Summary of Product Characteristics

1. Name of medicinal product

1.1 Product name

Genvoya™
Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide

1.2 Strength

150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine and tenofovir alafenamide fumarate equivalent to 10 mg of tenofovir alafenamide.

1.3 Pharmaceutical dosage form

Film-coated tablet (tablet).

2. Quality and Quantitative Formulation

2.1 Qualitative declaration

Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide

2.2 Quantitative declaration

Each tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine and tenofovir alafenamide fumarate equivalent to 10 mg of tenofovir alafenamide.

3. Pharmaceutical form

Green, capsule-shaped, film-coated tablet, debossed with “GSI” on one side of the tablet and “510” on the other side of the tablet.

4. Clinical Particulars

4.1. Therapeutic Indication

Genvoya is indicated for the treatment of adults and adolescents (aged 12 years and older with body weight at least 35 kg) infected with human immunodeficiency virus-1 (HIV-1) without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir (see sections 4.2 and 5.1).

4.2. Posology and Method of Administration

Therapy should be initiated by a physician experienced in the management of HIV infection.

Posology

Adults and adolescents aged 12 years and older, weighing at least 35 kg

One tablet to be taken once daily with food.

If the patient misses a dose of Genvoya within 18 hours of the time it is usually taken, the patient should take Genvoya with food as soon as possible and resume the normal dosing schedule. If a patient misses a dose of Genvoya by more than 18 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.

If the patient vomits within 1 hour of taking Genvoya another tablet should be taken.

Elderly

No dose adjustment of Genvoya is required in elderly patients (see sections 5.1 and 5.2).

Renal impairment

No dose adjustment of Genvoya is required in adults or adolescents (aged at least 12 years and of at least 35 kg body weight) with estimated creatinine clearance (CrCl) ≥ 30 mL/min.

Genvoya should not be initiated in patients with estimated CrCl < 30 mL/min as there are limited data available regarding the use of Genvoya in this population (see sections 5.1 and 5.2).

Genvoya should be discontinued in patients with estimated CrCl that declines below 30 mL/min during treatment (see sections 5.1 and 5.2).

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 sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of Genvoya in children younger than 12 years of age, or weighing < 35 kg, have not yet been established. No data are available.

Method of administration

Genvoya should be taken orally, once daily with food (see section 5.2). The film-coated tablet should not be chewed, crushed, or split.

4.3. Contraindications

Hypersensitivity to the active substances or to any of the excipients listed below:

Tablet core
Lactose (as monohydrate)
Microcrystalline cellulose
Croscarmellose sodium
Hydroxypropyl cellulose
Silicon dioxide
Sodium lauryl sulphate
Magnesium stearate

Film-coating
Polyvinyl alcohol
Titanium dioxide
Polyethylene glycol/Macrogol
Talc
FD&C Blue #2/Indigo carmine aluminium lake
Iron oxide yellow

Co-administration with the following medicinal products due to the potential for serious or life-threatening adverse reactions or loss of virologic response and possible resistance to Genvoya (see section 4.5):

- alpha 1-adrenoreceptor antagonists: alfuzosin
- antiarrhythmics: amiodarone, quinidine
- anticonvulsants: carbamazepine, phenobarbital, phenytoin
- antimycobacterials: rifampicin
- ergot derivatives: dihydroergotamine, ergometrine, ergotamine
- gastrointestinal motility agents: cisapride
- herbal products: St. John's wort (*Hypericum perforatum*)
- HMG Co-A reductase inhibitors: lovastatin, simvastatin
- neuroleptics: pimozide
- PDE-5 inhibitors: sildenafil for the treatment of pulmonary arterial hypertension
- sedatives/hypnotics: orally administered midazolam, triazolam

4.4. Special Warnings and Precautions for Use

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Patients co-infected with HIV and hepatitis B or C virus

Patients with chronic hepatitis B or C treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

The safety and efficacy of Genvoya in patients co-infected with HIV-1 and hepatitis C virus (HCV) have not been established. Tenofovir alafenamide is active against hepatitis B virus (HBV), but its clinical efficacy against this virus is under investigation and is not yet fully established.

Discontinuation of Genvoya therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis. Patients co-infected with HIV and HBV who discontinue Genvoya should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment.

Genvoya should not be administered concomitantly with medicinal products containing tenofovir disoproxil (as fumarate), lamivudine or adefovir dipivoxil used for the treatment of HBV infection.

Liver disease

The safety and efficacy of Genvoya in patients with significant underlying liver disorders have not been established.

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Mitochondrial dysfunction

Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or postnatally to nucleoside analogues. The main adverse reactions reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactataemia, hyperlipasaemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Immune Reactivation Syndrome

In HIV infected patients treated with CART, including with emtricitabine, immune reactivation syndrome has been reported. In HIV infected patients with severe immune deficiency at the time of institution of CART, 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 CART. 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 (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable, and these events can occur many months after initiation of treatment.

Opportunistic infections

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.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV disease and/or long-term exposure to CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Nephrotoxicity

A potential risk of nephrotoxicity resulting from chronic exposure to low levels of tenofovir due to dosing with tenofovir alafenamide cannot be excluded (see section 5.3).

Co-administration of other medicinal products

Some medicinal products should not be co-administered with Genvoya (see sections 4.3 and 4.5).

Other antiretroviral medicinal products

Genvoya should not be co-administered with other antiretroviral medicinal products (see section 4.5).

Contraception requirements

Female patients of childbearing potential should use either a hormonal contraceptive containing at least 30 µg ethinylestradiol and containing norgestimate as the progestagen or should use an alternative reliable method of contraception (see sections 4.5 and 4.6). The effect of co-administration of Genvoya with oral contraceptives containing progestagens other than norgestimate is not known and, therefore, should be avoided.

Excipients

Genvoya contains lactose monohydrate. Consequently, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

4.5. Interactions with other Medication

Genvoya should not be co-administered with other antiretroviral medicinal products. Therefore, information regarding drug-drug interactions with other antiretroviral products (including PIs and non-nucleoside reverse transcriptase inhibitors [NNRTIs]) is not provided (see section 4.4). Interaction studies have only been performed in adults.

Genvoya should not be administered concomitantly with medicinal products containing tenofovir disoproxil (as fumarate), lamivudine or adefovir dipivoxil used for the treatment of HBV infection.

Elvitegravir

Elvitegravir is primarily metabolised by CYP3A, and medicinal products that induce or inhibit CYP3A may affect the exposure of elvitegravir. Co-administration of Genvoya with medicinal products that induce CYP3A may result in decreased plasma concentrations of elvitegravir and reduced therapeutic effect of Genvoya (see "Concomitant use contraindicated" and section 4.3). Elvitegravir may have the potential to induce CYP2C9 and/or inducible uridine diphosphate glucuronosyltransferase (UGT) enzymes; as such it may decrease the plasma concentration of substrates of these enzymes.

Cobicistat

Cobicistat is a strong mechanism-based inhibitor of CYP3A and is also a CYP3A substrate. Cobicistat is also a weak CYP2D6 inhibitor and is metabolised, to a minor extent, by CYP2D6. Medicinal products that inhibit CYP3A may decrease the clearance of cobicistat, resulting in increased plasma concentrations of cobicistat.

Medicinal products that are highly dependent on CYP3A metabolism and have high first pass metabolism are the most susceptible to large increases in exposure when co-administered with cobicistat (see "Concomitant use contraindicated" and section 4.3).

Cobicistat is an inhibitor of the following transporters: P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP) 1B1 and OATP1B3. Co-administration with medicinal products that are substrates of P-gp, BCRP, OATP1B1 and OATP1B3 may result in increased plasma concentrations of these products.

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. Co-administration of emtricitabine with medicinal products that are eliminated by active tubular secretion may increase concentrations of emtricitabine, and/or the co-administered medicinal product. Medicinal products that decrease renal function may increase concentrations of emtricitabine.

Tenofovir alafenamide

Tenofovir alafenamide is transported by P-gp and BCRP. Medicinal products that strongly affect P-gp and BCRP activity may lead to changes in tenofovir alafenamide absorption. However, upon co-administration 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 administered alone. As such, tenofovir alafenamide exposures following administration of Genvoya are not expected to be further increased when used in combination with another P-gp inhibitor (e.g., ketoconazole). It is not known whether the co-administration of Genvoya and xanthine oxidase inhibitors (e.g., febuxostat) would increase systemic exposure to tenofovir. *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 of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Tenofovir alafenamide is not an inhibitor of CYP3A4 *in vivo*. Tenofovir alafenamide is a substrate of OATP *in vitro*. Inhibitors of OATP and BCRP include ciclosporin.

Concomitant use contraindicated

Co-administration of Genvoya and some medicinal products that are primarily metabolised by CYP3A may result in increased plasma concentrations of these products, which are associated with the potential for serious or life-threatening adverse reactions such as peripheral vasospasm or ischaemia (e.g., dihydroergotamine, ergotamine, ergometrine), or myopathy, including rhabdomyolysis (e.g., simvastatin, lovastatin), or prolonged or increased sedation or respiratory depression (e.g., orally administered midazolam or triazolam). Co-administration of Genvoya and other medicinal products primarily metabolised by CYP3A such as amiodarone, quinidine, cisapride, pimozide, alfuzosin and sildenafil for pulmonary arterial hypertension is contraindicated (see section 4.3).

Co-administration of Genvoya and some medicinal products that induce CYP3A such as St. John's wort (*Hypericum perforatum*), rifampicin, carbamazepine, phenobarbital, and phenytoin may result in significantly decreased cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance (see section 4.3).

Other interactions

Cobicistat and tenofovir alafenamide are not inhibitors of human UGT1A1 *in vitro*. It is not known whether cobicistat, emtricitabine, or tenofovir alafenamide are inhibitors of other UGT enzymes.

Interactions between the components of Genvoya and potential co-administered medicinal products are listed in Table 1 below (increase is indicated as "↑", decrease as "↓", no change as "↔"). The 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-drug interactions that may occur with Genvoya.

Table 1: Interactions between the individual components of Genvoya and other medicinal products

Medicinal product by therapeutic areas	**Effects on medicinal product levels.** **Mean percent change in AUC, C_{max}, C_{min}** [1]	**Recommendation concerning co-administration with Genvoya**
ANTI-INFECTIVES		
Antifungals		
Ketoconazole (200 mg twice daily)/ Elvitegravir (150 mg once daily)[2]	Elvitegravir: AUC: ↑ 48% C_{min}: ↑ 67% C_{max}: ↔ Concentrations of ketoconazole and/or cobicistat may increase with co-administration of Genvoya.	When administering with Genvoya, the maximum daily dose of ketoconazole should not exceed 200 mg per day. Caution is warranted and clinical monitoring is recommended during the co-administration.
Itraconazole[3] Voriconazole[3] Posaconazole[3] Fluconazole	Interaction not studied with any of the components of Genvoya. Concentrations of itraconazole, fluconazole and posaconazole may be increased when co-administered with cobicistat. Concentrations of voriconazole may increase or decrease when co-administered with Genvoya.	Clinical monitoring should be made upon co-administration with Genvoya. When administering with Genvoya, the maximum daily dose of itraconazole should not exceed 200 mg per day. An assessment of benefit/risk ratio is recommended to justify use of voriconazole with Genvoya.
Antimycobacterials		
Rifabutin (150 mg every other day)/ Elvitegravir (150 mg once daily)/ Cobicistat (150 mg once daily)	Co-administration of rifabutin, a potent CYP3A inducer, may significantly decrease cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Rifabutin: AUC: ↔ C_{min}: ↔ C_{max}: ↔ 25-O-desacetyl-rifabutin AUC: ↑ 525% C_{min}: ↑ 394% C_{max}: ↑ 384% Elvitegravir: AUC: ↓ 21% C_{min}: ↓ 67% C_{max}: ↔ Cobicistat: AUC: ↔ C_{min}: ↓ 66% C_{max}: ↔	Co-administration of Genvoya and rifabutin is not recommended. If the combination is needed, the recommended dose of rifabutin is 150 mg 3 times per week on set days (for example Monday-Wednesday-Friday). Increased monitoring for rifabutin-associated adverse reactions including neutropenia and uveitis is warranted due to an expected increase in exposure to desacetyl-rifabutin. Further dose reduction of rifabutin has not been studied. It should be kept in mind that a twice weekly dose of 150 mg may not provide an optimal exposure to rifabutin thus leading to a risk of rifamycin resistance and a treatment failure.

Medicinal product by therapeutic areas	**Effects on medicinal product levels.** **Mean percent change in AUC, C_{max}, C_{min}**[1]	**Recommendation concerning co-administration with Genvoya**
Anti-hepatitis C virus medicinal products		
Telaprevir (750 mg three times daily)/ Elvitegravir (150 mg once daily)/ Cobicistat (150 mg once daily)[4]	Telaprevir: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Elvitegravir: AUC: ↔ C_{min}: ↑ 29% C_{max}: ↔ Cobicistat: AUC: ↔ C_{min}: ↑ 232% C_{max}: ↔	Co-administration with telaprevir has the potential to adversely affect the intracellular activation and clinical antiviral efficacy of tenofovir alafenamide, therefore co-administration of Genvoya and telaprevir is not recommended.
Ledipasvir (90 mg once daily)/ Sofosbuvir (400 mg once daily)/ Elvitegravir (150 mg once daily)/ Cobicistat (150 mg once daily)/ Emtricitabine (200 mg once daily)/ Tenofovir alafenamide (10 mg once daily)[5]	Ledipasvir: AUC: ↑ 79% C_{min}: ↑ 93% C_{max}: ↑ 65% Sofosbuvir: AUC: ↑ 47% C_{min}: N/A C_{max}: ↑ 28% Sofosbuvir metabolite GS-566500: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Sofosbuvir metabolite GS-331007: AUC: ↑ 48% C_{min}: ↑ 66% C_{max}: ↔ Elvitegravir: AUC: ↔ C_{min}: ↑ 46% C_{max}: ↔ Cobicistat: AUC: ↑ 53% C_{min}: ↑ 225% C_{max}: ↔ Emtricitabine: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Tenofovir alafenamide: AUC: ↔ C_{min}: N/A C_{max}: ↔	No dose adjustment of ledipasvir/sofosbuvir and Genvoya is warranted upon co-administration.

Medicinal product by therapeutic areas	**Effects on medicinal product levels.** **Mean percent change in AUC, C_{max}, C_{min}[1]**	**Recommendation concerning co-administration with Genvoya**
Boceprevir	Interaction not studied with any of the components of Genvoya.	Co-administration with boceprevir has the potential to adversely affect the intracellular activation and clinical antiviral efficacy of tenofovir alafenamide, therefore co-administration of Genvoya and boceprevir is not recommended.
Macrolide antibiotics		
Clarithromycin	Interaction not studied with any of the components of Genvoya. Concentrations of clarithromycin and/or cobicistat may be altered with co-administration of Genvoya.	Clarithromycin dosing should be based on the patient's CrCl, taking into consideration the effect of cobicistat on CrCl and serum creatinine (see section 4.8). Patients with CrCl greater than or equal to 60 mL/min: No dose adjustment of clarithromycin is required. Patients with CrCl between 30 mL/min and 60 mL/min: The dose of clarithromycin should be reduced by 50%.
Telithromycin	Interaction not studied with any of the components of Genvoya. Concentrations of telithromycin and/or cobicistat may be altered with co-administration of Genvoya.	Clinical monitoring is recommended upon co-administration of Genvoya.
ANTICONVULSANTS		
Carbamazepine (200 mg twice daily)/ Elvitegravir (150 mg once daily)/ Cobicistat (150 mg once daily)	Co-administration of carbamazepine, a potent CYP3A inducer, may significantly decrease cobicistat plasma concentrations. Elvitegravir: AUC: ↓ 69% C_{min}: ↓ 97% C_{max}: ↓ 45% Cobicistat: AUC: ↓ 84% C_{min}: ↓ 90% C_{max}: ↓ 72% Carbamazepine: AUC: ↑ 43% C_{min}: ↑ 51% C_{max}: ↑ 40% Carbamazepine-10,11-epoxide: AUC: ↓ 35% C_{min}: ↓ 41% C_{max}: ↓ 27%	Carbamazepine decreases plasma concentrations of elvitegravir and cobicistat, which may result in loss of therapeutic effect and development of resistance. Co-administration of Genvoya with carbamazepine is contraindicated (see section 4.3).

Medicinal product by therapeutic areas	**Effects on medicinal product levels.** **Mean percent change in AUC, C_{max}, C_{min}**[1]	**Recommendation concerning co-administration with Genvoya**
GLUCOCORTICOIDS		
Inhaled/Nasal corticosteroids		
Fluticasone	Interaction not studied with any of the components of Genvoya. Concomitant use of inhaled or nasal fluticasone propionate and Genvoya may increase plasma concentrations of fluticasone, resulting in reduced serum cortisol concentrations.	Caution is warranted and clinical monitoring is recommended upon co-administration of Genvoya.
ANTACIDS		
Magnesium/aluminium-containing antacid suspension (20 mL single dose)/ Elvitegravir (50 mg single dose)/ Ritonavir (100 mg single dose)	Elvitegravir (antacid suspension after ± 2 hours): AUC: ↔ C_{min}: ↔ C_{max}: ↔ Elvitegravir (simultaneous administration): AUC: ↓ 45% C_{min}: ↓ 41% C_{max}: ↓ 47%	Elvitegravir plasma concentrations are lower with antacids due to local complexation in the gastrointestinal tract and not to changes in gastric pH. It is recommended to separate Genvoya and antacid administration by at least 4 hours. For information on other acid reducing agents (e.g., H_2-receptor antagonists and proton pump inhibitors), see "Studies conducted with other medicinal products".
FOOD SUPPLEMENTS		
Multivitamin supplements	Interaction not studied with any of the components of Genvoya.	As the effect of cationic complexation of elvitegravir cannot be excluded when Genvoya is co-administered with multivitamin supplements, it is recommended to separate Genvoya and multivitamin supplements dosing by at least 4 hours.
ORAL ANTI-DIABETICS		
Metformin	Interaction not studied with any of the components of Genvoya. Cobicistat reversibly inhibits MATE1, and concentrations of metformin may be increased when co-administered with Genvoya.	Careful patient monitoring and dose adjustment of metformin is recommended in patients who are taking Genvoya.

Medicinal product by therapeutic areas	**Effects on medicinal product levels.** **Mean percent change in AUC, C_{max}, C_{min}**[1]	**Recommendation concerning co-administration with Genvoya**
NARCOTIC ANALGESICS		
Methadone (80-120 mg)/ Elvitegravir (150 mg once daily)/ Cobicistat (150 mg once daily)	Methadone: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Cobicistat: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Elvitegravir: AUC: ↔ C_{min}: ↔ C_{max}: ↔	No dose adjustment of methadone is required.
Buprenorphine/Naloxone (16/4 to 24/6 mg)/ Elvitegravir (150 mg once daily)/ Cobicistat (150 mg once daily)	Buprenorphine: AUC: ↑ 35% C_{min}: ↑ 66% C_{max}: ↑ 12% Naloxone: AUC: ↓ 28% C_{max}: ↓ 28% Cobicistat: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Elvitegravir: AUC: ↔ C_{min}: ↔ C_{max}: ↔	No dose adjustment of buprenorphine/naloxone is required.
ORAL CONTRACEPTIVES		
Norgestimate (0.180/0.215 mg once daily)/ Ethinylestradiol (0.025 mg once daily)/ Elvitegravir (150 mg once daily)/ Cobicistat (150 mg once daily)[4]	Norgestimate: AUC: ↑ 126% C_{min}: ↑ 167% C_{max}: ↑ 108% Ethinylestradiol: AUC: ↓ 25% C_{min}: ↓ 44% C_{max}: ↔ Elvitegravir: AUC: ↔ C_{min}: ↔ C_{max}: ↔	Caution should be exercised when co-administering Genvoya and a hormonal contraceptive. The hormonal contraceptive should contain at least 30 µg ethinylestradiol and contain norgestimate as the progestagen or patients should use an alternative reliable method of contraception (see sections 4.4 and 4.6). The long-term effects of substantial increases in progesterone exposure are unknown. The effect of co-administration of Genvoya with oral contraceptives containing progestagens other than norgestimate is not known and therefore should be avoided.

Medicinal product by therapeutic areas	**Effects on medicinal product levels.** **Mean percent change in AUC, C_{max}, C_{min}**[1]	**Recommendation concerning co-administration with Genvoya**
ANTIARRHYTHMICS		
Digoxin (0.5 mg single dose)/ Cobicistat (150 mg multiple doses)	Digoxin: AUC: ↔ C_{max}: ↑ 41%	It is recommended that digoxin levels be monitored when digoxin is combined with Genvoya.
Disopyramide Flecainide Systemic lidocaine Mexiletine Propafenone	Interaction not studied with any of the components of Genvoya. Concentrations of these antiarrhythmic drugs may be increased when co-administered with cobicistat.	Caution is warranted and clinical monitoring is recommended upon co-administration with Genvoya.
ANTI-HYPERTENSIVES		
Metoprolol Timolol	Interaction not studied with any of the components of Genvoya. Concentrations of beta-blockers may be increased when co-administered with cobicistat.	Clinical monitoring is recommended and a dose decrease may be necessary when these agents are co-administered with Genvoya.
Amlodipine Diltiazem Felodipine Nicardipine Nifedipine Verapamil	Interaction not studied with any of the components of Genvoya. Concentrations of calcium channel blockers may be increased when co-administered with cobicistat.	Clinical monitoring of therapeutic effects and adverse reactions is recommended when these medicinal products are concomitantly administered with Genvoya.
ENDOTHELIN RECEPTOR ANTAGONISTS		
Bosentan	Interaction not studied with any of the components of Genvoya. Co-administration 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.
ANTICOAGULANTS		
Warfarin	Interaction not studied with any of the components of Genvoya. Concentrations of warfarin may be affected upon co-administration with Genvoya.	It is recommended that the international normalised ratio (INR) be monitored upon co-administration of Genvoya. INR should continue to be monitored during the first weeks following ceasing treatment with Genvoya.
Dabigatran	Interaction not studied with any of the components of Genvoya. Concentrations of dabigatran may be increased upon co-administration with Genvoya.	Clinical monitoring is recommended when dabigatran is co-administered with P-gp inhibitors. A coagulation test helps to identify patients with an increased bleeding risk due to increased dabigatran exposure.

Medicinal product by therapeutic areas	**Effects on medicinal product levels.** **Mean percent change in AUC, C_{max}, C_{min}**[1]	**Recommendation concerning co-administration with Genvoya**
INHALED BETA AGONIST		
Salmeterol	Interaction not studied with any of the components of Genvoya. Co-administration with Genvoya may result in increased plasma concentrations of salmeterol, which is associated with the potential for serious or life-threatening adverse reactions.	Concurrent administration of salmeterol and Genvoya is not recommended.
HMG CO-A REDUCTASE INHIBITORS		
Rosuvastatin (10 mg single dose)/ Elvitegravir (150 mg once daily)/ Cobicistat (150 mg once daily)	Elvitegravir: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Rosuvastatin: AUC: ↑ 38% C_{min}: N/A C_{max}: ↑ 89%	Concentrations of rosuvastatin are transiently increased when administered with elvitegravir and cobicistat. Dose modifications are not necessary when rosuvastatin is administered in combination with Genvoya.
Atorvastatin Pitavastatin	Interaction not studied with any of the components of Genvoya. Concentrations of atorvastatin and pitavastatin may be increased when administered with elvitegravir and cobicistat.	Co-administration of atorvastatin with Genvoya is not recommended. If the use of atorvastatin is considered strictly necessary, the lowest possible dose of atorvastatin should be administered with careful safety monitoring. Caution should be exercised when co-administering Genvoya with pitavastatin.
Pravastatin Fluvastatin	Interaction not studied with any of the components of Genvoya. Concentrations of these HMG Co-A reductase inhibitors are expected to transiently increase when administered with elvitegravir and cobicistat.	Dose modifications are not necessary when administered in combination with Genvoya.
Lovastatin Simvastatin	Interaction not studied with any of the components of Genvoya.	Co-administration of Genvoya and lovastatin and simvastatin is contraindicated (see section 4.3).

Medicinal product by therapeutic areas	**Effects on medicinal product levels.** **Mean percent change in AUC, C_{max}, C_{min}**[1]	**Recommendation concerning co-administration with Genvoya**
PHOSPHODIESTERASE TYPE 5 (PDE-5) INHIBITORS		
Sildenafil Tadalafil Vardenafil	Interaction not studied with any of the components of Genvoya. PDE-5 inhibitors are primarily metabolised by CYP3A. Co-administration with Genvoya may result in increased plasma concentrations of sildenafil and tadalafil, which may result in PDE-5 inhibitor-associated adverse reactions.	Co-administration of Genvoya and sildenafil for the treatment of pulmonary arterial hypertension is contraindicated. Caution should be exercised, including consideration of dose reduction, when co-administering 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 co-administered with Genvoya.
ANTIDEPRESSANTS		
Sertraline (50 mg single dose)/ Elvitegravir (150 mg once daily)/ Cobicistat (150 mg once daily)/ Emtricitabine (200 mg once daily)/ Tenofovir alafenamide (10 mg once daily)[5]	Elvitegravir: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Tenofovir alafenamide: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Sertraline: AUC: ↔ C_{min}: ↔ C_{max}: ↔	Concentrations of sertraline are not affected upon co-administration with Genvoya. No dose adjustment is required upon co-administration.
Tricyclic antidepressants (TCAs) Trazodone Selective serotonin reuptake inhibitors (SSRIs) Escitalopram	Interaction not studied with any of the components of Genvoya. Concentrations of antidepressant agents may be increased when co-administered with cobicistat.	Careful dose titration of the antidepressant and monitoring for antidepressant response is recommended.
IMMUNOSUPPRESSANTS		
Ciclosporin Sirolimus Tacrolimus	Interaction not studied with any of the components of Genvoya. Concentrations of these immunosuppressant agents may be increased when administered with cobicistat.	Therapeutic monitoring is recommended upon co-administration with Genvoya.

Medicinal product by therapeutic areas	**Effects on medicinal product levels.** **Mean percent change in AUC, C_{max}, C_{min}[1]**	**Recommendation concerning co-administration with Genvoya**
SEDATIVES/HYPNOTICS		
Buspirone Clorazepate Diazepam Estazolam Flurazepam Lorazepam Triazolam Zolpidem	Interaction not studied with any of the components of Genvoya. Triazolam is primarily metabolised by CYP3A. Co-administration with Genvoya may result in increased plasma concentrations of this medicinal product, which is associated with the potential for serious or life-threatening adverse reactions. Concentrations of other benzodiazepines, including diazepam, may be increased when administered with Genvoya. Based on non-CYP-mediated elimination pathways for lorazepam, no effect on plasma concentrations is expected upon co-administration with Genvoya.	Co-administration of Genvoya and triazolam is contraindicated (see section 4.3). With other sedatives/hypnotics, dose reduction may be necessary and concentration monitoring is recommended.
Orally administered midazolam (2.5 mg single dose)/ Tenofovir alafenamide (25 mg once daily) Intravenously administered midazolam (1 mg single dose)/ Tenofovir alafenamide (25 mg once daily)	Midazolam: AUC: ↔ C_{max}: ↔ Midazolam is primarily metabolised by CYP3A. Due to the presence of cobicistat, co-administration with Genvoya may result in increased plasma concentrations of this medicinal product, which is associated with the potential for serious or life-threatening adverse reactions.	Co-administration of Genvoya and orally administered midazolam is contraindicated (see section 4.3).
ANTI-GOUT		
Colchicine	Interaction not studied with any of the components of Genvoya. Co-administration with Genvoya may result in increased plasma concentrations of this medicinal product.	Dose reductions of colchicine may be required. Genvoya should not be co-administered with colchicine to patients with renal or hepatic impairment.

N/A = not applicable

[1] When data available from drug-drug interaction studies.

[2] These studies were performed with ritonavir boosted elvitegravir.

[3] These are medicinal products within class where similar interactions could be predicted.

[4] This study was conducted using elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate.

[5] This study was conducted using Genvoya

Studies conducted with other medicinal products

Based on drug-drug interaction studies conducted with Genvoya or the components of Genvoya, no clinically significant drug-drug interactions have been either observed or are

expected between the components of Genvoya and the following medicinal products: entecavir, famciclovir, ribavirin, famotidine, and omeprazole.

4.6 Pregnancy and Lactation

Women of childbearing potential / contraception in males and females

The use of Genvoya should be accompanied by the use of effective contraception (see sections 4.4 and 4.5).

Pregnancy

There are no adequate and well-controlled studies of Genvoya or its components in pregnant women. There are no or limited data (less than 300 pregnancy outcomes) from the use of Genvoya in pregnant women. However, a large amount of data on pregnant women (more than 1,000 exposed outcomes) indicate no malformative nor fetal/neonatal toxicity associated with emtricitabine.

Animal studies do not indicate direct or indirect harmful effects of elvitegravir, cobicistat, or emtricitabine, administered separately, with respect to fertility parameters, pregnancy, fetal development, parturition or postnatal development. Studies of tenofovir alafenamide in animals have shown no evidence of harmful effects of tenofovir alafenamide on fertility parameters, pregnancy, or fetal development (see section 4.8).

Genvoya should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Breast-feeding

It is not known whether elvitegravir, cobicistat, or tenofovir alafenamide are excreted in human milk. Emtricitabine is excreted in human milk. In animal studies it has been shown that elvitegravir, cobicistat, and tenofovir are excreted in milk.

There is insufficient information on the effects of elvitegravir, cobicistat, emtricitabine and tenofovir in newborns/infants. Therefore, Genvoya should not be used during breast-feeding.

In order to avoid transmission of HIV to the infant it is recommended that HIV infected women do not breast-feed their infants under any circumstances.

Fertility

There are no data on fertility from the use of Genvoya in humans. In animal studies there were no effects of elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide on mating or fertility parameters (see section 4.8).

4.7 Effects of ability to drive and use machinery

Patients should be informed that dizziness has been reported during treatment with Genvoya.

4.8 Undesirable effects

Summary of the safety profile

Assessment of adverse reactions is based on safety data from across all Phase 2 and 3 studies in which 2,396 patients received Genvoya. The most frequently reported adverse reactions in clinical studies through 96 weeks were nausea (10%), diarrhoea (7%), and headache (6%) (pooled data from Phase 3 clinical studies GS-US-292-0104 and GS-US-292-0111 in 866 treatment-naïve adult patients receiving Genvoya).

Tabulated summary of adverse reactions

The adverse reactions in Table 2 are listed by system organ class and frequency. Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100).

Table 2: Tabulated list of adverse reactions

Frequency	Adverse reaction
Blood and lymphatic system disorders	
Uncommon:	anaemia[1]
Psychiatric disorders	
Common:	abnormal dreams
Uncommon:	depression[2]
Nervous system disorders	
Common:	headache, dizziness
Gastrointestinal disorders	
Very common:	nausea
Common:	diarrhoea, vomiting, abdominal pain, flatulence
Uncommon:	dyspepsia
Skin and subcutaneous tissue disorders	
Common:	rash
Uncommon:	angioedema[1,3], pruritus
General disorders and administration site conditions	
Common:	fatigue

[1] This adverse reaction was not observed in the Phase 3 clinical studies for Genvoya but identified from clinical studies or post-marketing experience for emtricitabine when used with other antiretrovirals.

[2] This adverse reaction was not observed in the Phase 3 clinical studies for Genvoya but identified from clinical studies for elvitegravir when used with other antiretrovirals.

[3] This adverse reaction was identified through post-marketing surveillance for emtricitabine but was not observed in randomised controlled clinical studies in adults or paediatric HIV clinical studies of emtricitabine. The frequency category of uncommon was estimated from a statistical calculation based on the total number of patients exposed to emtricitabine in these clinical studies (n = 1,563).

Description of selected adverse reactions

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

Immune Reactivation Syndrome

In HIV infected patients with severe immune deficiency at the time of initiation of CART, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise.

Autoimmune disorders (such as Graves' disease) have also been reported; however, the reported time to onset is more variable, and these events can occur many months after initiation of treatment (see section 4.4).

Osteonecrosis

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to CART. The frequency of this is unknown (see section 4.4).

Changes in serum creatinine

Cobicistat increases serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function. In clinical studies of Genvoya, increases in serum creatinine occurred by Week 2 of treatment and remained stable through 96 weeks. In treatment-naïve patients, a mean change from baseline of 0.04 ± 0.11 mg/dL (3.5 ± 9.7 µmol/L) was observed after 96 weeks of treatment. Mean increases from baseline in the Genvoya group were smaller than in the elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil (as fumarate) 245 mg (E/C/F/TDF) group at Week 96 (difference −0.03, $p < 0.001$).

Changes in lipid laboratory tests

In studies in treatment-naïve patients, increases from baseline were observed in both treatment groups for the fasting lipid parameters total cholesterol, direct low-density lipoprotein (LDL)- and high-density lipoprotein (HDL)-cholesterol, and triglycerides at Week 96. The median increase from baseline for those parameters was greater in the Genvoya group compared with the E/C/F/TDF group at Week 96 ($p < 0.001$ for the difference between treatment groups for fasting total cholesterol, direct LDL- and HDL-cholesterol, and triglycerides). The median (Q1, Q3) change from baseline in total cholesterol to HDL-cholesterol ratio at Week 96 was 0.1 (-0.3, 0.7) in the Genvoya group and 0.0 (-0.4, 0.5) in the E/C/F/TDF group ($p < 0.001$ for the difference between treatment groups).

<u>Paediatric population</u>

The safety of Genvoya in HIV-1 infected, treatment-naïve paediatric patients aged 12 to < 18 years was evaluated through 48 weeks in an open-label clinical study (GS-US-292-0106). The safety profile in 50 adolescent patients who received treatment with Genvoya was similar to that in adults (see section 5.1).

<u>Other special populations</u>

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 (estimated glomerular filtration rate by Cockcroft-Gault method [$eGFR_{CG}$]: 30-69 mL/min) was evaluated through 24 weeks in an open-label clinical study (GS-US-292-0112). The

safety profile of Genvoya in patients with mild to moderate renal impairment was similar to that in patients with normal renal function (see section 5.1).

Patients co-infected with HIV and HBV

The safety of Genvoya was evaluated in approximately 70 HIV/HBV co-infected patients currently receiving treatment for HIV in an open-label clinical study (GS-US-292-1249). Based on this limited experience, the safety profile of Genvoya in patients with HIV/HBV co-infection appears to be similar to that in patients with HIV-1 monoinfection.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important.
It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

If overdose occurs the patient must be monitored for evidence of toxicity (see section 4.8). Treatment of overdose with Genvoya consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient.

As elvitegravir and cobicistat are highly bound to plasma proteins, it is unlikely that they would be significantly removed by haemodialysis or peritoneal dialysis. Emtricitabine can be removed by haemodialysis, which removes approximately 30% of the emtricitabine dose over a 3 hour dialysis period starting within 1.5 hours of emtricitabine dosing. Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54%. It is not known whether emtricitabine or tenofovir can be removed by peritoneal dialysis.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use; antivirals for treatment of HIV infections, combinations. ATC code: J05AR18.

Mechanism of action

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.

Cobicistat is a selective, mechanism-based inhibitor of cytochrome P450 (CYP) enzymes of the CYP3A subfamily. Inhibition of CYP3A-mediated metabolism by cobicistat enhances the systemic exposure of CYP3A substrates, such as elvitegravir, where bioavailability is limited and half-life is shortened by CYP3A-dependent metabolism.

Emtricitabine is a nucleoside reverse transcriptase inhibitor (NRTI) and nucleoside analogue of 2'-deoxycytidine. Emtricitabine is phosphorylated by cellular enzymes to form emtricitabine triphosphate. Emtricitabine triphosphate inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase (RT), which results in DNA chain-termination. Emtricitabine has activity against HIV-1, HIV-2, and HBV.

Tenofovir alafenamide is a nucleotide reverse transcriptase inhibitor (NtRTI) and phosphonoamidate 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 TDF in concentrating tenofovir in peripheral blood mononuclear cells (PBMCs) (including lymphocytes and other HIV target cells) and macrophages. Intracellular tenofovir is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV replication through incorporation into viral DNA by the HIV RT, which results in DNA chain-termination. Tenofovir has activity against HIV-1, HIV-2, and hepatitis B virus.

Antiviral activity *in vitro*

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.

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).

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

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

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, and O), including subtypes A, B, C, D, E, F, and G (EC_{50} values ranged from 0.10 to 12.0 nM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.91 to 2.63 nM).

Resistance

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

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

Reduced susceptibility to emtricitabine is associated with M184V/I mutations in HIV-1 RT.

HIV-1 isolates with reduced susceptibility to tenofovir alafenamide express 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 treatment-naïve patients
In a pooled analysis, genotyping was performed on plasma HIV-1 isolates from antiretroviral-naïve patients receiving Genvoya in Phase 3 studies GS-US-292-0104 and GS-US-292-0111 with HIV-1 RNA > 400 copies/mL at confirmed virologic failure, Week 96, or time of early study drug discontinuation. Up to Week 96, the development of one or more primary elvitegravir, emtricitabine, or tenofovir alafenamide resistance-associated mutations was observed in HIV-1 isolates from 10 of 19 patients with evaluable genotypic data from paired baseline and Genvoya treatment-failure isolates (10 of 866 patients [1.2%]) compared with 8 of 16 treatment-failure isolates from patients in the E/C/F/TDF treatment group (8 of 867 patients [0.9%]). Of the HIV-1 isolates from 10 patients with resistance development in the Genvoya group, the mutations that emerged were M184V/I (n = 9) and K65R/N (n = 2) in RT and T66T/A/I/V (n = 2), E92Q (n = 4), Q148Q/R (n = 1) and N155H (n = 2) in integrase. Of the HIV-1 isolates from 8 patients with resistance development in the E/C/F/TDF group, the mutations that emerged were M184V/I (n = 6) and K65R/N (n = 3) in RT and E92E/Q (n = 2), and Q148R (n = 2), and N155H/S (n = 2) in integrase. All HIV-1 isolates from patients in both treatment groups who developed resistance mutations to elvitegravir developed resistance mutations to both emtricitabine and elvitegravir.

In phenotypic analyses of patients in the resistance analysis population, 7 of 19 patients (37%) had HIV-1 isolates with reduced susceptibility to elvitegravir in the Genvoya group compared with HIV-1 isolates from 4 of 16 patients (25%) in the E/C/F/TDF group, HIV-1 isolates from 8 patients (42%) had reduced susceptibility to emtricitabine in the Genvoya group compared with HIV-1 isolates from 4 patients (25%) in the E/C/F/TDF group. One patient in the Genvoya group (1 of 19 [5.2%]) and 1 patient in the E/C/F/TDF group (1 of 16 [6.2%]) had reduced susceptibility to tenofovir.

In virologically suppressed patients
One patient with emergent HIV-1 resistance to Genvoya was identified (M184M/I) 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, n = 959).

Cross-resistance in HIV-1 infected, treatment-naïve or virologically suppressed patients
Elvitegravir-resistant viruses show varying degrees of cross-resistance to the INSTI 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-resistant viruses with the M184V/I substitution were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir, and zidovudine.

The K65R and K70E mutations result in reduced susceptibility to abacavir, didanosine, lamivudine, emtricitabine, and tenofovir, but retain sensitivity to zidovudine.

Clinical data

HIV-1 infected, treatment-naïve patients
In studies GS-US-292-0104 and GS-US-292-0111, patients were randomised in a 1:1 ratio to receive either Genvoya (n = 866) once daily or elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil (as fumarate) 245 mg (E/C/F/TDF) (n = 867) once daily. The mean age was 36 years (range 18-76), 85% were male, 57% were White, 25% were Black, and 10% were Asian. Nineteen percent of patients were identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.5 $\log_{10}$ copies/mL (range 1.3-7.0) and 23% had baseline viral loads > 100,000 copies/mL. The mean baseline CD4+ cell count was 427 cells/mm^3 (range 0-1,360) and 13% had a CD4+ cell count < 200 cells/mm^3.

Genvoya met the non-inferiority criteria in achieving HIV-1 RNA < 50 copies/mL when compared to E/C/F/TDF. Pooled treatment outcomes at 48 and 96 weeks are shown in Table 3.

Table 3: Pooled virologic outcomes of studies GS-US-292-0104 and GS-US-292-0111 at Weeks 48 and 96[a,b]

	Week 48		Week 96	
	Genvoya (n = 866)	E/C/F/TDF (n = 867)	Genvoya (n = 866)	E/C/F/TDF (n = 867)
HIV-1 RNA < 50 copies/mL	92%	90%	87%	85%
Treatment difference	2.0% (95% CI: -0.7% to 4.7%)		1.5% (95% CI: -1.8% to 4.8%)	
HIV-1 RNA ≥ 50 copies/mL[c]	4%	4%	5%	4%
No virologic data at Week 48 or 96 window	4%	6%	9%	11%
Discontinued study drug due to AE or death[d]	1%	2%	1%	2%
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[e]	2%	4%	6%	7%
Missing data during window but on study drug	1%	< 1%	2%	1%

	Week 48		Week 96	
	Genvoya (n = 866)	E/C/F/TDF (n = 867)	Genvoya (n = 866)	E/C/F/TDF (n = 867)
Proportion (%) of patients with HIV-1 RNA < 50 copies/mL by subgroup				
Age				
< 50 years	716/777 (92%)	680/753 (90%)	668/777 (86%)	639/753 (85%)
≥ 50 years	84/89 (94%)	104/114 (91%)	82/89 (92%)	100/114 (88%)
Sex				
Male	674/733 (92%)	673/740 (91%)	635/733 (87%)	631/740 (85%)
Female	126/133 (95%)	111/127 (87%)	115/133 (87%)	108/127 (85%)
Race				
Black	197/223 (88%)	177/213 (83%)	173/223 (78%)	168/213 (79%)
Non-black	603/643 (94%)	607/654 (93%)	577/643 (90%)	571/654 (87%)
Baseline viral load				
≤ 100,000 copies/mL	629/670 (94%)	610/672 (91%)	587/670 (88%)	573/672 (85%)
> 100,000 copies/mL	171/196 (87%)	174/195 (89%)	163/196 (83%)	166/195 (85%)
Baseline CD4+ cell count				
< 200 cells/mm^3	96/112 (86%)	104/117 (89%)	93/112 (83%)	97/117 (83%)
≥ 200 cells/mm^3	703/753 (93%)	680/750 (91%)	657/753 (87%)	642/750 (86%)
HIV-1 RNA < 20 copies/mL	84.4%	84.0%	81.5%	80.2%
Treatment difference	0.4% (95% CI: -3.0% to 3.8%)		1.5% (95% CI: -2.2% to 5.2%)	

E/C/F/TDF = elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate

a Week 48 window was between Day 294 and 377 (inclusive); Week 96 window was between Day 630 and 713 (inclusive).

b 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+ cell count (< 50 cells/μL, 50-199 cells/μL, or ≥ 200 cells/μL), and by region (US or ex-US).

c Included patients who had ≥ 50 copies/mL in the Week 48 or 96 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.

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

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

The mean increase from baseline in CD4+ cell count was 230 cells/mm^3 in Genvoya-treated patients and 211 cells/mm^3 in E/C/F/TDF-treated patients (p = 0.024) at Week 48, and 280 cells/mm^3 in Genvoya-treated patients and 266 cells/mm^3 in E/C/F/TDF-treated patients (p = 0.14) at Week 96.

HIV-1 infected virologically suppressed patients

In study GS-US-292-0109, the efficacy and safety of switching from either efavirenz (EFV)/emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF), FTC/TDF plus atazanavir (boosted by either cobicistat or ritonavir), or E/C/F/TDF to Genvoya were evaluated in a randomised, open-label study of virologically suppressed (HIV-1 RNA < 50 copies/mL) HIV-1 infected adults (n = 1,436). Patients must have been stably suppressed (HIV-1 RNA < 50 copies/mL) on their baseline regimen for at least 6 months and had HIV-1 with 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 21-77), 89% were male, 67% were White, and 19% were Black. The mean baseline CD4+ cell count was 697 cells/mm^3 (range 79-1,951). Patients were stratified by prior treatment regimen. At screening, 42% of patients were receiving FTC/TDF plus atazanavir (boosted by either cobicistat or ritonavir), 32% of patients were receiving E/C/F/TDF, and 26% of patients were receiving EFV/FTC/TDF.

Switching from a TDF-based regimen to Genvoya was superior in maintaining HIV-1 RNA < 50 copies/mL compared to staying on the baseline regimen (Table 4).

Table 4: Virologic outcomes of study GS-US-292-0109 at Week 48[a]

	Genvoya (n = 959)	Baseline regimen (n = 477)
HIV-1 RNA < 50 copies/mL	97%	93%
Treatment difference	4.1% (95% CI: 1.6% to 6.7%, p < 0.001[b])	
HIV-1 RNA ≥ 50 copies/mL[c]	1%	1%
No virologic data at Week 48 window	2%	6%
Discontinued study drug due to AE or death[d]	1%	1%
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[e]	1%	4%
Missing data during window but on study drug	0%	< 1%
Proportion (%) of patients with HIV-1 RNA < 50 copies/mL by prior treatment regimen		
EFV/FTC/TDF	96%	90%
FTC/TDF plus boosted atazanavir	97%	92%
E/C/F/TDF	98%	97%

EFV = efavirenz; FTC = emtricitabine; TDF = tenofovir disoproxil fumarate;
E/C/F/TDF = elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate

a Week 48 window was between Day 294 and 377 (inclusive).

b P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by the prior treatment regimen (EFV/FTC/TDF, FTC/TDF plus boosted atazanavir, or E/C/F/TDF).

c Included patients who had ≥ 50 copies/mL in the Week 48 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (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.

HIV-1 infected patients with mild to moderate renal impairment

In study GS-US-292-0112, the efficacy and safety of Genvoya were evaluated in an open-label clinical study of 242 HIV-1 infected patients with mild to moderate renal impairment ($eGFR_{CG}$: 30-69 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 were identified as Hispanic/Latino. At baseline, 80 patients (33%) had $eGFR_{CG}$ < 50 mL/min and 162 patients had $eGFR_{CG}$ ≥ 50 mL/min. At baseline, median eGFR was 56 mL/min. The mean baseline CD4+ cell count was 664 cells/mm^3 (range 126-1,813).

At Week 48, 92% (222/242 patients) maintained HIV-1 RNA < 50 copies/mL after switching to Genvoya. Three patients had virologic failure at Week 48.

Changes in measures of bone mineral density

In studies in treatment-naïve patients, Genvoya was associated with smaller reductions in bone mineral density (BMD; as measured by hip and lumbar spine DXA analysis) compared to E/C/F/TDF after 96 weeks of treatment. Small improvements in BMD were noted at

48 weeks after switching to Genvoya from a TDF-containing regimen compared to maintaining the TDF-containing regimen.

Changes in measures of renal function
In studies in treatment-naïve patients, Genvoya was associated with a lower impact on renal safety parameters (as measured by estimated glomerular filtration rate by Cockcroft-Gault method, urine protein to creatinine ratio, and urine albumin to creatinine ratio) compared to E/C/F/TDF after 96 weeks of treatment (see also section 4.4).

Paediatric population

In study GS-US-292-0106, the efficacy, safety, and pharmacokinetics of Genvoya were evaluated in an open-label study in HIV-1-infected, treatment-naïve adolescents. Fifty patients had a mean age of 15 years (range 12 to 17), were 44% male, 12% Asian, and 88% black. At baseline, mean plasma HIV-1 RNA was 4.6 $\log_{10}$ copies/mL, median CD4+ cell count was 456 cells/mm^3 (range: 95 to 1,110), and median CD4+% was 23% (range: 7 to 45%). Overall, 22% had baseline plasma HIV-1 RNA > 100,000 copies/mL.

At Week 48, the virologic response rate to Genvoya in treatment-naïve HIV-1 infected adolescents was similar to response rates in studies of treatment-naïve HIV-1 infected adults. In patients treated with Genvoya, 92% (46/50) achieved HIV-1 RNA < 50 copies/mL. The mean increase from baseline in CD4+ cell count at Week 48 was 224 cells/mm^3. Three patients had virologic failure at Week 48; there was no virologic resistance detected to Genvoya.

5.2 Pharmacokinetic properties

Absorption
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. The steady-state mean C_{max}, AUC_{tau}, and C_{trough} (mean ± SD) in HIV-1 infected patients, respectively, were 1.7 ± 0.39 µg/mL, 23 ± 7.5 µg•h/mL, and 0.45 ± 0.26 µg/mL for elvitegravir, which provides inhibitory quotient of ~10 (ratio of C_{trough}: protein binding-adjusted IC_{95} for wild-type HIV-1 virus). Corresponding steady-state mean C_{max}, AUC_{tau}, and C_{trough} (mean ± SD) were 1.1 ± 0.40 µg/mL, 8.3 ± 3.8 µg•h/mL, and 0.05 ± 0.13 µg/mL for cobicistat; 1.9 ± 0.5 µg/mL, 13 ± 4.5 µg•h/mL, and 0.14 ± 0.25 µg/mL for emtricitabine. Steady-state mean C_{max} and AUC_{tau} for tenofovir alafenamide were 0.16 ± 0.08 µg/mL and 0.21 ± 0.15 µg•h/mL, respectively.

For elvitegravir, C_{max} and AUC increased 22% and 36% with a light meal, and 56% and 91% with a high-fat meal, relative to fasting conditions. Cobicistat exposures were unaffected by a light meal and although there was a modest decrease of 24% and 18% in C_{max} and AUC respectively with a high-fat meal, no difference was observed in its pharmacoenhancing effect on elvitegravir. Emtricitabine exposures were unaffected by a light or high-fat meal. Relative to fasting conditions, the administration of Genvoya with a light meal (~400 kcal, 20% fat) or high-fat meal (~800 kcal, 50% fat) did not affect overall exposures of tenofovir alafenamide to a clinically meaningful extent (approximately 15% and 18% higher AUC with a light or high-fat meal, respectively, *versus* fasted).

Distribution

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

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

In vitro binding of emtricitabine to human plasma proteins was < 4% and independent of concentration over the range of 0.02-200 µg/mL. At peak plasma concentration, the mean plasma to blood drug concentration ratio was ~1.0 and the mean semen to plasma drug concentration ratio was ~4.0.

In vitro binding of tenofovir to human plasma proteins is < 0.7% and is independent of concentration over the range of 0.01-25 µg/mL. *Ex vivo* binding of tenofovir alafenamide to human plasma proteins in samples collected during clinical studies was approximately 80%.

Biotransformation

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, displaying considerably lower antiviral activity against HIV-1 and do not contribute to the overall antiviral activity of elvitegravir.

Cobicistat is metabolised via CYP3A (major)- and CYP2D6 (minor)-mediated oxidation and does not undergo glucuronidation. Following oral administration of [^{14}C]-cobicistat, 99% of circulating radioactivity in plasma was unchanged cobicistat.

In vitro studies indicate that emtricitabine is not an inhibitor of human CYP enzymes. Following administration of [^{14}C]-emtricitabine, complete recovery of the emtricitabine dose was achieved in urine (~86%) and faeces (~14%). Thirteen percent of the dose was recovered in the urine as three putative metabolites. The biotransformation of emtricitabine includes oxidation of the thiol moiety to form the 3'-sulfoxide diastereomers (~9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (~4% of dose). No other metabolites were identifiable.

Metabolism is a major elimination pathway for tenofovir alafenamide in humans, accounting for > 80% of an oral dose. *In vitro* studies have shown that tenofovir alafenamide is 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 245 mg oral dose of tenofovir disoproxil (as fumarate) in E/C/F/TDF.

In vitro, tenofovir alafenamide is not metabolised by CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Tenofovir alafenamide is minimally metabolised by CYP3A4.

Upon co-administration with the moderate CYP3A inducer probe efavirenz, tenofovir alafenamide exposure was not significantly affected. Following administration of tenofovir alafenamide, plasma [^{14}C]-radioactivity showed a time-dependent profile with tenofovir alafenamide as the most abundant species in the initial few hours and uric acid in the remaining period.

Elimination

Following oral administration of [^{14}C]-elvitegravir/ritonavir, 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. The median terminal plasma half-life of elvitegravir following administration of E/C/F/TDF is approximately 12.9 hours.

Following oral administration of [^{14}C]-cobicistat, 86% and 8.2% of the dose were recovered in faeces and urine, respectively. The median terminal plasma half-life of cobicistat following administration of E/C/F/TDF 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.

Emtricitabine is primarily excreted by the kidneys with complete recovery of the dose achieved in urine (approximately 86%) and faeces (approximately 14%). Thirteen percent of the emtricitabine dose was recovered in urine as three metabolites. The systemic clearance of emtricitabine averaged 307 mL/min. Following oral administration, the elimination half-life of emtricitabine is approximately 10 hours.

Renal excretion of intact tenofovir alafenamide is a minor pathway with < 1% of the dose eliminated in urine. Tenofovir alafenamide is mainly 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 eliminated from the body by the kidneys by both glomerular filtration and active tubular secretion.

Age, gender, and ethnicity

No clinically relevant pharmacokinetic differences due to gender or ethnicity have been identified for cobicistat-boosted elvitegravir, cobicistat, emtricitabine, or tenofovir alafenamide.

Population pharmacokinetics analysis of HIV-infected patients in Phase 2 and Phase 3 studies of Genvoya showed that within the age range studied (12 to 82 years), age did not have a clinically relevant effect on exposures of tenofovir alafenamide.

Exposures of elvitegravir, cobicistat, emtricitabine, tenofovir, and tenofovir alafenamide achieved in 24 paediatric patients aged 12 to < 18 years who received Genvoya in study GS-US-292-0106 were similar to exposures achieved in treatment-naïve adults following administration of Genvoya (Table 5).

Table 5: Pharmacokinetics of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in antiretroviral-naïve adolescents and adults

	Adolescents					Adults				
	Genvoya					Genvoya				
	EVG[a]	COBI[a]	FTC[a]	TAF[b]	TFV[b]	EVG[a]	COBI[a]	FTC[a]	TAF[c]	TFV[c]
AUC_{tau} (ng•h/mL)	23,840.1 (25.5)	8,240.8 (36.1)[b]	14,424.4 (23.9)	242.8 (57.8)	275.8 (18.4)	22,797.0 (34.7)	9,459.1 (33.9)	11,714.1 (16.6)	206.4 (71.8)	292.6 (27.4)
C_{max} (ng/mL)	2,229.6 (19.2)	1,202.4 (35.0)	2,265.0 (22.5)	121.7 (46.2)	14.6 (20.0)	2,113.1 (33.7)	1,450.3 (28.4)	2,056.3 (20.2)	162.2 (51.1)	15.2 (26.1)
C_{tau} (ng/mL)	300.8 (81.0)	25.0 (180.0)[d]	102.4 (38.9)[b]	N/A	10.0 (19.6)	287.3 (61.7)	20.6 (85.2)	95.2 (46.7)	N/A	10.6 (28.5)

EVG = elvitegravir; COBI = cobicistat; FTC = emtricitabine; TAF = tenofovir alafenamide fumarate; TFV = tenofovir
N/A = not applicable
Data are presented as mean (%CV).
a n = 24 adolescents; n = 19 adults
b n = 23 adolescents
c n = 539 (TAF) or 841 (TFV) adults
d n = 15 adolescents

Renal impairment

No clinically relevant differences in elvitegravir, cobicistat, tenofovir alafenamide, or tenofovir pharmacokinetics were observed between healthy subjects and patients with severe renal impairment (estimated CrCl > 15 but < 30 mL/min) in studies of cobicistat-boosted elvitegravir or of tenofovir alafenamide, respectively. Mean systemic emtricitabine exposure was higher in patients with severe renal impairment (CrCl < 30 mL/min) (33.7 µg•h/ml) than in subjects with normal renal function (11.8 µg•h/mL).

Hepatic impairment

Both elvitegravir and cobicistat are primarily metabolised and eliminated by the liver. A study of the pharmacokinetics of cobicistat-boosted elvitegravir was performed in non-HIV-1 infected patients with moderate hepatic impairment (Child-Pugh Class B). No clinically relevant differences in elvitegravir or cobicistat pharmacokinetics were observed between patients with moderate impairment and healthy subjects. No dose adjustment of elvitegravir or cobicistat is necessary for patients with mild to moderate hepatic impairment. The pharmacokinetics of emtricitabine have not been studied in patients with hepatic impairment; however, emtricitabine is not significantly metabolised by liver enzymes, so the impact of liver impairment should be limited. Clinically relevant changes in tenofovir pharmacokinetics in patients with hepatic impairment were not observed in patients with mild to moderate hepatic impairment, and no tenofovir alafenamide dose adjustment is required in patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of elvitegravir, cobicistat, or tenofovir alafenamide has not been studied.

Hepatitis B and/or hepatitis C virus co-infection

The pharmacokinetics of emtricitabine and tenofovir alafenamide have not been fully evaluated in patients co-infected with hepatitis B and/or C virus. 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.

5.3 Preclinical safety data

Elvitegravir was negative in an *in vitro* bacterial mutagenicity test (Ames test) and negative in an *in vivo* rat micronucleus assay at doses up to 2,000 mg/kg. In an *in vitro* chromosomal aberration test, elvitegravir was negative with metabolic activation; however, an equivocal response was observed without activation.

Cobicistat was not mutagenic or clastogenic in conventional genotoxicity assays. *Ex vivo* rabbit studies and *in vivo* dog studies suggest that cobicistat has a low potential for QT prolongation, and may slightly prolong the PR interval and decrease left ventricular function at concentrations at least 11-fold higher than the human exposure at the recommended 150 mg daily dose. In a human clinical study of 35 healthy subjects, echocardiograms performed at baseline and after receiving 150 mg cobicistat once daily for at least 15 days indicated no clinically significant change in left ventricular function.

Reproductive toxicity studies in rats and rabbits with cobicistat showed no effects on mating, fertility, pregnancy or fetal parameters. However increased post-implantation loss and decreased fetal weights were observed in rats associated with significant decreases in maternal body weights at 125 mg/kg/day.

Non-clinical data on emtricitabine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Elvitegravir, cobicistat, and emtricitabine have all demonstrated low carcinogenic potential in mice and rats.

Non-clinical studies of tenofovir alafenamide in rats and dogs revealed bone and kidney as the primary target organs of toxicity. Bone toxicity was observed as reduced bone mineral density in rats and dogs at tenofovir exposures at least four times greater than those expected after administration of Genvoya. A minimal infiltration of histiocytes was present in the eye in dogs at tenofovir alafenamide and tenofovir exposures of approximately 4 and 17 times greater, respectively, than those expected after administration of Genvoya.

Tenofovir alafenamide was not mutagenic or clastogenic in conventional genotoxicity assays.

Because there is a lower tenofovir exposure in rats and mice after the administration of tenofovir alafenamide compared to TDF, carcinogenicity studies and a rat peri-postnatal study were conducted only with TDF. No special hazard for humans was revealed in conventional studies of carcinogenic potential and toxicity to reproduction and development. Reproductive toxicity studies in rats and rabbits showed no effects on mating, fertility, pregnancy or fetal parameters. However, tenofovir disoproxil fumarate reduced the viability index and weight of pups in a peri-postnatal toxicity study at maternally toxic doses.

6. Pharmaceutical Particulars

6.1 List of excipients

Tablet core
Lactose (as monohydrate)
Microcrystalline cellulose
Croscarmellose sodium
Hydroxypropyl cellulose
Silicon dioxide
Sodium lauryl sulphate
Magnesium stearate

Film-coating
Polyvinyl alcohol
Titanium dioxide
Polyethylene glycol
Talc
Indigo carmine aluminium lake
Iron oxide yellow

6.2 Incompatibilities

None.

6.3 Shelf-life

24 months

6.4 Special precautions for storage

Store below 30 °C.

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

6.5 Nature and contents of container

Genvoya is supplied in a 100 mL, white, high-density polyethylene (HDPE) bottle with a polypropylene (PP) continuous-thread child-resistant cap lined with an induction activated aluminum foil liner.
Each bottle contains 30 tablets and either a canister or sachet containing three gram silica gel desiccant, and polyester coil packing material.

7. Name and Address of Manufacturing / Marketing Authorization Holder

Product licence holder:
Gilead Sciences International Limited
Granta Park, Abington
Cambridge CB21 6GT
United Kingdom

Manufactured by:
Patheon Inc., 2100 Syntex Court,
Mississauga, Ontario L5N 7K9
Canada

Released by:
Gilead Sciences Ireland UC
Carrigtohill, Co. Cork
Ireland

Imported by:
DCH Auriga (Thailand) Limited,
Bangkok, Thailand

8. Marketing Authorisation Number

9. Date of Authorisation

10. Date of revision of package insert

Issued: May 2016

TH-JAN2018-EU-MAY2016