients with emergent resistance to GENVOYA were identified (M184M/I; M184I + E92G; M184V + E92Q) as of Week 96 in a clinical study of virologically suppressed patients who switched from a regimen containing emtricitabine/tenofovir disoproxil fumarate and a third agent (Study 109, N = 959).

Cross Resistance

In HIV-1 Infected Treatment-Naïve Patients or Virologically Suppressed Patients: No cross-resistance has been demonstrated for elvitegravir-resistant HIV-1 isolates and emtricitabine or tenofovir, or for emtricitabine- or tenofovir-resistant isolates and elvitegravir.

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). Viruses expressing elvitegravir or raltegravir resistance mutations maintain susceptibility to dolutegravir.

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 Alafenamide: The K65R and K70E mutations result in reduced susceptibility to abacavir, didanosine, lamivudine, emtricitabine, and tenofovir, but retain sensitivity to zidovudine.

Multinucleoside resistant HIV-1 with a T69S double insertion mutation or with a Q151M mutation complex including K65R showed reduced susceptibility to tenofovir alafenamide.

HIV-1 containing the K103N or Y181C mutations associated with resistance to NNRTIs were susceptible to tenofovir alafenamide.

HIV-1 containing mutations associated with resistance to PIs, such as M46I, I54V, V82F/T, and L90M were susceptible to tenofovir alafenamide.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

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

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

– the highest doses evaluated in the 13-week, 26-week, and 39-week repeat-dose studies, respectively.

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

Tenofovir alafenamide: The general toxicology profile of tenofovir alafenamide has been studied in mice, rats, dogs and monkeys. The target organs were the kidney and bone. The effects on the kidneys included cortical tubular basophilia and tubular karyomegaly in both rats and dogs and additionally cortical tubular degeneration/regeneration in dogs. These effects did not appear to meaningfully affect renal function except for possibly related reduction in serum calcitriol (1,25-dihydroxyvitamin D3) that may be implicated in the bone effects (see below). The tenofovir alafenamide-related effects on the bone included decreases in bone mineral density and mineral content observed in both rats and dogs. In the 9-month dog study, animals dosed at 18/12 mg/kg/day (approximately 47 times the clinical exposure based on AUC) failed to mature skeletally. The NOAEL in the rat and dog was 25 mg/kg/day (approximately 13 times clinical tenofovir exposure based on AUC) and 2 mg/kg/day (approximately 4 times the clinical tenofovir exposure based on AUC), respectively. These effects were partially reversible upon treatment discontinuation.

Electrocardiographic effects occurred in the 9-month dog study and included prolongation of PR intervals at ≥ 6 mg/kg (approximately 15 times the clinical exposure based on AUC) and reduction in heart rate with an associated QT prolongation at 18/12 mg/kg (approximately 47 times the clinical exposure based on AUC); the heart rate changes were reversible following a three-month recovery period. The NOAEL was 2 mg/kg (approximately 4 times the clinical tenofovir exposure based on AUC). These effects might have been due to a reduction in triiodothryonine (T3) levels.

Carcinogenicity:

Elvitegravir: In 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/kg/day alone or in combination with 25 mg/kg/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/kg/day at exposures 12- to 27-fold, respectively in male and female, the human systemic exposure.

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.

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/kg/day (23 times the human systemic exposure at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (28 times the human systemic exposure at the therapeutic dose).

Tenofovir Alafenamide: Because there is a lower tenofovir exposure in rats and mice after tenofovir alafenamide administration compared to tenofovir disoproxil fumarate, carcinogenicity studies were conducted only with tenofovir disoproxil fumarate. Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate 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 300 mg therapeutic dose of tenofovir disoproxil fumarate for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures 10 times 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.

Genotoxicity:

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

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

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

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

Reproductive and Developmental Toxicology:

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

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

Elvitegravir did not affect fertility in male and female rats at approximately 16- and 30-fold higher exposures (AUC), respectively, than in humans at the therapeutic 150 mg daily dose.

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

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

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

Cobicistat did not affect fertility in male or female rats at daily exposures (AUC) approximately 4-fold higher than human exposures at the recommended 150 mg daily dose. Fertility was normal in the offspring of rats exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 1.2-fold higher than human exposures at the recommended 150 mg daily dose.

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

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

Tenofovir Alafenamide: There were no effects on fertility when tenofovir alafenamide was administered to male rats at a dose equivalent to 155 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 14 days prior to mating through day seven of gestation.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

GENVOYA®

elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide* tablets
*as tenofovir alafenamide hemifumarate

Read this carefully before you start taking **Genvoya** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Genvoya**.

Serious Warnings and Precautions

- **"Flare-ups" of Hepatitis B Virus infection**, in which the disease suddenly returns in a worse way than before, can occur if you also have hepatitis B and stop taking **Genvoya**. Do not stop taking **Genvoya** without your healthcare professional's advice. If you stop taking **Genvoya**, tell your healthcare professional immediately about any new, unusual or worsening symptoms that you notice after stopping treatment. After you stop taking **Genvoya**, your healthcare professional will still need to check your health and take blood tests to check your liver. **Genvoya** is not approved for the treatment of hepatitis B virus infection.

What is Genvoya used for?

Genvoya is used to treat HIV infection in adults and children who weigh at least 25 kg (55 lbs).

Genvoya is for people who do not have an HIV virus that is resistant to **Genvoya**. **Genvoya** has not been studied in children weighing less than 25 kg (55 lbs).

How does Genvoya work?

Genvoya lowers the amount of HIV in the blood (viral load).

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

Genvoya may help increase the count of CD4+ (T) cells. Lowering the amount of HIV in the blood and increasing the CD4+ (T) cells lower the chance of getting infections that happen when your immune system is weak.

Genvoya does not cure HIV infection or AIDS. The long-term effects of **Genvoya** are not known. People taking **Genvoya** may still get infections or other conditions that happen with HIV infection. Some of these conditions are pneumonia and *Mycobacterium avium* complex (MAC) infections. **It is very important that you see your healthcare professional on a regular basis while taking Genvoya.**

Genvoya has not been shown to reduce the risk of passing HIV to others through sexual contact or blood. Continue to practice safe sex. Use condoms to lower the chance of sexual

contact with body fluids such as semen, vaginal secretions, or blood. Do not re-use or share needles.

What are the ingredients in Genvoya?

Medicinal ingredients: elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide (as tenofovir alafenamide hemifumarate)

Non-medicinal ingredients: croscarmellose sodium, hydroxypropyl cellulose, indigo carmine aluminum lake, iron oxide yellow, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, silicon dioxide, sodium lauryl sulfate, talc and titanium dioxide.

Genvoya comes in the following dosage forms:

Genvoya is available as green, capsule-shaped tablets. Each tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine and 10 mg of tenofovir alafenamide (equivalent to 11.2 mg of tenofovir alafenamide hemifumarate).

Do not use Genvoya if:

- you are allergic to elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide or any of the other ingredients in **Genvoya**. (see **What are the ingredients in Genvoya?**)
- you are taking any medication listed below:

Drugs that must not be taken with Genvoya:

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

*Not available in Canada

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Genvoya. Talk about any health conditions or problems you may have, including if you:

- Have hepatitis B virus (HBV) infection and take **Genvoya**. Your HBV infection may get worse (flare-up) and symptoms worsen if you stop taking **Genvoya** (see **Serious Warnings and Precautions** box and **Serious Side Effects** table).
- Have a history of pancreatitis (swelling of the pancreas). If you develop symptoms of pancreatitis, such as nausea, vomiting and severe pain in the abdomen and/or back, tell your healthcare professional.
- Have kidney problems. Kidney problems, including kidney failure, have occurred in patients taking tenofovir. If you have kidney problems and are taking **Genvoya** along with certain medicines such as non-steroidal anti-inflammatory drugs, your kidney problems could get worse.
- Have a history of bone fracture, bone loss or osteoporosis. Bone loss has happened in some people who took **Genvoya**.
- Have lactic acidosis (high levels of acid in the blood). See the **Serious Side Effects** table for symptoms and tell your healthcare professional right away if you get these symptoms.
- Have severe liver problems including enlarged or fatty liver. See the **Serious Side Effects** table for symptoms and tell your healthcare professional right away if you get these symptoms.

If you have HBV infection and you stop taking **Genvoya**, your healthcare professional will need to check your health often and do blood tests regularly for several months to check your HBV infection. Tell your healthcare professional about any new or unusual symptoms you may have after you stop taking **Genvoya**.

Other warnings you should know about:

If you are pregnant or plan to become pregnant:

It is not known if **Genvoya** can harm your unborn child. Your healthcare professional will decide if you should take **Genvoya**.

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

If you are breast-feeding or plan to breast-feed:

Do not breast-feed if you have HIV because of the chance of passing the HIV virus to your baby. One of the medicinal ingredients of **Genvoya**, emtricitabine, can be passed to your baby in your breast milk and may cause harm to your baby. It is not known if the other medicinal ingredients can be passed to your baby in breast milk. If you are a woman who has or will have a baby, talk with your healthcare professional about the best way to feed your baby.

Blood Sugar and Fat Levels

Your blood sugar levels (glucose) or levels of fats (lipids) in your blood may increase with HIV treatment. Your healthcare professional may order blood tests for you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

If you are taking Genvoya, you should not take:

- Antiplatelets such as clopidogrel (Plavix®).
- Anticonvulsants such as oxcarbazepine
- Antipsychotics such as quetiapine (Seroquel®)
- Any other medicines to treat HIV-1 infection.
- Any other medicines that contain elvitegravir (STRIBILD®).
- Any other medicines that contain cobicistat (STRIBILD, Symtuza®, TYBOST®, Prezcobix®).
- Any other medicines that contain tenofovir (ATRIPLA®, BIKTARVY®, COMPLERA®, Delstrigo®, DESCOVY®, ODEFSEY®, STRIBILD, Symtuza®, TRUVADA®, VEMLIDY®, VIREAD®).
- Any other medicines that contain emtricitabine or lamivudine (ATRIPLA, BIKTARVY, COMPLERA, Delstrigo, DESCOVY, Dovato®, EMTRIVA®, ODEFSEY, STRIBILD, Symtuza, TRUVADA; 3TC, Combivir®, Heptovir®, Kivexa®, Triumeq®, Trizivir®).
- Any other medicines containing ritonavir (Norvir®, Kaletra®).
- Adefovir (HEPSERA®).

Also tell your healthcare professional if you take:

- Any medications, antacids, vitamins, and supplements containing magnesium, aluminum, calcium, iron, or zinc. These include antacids (for stomach ulcers, heartburn, or acid reflux), mineral supplements and vitamins that contain calcium or iron, and ulcer healing medication (sucralfate). Take medications, antacids, vitamins, and supplements containing magnesium, aluminum, calcium, iron, or zinc at least 2 hours before or after you take **Genvoya**.
- Antidepressants such as trazodone and Selective Serotonin Reuptake Inhibitors (SSRIs)
- Antifungals such as ketoconazole (Nizoral®), itraconazole (Sporanox®) and voriconazole (Vfend®)
- Antiarrhythmics such as amiodarone, digoxin, disopyramide, flecainide (Tambacor®), systemic lidocaine, mexiletine, propafenone and quinidine
- Antibacterials such as clarithromycin (Biaxin®) and telithromycin (Ketek®)
- Anticonvulsants such as ethosuximide
- Antimycobacterials such as rifabutin (Mycobutin®)
- Anticoagulants such as warfarin, dabigatran (Pradaxa®), edoxaban (Lixiana®)
- Antigout (colchicine)
- Antivirals such as elbasvir/grazoprevir (Zepatier®)
- Beta-blockers such as metoprolol (Lopressor®) and timolol
- Calcium channel blockers such as amlodipine (Norvasc®), diltiazem (Cardizem®), felodipine, nifedipine, and verapamil
- Corticosteroids such as betamethasone, budesonide, dexamethasone, fluticasone (Flonase®), mometasone, and triamcinolone

- Endothelial receptor antagonists such as bosentan (Tracleer®)
- Hormonal contraceptives such as norgestimate/ethinyl estradiol and drospirenone/ ethinyl estradiol
- Immunosuppressants such as cyclosporine (Neoral®), sirolimus (Rapamune®) and tacrolimus (Prograf®)
- Neuroleptics such as risperidone (Risperdal®) and perphenazine (Trilafon®)
- PDE-5 inhibitors such as sildenafil (Viagra®), tadalafil (Cialis®, Adcirca®), and vardenafil (Levitra®)
- Sedative/hypnotics such as diazepam (Valium®), flurazepam and buspirone

*Not marketed in Canada.

How to take Genvoya:

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

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

Only take medicine that has been prescribed specifically for you.

Do not give **Genvoya** to others or take medicine prescribed for someone else.

Do not use if seal over bottle opening is broken or missing.

Usual dose:

Adults and children weighing 25 kg or more:

- The usual dose of **Genvoya** is one tablet orally (by mouth) once a day. Try to take the tablet at the same time each day. Swallow with plenty of water.
- **Genvoya** must be taken with food.

Adults on Dialysis:

- If you are on dialysis, take your daily dose of **Genvoya** following dialysis**.**

Overdose:

If you think you, or a person you are caring for, have taken too much **Genvoya**, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

It is important that you do not miss any doses. If you miss a dose of **Genvoya** and it is less than 18 hours from the time you usually take **Genvoya**, then take the dose. If more than 18 hours has passed from the time you usually take **Genvoya**, then wait until the next scheduled daily

dose. **Do not** take more than 1 dose of **Genvoya** in a day. **Do not** take 2 doses at the same time. Call your healthcare professional if you are not sure what to do.

What are possible side effects from using Genvoya?

These are not all the possible side effects you may feel when taking **Genvoya**. If you experience any side effects not listed here, tell your healthcare professional.

The common side effects of **Genvoya** are:

- Diarrhea
- Nausea
- Headache
- Tiredness

Additional side effects may include:

- Gas
- Swelling in the face, lips, tongue or throat (angioedema)
- Hives

Changes in your immune system (Immune Reconstitution Inflammatory 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.

Autoimmune disorders (when the immune system attacks healthy body tissue), may also occur after you start taking medicines for HIV infection. Examples of this include: Graves' disease (which affects the thyroid gland), Guillain-Barré syndrome (which affects the nervous system), polymyositis (which affects the muscles), or autoimmune hepatitis (which affects the liver). Autoimmune disorders may occur many months after the start of treatment. Look for any other symptoms such as:

- high temperature (fever), redness, rash or swelling.
- joint or muscle pain.
- numbness or weakness beginning in the hands and feet and moving up towards the trunk of the body.
- palpitations (chest pain) or rapid heart rate.

If you notice these or any symptoms of inflammation or infection, tell your healthcare professional immediately.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE			
Lactic acidosis: feeling very weak or tired, unusual muscle pain, stomach pain with nausea and vomiting, feeling unusually cold especially in arms and legs, feeling dizzy or lightheaded, fast or irregular heartbeat, fast and deep breathing		✓	
VERY RARE			
Flare-ups of hepatitis B virus infection following drug discontinuation: jaundice (skin or the white part of eyes turn yellow), urine turns dark, bowel movements (stools) turn light in color, loss of appetite for several days or longer, nausea, stomach pain		✓	
Hepatotoxicity (severe liver problems) with hepatomegaly (liver enlargement) and steatosis (fat in the liver): jaundice (skin or the white part of eyes turn yellow), urine turns dark, bowel movements (stools) turn light in color, loss of appetite for several days or longer, nausea, stomach pain		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- **Genvoya** should be stored below 30°C. It should remain stable until the expiration date printed on the label.
- Keep **Genvoya** in its original container and keep the container tightly closed.
- Keep out of reach and sight of children.

If you want more information about Genvoya:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website (www.gilead.ca), or by calling 1-866-207-4267.

This leaflet was prepared by Gilead Sciences Canada, Inc.

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Gilead Sciences, Inc.
Foster City, CA 94404
USA

Gilead Sciences Canada, Inc.
Mississauga, ON L5N 2W3

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Marketing Status in United States

Drug Databases (https://www.fda.gov/Drugs/InformationOnDrugs/)

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

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Product Details for NDA 207561

GENVOYA (COBICISTAT; ELVITEGRAVIR; EMTRICITABINE; TENOFOVIR ALAFENAMIDE FUMARATE)
150MG;150MG;200MG;EQ 10MG BASE
Marketing Status: Prescription

Active Ingredient: COBICISTAT; ELVITEGRAVIR; EMTRICITABINE; TENOFOVIR ALAFENAMIDE FUMARATE
Proprietary Name: GENVOYA
Dosage Form; Route of Administration: TABLET; ORAL
Strength: 150MG;150MG;200MG;EQ 10MG BASE
Reference Listed Drug: Yes
Reference Standard: Yes
TE Code:
Application Number: N207561
Product Number: 001
Approval Date: Nov 5, 2015
Applicant Holder Full Name: GILEAD SCIENCES INC
Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=001&Appl_No=207561&Appl_type=N)