NEW ZEALAND DATA SHEET

GENVOYA® (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide) tablets

1 PRODUCT NAME

GENVOYA (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

GENVOYA is available as tablets. Each tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg emtricitabine and tenofovir alafenamide fumarate equivalent to 10 mg of tenofovir alafenamide. The tablets are film-coated, capsule shaped and green in colour. Each tablet is debossed with 'GSI' on one side and the number "510" on the other side.

Contains lactose.

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

3 PHARMACEUTICAL FORM

Each GENVOYA tablet is capsule shaped, film-coated and green in colour. Each tablet is debossed with 'GSI' on one side and the number '510' on the other side. The tablets are supplied in bottles with child resistant closures.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

GENVOYA is indicated as a single tablet regimen for the treatment of HIV-1 infection in adults and paediatric patients weighing at least 25 kg who are either treatment–naïve; or virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen (see section 5.1 Pharmacodynamic properties, Clinical trials). Patients must not have a history of treatment failure or known mutations associated with resistance to the antiretroviral components of GENVOYA.

GENVOYA is a fixed dose combination of one integrase inhibitor, one pharmacokinetic enhancer and two nucleos(t)ide HIV-1 reverse transcriptase inhibitors.

4.2 Dose and Method of Administration

Adults

The recommended dose of GENVOYA is one tablet once daily taken with food.

Children and Adolescents up to 18 Years of Age

In paediatric patients weighing ≥ 25 kg, the recommended dose of GENVOYA is one tablet once daily taken with food.

Clinical trials data in children 6 to < 12 years of age (weighing at least 25 kg) is limited to virologically suppressed children who were switched to GENVOYA; no clinical trials data is available in treatment-naïve children in this age group.

No data are available on which to make a dose recommendation for paediatric patients weighing less than 25 kg.

Elderly

No dose adjustment is required for elderly patients. Clinical trials of GENVOYA included 97 patients (80 receiving GENVOYA) aged 65 years and over. No differences in safety or efficacy have been observed between elderly patients and those between 8 and less than 65 years of age.

Renal Impairment

No dose adjustment of GENVOYA is required in adult patients with estimated creatinine clearance greater than or equal to 30 mL/min. The safety of GENVOYA has not been established in patients with estimated creatinine clearance that declines below 30 mL/min.

GENVOYA should not be initiated in patients with estimated creatinine clearance below 30 mL/minute as there are insufficient data available regarding the use of GENVOYA in this population.

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 section 5.2 Pharmacokinetic properties: Patients with hepatic impairment).

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 Section 4.6 Use in Pregnancy].

GENVOYA should not be initiated in pregnant individuals. An alternative regimen is recommended for individuals who become pregnant during therapy with GENVOYA (see Section 4.6 Use in Pregnancy).

4.3 Contraindications

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

Coadministration is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events, and with drugs that are potent inducers of CYP3A due to the potential for

loss of virologic response and possible resistance to GENVOYA as seen in Table 1. Therefore, coadministration is contraindicated with, but not limited to, the following drugs (See Table 1):

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 TAF. This may result in loss of therapeutic effect to GENVOYA.
Antimycobacterials	rifampin	Rifampin is a potent inducer of CYP450 metabolism and may cause significant decrease in the plasma concentration of elvitegravir, cobicistat, and TAF. This may result in loss of therapeutic effect to GENVOYA.
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 TAF. This may result in loss of therapeutic effect and development of resistance.
Lipid-modifying agents	lovastatin, simvastatin lomitapide	Potential for serious reactions such as myopathy, including rhabdomyolysis. Coadministration with lomitapide is contraindicated due to potential for markedly increased transaminases.

Drug Class	Drugs within Class that are Contraindicated with GENVOYA	Clinical Comment
Neuroleptics	pimozide	Potential for serious and/or life-threatening events such as cardiac arrhythmias.
PDE-5 inhibitors	sildenafil[a] for the treatment of pulmonary arterial hypertension	There is increased potential for sildenafil-associated adverse events (which include visual disturbances, hypotension, priapism, and syncope).
Sedative/hypnotics	orally administered midazolam, triazolam[b]	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.

*. Indicates that a drug-drug interaction trial was conducted.
a. See Drug Interactions, Table 2 for sildenafil when used for erectile dysfunction.
b. See Drug Interactions, Table 2 for parenterally administered midazolam

4.4 Special Warnings and Precautions for Use

General

Patients receiving GENVOYA or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of HIV transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines. Patients should also be informed that GENVOYA is not a cure for HIV infection.

HIV and Hepatitis B Virus (HBV) Co-infection

Discontinuation of GENVOYA therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis due to the emtricitabine and tenofovir alafenamide components of GENVOYA. Patients co-infected with HIV and HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping GENVOYA treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, discontinuation of anti-hepatitis B therapy is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Use with Other Anti-Viral Products

GENVOYA should not be coadministered with other antiretroviral products for treatment of HIV.

There are limited data on interactions of GENVOYA with HIV protease inhibitors and or NNRTI/s, but as a fixed dose combination for HIV, it is not expected that co-administration with other antiretrovirals would be required.

For treatment of HIV and Hepatitis C co-infection, GENVOYA should not be used in conjunction with protease inhibitors that are inhibitors of cathepsin A (such as the anti-hepatitis C agent boceprevir) due to potential drug-drug interactions including altered and/or suboptimal pharmacokinetics of tenofovir alafenamide.

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

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including emtricitabine, a component of GENVOYA. In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of antiretroviral therapy. Relevant examples include cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders have also been reported to occur in the setting of immune reconstitution; however, the reported time to onset is more variable, and these events can occur many months after initiation of treatment.

Paediatric Use

The safety, virologic, and immunologic responses of GENVOYA were evaluated in 50 treatment-naive, HIV-1 infected adolescent patients aged 12 to less than 18 years through Week 48 and in 23 virologically suppressed paediatric patients between the ages of 6 and less than 12 years through Week 24 in an open-label trial, Study 106 (see section 5.1 Pharmacodynamic properties, Clinical trials). Pharmacokinetic parameters evaluated in 24 adolescent patients receiving GENVOYA were similar to adults receiving GENVOYA. Pharmacokinetic parameters in 23 paediatric patients between the ages of 6 and less than 12 years receiving GENVOYA were generally higher than in adults; however, the increase was not considered clinically significant (see 5.2 Pharmacokinetic properties). The safety profile in adolescent and paediatric patients who received treatment with GENVOYA was similar to

that in adults (see 4.8 Undesirable effects). See 4.2 Dose and method of administration for dosing recommendations for patients weighing at least 25 kg. No data are available on which to make a dose recommendation for paediatric patients weighing less than 25 kg.

Use in the Elderly

Clinical trials of GENVOYA included 97 patients (80 receiving GENVOYA) aged 65 years and over. No differences in safety or efficacy have been observed between elderly patients and those between 8 and less than 65 years of age.

Renal Impairment

Post marketing cases of renal impairment, including acute renal failure, proximal renal tubulopathy (PRT), and Fanconi syndrome have been reported with tenofovir alafenamide containing products; while most of these cases were characterised 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.

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.

The safety, virologic, and immunologic responses of GENVOYA in HIV-1 infected adult patients with mild to moderate renal impairment (eGFR 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 (see section 5.2 Pharmacokinetic properties). The safety profile of GENVOYA in patients with mild to moderate renal impairment was similar to safety data from patients with normal renal function (see section 4.8 Undesirable effects).

No dose adjustment of GENVOYA is required in adult patients with estimated creatinine clearance greater than or equal to 30 mL/min. The safety of GENVOYA has not been established in adult patients with estimated creatinine clearance that declines below 30 mL/min or in paediatric patients with renal impairment see section 5.1 Pharmacodynamic properties, Clinical trials and 5.2 Pharmacokinetic properties).

GENVOYA should not be initiated in patients with estimated creatinine clearance below 30 mL/min as there are insufficient data available regarding the use of GENVOYA in this population (see section 4.2 Dose and method of administration).

No data are available to make dose recommendations in paediatric 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. 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 (see section 5.1 Pharmacodynamic properties, Clinical trials and 5.2 Pharmacokinetic properties).

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported with the use of antiretroviral nucleoside analogs, including 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).

4.5 Interaction with Other Medicines and Other Forms of Interaction

General

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

CYP3A Associated Drug-Drug Interactions

Cobicistat, a component of GENVOYA, is a strong inhibitor of cytochrome P450 (CYP3A) and a CYP3A substrate. Thus, coadministration of GENVOYA, with drugs that are primarily metabolised by CYP3A may result in increased plasma concentrations of such drugs (see 4.3 Contraindications). Coadministration of GENVOYA, with drugs that inhibit CYP3A may decrease the clearance of cobicistat, resulting in increased plasma concentration of cobicistat. Coadministration of GENVOYA with drugs that have active metabolite(s) formed by CYP3A may result in reduced plasma concentrations of these active metabolite(s). Cobicistat, is also an inhibitor of CYP2D6. The transporters that cobicistat inhibits included p-glycoprotein (P-gp), BCRP, OATP1B1 and OATP1B3. Thus, coadministration of GENVOYA with drugs that are primarily metabolised by CYP3A or CYP2D6, or are substrates of P-gp, BCRP, OATP1B1 or OATP1B3 may result in increased plasma concentrations of such drugs.

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

Established and Other Potentially Significant Interactions

GENVOYA is indicated for use as a complete regimen for the treatment of HIV-1 infection and should not be administered with other antiretroviral products. Therefore, information regarding drug-drug interactions with other antiretroviral products (including PIs and NNRTIs) is not provided. Drug interaction information for GENVOYA with potential concomitant drugs is summarised in Table 2. The drug interactions described are based on studies conducted with GENVOYA, or the components of GENVOYA, (elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide) as individual agents and/or in combination, or are potential drug interactions that may occur with GENVOYA.

The table is not all-inclusive (see section 4.3 Contraindications).

Table 2 Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect[b]	Clinical Comment
Alpha 1-Adrenoreceptor Antagonist: alfuzosin	↑ alfuzosin	Alfuzosin is primarily metabolised 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 greater than or equal to 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 telithromycis in coadministered with GENVOYA. Clinical monitoring is recommended upon coadministration with GENVOYA.

Concomitant Drug Class: Drug Name	Effect[b]	Clinical Comment
Anticoagulants: warfarin **Direct Oral Anticoagulants (DOACs):** apixaban rivaroxaban dabigatran edoxaban	↑ or ↓ warfarin ↑ DOACs	Concentrations of warfarin may be affected upon coadministration with GENVOYA. It is recommended that the international normalized ratio (INR) be monitored upon coadministration with GENVOYA. Coadministration of DOACs 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 not recommended 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 prescribing information of the coadministered DOAC.
Anticonvulsants: carbamazepine ethosuximide oxcarbazepine phenobarbital phenytoin	↑ ethosuximide ↓ elvitegravir ↓ cobicistat ↓ tenofovir alafenamide	Carbamazepine, a potent CYP3A inducer, decreases cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Coadministration of 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.
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.

Concomitant Drug Class: Drug Name	Effect[b]	Clinical Comment
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 and elvitegravir 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	↓ clopidogrel 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.
Benzodiazepines: diazepam lorazepam midazolam triazolam	↑ diazepam ↔lorazepam ↑ midazolam ↑ triazolam	Midazolam and triazolam are primarily metabolised 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.

Concomitant Drug Class: Drug Name	Effect[b]	Clinical Comment
Calcium Channel Blockers: amlodipine diltiazem felodipine nicardipine nifedipine verapamil	↑ calcium channel blockers	Concentrations of calcium channel blockers may be increased when coadministered with cobicistat. Caution is warranted and clinical monitoring is recommended upon coadministration with GENVOYA.
Corticosteroids: dexamethasone (oral)	↓ elvitegravir (with oral dexamethasone) ↓ cobicistat (with oral dexamethasone)	Coadministration of dexamethasone, a CYP3A inducer, may decrease cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Alternative corticosteroids should be considered.
betamethasone budesonide fluticasone mometasone triamcinolone	↑ corticosteroids	Coadministration with corticosteroids that are sensitive to CYP3A inhibition can increase the risk for Cushing's syndrome and adrenal suppression, which have been reported during postmarketing use of cobicistat-containing products. Consider the risk of systemic corticosteroid effects if GENVOYA is coadministered with corticosteroids that are sensitive to CYP3A inhibition. Alternative corticosteroids should be considered, particularly for long-term use. For coadministration of cutaneously-administered corticosteroids sensitive to CYP3A inhibition, refer to the prescribing information of the corticosteroid for conditions or uses that augment its systemic absorption.
Endothelin Receptor Antagonists: bosentan	↑ 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 ergotamine ergonovine methylergonovine	↑ ergot derivatives	Ergot derivatives are primarily metabolised 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.

Concomitant Drug Class: Drug Name	Effect[b]	Clinical Comment
GI Motility Agents: cisapride	↑ cisapride	Cisapride is primarily metabolised 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.
Hepatitis C Virus Antiviral Agents: boceprevir	Effect on boceprevir or tenofovir alafenamide concentrations unknown	Coadministration with boceprevir has the potential to adversely affect the intracellular activation and clinical antiviral efficacy of tenofovir alafenamide based on *in vitro* data. Coadministration of GENVOYA and boceprevir is not recommended.
Herbal Products: St. John's wort (Hypericum perforatum)	↓ elvitegravir ↓ cobicistat ↓ tenofovir alafenamide	Coadministration of St. John's wort, a potent CYP3A inducer, may significantly decrease cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Coadministration of GENVOYA with St. John's wort is contraindicated.
Lipid-modifying Agents: HMG CoA Reductase Inhibitors: atorvastatin lovastatin rosuvastatin simvastatin Other Lipid-modifying Agents: lomitapide	↑ HMG-CoA reductase inhibitors ↑ lomitapide	HMG CoA reductase inhibitors are primarily metabolised 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 possible dose of atorvastatin with careful monitoring upon coadministration with GENVOYA. 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. Coadministration with lomitapide is contraindicated due to potential for markedly increased transaminases.

Concomitant Drug Class: Drug Name	Effect[b]	Clinical Comment
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. Additional or alternative non-hormonal forms of contraception should be considered when estrogen based contraceptives are coadministered with GENVOYA. The long-term effects of substantial increases in progesterone exposure are unknown. The effect of coadministration of GENVOYA with oral contraceptives or hormonal contraceptives containing progestogens other than drospirenone, norgestimate, or less than 25 mcg of ethinyl estradiol, is not known.
Immunosuppressants: cyclosporine rapamycin sirolimus tacrolimus	↑ immunosuppressants	Concentrations of these immunosuppressant agents may be increased when coadministered with cobicistat. Therapeutic monitoring is recommended upon coadministration with GENVOYA.
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.
Narcotic Analgesics: fentanyl tramadol	↑ fentanyl ↑ tramadol	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.

Concomitant Drug Class: Drug Name	Effect[b]	Clinical Comment
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 medicines	↓ 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 (e.g. H2-receptor antagonists and proton pump inhibitors), see Drugs Without Clinically Significant Interactions.
Neuroleptics: perphenazine pimozide risperidone thioridazine	↑ neuroleptics	Pimozide is primarily metabolised 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 (PDE5) Inhibitors: sildenafil tadalafil vardenafil	↑ PDE5 inhibitors	PDE5 inhibitors are primarily metabolised by CYP3A. Coadministration with GENVOYA may result in increased plasma concentrations of sildenafil and tadalafil, which may result in PDE5 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.

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 with the following drugs:

- famciclovir
- famotidine
- ledipasvir/sofosbuvir
- omeprazole
- sertraline
- sofosbuvir
- sofosbuvir/velpatasvir
- sofosbuvir/velpatasvir/voxilaprevir

No clinically significant drug interactions are expected when GENVOYA is coadministered with the following drugs:

- entecavir
- ribavirin.

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

Concentrations of buprenorphine and norbuprenorphine are modestly increased and concentrations of naloxone are modestly decreased when coadministered with elvitegravir and cobicistat. There was no effect on opioid pharmacodynamics and the concentration changes are not considered clinically relevant. No dose adjustment of buprenorphine/naloxone is required upon coadministration with GENVOYA.

4.6 Fertility, Pregnancy and Lactation

Impairment of Fertility

No reproductive toxicity studies have been conducted with elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide in combination.

Elvitegravir: Elvitegravir did not affect fertility in male and female rats at daily exposures (AUC) greater than 10-fold higher than in 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 18-fold higher than human exposures at the recommended 150 mg daily dose.

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

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

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

Tenofovir alafenamide: There were no effects on fertility, mating performance or early embryonic development when tenofovir alafenamide was administered to male rats at a dose up to 160 mg/kg/day, 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.

Use in Pregnancy

Pregnancy Category B3.

There are no adequate and well controlled clinical studies of GENVOYA or its components in pregnant women. Animal reproductive studies have only been conducted with the individual pharmaceutical components and not the fixed dose combination. Animal reproductive studies are not always predictive of human response. Lower exposures of elvitegravir and cobicistat have been reported during pregnancy compared to postpartum. Treatment during pregnancy may be associated with an increased risk of treatment failure and an increased risk of HIV transmission to the child. Therefore, GENVOYA is not recommended during pregnancy. An alternative regimen is recommended for individuals who become pregnant during therapy with GENVOYA. Viral load should be closely monitored during pregnancy.

Elvitegravir: Studies in animals have shown no evidence of teratogenicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with elvitegravir during pregnancy, there were no toxicologically significant effects on developmental endpoints. The exposures at the embryo-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 dose of 150 mg/day.

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

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

Tenofovir alafenamide: Embryo-fetal development studies have been performed in rats and rabbits which revealed no evidence of embryolethality, fetotoxicity or teratogenicity due to tenofovir alafenamide. The embryo-fetal NOAELs in rats and rabbits occurred at TAF

exposures (AUC) similar to and 53 times higher than, respectively, the exposure in humans at the recommended daily dose.

Women of childbearing potential

Since there are no well controlled clinical studies with GENVOYA in pregnant women, adequate contraception is recommended for women of childbearing potential when taking GENVOYA.

Use in Lactation

In animal studies it has been shown that elvitegravir, cobicistat and tenofovir are secreted into milk. It is not known whether elvitegravir, cobicistat, or tenofovir alafenamide is secreted in human milk. In humans, samples of breast milk obtained from five HIV-1 infected mothers given TRUVADA (emtricitabine/tenofovir disoproxil fumarate) 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. Because of the potential for both HIV transmission and for serious adverse events in nursing infants, mothers should be instructed not to breast feed if they are receiving GENVOYA.

4.7 Effects on Ability to Drive and Use Machines

No studies on the effects of GENVOYA on the ability to drive and use machines have been performed.

4.8 Undesirable Effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

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

For additional safety information about elvitegravir, cobicistat and emtricitabine, in combination with other antiretroviral agents, consult the Product Information for these products.

Clinical Trials

Experience from Clinical Studies in Treatment-Naïve Patients

The safety assessment of GENVOYA is based on pooled data from two 144-week controlled clinical studies (Study 104 and Study 111) in which 1733 treatment-naïve patients received GENVOYA (N=866) or STRIBILD (N=867) once daily.

The most common adverse reaction (all Grades) reported in at least 10% of patients in the GENVOYA group was nausea. The proportion of patients who discontinued treatment with GENVOYA or STRIBILD due to adverse events, regardless of severity, was 1.3% and 3.3%, respectively. Table 3 displays the frequency of adverse reactions (all Grades) greater than or equal to 5% in the GENVOYA group.

Table 3 Treatment-Emergent Adverse Drug 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
GASTROINTESTINAL DISORDERS		
Diarrhea	7%	9%
Nausea	11%	13%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue	5%	4%
NERVOUS SYSTEM DISORDERS		
Headache	6%	5%

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 3 occurred at severity Grade 1.

In addition to the adverse reactions presented in Table 3, abdominal pain, dyspepsia, flatulence, rash, and vomiting occurred at a common frequency (≥1% and <10%; frequency based on all adverse events regardless of relationship to study drug) in the GENVOYA group.

Laboratory Abnormalities

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 4.

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

	GENVOYA N=866	STRIBILD N=867
Laboratory Parameter Abnormality[a]		
Creatine Kinase (≥ 10.0 x ULN)	11%	10%
LDL-cholesterol (fasted) (> 190 mg/dL)	11%	5%
Total cholesterol (fasted) (>300mg/dL)	4%	3%
AST (> 5.0 x ULN)	3%	4%
ALT (> 5.0 x ULN)	3%	3%
Amylase (> 2.0 x ULN)	3%	5%
Urine RBC (Hematuria) (>75 RBC/HPF)	3%	3%
Lipase[b]	5%	8%

a. Frequencies are based on treatment-emergent laboratory abnormalities.
b. Lipase test was performed only for subjects with serum amylase > 1.5 x upper limit of normal

The cobicistat component of GENVOYA has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function. In clinical studies with GENVOYA, increases in serum creatinine occurred by Week 2 of treatment and remained stable through 144 weeks. In treatment-naïve subjects, a mean change from baseline of 0.04 ± 0.12 mg/dL was observed after 144 weeks of treatment.

Serum Lipids

In the clinical trials of GENVOYA, a similar percentage of patients receiving GENVOYA and STRIBILD were on lipid lowering agents at baseline (4% and 5%, respectively). While receiving study drug through Week 144, an additional 5.5% of GENVOYA patients were started on lipid lowering agents, compared to 5.8% of STRIBILD patients.

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

Table 5 Lipid Values, Mean Change from Baseline, Reported in Patients Receiving GENVOYA or STRIBILD in Studies 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]
HDL-cholesterol (fasted)	47 [N=647]	+7 [N=647]	46 [N=627]	+3 [N=627]
LDL-cholesterol (fasted)	103 [N=643]	+20 [N=643]	107 [N=628]	+8 [N=628]
Triglycerides (fasted)	111 [N=647]	+29 [N=647]	115 [N=627]	17 [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 144values.

Experience from Clinical Studies in Virologically Suppressed Patients

No new adverse reactions to GENVOYA were identified through Week 96 in an open-label clinical study (Study 109) of virologically suppressed patients who switched from a TDF-containing combination regimen to GENVOYA (N=959).

Experience from Clinical Studies in Patients with Renal Impairment

The safety of GENVOYA in 248 HIV-1 infected patients who were either treatment-naïve (N=6) or virologically suppressed (N=242) with mild to moderate renal impairment (eGFR by Cockcroft-Gault method 30 - 69 mL/min) was evaluated through Week 144 in an open-label clinical study (Study 112). The safety profile of GENVOYA in patients with mild to moderate renal impairment was similar to patients with normal renal function (see section 5.1 Pharmacodynamic properties, Clinical trials).

In 84 renally impaired patients who switched to GENVOYA in Study 112 from antiviral regimens not containing tenofovir disoproxil fumarate, mean change from baseline in fasting lipid laboratory tests at Week 144 were -19 mg/dL in total cholesterol, -13 mg/dL in LDL cholesterol, -6 mg/dL in HDL cholesterol, 0.2 in total cholesterol to HDL ratio, and -22 mg/dL in triglycerides.

Experience from Clinical Studies in Paediatric Patients

The safety of GENVOYA was evaluated in 50 HIV-1 infected, treatment naïve patients between the ages of 12 to < 18 years (≥ 35 kg) through Week 48 and in 23 virologically suppressed patients between the ages of 6 to <12 years (≥ 25 kg) through Week 24 in an open-label clinical study (Study 106). In this study, the safety profile of GENVOYA was similar to that in adults.

Experience from Clinical Studies in Patients Coinfected with HIV-1 and Chronic Hepatitis B

The safety of tenofovir alafenamide (a component of GENVOYA) for the treatment of chronic hepatitis B is based on data from two randomised, double-blind, active-controlled studies in adults with compensated liver disease (Study 108 and Study 110).

The safety of GENVOYA in 72 HIV-suppressed adults coinfected with chronic hepatitis B was evaluated through Week 48 in an open-label clinical study (Study 1249) in which patients were switched from another antiretroviral regimen to GENVOYA. The safety profile of GENVOYA in patients coinfected with HIV-1 and chronic hepatitis B was similar to that in patients with HIV-1 monoinfection.

Postmarketing Experience

In addition to adverse reactions from clinical studies, the following adverse reactions were identified during post-approval use of products containing tenofovir alafenamide (TAF). Because these reactions were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

SKIN AND SUBCUTANEOUS TISSUE DISORDERS
Angioedema, urticaria

RENAL AND URINARY DISORDERS
Acute renal failure, proximal renal tubulopathy, Fanconi syndrome

4.9 Overdose

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 and ECG (QT interval) as well as observation of the clinical status of the patient. For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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

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

Emtricitabine: Limited clinical experience is available at doses higher than the therapeutic dose of emtricitabine 200 mg. In one clinical pharmacology study single doses of emtricitabine 1200 mg were administered to 11 patients. No severe adverse reactions were reported. The effects of higher doses are not known.

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

Tenofovir alafenamide: Limited clinical experience is available at doses higher than the therapeutic dose of tenofovir alafenamide. 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%.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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

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 (primarily CYP3A4 and CYP3A5). Inhibition of CYP3A-mediated metabolism by cobicistat enhances the systemic exposure of CYP3A substrates, such as elvitegravir, where bioavailability is limited and half-life is shortened by CYP3A-dependent metabolism.

Emtricitabine*:* Emtricitabine, a synthetic nucleoside analogue of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 RT by competing with the natural substrate 2'-deoxycytidine 5'-triphosphate by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5′-triphosphate is a weak inhibitor of mammalian DNA polymerases α, β, ε and mitochondrial DNA polymerase γ.

Tenofovir alafenamide: Tenofovir alafenamide is a phosphonamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). Tenofovir alafenamide is permeable into cells and due to increased plasma stability and intracellular activation through hydrolysis by cathepsin A, tenofovir alafenamide is more efficient than tenofovir disoproxil fumarate in loading tenofovir into peripheral blood mononuclear cells (PBMCs), including lymphocytes 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) and hepatitis B virus (HBV). *In vitro* 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 vitro* based on several assays including mitochondrial DNA analyses.

Antiviral Activity *In Vitro*

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 lymphoblastoid cells, monocyte/macrophage cells, and peripheral blood lymphocytes and the 50% effective concentration (EC_{50}) values were in the range of 0.02 to 1.7 nM. Elvitegravir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values ranged from 0.1 to 1.3 nM) and activity against HIV-2 (EC_{50} of 0.53 nM). The antiviral activity of elvitegravir with antiretroviral drugs in two-drug combination studies was additive to synergistic when combined with nucleotide reverse transcriptase inhibitors (NRTIs) (abacavir, didanosine, emtricitabine, 3TC, d4T, tenofovir, or AZT); non-nucleoside reverse transcriptase inhibitors (NNRTIs) (efavirenz, etravirine, or nevirapine); protease inhibitors (PI) (amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, or tipranavir); the integrase strand transfer inhibitor raltegravir; the fusion inhibitor enfuvirtide, or the CCR5 co-receptor antagonist, maraviroc. No antagonism was observed for these combinations.

Elvitegravir did not show inhibition of replication of HBV or hepatitis C virus (HCV) *in vitro*.

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

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

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.

Drug Resistance

In Cell Culture:

Elvitegravir: HIV-1 isolates with reduced susceptibility to elvitegravir have been selected in cell culture. Reduced susceptibility to elvitegravir was most commonly associated with the primary integrase substitutions T66I, E92Q, and Q148R. Additional integrase substitutions observed in cell culture selection included H51Y, F121Y, S147G, S153Y, E157Q, and R263K.

Elvitegravir showed cross-resistance *in vitro* to the raltegravir selected mutations T66A/K, Q148H/K, and N155H.

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

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

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 mutation in HIV-1 RT; in addition, a K70E mutation in HIV-1 RT has been transiently observed. HIV-1 isolates with the K65R mutation have low-level reduced susceptibility to abacavir, emtricitabine, tenofovir, and lamivudine. *In vitro* drug resistance selection studies with tenofovir alafenamide have shown no development of high-level resistance after extended culture.

In Clinical Studies:

In Treatment-Naïve Patients: In a pooled analysis of antiretroviral-naive patients receiving GENVOYA in GS-US-292-0104 (Study 104), GS-US-292-0111 (Study 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 L210W (N = 1) in reverse transcriptase and E92/Q (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, and 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 patient 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 (GS-US-292-0109 (Study 109), N = 959).

In Patients Coinfected with HIV-1 and Chronic Hepatitis B: In a clinical study of patients coinfected with HIV-1 and chronic hepatitis B who received GENVOYA for 48 weeks (GS-US-292-1249 (Study 1249), N = 72), no patient had HIV or HBV emergent resistance to GENVOYA.

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

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

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.

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 effect of multiple doses of elvitegravir 125 and 250 mg (0.83 and 1.67 times the dose in GENVOYA) (coadministered with 100 mg ritonavir to boost the blood levels of elvitegravir) on QTc interval was evaluated in a randomised, placebo- and active-controlled (moxifloxacin 400 mg) parallel group thorough QT study in 126 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on Fridericia's correction method (QTcF) was below 10 msec. In this study, there was no clinically relevant prolongation of the QTc interval.

The effect of a single dose of cobicistat 250 mg and 400 mg (1.67 and 2.67 times the dose in GENVOYA) on QTc interval was evaluated in a randomised, placebo- and active-controlled (moxifloxacin 400 mg) four-period crossover thorough QT study in 48 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on individual correction method (QTc) was below 10 msec, the threshold for regulatory concern. Prolongation of the PR interval was noted in subjects receiving cobicistat in the same study. The maximum mean (95% upper confidence bound) difference in PR from placebo after baseline-correction was 9.5 (12.1) msec for 250 mg dose and 20.2 (22.8) for 400 mg dose cobicistat. Because the 150 mg cobicistat dose used in the 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. In a thorough QT/QTc study in 48 healthy subjects, 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 volunteers with normal renal function (eGFR ≥ 80 mL/min; N = 18) and mild to moderate renal impairment (eGFR: 50-79 mL/min; N = 12). A statistically significant change of $eGFR_{CG}$ from baseline was observed after 7 days of treatment with cobicistat 150 mg among subjects with normal renal function (-9.9 ± 13.1 mL/min) and mild to moderate renal impairment (-11.9 ± 7.0 mL/min). These decreases in $eGFR_{CG}$ were reversible after cobicistat was discontinued. The actual glomerular filtration rate, as determined by the clearance of probe drug iohexol, was not altered from baseline following treatment of cobicistat among subjects with normal renal function and mild to moderate renal impairment, indicating cobicistat inhibits tubular secretion of creatinine, reflected as a reduction in $eGFR_{CG}$, without affecting the actual glomerular filtration rate.

Clinical Trials

The efficacy and safety of GENVOYA in HIV-1 infected, treatment-naïve adults are based on 144-week data from two randomised, double-blind, active-controlled trials, Studies 104 and 111 (N=1733). The efficacy and safety of GENVOYA in virologically-suppressed HIV-1 infected adults are based on 96-week data from a randomised, open-label, active-controlled trial, 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 144-week data from an open-label trial, Study 112 (N=242). The efficacy and safety of GENVOYA in HIV-1 infected, paediatric patients are based on 48-week data in treatment-naïve patients between the ages of 12 to < 18 years (≥ 35 kg) (N=50) and 24-week data in virologically suppressed patients between the ages of 6 to < 12 years (≥ 25 kg) (N=23) from an open-label trial, Study 106.

Treatment-Naïve Patients

In both Study 104 and Study 111, patients were randomised 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 $\log_{10}$ copies/mL (range 1.3–7.0). The mean baseline CD4+ cell count was 427 cells/µL// (range 0-1360) and 13% had CD4+ cell counts less than 200 cells/µL. Twenty-three percent of patients had baseline viral loads greater than 100,000 copies/mL.

In both studies, patients were stratified by baseline HIV-1 RNA (≤ 100,000 copies/mL, > 100,000 copies/mL to ≤ 400,000 copies/mL, or > 400,000 copies/mL), by CD4 count (< 50 cells/µL, 50-199 cells/µL, or ≥ 200 cells/µL), and by region (US or ex-US).

Treatment outcomes of Studies 104 and 111 through 48 and 144 weeks are presented in Table 6.

Table 6 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)**
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%)	
HIV-1 RNA ≥ 50 copies/mL[c]	4%	4%	5%	4%
No Virologic Data at Week 48 or 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 ≥ 50 years	716/777 (92%) 84/89 (94%)	680/753 (90%) 104/114 (91%)	647/777 (83%) 82/89 (92%)	602/753 (80%) 92/114 (81%)
Sex Male Female	674/733 (92%) 126/133 (95%)	673/740 (91%) 111/127 (87%)	616/733 (84%) 113/133 (85%)	603/740 (81%) 91/127 (72%)
Race Black Nonblack	197/223 (88%) 603/643 (94%)	177/213 (83%) 607/654 (93%)	168/223 (75%) 561/643 (87%)	152/213 (71%) 542/654 (83%)

	Week 48		Week 144	
	GENVOYA (N=866)	STRIBILD (N=867)	GENVOYA (N=866)	STRIBILD (N=867)
Baseline Viral Load ≤ 100,000 copies/mL > 100,000 copies/mL	629/670 (94%) 171/196 (87%)	610/672 (91%) 174/195 (89%)	567/670 (85%) 162/196 (83%)	537/672 (80%) 157/195 (81%)
Baseline CD4+ cell count < 200 cells/µL ≥ 200 cells/µL	96/112 (86%) 703/753 (93%)	104/117 (89%) 680/750 (91%)	93/112 (83%) 635/753 (84%)	94/117 (80%) 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; e.g., withdrew consent, loss to follow-up, etc.

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 mean increase from baseline in CD4+ cell count at Week 144 was 326 cells/µL in GENVOYA-treated patients and 305 cells/µL in STRIBILD-treated patients (p = 0.06).

***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) change from baseline to Week 144 were assessed by dual-energy X-ray absorptiometry (DXA). As shown in Table 7, in patients who had both baseline and Week 144 measurements (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 7 Measures of Bone Mineral Density in Studies 104 and 111 (Week 144 analysis)

	GENVOYA	STRIBILD	Treatment Difference
Hip DXA Analysis	N=690	N=683	
Mean Percent Change in BMD	-0.8%	-3.4%	2.62% p < 0.001
Subjects with Categorical Change: > 3% Decrease in BMD > 3% Increase in BMD	 28% 13%	 55% 6%	 --
Subjects with No Decrease in BMD	40%	19%	--
Lumbar Spine DXA Analysis	N=702	N=686	
Mean Percent Change in BMD	-0.9%	-3.0%	2.04% p < 0.001

	GENVOYA	STRIBILD	Treatment Difference
Subjects with Categorical Change:			
> 3% Decrease in BMD	30%	49%	--
> 3% Increase in BMD	13%	7%	
Subjects with No Decrease in BMD	39%	22%	--

***Changes in Renal Laboratory Tests*:** Laboratory tests were performed in Studies 104 and 111 to compare the effect of TAF, administered as a component of GENVOYA, to that of TDF, administered as a component of STRIBILD, on renal laboratory parameters. As shown in Table 8, statistically significant differences were observed between treatment groups that favoured GENVOYA. In these studies, there were statistically significant differences between treatment groups for increases in serum creatinine and changes in proteinuria, including Urine Protein to Creatinine Ratio (UPCR), Urine Albumin to Creatinine Ratio (UACR), urinary retinol binding protein (RBP) to creatinine ratio, and urine beta-2-microglobulin to creatinine ratio that favoured GENVOYA.

Table 8 Change from Baseline in Renal Laboratory Tests in Studies 104 and 111 (Week 144 analysis)

	GENVOYA N=866	STRIBILD N=867	Treatment Difference
Serum Creatinine (mg/dL)[a]	0.04 ± 0.12	0.07 ± 0.13	-0.04 p < 0.001
Proteinuria by Urine Dipstick[b]	40%	45%	p = 0.027
Urine Protein to Creatinine Ratio [UPCR] [c]	-10.5%	25.2%	p < 0.001
Urine Albumin to Creatinine Ratio [UACR] [c]	-5.2%	5.2%	p < 0.001
Urine RBP to Creatinine Ratio[c]	34.8%	111%	p < 0.001
Urine Beta-2-Microglobulin to Creatinine Ratio[c]	-25.7%	53.8%	p < 0.001

a. Mean change ± SD. Treatment difference was from the analysis of covariance model
b. Includes all severity grades (1-3).
c. Median percent change.
d. Week 96 analysis

Virologically-Suppressed Patients

In Study 109, the efficacy and safety of switching from either ATRIPLA® (tenofovir DF/emtricitabine/efavirenz), TRUVADA® (tenofovir DF/emtricitabine) plus atazanavir (boosted by either cobicistat or ritonavir), or STRIBILD to GENVOYA were evaluated in a randomised, open-label trial 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 randomised 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 21-72), 89% were male, 67% were White, and 19% were Black. The mean baseline CD4+ cell count was 697 cells/μL (range 79-1951).

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.

Treatment outcomes of Study 109 through 48 and 96 weeks are presented in Table 9.

Table 9 Virologic Outcomes of Study 109 at Week 48[a] and 96[b]

	Week 48		Week 96	
	GENVOYA (N=959)	**Baseline Regimen (N=477)**	**GENVOYA (N = 959)**	**Baseline Regimen (N = 477)**
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%)	
HIV-1 RNA ≥ 50 copies/mL[c]	1%	1%	2%	2%
No Virologic Data at Week 48 or 96 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 the 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; patients who had new antiretroviral added.
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; e.g., withdrew consent, loss to follow-up, etc.

At Week 96, 90% (227/251) of patients who had received ATRIPLA as their prior treatment regimen remained suppressed (HIV-1 RNA < 50 copies/mL) after switching to GENVOYA vs. 86% (108/125) of patients who stayed on ATRIPLA; 92% (370/402) of patients who had received TRUVADA plus boosted atazanavir and switched to GENVOYA remained suppressed vs. 88% (175/199) who stayed on TRUVADA plus boosted atazanavir; 96% (293/306) of patients who had received STRIBILD and switched to GENVOYA remained suppressed vs. 93% (142/153) who stayed on STRIBILD.

At Week 96, switching to GENVOYA was superior (p=0.017) in maintaining HIV-1 RNA < 50 copies/mL when compared to patients who stayed on their baseline regimen.

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

Bone Mineral Density: In Study 109, changes in BMD were assessed by DXA in patients who had both baseline and Week 96 measurements (N = 809 and 821 in the GENVOYA arm and N = 396 and 401 in patients who remained on their baseline regimen, for hip and spine, respectively). Results are summarised in Table 10.

Table 10 Measures of Bone Mineral Density in Study 109 (Week 96 analysis)

	GENVOYA	Baseline Regimen	Treatment Difference
Hip DXA Analysis	**N=809**	**N=396**	
Mean Percent Change in BMD	2.4%	-0.5%	2.9% p < 0.001
Patients with Categorical Change: > 3% Decrease in BMD > 3% Increase in BMD	 2% 35%	 15% 9%	 --
Subjects with No Decrease in BMD	82%	43%	--
Lumbar Spine DXA Analysis	**N=821**	**N=401**	
Mean Percent Change in BMD	2.1%	-0.1%	2.2% p < 0.001
Subjects with Categorical Change: > 3% Decrease in BMD > 3% Increase in BMD	 6% 37%	 17% 18%	 --
Subjects with No Decrease in BMD	75%	47%	--

Changes in Renal Laboratory Tests: 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 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 the 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%; in urine beta-2-microglobulin to creatinine ratio it was −52% vs. 19% (p < 0.001 for all comparisons).

HIV-1 Infected Patients with Renal Impairment

In Study 112, the efficacy and safety of GENVOYA were evaluated in an open-label clinical trial of 242 HIV-1 infected patients with mild to moderate renal impairment (eGFR by Cockcroft-Gault method between 30 to 69 mL/min). 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 eGFR was 56 mL/minute, and 33% of patients had an eGFR of less than 50 mL/min. The mean baseline CD4+ cell count was 664 cells/µL (range 126-1813). At Week 24, 95.0% (230/242 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.

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.

Changes from baseline in renal laboratory tests in Study 112 are summarised in Table 11.

Table 11 Change from Baseline in Renal Laboratory Tests at Week 144 in Virologically Suppressed Patients with Renal Impairment who Switched to GENVOYA in Study 112 (Week 144 analysis)

	GENVOYA N=242
Serum Creatinine (mg/dL)[a]	-0.05 ± 0.29
Improvement in Proteinuria by Urine Dipstick[b]	56/66 (85%)
Urine Protein to Creatinine Ratio [UPCR][c]	-45.7%
Urine Albumin to Creatinine Ratio [UACR][c]	-35.1%
Urine RBP to Creatinine Ratio[c]	-63.8%
Urine Beta-2-Microglobulin to Creatinine Ratio[c]	-81.9%

a. Mean change ± SD.
b. An improvement of at least 1 toxicity grade from baseline.
c. Median percent change

Multiple assessments of renal function indicate that improvements in renal function occur as early as 1 week after switching to GENVOYA and persist through 144 weeks. The prevalence of clinically significant proteinuria (UPCR > 200 mg/g) and albuminuria (UACR ≥ 30 mg/g) decreased from 42% at baseline to 16% at Week 144 and 49% at baseline to 32% at Week 144, respectively. Other renal assessments, including fractional excretion of uric acid, serum cystatin C, and serum phosphorus showed small changes from baseline through Week 144.

In patients whose prior antiretroviral regimen did not include tenofovir disoproxil fumarate (N=84), mean change from baseline in serum creatinine at Week 144 was 0.01 ± 0.31 mg/dL; 73% (11/15 patients) had an improvement in proteinuria as measured by urine dipstick. Median percent change in UPCR and UACR at Week 144 were -9% and -4%, respectively. Median percent change in urine RBP to creatinine ratio, and urine beta-2-microglobulin to creatinine ratio at Week 144 were 15% and -6%, respectively.

In virologically suppressed patients with renal impairment who switched to GENVOYA, mean percentage increases from baseline at Week 144 were observed in hip and spine BMD. 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 and spine.

Paediatric Patients

In Study 106, the efficacy, safety, and pharmacokinetics of GENVOYA in HIV-1-infected patients were evaluated in open-label studies in treatment-naïve patients between the ages of 12 to < 18 years (≥ 35 kg) (N=50) and in virologically suppressed patients between the ages of 6 to < 12 years (≥ 25 kg) (N=23).

Cohort 1: Treatment-naïve adolescents (12 to < 18 years; ≥ 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/µL (range: 95 to 1110), and median CD4+% was 23% (range: 7% to 45%). 22% had baseline plasma HIV-1 RNA > 100,000 copies/mL.

Among the patients in Cohort 1 treated with GENVOYA, 92% (46/50) achieved HIV-1 RNA < 50 copies/mL at Week 48. The mean increase from baseline in CD4+ cell count at Week 48 was 224 cells/µL. Three of 50 patients had virologic failure at Week 48; no emergent resistance to GENVOYA was detected through Week 48.

Among the patients in Cohort 1 who had both baseline and Week 48 measurements (N=47 and 44 for the lumbar spine and total body less head [TBLH], respectively), mean BMD increased from baseline to Week 48, +4.2% at the lumbar spine and +1.3% for TBLH.

Cohort 2: Virologically suppressed children (6 to < 12 years; ≥ 25 kg): In Study 106, 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. Cohort 2 of Study 106 did not include any child below 8 years of age; the lowest body weight of any child treated in cohort 2 was 26 kg. Cohort 2 was limited to virologically suppressed children who switched to GENVOYA. At baseline, median CD4+ cell count was 969 cells/µL (range: 603 to 1421), and median CD4+% was 39% (range: 30% to 51%). After switching to GENVOYA, 100% (23/23) of patients in Cohort 2 remained suppressed (HIV-1 RNA <50 copies/mL) at Week 24. The mean change from baseline in CD4+ cell count at Week 24 was -150 cells/µL. No patient qualified for resistance analysis through Week 24.

Among the patients in Cohort 2 who had both baseline and Week 24 measurements (N=21 and 23, for lumbar spine and TBLH, respectively), mean BMD increased from baseline to Week 24,+2.9% at the lumbar spine and +1.7% for TBLH.

Patients Coinfected with HIV-1 and Chronic Hepatitis B

In Study 1249, the efficacy and safety of GENVOYA were evaluated in an open-label study in adults coinfected with HIV-1 and chronic hepatitis B. Seventy-two patients were HIV-suppressed (HIV-1 RNA < 50 copies/mL) for at least 6 months with or without suppression of HBV DNA and had compensated liver function. Sixty-nine of the 72 patients were on prior TDF-containing antiretroviral therapy. The mean age was 50 years (range: 28 to 67), 92% of patients were male, 69% were White, 18% were Black, and 10% were Asian. The mean baseline CD4+ cell count was 636 cells/µL (range 263-1498). 86% (62/72 patients) were

HBV suppressed (HBV DNA < 29 IU/mL) and 42% (30/72) of patients were HBeAg positive at baseline.

At Week 48, 92% (66/72 HIV-suppressed patients) maintained HIV-1 RNA < 50 copies/mL after switching to GENVOYA. The mean change from baseline in CD4+ cell count at Week 48 was -2 cells/µL.

Ninety-two percent (66/72 HIV-suppressed patients) had HBV DNA < 29 IU/mL using missing = failure analysis at Week 48. ALT normalisation was achieved in 50% patients (i.e., 4 of 8 patients who had ALT data available at Week 48).

5.2 Pharmacokinetic Properties

Absorption and Bioavailability

Elvitegravir, Cobicistat, Emtricitabine and Tenofovir Alafenamide: Following oral administration with food in HIV-1 infected patients, peak plasma concentrations were observed approximately 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 12 for pharmacokinetic parameters).

Table 12. Pharmacokinetic Parameters of Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir Alafenamide Exposure Following Oral Administration in HIV-Infected Adults

Parameter Mean ± SD [range: min:max]	Elvitegravir[a]	Cobicistat[b]	Emtricitabine[b]	Tenofovir Alafenamide[c]
C_{max} (µg/mL)	1.7 ± 0.4 [0.4:3.7]	1.1 ± 0.4 [0.1:2.1]	1.9 ± 0.5 [0.6:3.6]	0.16 ± 0.08 [0.02:0.97]
AUC_{tau} (µg•h/mL)	23.0 ± 7.5 [4.4:69.8]	8.3 ± 3.8 [0.5:18.3]	12.7 ± 4.5 [5.2:34.1]	0.21 ± 0.15 [0.05:1.9]
C_{trough} (µg/mL)	0.45 ± 0.26 [0.05:2.34]	0.05 ± 0.13 [0.01:0.92]	0.14 ± 0.25 [0.04:1.94]	NA

SD = Standard Deviation; 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.

Effect of Food on Oral Distribution

Relative to fasting conditions, the 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, the 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, the 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.

Distribution, Metabolism and Elimination

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. Elvitegravir undergoes primarily oxidative metabolism via CYP3A, and is secondarily glucuronidated via UGT1A1/3 enzymes. Following oral administration of boosted [^{14}C]elvitegravir, elvitegravir was the predominant species in plasma, representing ~ 94% of the circulating radioactivity. Aromatic and aliphatic hydroxylation or glucuronidation metabolites are present in very low levels, display considerably lower anti-HIV activity and do not contribute to the overall antiviral activity of elvitegravir. 94.8% of the dose was recovered in faeces, consistent with the hepatobiliary excretion of elvitegravir; 6.7% of the administered dose was recovered in urine as unchanged elvitegravir. The median terminal plasma half-life of elvitegravir following administration of STRIBILD is approximately 12.9 hours. Elvitegravir plasma exposures are non-linear and less than dose proportional, likely due to solubility-limited absorption.

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

Cobicistat is metabolised via CYP3A (major)- and CYP2D6 (minor)-mediated oxidation and does not undergo glucuronidation. Following oral administration of [14C] cobicistat, 99% of circulating radioactivity in plasma was unchanged cobicistat. Low levels of metabolites are observed in urine and faeces and do not contribute to the CYP3A inhibitory activity of cobicistat. Eighty-six percent and 8.2% of the dose were recovered in feces and urine, respectively. The median terminal plasma half-life of cobicistat following administration of STRIBILD is approximately 3.5 hours and the associated cobicistat exposures provide elvitegravir C_{trough} approximately 10-fold above the protein-binding adjusted IC_{95} for wild-type HIV-1 virus. Cobicistat exposures are non-linear and greater than dose-proportional over the range of 50 mg to 400 mg, consistent with a mechanism-based CYP3A inhibitor.

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. Following administration of radiolabelled emtricitabine approximately 86% is recovered in the urine and 13% is recovered as metabolites. The metabolites of emtricitabine include 3′-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of EMTRIVA, the plasma emtricitabine half-life is approximately 10 hours.

Tenofovir alafenamide: The binding of tenofovir to human plasma proteins is less than 0.7% and is independent of concentration over the range of 0.01 to 25 micrograms/mL. The binding of tenofovir alafenamide to human plasma proteins in samples collected during clinical studies was approximately 80%.

Distribution studies in dogs showed 5.7 to 15-fold higher ^{14}C-radioactivity in lymphoid tissues (iliac, axillary, inguinal and mesenteric lymph nodes, and spleen) 24 hours following administration of an equivalent dose of [^{14}C]-tenofovir alafenamide relative to [^{14}C]-tenofovir disoproxil fumarate.

Metabolism is a major excretion pathway for tenofovir alafenamide in humans, accounting for > 80% of an oral dose. *In vitro* studies have shown that tenofovir alafenamide is metabolised to tenofovir (major metabolite) by cathepsin A in PBMCs (including lymphocytes and other HIV target cells) and macrophages; and by carboxylesterase-1 in hepatocytes. *In vivo*, tenofovir alafenamide is hydrolysed 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 metabolised by CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Tenofovir alafenamide is minimally metabolised by CYP3A4. Upon coadministration with the moderate CYP3A inducer probe efavirenz, tenofovir alafenamide exposure was not significantly affected. 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*.

Tenofovir alafenamide is eliminated following metabolism to tenofovir. Tenofovir alafenamide and tenofovir have a median plasma half-life of 0.51 and 32.37 hours, respectively. Tenofovir is renally eliminated by both glomerular filtration and active tubular secretion. 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 to 180 hours within PBMCs.

Age, Gender and Ethnicity

No clinically relevant pharmacokinetic differences due to gender have been identified for cobicistat-boosted elvitegravir, emtricitabine, or tenofovir alafenamide and no dosage adjustment is recommended based on gender.

Pharmacokinetic differences for cobicistat-boosted elvitegravir, emtricitabine, or tenofovir alafenamide due to ethnicity are unclear, however, based on population pharmacokinetic analyses, no dosage adjustment is recommended based on ethnicity.

Clinical trials of GENVOYA included 97 patients (80 receiving GENVOYA) aged 65 years and over. No dose adjustment is required for elderly patients. Pharmacokinetic pharmacodynamic analyse of HIV-infected patients in Phase 2 and Phase 3 studies 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.

Exposures of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide achieved in 24 paediatric patients aged 12 to < 18 years who received GENVOYA in Study 106 were similar to exposures achieved in treatment-naïve adults following administration of GENVOYA.

Exposures of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide achieved in 23 paediatric patients between the ages of 6 to < 12 years (≥ 25 kg) who received GENVOYA in Study 106 were generally higher (20–80%) than exposures achieved in adults; however, the increase was not considered clinically significant as the safety profiles were similar in adult and paediatric patients.

Patients with Impaired Renal Function

No clinically relevant differences in elvitegravir, cobicistat, tenofovir alafenamide, or tenofovir pharmacokinetics were observed between healthy subjects (N=13) and subjects with severe renal impairment (N=14) (estimated creatinine clearance less than 30 mL/min) in studies of cobicistat-boosted elvitegravir or of tenofovir alafenamide, respectively. There are no pharmacokinetic data on elvitegravir, cobicistat, or tenofovir alafenamide in subjects with estimated creatinine clearance less than 15 mL/min.

The safety, virologic, and immunologic responses of GENVOYA in HIV-1 infected patients with mild to moderate renal impairment (eGFR 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, GS-US-292-0112 (Study 112). The safety profile of GENVOYA in subjects with mild to moderate renal impairment was similar to that inpatients with normal renal function.

Patients with Hepatic Impairment

Elvitegravir and cobicistat: Both elvitegravir and cobicistat are primarily metabolised and eliminated by the liver. A study of pharmacokinetics of cobicistat-boosted elvitegravir was performed in non-HIV-1 infected subjects with moderate hepatic impairment. No clinically relevant differences in elvitegravir or cobicistat pharmacokinetics were observed between subjects with moderate impairment and healthy subjects. No 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 subjects with hepatic impairment; however, emtricitabine is not significantly metabolised 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.

Hepatitis B and/or Hepatitis C Virus Coinfection

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

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

Assessment of Drug Interactions

Drug-drug interaction studies were conducted with GENVOYA or various combinations of GENVOYA components including elvitegravir (coadministered with cobicistat or ritonavir).

As GENVOYA should not be administered with other antiretroviral medications, information regarding drug-drug interactions with other antiretrovirals agents is not provided (see section 4.4 Special warnings and precautions for use).

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

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

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

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.

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

Tenofovir alafenamide: Tenofovir alafenamide is a substrate of P-glycoprotein (P-gp) and BCRP. 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 interaction 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 CYP3A4 *in vivo*.

Drug Interaction Studies

The effects of coadministered drugs on the exposure of elvitegravir are shown in Table 13. The effects of coadministered drugs on the exposure of tenofovir alafenamide are shown in Table 14. The effects of GENVOYA or its components on the exposure of coadministered drugs are shown in Table 15.

Table 13 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	Mean Ratio of Elvitegravir Pharmacokinetic Parameters (90% CI)[b]; No effect = 1.00		
					C_{max}	AUC	C_{min}
Antacids	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)
	20 mL single dose simultaneously administered with elvitegravir	50 single dose	Ritonavir 100 single dose	13	0.53 (0.47, 0.60)	0.55 (0.50, 0.60)	0.59 (0.52, 0.67)
Atorvastatin	10 single dose	150 once daily[d]	Cobicistat 150 once daily[d]	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)

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose (mg)	Cobicistat or Ritonavir Booster Dose (mg)	N	Mean Ratio of Elvitegravir Pharmacokinetic Parameters (90% CI)[b]; No effect = 1.00		
					C_{max}	AUC	C_{min}
Famotidine[c]	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[d]	Cobicistat 150 once daily[d]	30	0.98 (0.90, 1.07)	1.11 (1.02, 1.20)	1.46 (1.28, 1.66)
Omeprazole[c]	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[d]	Cobicistat 150 once daily[d]	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[d]	Cobicistat 150 once daily[d]	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 once daily[e]	150 once daily[d]	Cobicistat 150 once daily[d]	29	0.79 (0.75, 0.85)	0.94 (0.88, 1.00)	1.32 (1.17, 1.49)
Telaprevir	750 three times daily	150 once daily[f]	Cobicistat 150 once daily[f]	16	0.79 (0.74, 0.85)	0.84 (0.79, 0.89)	1.29 (1.14, 1.46)

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. Study conducted with GENVOYA.

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

Table 14 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	Mean Ratio of Tenofovir Alafenamide 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	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[c]	24	0.80 (0.68, 0.94)	0.87 (0.81, 0.94)	NC
Sofosbuvir/ Velpatasvir/ Voxilaprevir	400/100/100 + 100 Voxilaprevir once daily[d]	10 once daily[c]	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. All No Effect Boundaries are 70% -143% unless otherwise specified..
c. Study conducted with GENVOYA.
d. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Table 15 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	Mean Ratio of Coadministered Drug Pharmacokinetic Parameters (90% CI)[b]; No effect = 1.00		
						C_{max}	AUC	C_{min}
Atorvastatin	10 single dose	150 once daily[d]	150 once daily[d]	10 once daily[f]	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	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	12	1.40 (1.32, 1.49)	1.43 (1.36, 1.52)	1.51 (1.41, 1.62)
Carbamazepine-10,11-epoxide						0.73 (0.70, 0.78)	0.65 (0.63, 0.66)	0.59 (0.57, 0.61)
Desipramine[c]	50 single dose	N/A	150 once daily	N/A	8	1.24 (1.08, 1.44)	1.65 (1.36, 2.02)	NC

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose[b] (mg)	Cobicistat Booster Dose (mg)	Tenofovir Alafenamide (mg)	N	Mean Ratio of Coadministered Drug Pharmacokinetic Parameters (90% CI)[b]; No effect = 1.00		
						C_{max}	AUC	C_{min}
Digoxin[c]	0.5 single dose	N/A	150 once daily	N/A	22	1.41 (1.29, 1.55)	1.08 (1.00, 1.17)	NC
Ledipasvir	90 once daily	150 once daily[f]	150 once daily[f]	10 once daily[f]	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[i]						1.29 (1.24, 1.35)	1.48 (1.44, 1.53)	1.66 (1.60, 1.73)
Norgestimate[c]/ ethinyl estradiol[c]	0.180/0.215/ 0.250 norgestimate once daily	150 once daily[d]	150 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)
Norelgelstromin	0.180/0.215/ 0.250 norgestimate once daily / 0.025 ethinyl estradiol once daily	NA	NA	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	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[f]	150 once daily[f]	10 once daily[f]	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	12	1.09 (0.98, 1.20[g]	0.92 (0.83, 1.03)[g]	0.94 (0.85, 1.04[g]
25-O-desacetyl-rifabutin					12	4.84 (4.09, 5.74)[g]	6.25 (5.08, 7.69)[g]	4.94 (4.04, 6.04)[g]
Rosuvastatin	10 single dose	150 once daily	150 once daily	N/A	10	1.89[h] (1.48 ,2.42)	1.38 (1.14, 1.67)	NA
Sofosbuvir	400/100 once daily	150 once daily[f]	150 once daily[f]	10 once daily[f]	24	1.23 (1.07, 1.42)	1.37 (1.24, 1.52)	NA
GS-331007[i]						1.29 (1.25, 1.33)	1.48 (1.43, 1.53)	1.58 (1.52, 1.65)
Velpatasvir						1.30 (1.17, 1.45)	1.50 (1.35, 1.66)	1.60 (1.44, 1.78)
Sofosbuvir	400/100/ 100+100[j] once daily	150 once daily[f]	150 once daily[f]	10 once daily[f]	29	1.27 (1.09, 1.48)	1.22 (1.12, 1.32)	NA
GS-331007[i]						1.28 (1.25, 1.32)	1.43 (1.39, 1.47)	NA

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose[b] (mg)	Cobicistat Booster Dose (mg)	Tenofovir Alafenamide (mg)	N	Mean Ratio of Coadministered Drug Pharmacokinetic Parameters (90% CI)[b]; No effect = 1.00		
						C_{max}	AUC	C_{min}
Velpatasvir						0.96 (0.89, 1.04)	1.16 (1.06, 1.27)	1.46 (1.30, 1.64)
Voxilaprevir						1.92 (1.63, 2.26)	2.71 (2.30, 3.19)	4.50 (3.68, 5.50)
Telaprevir	750 three times daily	150 once daily[d]	150 once daily[d]	NA	15	1.06 (0.97, 1.16)	1.13 (1.00, 1.29)	1.15 (1.05, 1.25)

N/A = Not Applicable/Not Available;

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

5.3 Preclinical Safety Data

Genotoxicity

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

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

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

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

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

Carcinogenicity

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

Elvitegravir: In a long-term carcinogenicity study in mice, no tumourigenic response was seen with doses of up to 2000 mg/kg/day, with the highest dose also being given together

with 25 mg/kg/day ritonavir. Respective elvitegravir exposures (AUC) with this dose were approximately 3.1 and 14 times the human exposure with the 150 mg/day dose. No tumourigenic response was seen in a long-term study in rats with doses up to 2000 mg/kg/day (12 times in males and 27 times in females the human exposure (AUC) with the therapeutic dose).

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

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

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

GENVOYA tablets contain the following ingredients as excipients:
Tablet core: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hyprolose, silicon dioxide, sodium lauryl sulfate, and magnesium stearate.

Film-coating: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, indigo carmine aluminum lake, and iron oxide yellow.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf Life

3 years

6.4 Special Precautions for Storage

GENVOYA should be stored below 25 °C.

6.5 Nature and Contents of Container

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

6.6 Special Precautions for Disposal

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

7 MEDICINE SCHEDULE

PRESCRIPTION ONLY MEDICINE

8 SPONSOR

Gilead Sciences (NZ)
c/- Grant Thornton New Zealand Limited
L4, 152 Fanshawe Street,
Auckland 1010
New Zealand
Tel: 0800 443 933

9 DATE OF FIRST APPROVAL

17 January 2017

10 DATE OF REVISION OF THE TEXT

03 July 2024

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
2.0	Inclusion of 'Contains lactose'
6.3	Change to Shelf Life