Gendevra®
(elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide (as fumarate)) Film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Gendevra®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated 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.

Excipient(s) with known effect

Each tablet contains 58 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Green, capsule-shaped, film-coated tablet of dimensions 19 mm x 8.5 mm, debossed with “GSI” on one side of the tablet and “510” on the other side of the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gendevra is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir as follows:

- In adults and adolescents aged from 12 years and with body weight at least 35 kg
- In children aged from 6 years and with body weight at least 25 kg for whom alternative regimens are unsuitable due to toxicities.

See sections 4.2, 4.4 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 paediatric patients aged 6 years and older, weighing at least 25 kg
One tablet to be taken once daily with food.

If the patient misses a dose of Gendevra within 18 hours of the time it is usually taken, the patient should take Gendevra with food as soon as possible and resume the normal dosing schedule. If a patient misses a dose of Gendevra 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 Gendevra another tablet should be taken.

Special populations

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

Renal impairment
No dose adjustment of Gendevra 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. Gendevra should be discontinued in patients with estimated CrCl that declines below 30 mL/min during treatment (see section 5.2).

No dose adjustment of Gendevra is required in adults with end stage renal disease (estimated CrCl < 15 mL/min) on chronic haemodialysis; however, Gendevra should generally be avoided but may be used in these patients if the potential benefits are considered to outweigh the potential risks (see sections 4.4 and 5.2). On days of haemodialysis, Gendevra should be administered after completion of haemodialysis treatment.

Gendevra should be avoided in patients with estimated CrCl ≥ 15 mL/min and < 30 mL/min, or < 15 mL/min who are not on chronic haemodialysis, as the safety of Gendevra has not been established in these populations.

No data are available to make dose recommendations in children aged less than 12 years with renal impairment or in children less than 18 years with end stage renal disease.

Hepatic impairment
No dose adjustment of Gendevra is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Gendevra has not been studied in patients with severe hepatic impairment (Child-Pugh Class C); therefore, Gendevra 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 Gendevra in children younger than 6 years of age, or weighing < 25 kg, have not yet been established. No data are available.

Method of administration
Gendevra should be taken orally, once daily with food (see section 5.2). Due to the bitter taste, it is recommended that the film-coated tablet not be chewed or crushed. For patients who are unable to swallow the tablet whole, the tablet may be split in half and both halves taken one after the other, ensuring that the full dose is taken immediately.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Co-administration is contraindicated with medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious or life-threatening adverse reactions. Therefore Gendevra should not be co-administered with medicinal products that include, but are not limited to, the following (see sections 4.4 and 4.5):

- alpha 1-adrenoreceptor antagonists: alfuzosin
- antiarrhythmics: amiodarone, quinidine
- ergot derivatives: dihydroergotamine, ergometrine, ergotamine
- gastrointestinal motility agents: cisapride
- HMG Co-A reductase inhibitors: lovastatin, simvastatin
- lipid-modifying agent: lomitapide

- neuroleptics/ antipsychotics: pimozide, lurasidone
- PDE-5 inhibitors: sildenafil for the treatment of pulmonary arterial hypertension
- sedatives/hypnotics: orally administered midazolam, triazolam

Co-administration is contraindicated with medicinal products that are strong inducers of CYP3A due to the potential for loss of virologic response and possible resistance to Gendevra. Therefore, Gendevra should not be co-administered with medicinal products that include, but are not limited to, the following (see sections 4.4 and 4.5):

- anticonvulsants: carbamazepine, phenobarbital, phenytoin
- antimycobacterials: rifampicin
- herbal products: St. John's wort (*Hypericum perforatum*)

Co-administration with dabigatran etexilate, a P-glycoprotein (P-gp) substrate, is contraindicated (see section 4.5).

4.4 Special warnings and precautions for use

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 Gendevra 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). Discontinuation of Gendevra 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 Gendevra should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment.

Liver disease

The safety and efficacy of Gendevra 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 following exposure *in utero*

Nucleos(t)ide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or postnatally to nucleoside analogues; these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders

(hyperlactataemia, hyperlipasaemia). These events have often been transitory. Late onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed *in utero* to nucleos(t)ide analogues, who present with severe clinical findings of unknown aetiology, particularly neurologic findings. 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 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 and autoimmune hepatitis) 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 Gendevra 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

Post-marketing cases of renal impairment, including acute renal failure and proximal renal tubulopathy have been reported with tenofovir alafenamide-containing products. 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).

It is recommended that renal function is assessed in all patients prior to, or when initiating, therapy with Gendevra and that it is also monitored during therapy in all patients as clinically appropriate. In patients who develop clinically significant decreases in renal function, or evidence of proximal renal tubulopathy, discontinuation of Gendevra should be considered.

Patients with end stage renal disease on chronic haemodialysis

Gendevra should generally be avoided but may be used in adults with end stage renal disease (estimated CrCl < 15 mL/min) on chronic haemodialysis if the potential benefits outweigh the potential risks (see section 4.2). In a study of Gendevra in HIV-1 infected adults with end stage renal disease (estimated CrCl < 15 mL/min) on chronic haemodialysis, efficacy was maintained through 48 weeks but emtricitabine exposure was significantly higher than in patients with normal renal function. Although there were no new safety issues identified, the implications of increased emtricitabine exposure remain uncertain (see sections 4.8 and 5.2).

Co-administration of other medicinal products

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

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

Gendevra should not be administered concomitantly with medicinal products containing tenofovir alafenamide, tenofovir disoproxil, lamivudine or adefovir dipivoxil used for the treatment of HBV infection (see section 4.5).

Contraception requirements
Female patients of childbearing potential should use either a hormonal contraceptive containing at least 30 µg ethinyloestradiol and containing drospirenone or norgestimate as the progestogen or should use an alternative reliable method of contraception (see sections 4.5 and 4.6). The use of Gendevra with oral contraceptives containing other progestogens should be avoided (see section 4.5). Plasma concentrations of drospirenone are expected to be increased following co-administration with Gendevra and clinical monitoring is recommended due to the potential for hyperkalaemia (see section 4.5).

Pregnancy

Treatment with cobicistat and elvitegravir during the second and third trimesters of pregnancy has been shown to result in lower elvitegravir exposures (see section 5.2). Cobicistat levels decrease and may not provide sufficient boosting. The substantial reduction in elvitegravir exposure may result in virological failure and an increased risk of mother-to-child transmission of HIV infection. Therefore, therapy with Gendevra should not be initiated during pregnancy, and women who become pregnant during therapy with Gendevra should be switched to an alternative regimen (see section 4.6).

Paediatric population

Reductions in BMD (≥ 4%) of the spine and total-body-less-head (TBLH) have been reported in patients aged between 7 to < 12 years weighing at least 25 kg receiving Genvoya for 48 weeks in study GS-US-292-0106 (see section 4.8). The long-term effects of changes in BMD on the growing bone, including the risk of fracture, are uncertain. A multidisciplinary approach is recommended to decide the appropriate monitoring during treatment.

Excipients

Gendevra contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

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

Gendevra should not be administered concomitantly with medicinal products containing tenofovir alafenamide, tenofovir disoproxil, 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 Gendevra with medicinal products that induce CYP3A may result in decreased plasma concentrations of elvitegravir and reduced therapeutic effect of Gendevra (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 have active metabolite(s) formed by CYP3A may result in reduced plasma concentrations of these active metabolite(s).

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-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 Gendevra, 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 Gendevra are not expected to be further increased when used in combination with another P-gp and/or BCRP inhibitor (e.g., ketoconazole). Based on data from an *in vitro* study, co-administration of tenofovir alafenamide and xanthine oxidase inhibitors (e.g., febuxostat) is not expected to increase systemic exposure to tenofovir *in vivo*. *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 or inducer of CYP3A *in vivo*. Tenofovir alafenamide is a substrate of OATP *in vitro*. Inhibitors of OATP and BCRP include ciclosporin.

Concomitant use contraindicated

Co-administration of Gendevra 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 Gendevra and other medicinal products primarily metabolised by CYP3A such as amiodarone, lomitapide, quinidine, cisapride, pimozide, lurasidone, alfuzosin and sildenafil for pulmonary arterial hypertension is contraindicated (see section 4.3).

Co-administration of Gendevra 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 Gendevra 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 Gendevra, or the components of Gendevra (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide), as individual agents and/or in combination, or are potential drug-drug interactions that may occur with Gendevra.

Table 1: Interactions between the individual components of Gendevra 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 Gendevra**
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 Gendevra.	When administering with Gendevra, 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 Gendevra. 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 Gendevra.	Clinical monitoring should be made upon co-administration with Gendevra. When administering with Gendevra, 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 Gendevra.

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 Gendevra
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 Gendevra 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 Gendevra
Anti-hepatitis C virus medicinal products		
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 Gendevra 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 Gendevra
Sofosbuvir (400 mg once daily)/ Velpatasvir (100 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]	Sofosbuvir: AUC: ↑ 37% C_{min}: N/A C_{max}: ↔ Sofosbuvir metabolite GS-331007: AUC: ↑ 48% C_{min}: ↑ 58% C_{max}: ↔ Velpatasvir: AUC: ↑ 50% C_{min}: ↑ 60% C_{max}: ↑ 30% Elvitegravir: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Cobicistat: AUC: ↔ C_{min}: ↑ 103% C_{max}: ↔ Emtricitabine: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Tenofovir alafenamide: AUC: ↔ C_{min}: N/A C_{max}: ↓ 20%	No dose adjustment of sofosbuvir/velpatasvir and Gendevra 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 Gendevra
Sofosbuvir/Velpatasvir/ Voxilaprevir (400 mg/100 mg/100 mg+100 mg once daily)[7]/ Elvitegravir (150 mg once daily)/ Cobicistat (150 mg once daily)/ Emtricitabine (200 mg once daily)/ Tenofovir alafenamide (10 mg once daily)[5]	Sofosbuvir: AUC: ↔ C_{min}: N/A C_{max}: ↑ 27% Sofosbuvir metabolite GS-331007: AUC: ↑ 43% C_{min}: N/A C_{max}: ↔ Velpatasvir: AUC: ↔ C_{min}: ↑ 46% C_{max}: ↔ Voxilaprevir: AUC: ↑ 171% C_{min}: ↑ 350% C_{max}: ↑ 92% Elvitegravir: AUC: ↔ C_{min}: ↑ 32% C_{max}: ↔ Cobicistat: AUC: ↑ 50% C_{min}: ↑ 250% C_{max}: ↔ Emtricitabine: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Tenofovir alafenamide: AUC: ↔ C_{min}: N/A C_{max}: ↓ 21%	No dose adjustment of sofosbuvir/velpatasvir/voxilaprevir and Gendevra is warranted upon co-administration.
Macrolide antibiotics		
Clarithromycin	Interaction not studied with any of the components of Gendevra. Concentrations of clarithromycin and/or cobicistat may be altered with co-administration of Gendevra.	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%.

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 Gendevra
Telithromycin	Interaction not studied with any of the components of Gendevra. Concentrations of telithromycin and/or cobicistat may be altered with co-administration of Gendevra.	Clinical monitoring is recommended upon co-administration of Gendevra.
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 Gendevra 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 Gendevra
GLUCOCORTICOIDS		
Corticosteroids		
Corticosteroids primarily metabolised by CYP3A (including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone).	Interaction not studied with any of the components of Gendevra. Plasma concentrations of these medicinal products may be increased when co-administered with Gendevra, resulting in reduced serum cortisol concentrations.	Concomitant use of Gendevra and corticosteroids that are metabolised by CYP3A (e.g. fluticasone propionate or other inhaled or nasal corticosteroids) may increase the risk of development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. Co-administration with CYP3A-metabolised corticosteroids is not recommended unless the potential benefit to the patient outweighs the risk, in which case patients should be monitored for systemic corticosteroid effects. Alternative corticosteroids which are less dependent on CYP3A metabolism e.g. beclomethasone for intranasal or inhalational use 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.
MEDICINAL PRODUCTS or ORAL SUPPLEMENTS CONTAINING POLYVALENT CATIONS (e.g. Mg, Al, Ca, Fe, Zn)		
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 Gendevra and administration of antacids, medicinal products or oral supplements containing polyvalent cations 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".

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 Gendevra
Calcium or iron supplements (including multivitamins) Other cation-containing antacids Cation-containing laxatives Sucralfate Buffered medicinal products	Interaction not studied with any of the components of Gendevra. Elvitegravir plasma concentrations are expected to be lower with antacids, medicinal products or oral supplements containing polyvalent cations, due to local complexation in the gastrointestinal tract and not to changes in gastric pH.	
ORAL ANTI-DIABETICS		
Metformin	Interaction not studied with any of the components of Gendevra. Cobicistat reversibly inhibits MATE1, and concentrations of metformin may be increased when co-administered with Gendevra.	Careful patient monitoring and dose adjustment of metformin is recommended in patients who are taking Gendevra.
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}: ↔ 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.

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 Gendevra
ORAL CONTRACEPTIVES		
Drospirenone/Ethinyloestradiol (3 mg/0.02 mg single dose)/ Cobicistat (150 mg once daily)	Interaction not studied with Gendevra. *Expected* Drospirenone: AUC: ↑	Plasma concentrations of drospirenone may be increased when co-administered with cobicistat-containing products. Clinical monitoring is recommended due to the potential for hyperkalaemia. Caution should be exercised when co-administering Gendevra and a hormonal contraceptive. The hormonal contraceptive should contain at least 30 µg ethinyloestradiol and contain drospirenone or norgestimate as the progestogen 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 progestogen exposure are unknown.
Norgestimate (0.180/0.215/0.250 mg once daily)/ Ethinyloestradiol (0.025 mg once daily)/ Emtricitabine/Tenofovir alafenamide (200/25 mg once daily)[6]	Norelgestromin: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Norgestrel: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Ethinyloestradiol: AUC: ↔ C_{min}: ↔ C_{max}: ↔	
Norgestimate (0.180/0.215 mg once daily)/ Ethinyloestradiol (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% Ethinyloestradiol: AUC: ↓ 25% C_{min}: ↓ 44% C_{max}: ↔ Elvitegravir: AUC: ↔ C_{min}: ↔ C_{max}: ↔	
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 Gendevra.
Disopyramide Flecainide Systemic lidocaine Mexiletine Propafenone	Interaction not studied with any of the components of Gendevra. 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 Gendevra.
ANTI-HYPERTENSIVES		
Metoprolol Timolol	Interaction not studied with any of the components of Gendevra. 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 Gendevra.

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 Gendevra
Amlodipine Diltiazem Felodipine Nicardipine Nifedipine Verapamil	Interaction not studied with any of the components of Gendevra. 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 Gendevra.
ENDOTHELIN RECEPTOR ANTAGONISTS		
Bosentan	Interaction not studied with any of the components of Gendevra. Co-administration with Gendevra 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		
Dabigatran	Interaction not studied with any of the components of Gendevra. Co-administration with Gendevra may increase dabigatran plasma concentrations with similar effects as seen with other strong P-gp inhibitors.	Co-administration of Gendevra with dabigatran is contraindicated.
Apixaban Rivaroxaban Edoxaban	Interaction not studied with any of the components of Gendevra. Co-administration with Gendevra may result in increased plasma concentrations of the DOAC, which may lead to an increased bleeding risk.	Co-administration of apixaban, rivaroxaban or edoxaban is not recommended with Gendevra.
Warfarin	Interaction not studied with any of the components of Gendevra. Concentrations of warfarin may be affected upon co-administration with Gendevra.	It is recommended that the international normalised ratio (INR) be monitored upon co-administration of Gendevra. INR should continue to be monitored during the first weeks following ceasing treatment with Gendevra.
ANTIPLATELETS		
Clopidogrel	Interaction not studied with any of the components of Gendevra. Co-administration of clopidogrel with cobicistat is expected to decrease clopidogrel active metabolite plasma concentrations, which may reduce the antiplatelet activity of clopidogrel.	Co-administration of Gendevra with clopidogrel is not recommended.
Prasugrel	Interaction not studied with any of the components of Gendevra. Gendevra is not expected to have a clinically relevant effect on plasma concentrations of the active metabolite of prasugrel.	No dose adjustment of prasugrel is required.

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 Gendevra
INHALED BETA AGONIST		
Salmeterol	Interaction not studied with any of the components of Gendevra. Co-administration with Gendevra 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 Gendevra 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 Gendevra.
Atorvastatin (10 mg single dose)/Elvitegravir (150 mg once daily)/Cobicistat (150 mg once daily)/Emtricitabine (200 mg once daily)/Tenofovir alafenamide (10 mg once daily)	Atorvastatin: AUC: ↑ 160% C_{min}: N/A C_{max}: ↑ 132% Elvitegravir: AUC: ↔ C_{min}: ↔ C_{max}: ↔	Concentrations of atorvastatin are increased when co-administered with elvitegravir and cobicistat. Start with the lowest possible dose of atorvastatin with careful monitoring upon co-administration with Gendevra.
Pitavastatin	Interaction not studied with any of the components of Gendevra. Concentrations of pitavastatin may be increased when administered with elvitegravir and cobicistat.	Caution should be exercised when co-administering Gendevra with pitavastatin.
Pravastatin Fluvastatin	Interaction not studied with any of the components of Gendevra. 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 Gendevra.
Lovastatin Simvastatin	Interaction not studied with any of the components of Gendevra.	Co-administration of Gendevra and lovastatin and simvastatin is contraindicated (see section 4.3).
LIPID-MODIFYING AGENTS		

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 Gendevra
Lomitapide	Interaction not studied with any of the components of Gendevra. Lomitapide is highly dependent on CYP3A for its metabolism and co-administration with Gendevra may result in increased concentrations of lomitapide and potential for markedly increased transaminases.	Coadministration with lomitapide is contraindicated (see section 4.3).
PHOSPHODIESTERASE TYPE 5 (PDE-5) INHIBITORS		
Sildenafil Tadalafil Vardenafil	Interaction not studied with any of the components of Gendevra. PDE-5 inhibitors are primarily metabolised by CYP3A. Co-administration with Gendevra may result in increased plasma concentrations of sildenafil and tadalafil, which may result in PDE-5 inhibitor-associated adverse reactions.	Co-administration of Gendevra and sildenafil for the treatment of pulmonary arterial hypertension is contraindicated. Caution should be exercised, including consideration of dose reduction, when co-administering Gendevra 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 Gendevra.
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 Gendevra. 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 Gendevra. 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.

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 Gendevra
IMMUNOSUPPRESSANTS		
Ciclosporin Sirolimus Tacrolimus	Interaction not studied with any of the components of Gendevra. Concentrations of these immunosuppressant agents may be increased when administered with cobicistat.	Therapeutic monitoring is recommended upon co-administration with Gendevra.
SEDATIVES/HYPNOTICS		
Buspirone Clorazepate Diazepam Estazolam Flurazepam Lorazepam Triazolam Zolpidem	Interaction not studied with any of the components of Gendevra. Triazolam is primarily metabolised by CYP3A. Co-administration with Gendevra 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 Gendevra. Based on non-CYP-mediated elimination pathways for lorazepam, no effect on plasma concentrations is expected upon co-administration with Gendevra.	Co-administration of Gendevra 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 Gendevra 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 Gendevra and orally administered midazolam 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 Gendevra
ANTI-GOUT		
Colchicine	Interaction not studied with any of the components of Gendevra. Co-administration with Gendevra may result in increased plasma concentrations of this medicinal product.	Dose reductions of colchicine may be required. Gendevra should not be co-administered with colchicine to patients with renal or hepatic impairment.

N/A = not applicable
DOAC = direct oral anticoagulant
[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.
[5] This study was conducted using Gendevra.
[6] This study was conducted using emtricitabine/tenofovir alafenamide.
[7] This study was conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Studies conducted with other medicinal products

Based on drug-drug interaction studies conducted with Gendevra or the components of Gendevra, no clinically significant drug-drug interactions have been either observed or are expected between the components of Gendevra and the following medicinal products: entecavir, famciclovir, ribavirin, famotidine, and omeprazole.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / contraception in males and females

The use of Gendevra 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 Gendevra or its components in pregnant women. There are no or limited data (less than 300 pregnancy outcomes) from the use of Gendevra in pregnant women. However, a large amount of data on pregnant women (more than 1,000 exposed outcomes) indicate no malformative nor foetal/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, foetal 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 foetal development (see section 5.3).

Treatment with cobicistat and elvitegravir during the second and third trimesters of pregnancy has been shown to result in lower elvitegravir exposure (see section 5.2). Cobicistat levels decrease and may not provide sufficient boosting. The substantial reduction in elvitegravir exposure may result in virological failure and an increased risk of mother-to-child transmission of HIV infection. Therefore, therapy with Gendevra should not be initiated during pregnancy, and women who become pregnant during therapy with Gendevra should be switched to an alternative regimen (see section 4.4).

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, Gendevra should not be used during breast-feeding.

In order to avoid transmission of HIV to the infant it is recommended that women living with HIV do not breast-feed their infants.

Fertility

There are no data on fertility from the use of Gendevra in humans. In animal studies there were no effects of elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide on mating or fertility parameters (see section 5.3).

4.7 Effects on ability to drive and use machines

Gendevra may have minor influence on the ability to drive and use machines. Patients should be informed that dizziness has been reported during treatment with Gendevra.

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 with Gendevra and from post-marketing experience. The most frequently reported adverse reactions in clinical studies through 144 weeks were nausea (11%), diarrhoea (7%), and headache (6%).

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:	suicidal ideation and suicide attempt (in patients with a pre-existing history of depression or psychiatric illness), 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[3,4], pruritus, urticaria[4]
General disorders and administration site conditions	
Common:	fatigue

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

[3] This adverse reaction was identified through post-marketing surveillance for emtricitabine-containing products.

[4] This adverse reaction was identified through post-marketing surveillance for tenofovir alafenamide-containing products.

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 and autoimmune hepatitis) 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 Gendevra, increases in serum creatinine occurred by Week 2 of treatment and remained stable through 144 weeks. In treatment-naïve patients, a mean change from baseline of 0.04 ± 0.12 mg/dL (3.5 ± 10.6 µmol/L) was observed after 144 weeks of treatment. Mean increases from baseline in the Gendevra 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 144 (difference −0.04, $p < 0.001$).

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 144. The median increase from baseline for those parameters was greater in the Gendevra group compared with the E/C/F/TDF group

at Week 144 ($p < 0.001$ 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 144 was 0.2 (-0.3, 0.7) in the Gendevra group and 0.1 (-0.4, 0.6) in the E/C/F/TDF group ($p = 0.006$ for the difference between treatment groups).

Paediatric population

The safety of Gendevra was evaluated through 48 weeks in HIV-1 infected adolescent patients aged 12 to < 18 years weighing ≥ 35 kg, (n = 100), and in children aged 7 to < 12 years weighing > 25 kg (n = 52). The safety profile in paediatric patients who received treatment with Gendevra was similar to that in adults. After 48 weeks of treatment with Genvoya, reductions in BMD of the spine and of the TBLH ≥ 4% have been reported in 2.1% (1/47) and 0.0% of adolescents and in 12.2% (6/49) and 3.9% (2/51) of children aged 7 to < 12 years weighing at least 25 kg.

Other special populations

Patients with renal impairment
The safety of Gendevra 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 144 weeks in an open-label clinical study (GS-US-292-0112). The safety profile of Gendevra in patients with mild to moderate renal impairment was similar to that in patients with normal renal function (see section 5.1).

The safety of Gendevra in 55 virologically suppressed HIV-1 infected patients with end stage renal disease ($eGFR_{CG}$ < 15 mL/min) on chronic haemodialysis was evaluated through 48 weeks in a single arm, open-label clinical study (GS-US-292-1825). There were no new safety issues identified in patients with end stage renal disease on chronic haemodialysis receiving Gendevra (see section 5.2).

Patients co-infected with HIV and HBV
The safety of Gendevra was evaluated in 72 HIV/HBV co-infected patients receiving treatment for HIV in an open-label clinical study (GS-US-292-1249), through Week 48, in which patients were switched from another antiretroviral regimen (which included tenofovir disoproxil in 69 of 72 patients) to Gendevra. Based on these limited data, the safety profile of Gendevra in patients with HIV/HBV co-infection was 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.

You can report any side effects to the Ministry of Health by clicking on the link "Report side effects due to medical treatment" that is located on the Ministry of Health homepage (www.health.gov.il) which redirects to the online form for reporting side effects or by clicking on the link: https://sideeffects.health.gov.il.

4.9 Overdose

If overdose occurs the patient must be monitored for evidence of toxicity (see section 4.8). Treatment of overdose with Gendevra 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 deoxyribonucleic acid (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 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 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 HBV.

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 Gendevra 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 144, or time of early study drug discontinuation. Up to Week 144, the development of one or more primary elvitegravir, emtricitabine, or tenofovir alafenamide resistance-associated mutations was observed in HIV-1 isolates from 12 of 22 patients with evaluable genotypic data from paired baseline and Gendevra 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 E/C/F/TDF treatment group (12 of 867 patients [1.4%]). Of the HIV-1 isolates from 12 patients with resistance development in the Gendevra group, the mutations that emerged were M184V/I (n = 11) 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 12 patients with resistance development in the E/C/F/TDF group, the mutations that emerged were M184V/I (n = 9), K65R/N (n = 4), and L210W (n = 1) in RT and E92Q/V (n = 4), and Q148R (n = 2), and N155H/S (n = 3) in integrase. Most 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 final resistance analysis population, 7 of 22 patients (32%) had HIV-1 isolates with reduced susceptibility to elvitegravir in the Gendevra group compared with HIV-1 isolates from 7 of 20 patients (35%) in the E/C/F/TDF group, HIV-1 isolates from 8 patients (36%) had reduced susceptibility to emtricitabine in the Gendevra group compared with HIV-1 isolates from 7 patients (35%) in the E/C/F/TDF group. One patient in the Gendevra group (1 of 22 [4.5%]) and 2 patients in the E/C/F/TDF group (2 of 20 [10%]) had reduced susceptibility to tenofovir.

In virologically suppressed patients
Three patients with emergent HIV-1 resistance to Gendevra were identified (M184M/I; M184I+E92G; M184V+E92Q) up to Week 96 in a clinical study of virologically suppressed patients who switched from a regimen containing emtricitabine/tenofovir disoproxil and a third agent (GS-US-292-0109, n = 959).

In patients co-infected with HIV and HBV
In a clinical study of HIV virologically suppressed patients co-infected with chronic hepatitis B, who received Gendevra for 48 weeks (GS-US-292-1249, n = 72), 2 patients qualified for resistance analysis. In these 2 patients, no amino acid substitutions associated with resistance to any of the components of Gendevra were identified in HIV-1 or HBV.

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 Gendevra (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.

Gendevra demonstrated statistical superiority in achieving HIV-1 RNA < 50 copies/mL when compared to E/C/F/TDF at Week 144. The difference in percentage was 4.2% (95% CI: 0.6% to 7.8%). Pooled treatment outcomes at 48 and 144 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 144[a,b]

	Week 48		Week 144	
	Gendevra (n = 866)	**E/C/F/TDF (n = 867)**	**Gendevra (n = 866)**	**E/C/F/TDF (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%

	Week 48		Week 144	
	Gendevra (n = 866)	**E/C/F/TDF (n = 867)**	**Gendevra (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%)	647/777 (83%)	602/753 (80%)
≥ 50 years	84/89 (94%)	104/114 (91%)	82/89 (92%)	92/114 (81%)
Sex				
Male	674/733 (92%)	673/740 (91%)	616/733 (84%)	603/740 (81%)
Female	126/133 (95%)	111/127 (87%)	113/133 (85%)	91/127 (72%)
Race				
Black	197/223 (88%)	177/213 (83%)	168/223 (75%)	152/213 (71%)
Non-black	603/643 (94%)	607/654 (93%)	561/643 (87%)	542/654 (83%)
Baseline viral load				
≤ 100,000 copies/mL	629/670 (94%)	610/672 (91%)	567/670 (85%)	537/672 (80%)
> 100,000 copies/mL	171/196 (87%)	174/195 (89%)	162/196 (83%)	157/195 (81%)
Baseline CD4+ cell count				
< 200 cells/mm^3	96/112 (86%)	104/117 (89%)	93/112 (83%)	94/117 (80%)
≥ 200 cells/mm^3	703/753 (93%)	680/750 (91%)	635/753 (84%)	600/750 (80%)
HIV-1 RNA < 20 copies/mL	84.4%	84.0%	81.1%	75.8%
Treatment difference	0.4% (95% CI: -3.0% to 3.8%)		5.4% (95% CI: 1.5% to 9.2%)	

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

a Week 48 window was between Day 294 and 377 (inclusive); Week 144 window was between Day 966 and 1,049 (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 Includes 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.

The mean increase from baseline in CD4+ cell count was 230 cells/mm^3 in Gendevra-treated patients and 211 cells/mm^3 in E/C/F/TDF-treated patients (p = 0.024) at Week 48, and 326 cells/mm^3 in Gendevra-treated patients and 305 cells/mm^3 in E/C/F/TDF-treated patients (p = 0.06) at Week 144.

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, FTC/tenofovir disoproxil plus atazanavir (boosted by either cobicistat or ritonavir), or E/C/F/TDF to Gendevra 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 Gendevra prior to study entry. Patients were randomised in a 2:1 ratio to either switch to Gendevra 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/tenofovir disoproxil 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/tenofovir disoproxil.

Switching from a tenofovir disoproxil-based regimen to Gendevra 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 Weeks 48[a] and 96[b]

	Week 48		Week 96	
	Gendevra (n = 959)	**Baseline regimen (n = 477)**	**Gendevra (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%, p < 0.001[c])		3.7% (95% CI: 0.4% to 7.0%, p < 0.017[c])	
HIV-1 RNA ≥ 50 copies/mL[d]	1%	1%	2%	2%
No virologic data at Week 48/ Week 96 window	2%	6%	5%	9%
Discontinued study drug due to AE or death[e]	1%	1%	1%	3%
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[f]	1%	4%	3%	6%
Missing data during window but on study drug	0%	< 1%	1%	< 1%
Proportion (%) of patients with HIV-1 RNA < 50 copies/mL by prior treatment regimen				
EFV/FTC/tenofovir disoproxil	96%	90%	90%	86%
FTC/tenofovir disoproxil plus boosted atazanavir	97%	92%	92%	88%
E/C/F/TDF	98%	97%	96%	93%

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

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

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

c 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/tenofovir disoproxil, FTC/tenofovir disoproxil plus boosted atazanavir, or E/C/F/TDF).

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

e 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.

f 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 Gendevra 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 Gendevra. 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 144, 83.1% (197/237 patients) maintained HIV-1 RNA < 50 copies/mL after switching to Gendevra.

In Study GS-US-292-1825, the efficacy and safety of Gendevra were evaluated in a single-arm, open-label clinical study in which 55 HIV-1 infected adults with end stage renal disease ($eGFR_{CG}$ < 15 mL/min) on chronic haemodialysis for at least 6 months before switching to Gendevra. Patients were virologically suppressed (HIV-1 RNA < 50 copies/mL) for at least 6 months before switching to Gendevra.

The mean age was 48 years (range 23-64). Seventy-six percent were male, 82% were Black and 18% were White. Fifteen percent of patients identified as Hispanic/Latino. The mean baseline CD4+ cell count was 545 cells/mm^3 (range 205-1473). At Week 48, 81.8% (45/55 patients) maintained HIV-1 RNA < 50 copies/mL after switching to Gendevra. There were no clinically significant changes in fasting lipid laboratory tests in patients who switched to Gendevra.

Patients co-infected with HIV and HBV
In open-label Study GS-US-292-1249, the efficacy and safety of Gendevra were evaluated in adult patients co-infected with HIV-1 and chronic hepatitis B. Sixty-nine of the 72 patients were on prior tenofovir disoproxil-containing antiretroviral therapy. At the start of treatment with Gendevra, the 72 patients had been 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. The mean age was 50 years (range 28-67), 92% of patients were male, 69% were White, 18% were Black, and 10% were Asian. The mean baseline CD4+ cell count was 636 cells/mm^3 (range 263-1,498). Eighty-six percent of patients (62/72) were HBV suppressed (HBV DNA < 29 IU/mL) and 42% (30/72) were HBeAg positive at baseline.

Of the patients who were HBeAg positive at baseline, 1/30 (3.3%) achieved seroconversion to anti-HBe at Week 48. Of the patients who were HBsAg positive at baseline, 3/70 (4.3%) achieved seroconversion to anti-HBs at Week 48.

At Week 48, 92% of patients (66/72) maintained HIV-1 RNA < 50 copies/mL after switching to Gendevra. The mean change from baseline in CD4+ cell count at Week 48 was -2 cells/mm^3. Ninety-two percent (66/72 patients) had HBV DNA < 29 IU/mL using missing = failure analysis at Week 48. Of the 62 patients who were HBV suppressed at baseline, 59 remained suppressed and 3 had missing data. Of the 10 patients who were not HBV suppressed at baseline (HBV DNA ≥ 29 IU/mL), 7 became suppressed, 2 remained detectable, and 1 had missing data.

There are limited clinical data on the use of Gendevra in HIV/HBV co-infected patients who are treatment-naïve.

Changes in measures of bone mineral density
In studies in treatment-naïve patients, Gendevra was associated with smaller reductions in bone mineral density (BMD) compared to E/C/F/TDF as measured by DXA analysis of hip (mean change: −0.8% versus −3.4%, p < 0.001) and lumbar spine (mean change: −0.9% versus −3.0%, p < 0.001) after 144 weeks of treatment.

Improvements in BMD were noted at 96 weeks after switching to Gendevra from a tenofovir disoproxil-containing regimen compared to maintaining the tenofovir disoproxil-containing regimen.

Changes in measures of renal function
In studies in treatment-naïve patients, Gendevra was associated with a lower impact on renal safety parameters (as measured after 144 weeks treatment by estimated glomerular filtration rate by Cockcroft-Gault method, and urine protein to creatinine ratio and after 96 weeks treatment by urine albumin to creatinine ratio) compared to E/C/F/TDF (see also section 4.4). Through 144 weeks of treatment, no subject discontinued Gendevra due to a treatment-emergent renal adverse event compared with 12 subjects who discontinued E/C/F/TDF (p < 0.001).

An improved renal safety profile was maintained through Week 96 in patients who switched to Gendevra compared with those who stayed on a tenofovir disoproxil-containing regimen.

Paediatric population

Study GS-US-292-0106
In Study GS-US-292-0106, the efficacy, safety, and pharmacokinetics of Gendevra were evaluated in an open-label study in HIV-1-infected, treatment-naïve adolescents between the ages of 12 to

< 18 years, weighing ≥ 35 kg (n = 50) in Cohort 1, and in virologically-suppressed children between the ages of 7 to < 12 years, weighing > 25 kg (n = 52) in Cohort 2.

Patients in Cohort 1 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 Gendevra 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 Gendevra, 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 Gendevra.

Patients in Cohort 2 had a mean age of 10 years (range: 7 to 11), a mean baseline weight of 32 kg (range: 26 to 58), were 42% male, 25% Asian, and 71% Black. At baseline, median CD4+ cell count was 926 cells/mm^3 (range: 336 to 1,611), and median CD4+% was 38% (range: 23 to 51%).

After switching to Gendevra, 98% (51/52) of patients in Cohort 2 remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 48. The mean change from baseline in CD4+ cell count and percentage at Week 48 was -66 cells/mm^3 and -0.6%, respectively. One of 52 patients met the criteria for inclusion in the resistance analysis population through Week 48; no emergent resistance to Gendevra was detected through Week 48.

Study GS-US-292-1515
In Study GS-US-292-1515, the efficacy and safety of Gendevra were evaluated in an open-label study in HIV-1-infected, virologically-suppressed adolescents between the ages of 12 and 18 years, weighing ≥ 35 kg (n = 50).

Patients in the study had a median age of 15 years (range: 12 to 17 years), 64% were female and 98% were Black. At baseline, median CD4+ cell count was 742 cells/mm^3 (range: 255 to 1,246) and median CD4+% was 34% (range: 21 to 53%).

After switching to Gendevra, 90% (45/50) of patients remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 48. The mean change from baseline in CD4+ cell count and percentage at Week 48 was -43 cells/mm^3 and -0.1%, respectively. Five subjects had virologic failure through the end of the study; no phenotypic or genotypic resistance to Gendevra was detected.

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 Gendevra 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 Gendevra 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.

Pharmacokinetics in special populations

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.

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

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

	Adolescents aged 12 to < 18 years, ≥ 35 kg					Adults				
	Gendevra					Gendevra				
	EVG[a]	COBI[a]	FTC[a]	TAF[b]	TFV[b]	EVG[e]	COBI[e]	FTC[e]	TAF[f]	TFV[f]
AUC_{tau} (ng•h/mL)	23,840.1 (25.5)	8,240.8 (36.1)[b]	14,424.4 (23.9)	242.8[c] (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.
b n = 23 adolescents.
c $AUC_{last.}$
d n = 15 adolescents.
e n = 19 adults.
f n = 539 (TAF) or 841 (TFV) adults.

Mean exposures of elvitegravir, cobicistat, emtricitabine, tenofovir, and tenofovir alafenamide achieved in children aged 8 to < 12 years (> 25 kg; n = 23) who received Gendevra in study GS-US-292-0106 were higher (20 to 80%) than the mean exposures achieved in adults (Table 6).

Table 6: Pharmacokinetics of elvitegravir, cobicistat, emtricitabine, tenofovir, and tenofovir alafenamide in virologically-suppressed children (aged 8 to < 12 years, > 25 kg) and adults

	Children aged 8 to < 12 years, > 25 kg					Adults				
	Gendevra					Gendevra				
	EVG[a]	COBI[a]	FTC[a]	TAF[a]	TFV[a]	EVG[e]	COBI[e]	FTC[e]	TAF[f]	TFV[f]
AUC_{tau} (ng•h/mL)	33,813.9 (57.8)[b]	15,890.7 (51.7)[c]	20,629.2 (18.9)[b]	332.9[d] (44.8)	440.2 (20.9)	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)	3,055.2 (38.7)	2,079.4 (46.7)	3,397.4 (27.0)	313.3 (61.2)	26.1 (20.8)	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)	370.0 (118.5)	96.0 (168.7)	114.9 (24.1)	N/A	15.1 (24.9)	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 = 23 children.
b n = 22 children.
c n = 20 children.
d $AUC_{last.}$
e n = 19 adults.
f n = 539 (TAF) or 841 (TFV) adults.

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 ml/min and but < 30 mL/min) in Phase 1 studies of cobicistat-boosted elvitegravir or of tenofovir alafenamide, respectively. In a separate Phase 1 study of emtricitabine alone, mean systemic emtricitabine exposure was higher in patients with severe renal impairment (estimated CrCl < 30 mL/min) (33.7 µg•h/mL) than in subjects with normal renal function

(11.8 µg•h/mL). The safety of Gendevra has not been established in patients with severe renal impairment (estimated CrCl ≥ 15 mL/min and < 30 mL/min).

Exposures of emtricitabine and tenofovir in 12 patients with end stage renal disease (estimated CrCl < 15 mL/min) on chronic haemodialysis who received Gendevra in Study GS-US-292-1825 were significantly higher than in patients with normal renal function. No clinically relevant differences in elvitegravir, cobicistat, or tenofovir alafenamide pharmacokinetics were observed in patients with end stage renal disease on chronic haemodialysis as compared to those with normal renal function. There were no new safety issues identified in patients with end stage renal disease on chronic haemodialysis receiving Gendevra (see section 4.8).

There are no pharmacokinetic data on elvitegravir, cobicistat, emtricitabine or tenofovir alafenamide in patients with end stage renal disease (estimated CrCl < 15 mL/min) not on chronic haemodialysis. The safety of elvitegravir, cobicistat, emtricitabine or tenofovir alafenamide has not been established in these patients.

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 hepatic impairment and subjects with normal hepatic function. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of elvitegravir or cobicistat has not been studied.

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 the pharmacokinetics of tenofovir alafenamide or its metabolite tenofovir were not observed in patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, total plasma concentrations of tenofovir alafenamide and tenofovir are lower than those seen in subjects with normal hepatic function. When corrected for protein binding, unbound (free) plasma concentrations of tenofovir alafenamide in severe hepatic impairment and normal hepatic function are similar.

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.

Pregnancy and postpartum
The results reported from a prospective study (IMPAACT P1026s) showed that treatment with cobicistat and elvitegravir-containing regimens during pregnancy results in lower elvitegravir and cobicistat exposures (Table 7).

Table 7: Changes in pharmacokinetic parameters from the IMPAACT P1026s study for elvitegravir and cobicistat in women receiving cobicistat and elvitegravir-containing regimens during the second and third trimesters of pregnancy compared to paired postpartum data

Comparison to paired postpartum data, n	Mean % change of elvitegravir pharmacokinetic parameters[a]			Mean % change of cobicistat pharmacokinetic parameters[a]		
	AUC_{24}	C_{max}	C_{24}	AUC_{24}	C_{max}	C_{24}
2T/PP, n = 14	↓ 24%[b]	↓ 8%	↓ 81%[b]	↓ 44%[b]	↓ 28%[b]	↓ 60%[b]
3T/PP, n = 24	↓ 44%[b]	↓ 28%[b]	↓ 89%[b]	↓ 59%[b]	↓ 38%[b]	↓ 76%[b]

2T = second trimester; 3T = third trimester; PP =postpartum
a paired comparisons
b P<0.10 compared with postpartum

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 foetal parameters. However increased post-implantation loss and decreased foetal 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 4 times greater than those expected after administration of Gendevra. 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 Gendevra.

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 tenofovir disoproxil, carcinogenicity studies and a rat peri-postnatal study were conducted only with tenofovir disoproxil. 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 foetal parameters. However, tenofovir disoproxil 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

Microcrystalline cellulose (E460)
Silicon dioxide (E551)
Croscarmellose sodium
Lactose (as monohydrate)
Magnesium stearate
Sodium lauryl sulfate
Hydroxypropyl cellulose (E463)

Film-coating

Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Polyethylene glycol (E1521)
Talc (E553b)
Indigo carmine aluminium lake (E132)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry of the product is indicated on the packaging materials.

6.4 Special precautions for storage

No special storage conditions. It is recommended to store at room temperature. Store in the original package in order to protect from moisture. Keep the bottle tightly closed.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with a polypropylene continuous-thread, child-resistant cap, lined with an induction activated aluminium foil liner containing 30 film-coated tablets. Each bottle contains silica gel desiccant and polyester coil.

The following pack sizes are available: outer cartons containing 1 bottle of 30 film-coated tablets

6.6 Special precautions for disposal

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

7. MANUFACTURER

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County Cork
Ireland

8. REGISTRATION HOLDER

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