ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Vitekta 85 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 85 mg of elvitegravir.

Excipient with known effect: Each tablet contains 6.2 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Green, pentagon-shaped, film-coated tablet of dimensions 8.9 mm x 8.7 mm, debossed with "GSI" on one side of the tablet and "85" on the other side of the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vitekta co-administered with a ritonavir-boosted protease inhibitor and with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults who are infected with HIV-1 without known mutations associated with resistance to elvitegravir (see sections 4.2 and 5.1).

4.2 Posology and method of administration

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

Posology
Vitekta must be administered in combination with a ritonavir-boosted protease inhibitor.

The Summary of Product Characteristics for the co-administered ritonavir-boosted protease inhibitor should be consulted.

The recommended dose of Vitekta is one 85 mg tablet or one 150 mg tablet taken orally once daily with food. The choice of dose of Vitekta depends on the co-administered protease inhibitor (see Table 1 and sections 4.4 and 4.5). For use of the 150 mg tablet, please refer to the Summary of Product Characteristics for Vitekta 150 mg tablets.

Vitekta should be administered once daily as follows:
- Either at the same time as a once daily ritonavir-boosted protease inhibitor
- Or with the first dose of a twice daily ritonavir-boosted protease inhibitor.

Table 1: Recommended dosing regimens

Dose of Vitekta	Dose of co-administered ritonavir-boosted protease inhibitor
85 mg once daily	atazanavir 300 mg and ritonavir 100 mg once daily
	lopinavir 400 mg and ritonavir 100 mg twice daily
150 mg once daily	darunavir 600 mg and ritonavir 100 mg twice daily
	fosamprenavir 700 mg and ritonavir 100 mg twice daily

There are no data to recommend the use of Vitekta with dosing frequencies or HIV-1 protease inhibitors other than those presented in Table 1.

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

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

Special populations

Elderly
No data are available on which to make a dose recommendation for patients over the age of 65 years (see section 5.2).

Renal impairment
No dose adjustment of Vitekta is required for patients with renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment of Vitekta is required in patients with mild (Child-Pugh Class A) or moderate hepatic impairment (Child-Pugh Class B). Elvitegravir has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of elvitegravir in children aged 0 to less than 18 years have not yet been established (see section 5.1). No data are available.

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

4.3 Contraindications

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

Co-administration with the following medicinal products due to the potential for loss of virologic response and possible development of resistance (see section 4.5):
- anticonvulsants: carbamazepine, phenobarbital, phenytoin
- antimycobacterials: rifampicin
- herbal products: St. John's wort (*Hypericum perforatum*)

4.4 Special warnings and precautions for use

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

The use of Vitekta with HIV-1 protease inhibitors or dosing frequencies other than those presented in Table 1 may result in inadequate or elevated plasma levels of elvitegravir and/or the co-administered medicinal products.

Resistance
Elvitegravir-resistant viruses show cross-resistance to the integrase strand transfer inhibitor raltegravir in most cases (see section 5.1).

Elvitegravir has a relatively low genetic barrier to resistance. Therefore, whenever possible, Vitekta should be administered with a fully active ritonavir-boosted protease inhibitor and a second fully active antiretroviral agent to minimise the potential for virologic failure and the development of resistance (see section 5.1).

Co-administration of other medicinal products
Elvitegravir is primarily metabolised by CYP3A. Co-administration of Vitekta with strong CYP3A inducers (including St. John's wort [*Hypericum perforatum*], rifampicin, carbamazepine, phenobarbital and phenytoin) is contraindicated (see sections 4.3 and 4.5). Co-administration of Vitekta with moderate CYP3A inducers (including, but not limited to, efavirenz and bosentan) is not recommended (see section 4.5).

Due to the need for co-administration of Vitekta with a ritonavir-boosted protease inhibitor, prescribers should consult the Summary of Product Characteristics of the co-administered protease inhibitor and ritonavir for a description of contraindicated medicinal products and other significant drug-drug interactions that may cause potentially life-threatening adverse reactions or loss of therapeutic effect and possible development of resistance.

Atazanavir/ritonavir and lopinavir/ritonavir have been shown to significantly increase the plasma concentrations of elvitegravir (see section 4.5). When used in combination with atazanavir/ritonavir and lopinavir/ritonavir, the dose of Vitekta should be decreased from 150 mg once daily to 85 mg once daily (see section 4.2).

Co-administration of Vitekta and related active substances: Vitekta must be used in combination with a ritonavir-boosted protease inhibitor. Vitekta should not be used with a protease inhibitor boosted by another agent as dosing recommendations for such combinations have not been established. Boosting elvitegravir with an agent other than ritonavir may result in suboptimal plasma concentrations of elvitegravir and/or the protease inhibitor leading to loss of therapeutic effect and possible development of resistance.

Vitekta should not be used in combination with products containing elvitegravir or pharmacokinetic boosting agents other than ritonavir.

Contraception requirements
Female patients of childbearing potential should use either a hormonal contraceptive containing at least 30 µg ethinylestradiol and containing norgestimate as the progestagen or should use an alternative reliable method of contraception (see sections 4.5 and 4.6). Co-administration of elvitegravir with oral contraceptives containing progestagens other than norgestimate have not been studied and, therefore, should be avoided.

Patients using oestrogens as hormone replacement therapy should be clinically monitored for signs of oestrogen deficiency (see section 4.5).

Opportunistic infections
Patients receiving Vitekta 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.

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

Physicians should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV).

Liver disease
Elvitegravir has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). No dose adjustment of Vitekta is required in patients with mild (Child-Pugh Class A) or moderate hepatic impairment (Child-Pugh Class B) (see sections 4.2 and 5.2).

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.

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 are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

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

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.

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

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Interactions with CYP3A inducers
Elvitegravir is primarily metabolised by CYP3A (see section 5.2). Medicinal products that are strong (causing a > 5-fold increase in substrate clearance) or moderate (causing a 2-5 fold increase in substrate clearance) inducers of CYP3A are expected to decrease plasma concentrations of elvitegravir.

Concomitant use contraindicated
Co-administration of Vitekta with medicinal products that are strong inducers of CYP3A is contraindicated as the expected decrease in plasma concentrations of elvitegravir can lead to loss of therapeutic effect and possible development of resistance to elvitegravir (see section 4.3).

Concomitant use not recommended
Co-administration of Vitekta with medicinal products that are moderate inducers of CYP3A (including, but not limited to, efavirenz and bosentan) is not recommended as the expected decrease in plasma concentrations of elvitegravir can lead to loss of therapeutic effect and possible development of resistance to elvitegravir (see section 4.4).

Interactions requiring dose adjustment of Vitekta
Elvitegravir undergoes oxidative metabolism by CYP3A (major route), and glucuronidation by UGT1A1/3 enzymes (minor route). Co-administration of Vitekta with medicinal products that are potent inhibitors of UGT1A1/3 may result in increased elvitegravir plasma concentrations and dose modifications may be required. For example, atazanavir/ritonavir and lopinavir/ritonavir (potent UGT1A1/3 inhibitors) have been shown to significantly increase the plasma concentrations of elvitegravir (see Table 2). Accordingly, when used in combination with atazanavir/ritonavir and lopinavir/ritonavir, the dose of Vitekta should be decreased from 150 mg once daily to 85 mg once daily (see sections 4.2 and 4.4).

Other interactions
Elvitegravir is a modest inducer and may have the potential to induce CYP2C9 and/or inducible UGT enzymes. As such, elvitegravir may decrease the plasma concentration of substrates of CYP2C9 (such as warfarin) or UGT (such as ethinyl estradiol). In addition, *in vitro* studies have shown that elvitegravir is a weak to modest inducer of CYP1A2, CYP2C19 and CYP3A enzymes. Elvitegravir would also have potential to be a weak to modest inducer of CYP2B6 and CYP2C8 enzymes, as these enzymes are regulated in a similar manner to CYP2C9 and CYP3A. However, clinical data have shown there are no clinically relevant changes in the exposure of methadone (which is primarily metabolised by CYP2B6 and CYP2C19) following co-administration with boosted elvitegravir *versus* administration of methadone alone (see Table 2).

Elvitegravir is a substrate for OATP1B1 and OATP1B3, and an inhibitor of OATP1B3 *in vitro*. The *in vivo* relevance of these interactions is not clear.

Interactions between elvitegravir and potential co-administered medicinal products are listed in Table 2 below (increase is indicated as "↑", decrease as "↓", no change as "↔"). These interactions are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of therapeutic effect.

Where interactions were studied, the effect on Vitekta was determined by comparing the pharmacokinetics of boosted elvitegravir (using either ritonavir or cobicistat as a pharmacokinetic enhancer) in the absence and presence of the co-administered medicinal product. No interactions were studied using unboosted elvitegravir. Except where indicated in Table 2, the dose of boosted elvitegravir or co-administered medicinal product was the same when administered alone or in combination. The pharmacokinetic parameters of the protease inhibitors presented in Table 2 were assessed in the presence of ritonavir.

Although there may be no actual or predicted interactions between a medicinal product and elvitegravir, there may be interactions between a medicinal product and ritonavir and/or the protease

inhibitor co-administered with elvitegravir. The prescriber should always refer to the Summary of Product Characteristics for ritonavir, or the protease inhibitor.

Table 2: Interactions between elvitegravir and other medicinal products

Medicinal product by therapeutic areas	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with ritonavir-boosted elvitegravir
ANTIRETROVIRALS		
HIV protease inhibitors		
Atazanavir (300 mg once daily) Elvitegravir (200 mg once daily) Ritonavir (100 mg once daily)	Atazanavir/Ritonavir has been shown to significantly increase the plasma concentrations of elvitegravir. Elvitegravir: AUC: ↑ 100% C_{max}: ↑ 85% C_{min}: ↑ 188% Atazanavir: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 35%	When used in combination with atazanavir, the dose of Vitekta should be 85 mg once daily. When used in combination with Vitekta, the recommended dose of atazanavir is 300 mg with ritonavir 100 mg once daily. There are no data available to make dosing recommendations for co-administration with other doses of atazanavir (see section 4.2).
Atazanavir (300 mg once daily) Elvitegravir (85 mg once daily) Ritonavir (100 mg once daily)	Elvitegravir: AUC: ↔* C_{max}: ↔* C_{min}: ↑ 38%* Atazanavir: AUC: ↔** C_{max}: ↔** C_{min}: ↔** *when compared to elvitegravir/ritonavir 150/100 mg once daily. **when compared to atazanavir/ritonavir 300/100 mg once daily.	
Darunavir (600 mg twice daily) Elvitegravir (125 mg once daily) Ritonavir (100 mg twice daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 17%	When used in combination with darunavir, the dose of Vitekta should be 150 mg once daily. There are no data available to make dosing recommendations for co-administration with other doses of darunavir (see section 4.2).
Fosamprenavir (700 mg twice daily) Elvitegravir (125 mg once daily) Ritonavir (100 mg twice daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Fosamprenavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔	When used in combination with fosamprenavir, the dose of Vitekta should be 150 mg once daily. There are no data available to make dosing recommendations for co-administration with other doses of fosamprenavir (see section 4.2).

Medicinal product by therapeutic areas	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with ritonavir-boosted elvitegravir
Lopinavir/Ritonavir (400/100 mg twice daily) Elvitegravir (125 mg once daily)	Lopinavir/Ritonavir has been shown to significantly increase the plasma concentrations of elvitegravir. Elvitegravir: AUC: ↑ 75% C_{max}: ↑ 52% C_{min}: ↑ 138% Lopinavir: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 8%	When used in combination with lopinavir/ritonavir, the dose of Vitekta should be 85 mg once daily. There are no data available to make dosing recommendations for co-administration with other doses of lopinavir/ritonavir (see section 4.2).
Tipranavir (500 mg twice daily) Elvitegravir (200 mg once daily) Ritonavir (200 mg twice daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tipranavir: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 11%	Due to insufficient clinical data, the combination of elvitegravir with tipranavir is not recommended (see section 4.2).
NRTIs		
Didanosine (400 mg once daily) Elvitegravir (200 mg once daily) Ritonavir (100 mg once daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Didanosine: AUC: ↓ 16% C_{max}: ↓ 16%	As didanosine is administered on an empty stomach, didanosine should be administered at least one hour before or two hours after Vitekta (which is administered with food). Clinical monitoring is recommended.
Zidovudine (300 mg twice daily) Elvitegravir (200 mg once daily) Ritonavir (100 mg once daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Zidovudine: AUC: ↔ C_{max}: ↔	No dose adjustment is required when Vitekta is co-administered with zidovudine.
Stavudine (40 mg once daily) Elvitegravir (200 mg once daily) Ritonavir (100 mg once daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Stavudine: AUC: ↔ C_{max}: ↔	No dose adjustment is required when Vitekta is co-administered with stavudine.
Abacavir (600 mg once daily) Elvitegravir (200 mg once daily) Ritonavir (100 mg once daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Abacavir: AUC: ↔ C_{max}: ↔	No dose adjustment is required when Vitekta is co-administered with abacavir.

Medicinal product by therapeutic areas	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with ritonavir-boosted elvitegravir
Tenofovir disoproxil fumarate (300 mg once daily) Emtricitabine (200 mg once daily) Elvitegravir (50 mg once daily) Ritonavir (100 mg once daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔	No dose adjustment is required when Vitekta is co-administered with tenofovir disoproxil fumarate or with emtricitabine.
NNRTIs		
Efavirenz	Interaction not studied with elvitegravir. Co-administration of efavirenz and elvitegravir is expected to decrease elvitegravir plasma concentrations which may result in loss of therapeutic effect and possible development of resistance.	Co-administration is not recommended (see section 4.4).
Etravirine (200 mg twice daily) Elvitegravir (150 mg once daily) Ritonavir (100 mg once daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Etravirine: AUC: ↔ C_{max}: ↔ C_{min}: ↔	No dose adjustment is required when Vitekta is co-administered with etravirine.
Nevirapine	Interaction not studied with elvitegravir. Co-administration of nevirapine and elvitegravir is expected to decrease elvitegravir plasma concentrations which may result in loss of therapeutic effect and possible development of resistance.	Co-administration is not recommended (see section 4.4).
Rilpivirine	Interaction not studied with elvitegravir.	Co-administration of elvitegravir and rilpivirine is not expected to change elvitegravir plasma concentrations, therefore no dose adjustment of Vitekta is required.
CCR5 antagonists		
Maraviroc (150 mg twice daily) Elvitegravir (150 mg once daily) Ritonavir (100 mg once daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Maraviroc:[§] AUC: ↑ 186% C_{max}: ↑ 115% C_{min}: ↑ 323%	No dose adjustment is required when Vitekta is co-administered with maraviroc. [§]Due to inhibition of CYP3A by ritonavir, maraviroc exposure is significantly increased.

Medicinal product by therapeutic areas	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with ritonavir-boosted elvitegravir
ANTACIDS		
Magnesium/aluminum-containing antacid suspension (20 mL single dose) Elvitegravir (50 mg once daily) Ritonavir (100 mg once daily)	Elvitegravir (antacid suspension given ± 4 hours from elvitegravir administration): AUC: ↔ C_{max}: ↔ C_{min}: ↔ Elvitegravir (simultaneous antacid administration): AUC: ↓ 45% C_{max}: ↓ 47% C_{min}: ↓ 41%	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 Vitekta and antacid administration by at least 4 hours.
FOOD SUPPLEMENTS		
Multivitamin supplements	Interaction not studied with elvitegravir.	As the effect of cationic complexation of elvitegravir cannot be excluded when co-administered with multivitamin supplements, it is recommended to separate Vitekta and multivitamin supplements dosing by at least 4 hours.
NARCOTIC ANALGESICS		
Methadone (80-120 mg once daily) Elvitegravir (150 mg once daily) Cobicistat (150 mg once daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Methadone: AUC: ↔ C_{max}: ↔ C_{min}: ↔	No dose adjustment is required when Vitekta is co-administered with methadone.
Buprenorphine/Naloxone (16/4 mg to 24/6 mg daily) Elvitegravir (150 mg once daily) Cobicistat (150 mg once daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Buprenorphine: AUC: ↑ 35% C_{max}: ↑ 12% C_{min}: ↑ 66% Naloxone: AUC: ↓ 28% C_{max}: ↓ 28%	No dose adjustment is required when Vitekta is co-administered with buprenorphine/naloxone.
ANTI-INFECTIVES		
Antifungals		
Ketoconazole (200 mg twice daily) Elvitegravir (150 mg once daily) Ritonavir (100 mg once daily)	Elvitegravir: AUC: ↑ 48% C_{max}: ↔ C_{min}: ↑ 67% ↑ Ketoconazole[§]	No dose adjustment is required when Vitekta is co-administered with ketoconazole. [§]Due to inhibition of CYP3A by ritonavir, ketoconazole exposure is increased.

Medicinal product by therapeutic areas	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with ritonavir-boosted elvitegravir
HCV protease inhibitors		
Telaprevir (750 mg three times daily)/ Elvitegravir (85 mg once daily) Atazanavir (300 mg once daily) Ritonavir (100 mg once daily)	Telaprevir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 40%* *Compared to atazanavir/ritonavir 300/100 mg plus elvitegravir 85 mg once daily.	No dose adjustment is required when Vitekta is co-administered with ritonavir-boosted atazanavir plus telaprevir.
Antimycobacterials		
Rifabutin (150 mg once every other day) Elvitegravir (300 mg once daily) Ritonavir (100 mg once daily)	Elvitegravir: AUC: ↔* C_{max}: ↔* C_{min}: ↔* Rifabutin: AUC: ↔** C_{max}: ↔** C_{min}: ↔**	Co-administration of Vitekta 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). No dose adjustment of Vitekta is required when co-administered with reduced dose of 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. §Due to inhibition of CYP3A by ritonavir, 25-O-desacetyl-rifabutin exposure is increased.
	25-O-desacetyl-rifabutin:§ AUC: ↑ 851%* C_{max}: ↑ 419%** C_{min}: ↑ 1,836%** *when compared to elvitegravir/ritonavir 300/100 mg once daily. **when compared to rifabutin 300 mg once daily. Total antimycobacterial activity was increased by 50%.	
ANTICOAGULANTS		
Warfarin	Interaction not studied with elvitegravir. Concentrations of warfarin may be affected upon co-administration with elvitegravir.	It is recommended that the international normalised ratio (INR) be monitored upon co-administration of Vitekta. INR should continue to be monitored during the first weeks following cessation of treatment with Vitekta.
H_2-RECEPTOR ANTAGONISTS		
Famotidine (40 mg once daily) Elvitegravir (150 mg once daily) Cobicistat (150 mg once daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔	No dose adjustment is required when Vitekta is co-administered with famotidine.

Medicinal product by therapeutic areas	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with ritonavir-boosted elvitegravir
HMG-CoA REDUCTASE INHIBITORS		
Rosuvastatin (10 mg single dose) Elvitegravir (150 mg once daily) Cobicistat (150 mg once daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Rosuvastatin: AUC: ↑ 38% C_{max}: ↑ 89% C_{min}: ↑ 43%	No dose adjustment is required when Vitekta is co-administered with rosuvastatin.
Atorvastatin Fluvastatin Pitavastatin Pravastatin	Interaction not studied with elvitegravir. Plasma concentrations of OATP substrates are not expected to change upon co-administration of elvitegravir. Plasma concentrations of elvitegravir are not expected to change upon co-administration of OATP substrates/inhibitors.	No dose adjustment is required when Vitekta is co-administered with atorvastatin, fluvastatin, pitavastatin or pravastatin.
ORAL CONTRACEPTIVES		
Norgestimate (0.180/0.215 mg once daily) Ethinylestradiol (0.025 mg once daily) Elvitegravir (150 mg once daily) Cobicistat (150 mg once daily)[1]	Norgestimate: AUC: ↑ 126% C_{max}: ↑ 108% C_{min}: ↑ 167% Ethinylestradiol: AUC: ↓ 25% C_{max}: ↔ C_{min}: ↓ 44% Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔	Caution should be exercised when co-administering Vitekta and a hormonal contraceptive. The hormonal contraceptive should contain at least 30 µg ethinylestradiol and contain norgestimate as the progestagen or patients should use an alternative reliable method of contraception (see sections 4.4 and 4.6). The long-term effects of substantial increases in progesterone exposure are unknown. Co-administration of elvitegravir with oral contraceptives containing progestagens other than norgestimate has not been studied and therefore should be avoided.
PROTON PUMP INHIBITORS		
Omeprazole (40 mg once daily) Elvitegravir (50 mg once daily Ritonavir (100 mg once daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔	No dose adjustment is required when Vitekta is co-administered with omeprazole.

[1] This study was conducted using the fixed-dose combination tablet elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / contraception in males and females

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

Pregnancy

There are no or limited clinical data with elvitegravir in pregnant women.

Animal studies do not indicate direct or indirect harmful effects of elvitegravir with respect to reproductive toxicity. However, the maximum exposures evaluated in the rabbit were not in excess of those achieved therapeutically (see section 5.3).

Vitekta should not be used during pregnancy unless the clinical condition of the woman requires treatment with elvitegravir.

Breast-feeding
It is unknown whether elvitegravir/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in rats have shown excretion of elvitegravir in milk. A risk to the newborns/infants cannot be excluded. Therefore, Vitekta should not be used during breast-feeding.

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

Fertility
No human data on the effect of elvitegravir on fertility are available. Animal studies do not indicate harmful effects of elvitegravir on fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
Assessment of adverse reactions is based on data from a controlled clinical study (GS-US-183-0145) in which 712 HIV-1 infected, antiretroviral treatment-experienced adults received elvitegravir (n = 354) or raltegravir (n = 358) each administered with a background regimen consisting of a fully active ritonavir-boosted protease inhibitor and other antiretroviral agents. Of these 712 patients, 543 (269 elvitegravir and 274 raltegravir) and 439 (224 elvitegravir and 215 raltegravir) received at least 48 and 96 weeks of treatment, respectively.

The most frequently reported adverse reactions to elvitegravir were diarrhoea (7.1%) and nausea (4.0%) (see Table 3).

Tabulated summary of adverse reactions
Adverse reactions to elvitegravir from clinical study experience are listed in Table 3 below, by body system organ class and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as common (≥ 1/100 to < 1/10) or uncommon (≥ 1/1,000 to < 1/100).

Table 3: Tabulated summary of adverse reactions to elvitegravir based on experience for 96 weeks from clinical study GS-US-183-0145

Frequency	Adverse reaction
Psychiatric disorders:	
Uncommon	suicidal ideation and suicide attempt (in patients with a pre-existing history of depression or psychiatric illness), depression, insomnia
Nervous system disorders:	
Common	headache
Uncommon	dizziness, paraesthesia, somnolence, dysgeusia
Gastrointestinal disorders:	
Common	abdominal pain, diarrhoea, vomiting, nausea
Uncommon	dyspepsia, abdominal distension, flatulence
Skin and subcutaneous tissue disorders:	
Common	rash
General disorders and administration site conditions:	
Common	fatigue

Description of selected adverse reactions

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

Immune Reactivation Syndrome
In HIV infected patients with severe immune deficiency at the time of initiation of CART, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

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

Diarrhoea
In study GS-US-183-0145, diarrhoea was reported as an adverse reaction in 7.1% of subjects in the elvitegravir group and in 5.3% of subjects in the raltegravir group. In these subjects, diarrhoea was mild to moderate in severity and did not result in discontinuation of study drug.

Paediatric population
No data are available for children below 18 years of age. Vitekta is not recommended in this population (see section 4.2).

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

4.9 Overdose

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

There is no specific antidote for overdose with elvitegravir. As elvitegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, other antivirals, ATC code: J05AX11.

Mechanism of action and pharmacodynamic effects
Elvitegravir is an HIV-1 integrase strand transfer inhibitor (INSTI). Integrase is an HIV-1 encoded enzyme that is required for viral replication. Inhibition of integrase prevents the integration of HIV-1 DNA into host genomic DNA, blocking the formation of the HIV-1 provirus and propagation of the viral infection. Elvitegravir does not inhibit human topoisomerases I or II.

Antiviral activity *in vitro*
The antiviral activity of elvitegravir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cells, monocyte/macrophage cells, and peripheral blood lymphocytes and the 50% effective concentration (EC_{50}) values were in the range of 0.02 to 1.7 nM. Elvitegravir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values ranged from 0.1 to 1.3 nM) and activity against HIV-2 (EC_{50} of 0.53 nM). The *in vitro* antiviral activity of elvitegravir when combined with antiretroviral drugs from the nucleoside reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI), integrase strand transfer inhibitor, fusion inhibitor, or CCR5 co-receptor antagonist classes showed no antagonism.

Elvitegravir did not show inhibition of replication of HBV or HCV *in vitro*.

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

Cross resistance
Elvitegravir-resistant viruses show varying degrees of cross-resistance to the integrase strand transfer inhibitor raltegravir depending on the type and number of substitutions. Viruses expressing the T66I/A substitutions maintain susceptibility to raltegravir, while most other patterns of elvitegravir-associated substitutions are associated with reduced susceptibility to raltegravir. With the exception of Y143C/R/H, HIV-1 with the primary raltegravir-associated substitutions T66K, Q148H/K/R, or N155H in integrase is associated with reduced susceptibility to elvitegravir.

In treatment-experienced patients
In an analysis of HIV-1 isolates from treatment-failure subjects in study GS-US-183-0145 through week 96, the development of one or more primary elvitegravir resistance-associated substitutions was observed in 23 of the 86 subjects with evaluable genotypic data from paired baseline and elvitegravir treatment-failure isolates (23/351 elvitegravir-treated subjects, 6.6%). Similar rates of raltegravir resistance development occurred in the HIV-1 from subjects treated with raltegravir (26/351 raltegravir-treated subjects, 7.4%). The most common substitutions that emerged in HIV-1 isolates from elvitegravir-treated subjects were T66I/A (n = 8), E92Q/G (n = 7), T97A (n = 4), S147G (n = 4), Q148R (n = 4), and N155H (n = 5) in integrase. In phenotypic analyses of HIV-1 isolates with resistance substitutions from elvitegravir-treated subjects, 14/20 (70%) had reduced susceptibility to elvitegravir and 12/20 (60%) had reduced susceptibility to raltegravir.

Clinical experience

In treatment-experienced HIV-1 infected patients

The efficacy of elvitegravir is primarily based on the analyses through 96 weeks from one randomised, double-blind, active-controlled study, study GS-US-183-0145, in treatment-experienced, HIV-1 infected patients (n = 702).

In study GS-US-183-0145, patients were randomised in a 1:1 ratio to receive either elvitegravir (150 mg or 85 mg) once daily or raltegravir 400 mg twice daily, each administered with a background regimen (BR) containing a fully-active ritonavir-boosted protease inhibitor (either atazanavir, darunavir, fosamprenavir, lopinavir or tipranavir) and a second agent. The BR was selected by the investigator based on genotypic/phenotypic resistance testing and prior antiretroviral treatment history. Randomisation was stratified by screening HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) and the class of the second agent (NRTI or other classes). Virologic response rate was evaluated in both treatment arms. Virologic response was defined as achieving an undetectable viral load (HIV-1 RNA < 50 copies/mL).

Baseline characteristics and treatment outcomes through 96 weeks for study GS-US-183-0145 are presented in Tables 4 and 5 respectively.

Table 4: Demographic and baseline disease characteristics of antiretroviral treatment-experienced HIV-1 infected adult subjects in study GS-US-183-0145

	Elvitegravir + background regimen n = 351	**Raltegravir + background regimen n = 351**
Demographic characteristics		
Median age, years (min-max)	44 (20-78)	45 (19-74)
Sex		
Male	83.2%	80.9%
Female	16.8%	19.1%
Ethnicity		
White	60.1%	64.4%
Black/African American	35.6%	32.2%
Asian	2.6%	1.4%
Other	1.7%	2.0%
Baseline disease characteristics		
Median baseline plasma HIV-1 RNA (range) log_{10} copies/mL	4.35 (1.69-6.63)	4.42 (1.69-6.10)
Percentage of subjects with viral load > 100,000 copies/mL	25.6	25.6
Median baseline CD4+ cell count (range), cells/mm^3	227.0 (2.0-1,374.0)	215.0 (1.0-1,497.0)
Percentage of subjects with CD4+ cell counts ≤ 200 cells/mm^3	44.4	44.9
Baseline genotypic sensitivity score[a]		
0	1%	< 1%
1	14%	15%
2	81%	83%
3	3%	2%

a Genotypic sensitivity scores are calculated by summing up drug susceptibility values (1 = sensitive; 0 = reduced susceptibility) on all drugs in the baseline background regimen.

Table 5: Virologic outcome of randomised treatment of study GS-US-183-0145 at week 48 and week 96 (snapshot analysis)[a]

	Week 48		Week 96	
	Elvitegravir + background regimen n = 351	**Raltegravir + background regimen n = 351**	**Elvitegravir + background regimen n = 351**	**Raltegravir + background regimen n = 351**
Virologic success HIV-1 RNA < 50 copies/mL	60%	58%	52%	53%
Treatment difference	2.2% (95% CI = -5.0%, 9.3%)		-0.5% (95% CI = -7.9%, 6.8%)	
Virologic failure[b]	33%	32%	36%	31%
No virologic data at week 48 or week 96 window	7%	11%	12%	16%
Discontinued study drug due to AE or death[c]	2%	5%	3%	7%
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[d]	4%	5%	8%	9%
Missing data during window but on study drug	1%	1%	1%	1%

a Week 48 window is between day 309 and 364 (inclusive), week 96 window is between day 645 and 700 (inclusive).
b Includes subjects who had ≥ 50 copies/mL in the week 48 or week 96 window, subjects who discontinued early due to lack or loss of efficacy, subjects who had a viral load ≥ 50 copies/mL at time of change in background regimen, subjects who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral load of ≥ 50 copies/mL.
c Includes patients who discontinued due to an AE or death at any time point from day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
d Includes subjects who discontinued for reasons other than an AE, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

Elvitegravir was non-inferior in achieving HIV-1 RNA < 50 copies/mL when compared to raltegravir.

Among subjects with a genotypic sensitivity score of ≤ 1, 76% and 69% had HIV-1 RNA < 50 copies/mL at week 48 in the elvitegravir and raltegravir treatment arms, respectively. Among subjects with a genotypic sensitivity score > 1, 57% and 56% had HIV-1 RNA < 50 copies/mL at week 48 in the elvitegravir and raltegravir treatment arms, respectively.

In study GS-US-183-0145, the mean increase from baseline in CD4+ cell count at week 96 was 205 cells/mm^3 in the elvitegravir-treated patients and 198 cells/mm^3 in the raltegravir-treated patients.

In study GS-US-183-0145, subgroup analyses by co-administered protease inhibitor showed similar rates of virologic success for elvitegravir and raltegravir within each protease inhibitor subgroup at weeks 48 and 96 (HIV-1 RNA < 50 copies/mL) (Table 6).

Table 6: Virologic success by co-administered protease inhibitor in study GS-US-183-0145 at week 48 and week 96 (snapshot analysis)

			Elvitegravir *versus* raltegravir
HIV-1 RNA < 50 copies/mL, n/N (%)	**Elvitegravir (N = 351)**	**Raltegravir (N = 351)**	**Difference in percentages (95% CI)[a]**
Virologic success at week 48			
Darunavir/ritonavir	126/202 (62.4%)	122/207 (58.9%)	3.4% (-6.0% to 12.9%)
Lopinavir/ritonavir	39/68 (57.4%)	37/68 (54.4%)	2.9% (-13.7% to 19.6%)
Atazanavir/ritonavir	34/61 (55.7%)	28/51 (54.9%)	0.8% (-17.7% to 19.3%)
Fosamprenavir/ritonavir	8/14 (57.1%)	10/18 (55.6%)	1.6% (-33.0% to 36.2%)
Tipranavir/ritonavir	3/6 (50.0%)	5/7 (71.4%)	-21.4% (-73.6% to 30.7%)
Virologic success at week 96			
Darunavir/ritonavir	105/202 (52.0%)	112/207 (54.1%)	-2.1% (-11.8% to 7.5%)
Lopinavir/ritonavir	36/68 (52.9%)	37/68 (54.4%)	-1.5% (-18.2% to 15.3%)
Atazanavir/ritonavir	33/61 (54.1%)	23/51 (45.1%)	9.0% (-9.5% to 27.5%)
Fosamprenavir/ritonavir	7/14 (50.0%)	11/18 (61.1%)	-11.1% (-45.7% to 23.4%)
Tipranavir/ritonavir	3/6 (50.0%)	3/7 (42.9%)	7.1% (-47.1% to 61.4%)

a The difference in proportions and its 95% CIs between randomised treatment groups is based on normal approximation.

Although limited by the small number of female subjects in study GS-US-183-0145, subgroup analysis by gender showed that the rates of virologic success in female subjects at weeks 48 and 96 (HIV-1 RNA < 50 copies/mL) were numerically lower in the elvitegravir treatment arm than in the raltegravir treatment arm. Virologic success rates at week 48 for elvitegravir and raltegravir were 47.5% (28/59) and 62.7% (42/67) (difference: -12.3% [95% CI: -30.1% to 5.5%]), respectively, for female subjects, and 62.3% (182/292) and 56.3% (160/284) (difference: 5.3% [95% CI: -2.5% to 13.2%]), respectively, for male subjects. Virologic success rates at week 96 for elvitegravir and raltegravir were 39.0% (23/59) and 52.2% (35/67) (difference: -8.4% [95% CI: -26.1% to 9.2%]), respectively, for female subjects, and 55.1% (161/292) and 53.2% (151/284) (difference: 1.5% [95% CI: -6.5% to 9.6%]), respectively, for male subjects.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with elvitegravir in one or more subsets of the paediatric population in the treatment of HIV-1 infection (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following oral administration of ritonavir-boosted elvitegravir with food in HIV-1 infected subjects, elvitegravir peak plasma concentrations were observed 4 hours post-dose. The steady-state mean C_{max}, AUC_{tau}, and C_{trough} (mean ± SD) following multiple doses of elvitegravir plus a ritonavir-boosted protease inhibitor (150 mg elvitegravir with darunavir or fosamprenavir; 85 mg elvitegravir with atazanavir or lopinavir) in HIV-1 infected subjects were 1.4 ± 0.39 µg/mL, 18 ± 6.8 µg•h/mL, and 0.38 ± 0.22 µg/mL for elvitegravir, respectively. The absolute oral bioavailability has not been determined.

Relative to fasting conditions, the administration of boosted elvitegravir as the fixed-dose combination 150 mg elvitegravir/150 mg cobicistat/200 mg emtricitabine/245 mg tenofovir disoproxil with a light meal (approximately 373 kcal, 20% fat) or high-fat meal (approximately 800 kcal, 50% fat) resulted in increased exposures of elvitegravir. The C_{max} and AUC_{tau} of elvitegravir increased 22% and 36% with a light meal, while increasing 56% and 91% with a high-fat meal, respectively.

Distribution
Elvitegravir is 98-99% bound to human plasma proteins and the binding is independent of drug concentration over the range of 1.0 ng/mL to 1.6 µg/mL. The mean plasma to blood drug concentration ratio is 1.37.

Biotransformation
Elvitegravir undergoes oxidative metabolism by CYP3A (major route), and glucuronidation via UGT1A1/3 enzymes (minor route).

Ritonavir inhibits CYP3A, thereby substantially increasing the plasma concentrations of elvitegravir. Administration of once-daily ritonavir (20-200 mg) results in an increased elvitegravir exposure following repeat once-daily administration, with elvitegravir exposure reaching a plateau with approximately 100 mg of ritonavir. Further increases in ritonavir dose do not result in further increases in elvitegravir exposure. Vitekta is indicated for use only when co-administered with ritonavir as a boosting agent.

Mean steady-state exposure (AUC_{tau}) of unboosted elvitegravir is ~ 20% lower after multiple dosing *versus* a single dose, indicating modest autoinduction of its metabolism. Upon boosting with ritonavir (100 mg), net inhibition of elvitegravir metabolism is observed with significantly increased systemic exposures (20-fold higher AUC), high trough concentrations, and longer median elimination half-life (9.5 *versus* 3.5 hours).

Following oral administration of a single dose of ritonavir-boosted [^{14}C]elvitegravir, elvitegravir was the predominant species in plasma, representing approximately 94% and 61% of the circulating radioactivity at 32 and 48 hours, respectively. Metabolites produced by aromatic and aliphatic hydroxylation or glucuronidation are present in very low levels and do not contribute to the overall antiviral activity of elvitegravir.

Elimination
Following oral administration of ritonavir-boosted [^{14}C]elvitegravir, 94.8% of the dose was recovered in faeces, consistent with the hepatobiliary elimination of elvitegravir; 6.7% of the administered dose was recovered in urine as metabolites. The median terminal plasma half-life of ritonavir-boosted elvitegravir is approximately 8.7 to 13.3 hours.

Linearity/non-linearity
Elvitegravir plasma exposures are non-linear and less than dose-proportional, likely due to solubility-limited absorption.

Elderly
Pharmacokinetics of elvitegravir have not been fully evaluated in the elderly (over 65 years of age).

Gender
No clinically relevant pharmacokinetic differences due to gender have been identified for boosted elvitegravir.

Ethnicity
No clinically relevant pharmacokinetic differences due to ethnicity have been identified for boosted elvitegravir.

Paediatric population
The pharmacokinetics of elvitegravir in paediatric subjects have not been established.

Renal impairment
A study of the pharmacokinetics of boosted elvitegravir was performed in non HIV-1 infected subjects with severe renal impairment (estimated creatinine clearance below 30 mL/min). No clinically relevant differences in elvitegravir pharmacokinetics were observed between subjects with severe

renal impairment and healthy subjects. No dose adjustment of Vitekta is required for patients with renal impairment.

Hepatic impairment
Elvitegravir is primarily metabolised and eliminated by the liver. A study of the pharmacokinetics of boosted elvitegravir was performed in non-HIV-1 infected subjects with moderate hepatic impairment (Child-Pugh Class B). No clinically relevant differences in elvitegravir pharmacokinetics were observed between subjects with moderate impairment and healthy subjects. No dose adjustment of Vitekta is necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of elvitegravir has not been studied.

Hepatitis B and/or hepatitis C virus co-infection
Limited data from population pharmacokinetic analysis (n = 56) indicated that hepatitis B and/or C virus infection had no clinically relevant effect on the exposure of boosted elvitegravir.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. The maximum doses of elvitegravir tested in the developmental toxicity studies in rats and rabbits corresponded to exposures that are approximately 29-fold and 0.2-fold the human therapeutic exposure, respectively.

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.

Elvitegravir did not show any carcinogenic potential in long-term oral carcinogenicity studies in mice and rats.

The active substance elvitegravir is persistent in the environment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Croscarmellose sodium
Hydroxypropyl cellulose
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose
Sodium lauryl sulfate

Film-coating
Indigo carmine aluminium lake (E132)
Macrogol 3350 (E1521)
Polyvinyl alcohol (partially hydrolysed) (E1203)
Talc (E553B)
Titanium dioxide (E171)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with a child-resistant closure containing 30 film-coated tablets.

Pack size: 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. MARKETING AUTHORISATION HOLDER

Gilead Sciences International Limited
Cambridge
CB21 6GT
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/883/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 November 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Vitekta 150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg of elvitegravir.

Excipient with known effect: Each tablet contains 10.9 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Green, triangle-shaped, film-coated tablet of dimensions 10.9 mm × 10.9 mm, debossed with "GSI" on one side of the tablet and "150" on the other side of the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vitekta co-administered with a ritonavir-boosted protease inhibitor and with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults who are infected with HIV-1 without known mutations associated with resistance to elvitegravir (see sections 4.2 and 5.1).

4.2 Posology and method of administration

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

Posology
Vitekta must be administered in combination with a ritonavir-boosted protease inhibitor.

The Summary of Product Characteristics for the co-administered ritonavir-boosted protease inhibitor should be consulted.

The recommended dose of Vitekta is one 85 mg tablet or one 150 mg tablet taken orally once daily with food. The choice of dose of Vitekta depends on the co-administered protease inhibitor (see Table 1 and sections 4.4 and 4.5). For use of the 85 mg tablet, please refer to the Summary of Product Characteristics for Vitekta 85 mg tablets.

Vitekta should be administered once daily as follows:
- Either at the same time as a once daily ritonavir-boosted protease inhibitor
- Or with the first dose of a twice daily ritonavir-boosted protease inhibitor.

Table 1: Recommended dosing regimens

Dose of Vitekta	Dose of co-administered ritonavir-boosted protease inhibitor
85 mg once daily	atazanavir 300 mg and ritonavir 100 mg once daily
	lopinavir 400 mg and ritonavir 100 mg twice daily
150 mg once daily	darunavir 600 mg and ritonavir 100 mg twice daily
	fosamprenavir 700 mg and ritonavir 100 mg twice daily

There are no data to recommend the use of Vitekta with dosing frequencies or HIV-1 protease inhibitors other than those presented in Table 1.

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

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

Special populations

Elderly
No data are available on which to make a dose recommendation for patients over the age of 65 years (see section 5.2).

Renal impairment
No dose adjustment of Vitekta is required for patients with renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment of Vitekta is required in patients with mild (Child-Pugh Class A) or moderate hepatic impairment (Child-Pugh Class B). Elvitegravir has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of elvitegravir in children aged 0 to less than 18 years have not yet been established (see section 5.1). No data are available.

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

4.3 Contraindications

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

Co-administration with the following medicinal products due to the potential for loss of virologic response and possible development of resistance (see section 4.5):
- anticonvulsants: carbamazepine, phenobarbital, phenytoin
- antimycobacterials: rifampicin
- herbal products: St. John's wort (*Hypericum perforatum*)

4.4 Special warnings and precautions for use

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

The use of Vitekta with HIV-1 protease inhibitors or dosing frequencies other than those presented in Table 1 may result in inadequate or elevated plasma levels of elvitegravir and/or the co-administered medicinal products.

Resistance
Elvitegravir-resistant viruses show cross-resistance to the integrase strand transfer inhibitor raltegravir in most cases (see section 5.1).

Elvitegravir has a relatively low genetic barrier to resistance. Therefore, whenever possible, Vitekta should be administered with a fully active ritonavir-boosted protease inhibitor and a second fully active antiretroviral agent to minimise the potential for virologic failure and the development of resistance (see section 5.1).

Co-administration of other medicinal products
Elvitegravir is primarily metabolised by CYP3A. Co-administration of Vitekta with strong CYP3A inducers (including St. John's wort [*Hypericum perforatum*], rifampicin, carbamazepine, phenobarbital and phenytoin) is contraindicated (see sections 4.3 and 4.5). Co-administration of Vitekta with moderate CYP3A inducers (including, but not limited to, efavirenz and bosentan) is not recommended (see section 4.5).

Due to the need for co-administration of Vitekta with a ritonavir-boosted protease inhibitor, prescribers should consult the Summary of Product Characteristics of the co-administered protease inhibitor and ritonavir for a description of contraindicated medicinal products and other significant drug-drug interactions that may cause potentially life-threatening adverse reactions or loss of therapeutic effect and possible development of resistance.

Atazanavir/ritonavir and lopinavir/ritonavir have been shown to significantly increase the plasma concentrations of elvitegravir (see section 4.5). When used in combination with atazanavir/ritonavir and lopinavir/ritonavir, the dose of Vitekta should be decreased from 150 mg once daily to 85 mg once daily (see section 4.2). Please refer to the Summary of Product Characteristics for Vitekta 85 mg tablets.

Co-administration of Vitekta and related active substances: Vitekta must be used in combination with a ritonavir-boosted protease inhibitor. Vitekta should not be used with a protease inhibitor boosted by another agent as dosing recommendations for such combinations have not been established. Boosting elvitegravir with an agent other than ritonavir may result in suboptimal plasma concentrations of elvitegravir and/or the protease inhibitor leading to loss of therapeutic effect and possible development of resistance.

Vitekta should not be used in combination with products containing elvitegravir or pharmacokinetic boosting agents other than ritonavir.

Contraception requirements
Female patients of childbearing potential should use either a hormonal contraceptive containing at least 30 µg ethinylestradiol and containing norgestimate as the progestagen or should use an alternative reliable method of contraception (see sections 4.5 and 4.6). Co-administration of elvitegravir with oral contraceptives containing progestagens other than norgestimate have not been studied and, therefore, should be avoided.

Patients using oestrogens as hormone replacement therapy should be clinically monitored for signs of oestrogen deficiency (see section 4.5).

Opportunistic infections
Patients receiving Vitekta 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.

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

Physicians should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV).

Liver disease
Elvitegravir has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). No dose adjustment of Vitekta is required in patients with mild (Child-Pugh Class A) or moderate hepatic impairment (Child-Pugh Class B) (see sections 4.2 and 5.2).

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.

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 are cytomegalovirus retinitis, generalised and or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

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

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.

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

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Interactions with CYP3A inducers
Elvitegravir is primarily metabolised by CYP3A (see section 5.2). Medicinal products that are strong (causing a > 5-fold increase in substrate clearance) or moderate (causing a 2-5 fold increase in substrate clearance) inducers of CYP3A are expected to decrease plasma concentrations of elvitegravir.

Concomitant use contraindicated
Co-administration of Vitekta with medicinal products that are strong inducers of CYP3A is contraindicated as the expected decrease in plasma concentrations of elvitegravir can lead to loss of therapeutic effect and possible development of resistance to elvitegravir (see section 4.3).

Concomitant use not recommended
Co-administration of Vitekta with medicinal products that are moderate inducers of CYP3A (including, but not limited to, efavirenz and bosentan) is not recommended as the expected decrease in plasma concentrations of elvitegravir can lead to loss of therapeutic effect and possible development of resistance to elvitegravir (see section 4.4).

Interactions requiring dose adjustment of Vitekta
Elvitegravir undergoes oxidative metabolism by CYP3A (major route), and glucuronidation by UGT1A1/3 enzymes (minor route). Co-administration of Vitekta with medicinal products that are potent inhibitors of UGT1A1/3 may result in increased elvitegravir plasma concentrations and dose modifications may be required. For example, atazanavir/ritonavir and lopinavir/ritonavir (potent UGT1A1/3 inhibitors) have been shown to significantly increase the plasma concentrations of elvitegravir (see Table 2). Accordingly, when used in combination with atazanavir/ritonavir and lopinavir/ritonavir, the dose of Vitekta should be decreased from 150 mg once daily to 85 mg once daily (see sections 4.2 and 4.4). Please refer to the Summary of Product Characteristics for Vitekta 85 mg tablets.

Other interactions
Elvitegravir is a modest inducer and may have the potential to induce CYP2C9 and/or inducible UGT enzymes. As such, elvitegravir may decrease the plasma concentration of substrates of CYP2C9 (such as warfarin) or UGT (such as ethinyl estradiol). In addition, *in vitro* studies have shown that elvitegravir is a weak to modest inducer of CYP1A2, CYP2C19 and CYP3A enzymes. Elvitegravir would also have potential to be a weak to modest inducer of CYP2B6 and CYP2C8 enzymes, as these enzymes are regulated in a similar manner to CYP2C9 and CYP3A. However, clinical data have shown there are no clinically relevant changes in the exposure of methadone (which is primarily metabolised by CYP2B6 and CYP2C19) following co-administration with boosted elvitegravir *versus* administration of methadone alone (see Table 2).

Elvitegravir is a substrate for OATP1B1 and OATP1B3, and an inhibitor of OATP1B3 *in vitro*. The *in vivo* relevance of these interactions is not clear.

Interactions between elvitegravir and potential co-administered medicinal products are listed in Table 2 below (increase is indicated as "↑", decrease as "↓", no change as "↔"). These interactions are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of therapeutic effect.

Where interactions were studied, the effect on Vitekta was determined by comparing the pharmacokinetics of boosted elvitegravir (using either ritonavir or cobicistat as a pharmacokinetic enhancer) in the absence and presence of the co-administered medicinal product. No interactions were studied using unboosted elvitegravir. Except where indicated in Table 2, the dose of boosted elvitegravir or co-administered medicinal product was the same when administered alone or in

combination. The pharmacokinetic parameters of the protease inhibitors presented in Table 2 were assessed in the presence of ritonavir.

Although there may be no actual or predicted interactions between a medicinal product and elvitegravir, there may be interactions between a medicinal product and ritonavir and/or the protease inhibitor co-administered with elvitegravir. The prescriber should always refer to the Summary of Product Characteristics for ritonavir, or the protease inhibitor.

Table 2: Interactions between elvitegravir and other medicinal products

Medicinal product by therapeutic areas	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with ritonavir-boosted elvitegravir
ANTIRETROVIRALS		
HIV protease inhibitors		
Atazanavir (300 mg once daily) Elvitegravir (200 mg once daily) Ritonavir (100 mg once daily)	Atazanavir/Ritonavir has been shown to significantly increase the plasma concentrations of elvitegravir. Elvitegravir: AUC: ↑ 100% C_{max}: ↑ 85% C_{min}: ↑ 188% Atazanavir: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 35%	When used in combination with atazanavir, the dose of Vitekta should be 85 mg once daily. When used in combination with Vitekta, the recommended dose of atazanavir is 300 mg with ritonavir 100 mg once daily. There are no data available to make dosing recommendations for co-administration with other doses of atazanavir (see section 4.2).
Atazanavir (300 mg once daily) Elvitegravir (85 mg once daily) Ritonavir (100 mg once daily)	Elvitegravir: AUC: ↔* C_{max}: ↔* C_{min}: ↑ 38%* Atazanavir: AUC: ↔** C_{max}: ↔** C_{min}: ↔** *when compared to elvitegravir/ritonavir 150/100 mg once daily. **when compared to atazanavir/ritonavir 300/100 mg once daily.	
Darunavir (600 mg twice daily) Elvitegravir (125 mg once daily) Ritonavir (100 mg twice daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 17%	When used in combination with darunavir, the dose of Vitekta should be 150 mg once daily. There are no data available to make dosing recommendations for co-administration with other doses of darunavir (see section 4.2).

Fosamprenavir (700 mg twice daily) Elvitegravir (125 mg once daily) Ritonavir (100 mg twice daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Fosamprenavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔	When used in combination with fosamprenavir, the dose of Vitekta should be 150 mg once daily. There are no data available to make dosing recommendations for co-administration with other doses of fosamprenavir (see section 4.2).
Lopinavir/Ritonavir (400/100 mg twice daily) Elvitegravir (125 mg once daily)	Lopinavir/Ritonavir has been shown to significantly increase the plasma concentrations of elvitegravir. Elvitegravir: AUC: ↑ 75% C_{max}: ↑ 52% C_{min}: ↑ 138% Lopinavir: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 8%	When used in combination with lopinavir/ritonavir, the dose of Vitekta should be 85 mg once daily. There are no data available to make dosing recommendations for co-administration with other doses of lopinavir/ritonavir (see section 4.2).
Tipranavir (500 mg twice daily) Elvitegravir (200 mg once daily) Ritonavir (200 mg twice daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tipranavir: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 11%	Due to insufficient clinical data, the combination of elvitegravir with tipranavir is not recommended (see section 4.2).
NRTIs		
Didanosine (400 mg once daily) Elvitegravir (200 mg once daily) Ritonavir (100 mg once daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Didanosine: AUC: ↓ 14% C_{max}: ↓ 16%	As didanosine is administered on an empty stomach, didanosine should be administered at least one hour before or two hours after Vitekta (which is administered with food). Clinical monitoring is recommended.
Zidovudine (300 mg twice daily) Elvitegravir (200 mg once daily) Ritonavir (100 mg once daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Zidovudine: AUC: ↔ C_{max}: ↔	No dose adjustment is required when Vitekta is co-administered with zidovudine.
Stavudine (40 mg once daily) Elvitegravir (200 mg once daily) Ritonavir (100 mg once daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Stavudine: AUC: ↔ C_{max}: ↔	No dose adjustment is required when Vitekta is co-administered with stavudine.

Abacavir (600 mg once daily) Elvitegravir (200 mg once daily) Ritonavir (100 mg once daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Abacavir: AUC: ↔ C_{max}: ↔	No dose adjustment is required when Vitekta is co-administered with abacavir.
Tenofovir disoproxil fumarate (300 mg once daily) Emtricitabine (200 mg once daily) Elvitegravir (50 mg once daily) Ritonavir (100 mg once daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔	No dose adjustment is required when Vitekta is co-administered with tenofovir disoproxil fumarate or with emtricitabine.
NNRTIs		
Efavirenz	Interaction not studied with elvitegravir. Co-administration of efavirenz and elvitegravir is expected to decrease elvitegravir plasma concentrations which may result in loss of therapeutic effect and possible development of resistance.	Co-administration is not recommended (see section 4.4).
Etravirine (200 mg twice daily) Elvitegravir (150 mg once daily) Ritonavir (100 mg once daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Etravirine: AUC: ↔ C_{max}: ↔ C_{min}: ↔	No dose adjustment is required when Vitekta is co-administered with etravirine.
Nevirapine	Interaction not studied with elvitegravir. Co-administration of nevirapine and elvitegravir is expected to decrease elvitegravir plasma concentrations which may result in loss of therapeutic effect and possible development of resistance.	Co-administration is not recommended (see section 4.4).
Rilpivirine	Interaction not studied with elvitegravir.	Co-administration of elvitegravir and rilpivirine is not expected to change elvitegravir plasma concentrations, therefore no dose adjustment of Vitekta is required.

CCR5 antagonists		
Maraviroc (150 mg twice daily) Elvitegravir (150 mg once daily) Ritonavir (100 mg once daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Maraviroc:[§] AUC: ↑ 186% C_{max}: ↑ 115% C_{min}: ↑ 323%	No dose adjustment is required when Vitekta is co-administered with maraviroc. [§]Due to inhibition of CYP3A by ritonavir, maraviroc exposure is significantly increased.
ANTACIDS		
Magnesium/aluminum-containing antacid suspension (20 mL single dose) Elvitegravir (50 mg once daily) Ritonavir (100 mg once daily)	Elvitegravir (antacid suspension given ± 4 hours from elvitegravir administration): AUC: ↔ C_{max}: ↔ C_{min}: ↔ Elvitegravir (simultaneous antacid administration): AUC: ↓ 45% C_{max}: ↓ 47% C_{min}: ↓ 41%	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 Vitekta and antacid administration by at least 4 hours.
FOOD SUPPLEMENTS		
Multivitamin supplements	Interaction not studied with elvitegravir.	As the effect of cationic complexation of elvitegravir cannot be excluded when co-administered with multivitamin supplements, it is recommended to separate Vitekta and multivitamin supplements dosing by at least 4 hours.
NARCOTIC ANALGESICS		
Methadone (80-120 mg once daily) Elvitegravir (150 mg once daily) Cobicistat (150 mg once daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Methadone: AUC: ↔ C_{max}: ↔ C_{min}: ↔	No dose adjustment is required when Vitekta is co-administered with methadone.
Buprenorphine/Naloxone (16/4 mg to 24/6 mg daily) Elvitegravir (150 mg once daily) Cobicistat (150 mg once daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Buprenorphine: AUC: ↑ 35% C_{max}: ↑ 12% C_{min}: ↑ 66% Naloxone: AUC: ↓ 28% C_{max}: ↓ 28%	No dose adjustment is required when Vitekta is co-administered with buprenorphine/naloxone.

ANTI-INFECTIVES		
Antifungals		
Ketoconazole (200 mg twice daily) Elvitegravir (150 mg once daily) Ritonavir (100 mg once daily)	Elvitegravir: AUC: ↑ 48% C_{max}: ↔ C_{min}: ↑ 67% ↑ Ketoconazole[§]	No dose adjustment is required when Vitekta is co-administered with ketoconazole. [§]Due to inhibition of CYP3A by ritonavir, ketoconazole exposure is increased.
Antimycobacterials		
Rifabutin (150 mg once every other day) Elvitegravir (300 mg once daily) Ritonavir (100 mg once daily)	Elvitegravir: AUC: ↔[*] C_{max}: ↔[*] C_{min}: ↔[*] Rifabutin: AUC: ↔[**] C_{max}: ↔[**] C_{min}: ↔[**]	Co-administration of Vitekta 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). No dose adjustment of Vitekta is required when co-administered with reduced dose of 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. [§]Due to inhibition of CYP3A by ritonavir, 25-O-desacetyl-rifabutin exposure is increased.
	25-O-desacetyl-rifabutin:[§] AUC: ↑ 851%[**] C_{max}: ↑ 440%[**] C_{min}: ↑ 1,836%[**] [*]when compared to elvitegravir/ritonavir 300/100 mg once daily. [**]when compared to rifabutin 300 mg once daily. Total antimycobacterial activity was increased by 50%.	
ANTICOAGULANTS		
Warfarin	Interaction not studied with elvitegravir. Concentrations of warfarin may be affected upon co-administration with elvitegravir.	It is recommended that the international normalised ratio (INR) be monitored upon co-administration of Vitekta. INR should continue to be monitored during the first weeks following cessation of treatment with Vitekta.
H_2-RECEPTOR ANTAGONISTS		
Famotidine (40 mg once daily) Elvitegravir (150 mg once daily) Cobicistat (150 mg once daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔	No dose adjustment is required when Vitekta is co-administered with famotidine.
HMG-CoA REDUCTASE INHIBITORS		
Rosuvastatin (10 mg single dose) Elvitegravir (150 mg once daily) Cobicistat (150 mg once daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Rosuvastatin: AUC: ↑ 38% C_{max}: ↑ 89% C_{min}: ↑ 43%	No dose adjustment is required when Vitekta is co-administered with rosuvastatin.

Atorvastatin Fluvastatin Pitavastatin Pravastatin	Interaction not studied with elvitegravir. Plasma concentrations of OATP substrates are not expected to change upon co-administration of elvitegravir. Plasma concentrations of elvitegravir are not expected to change upon co-administration of OATP substrates/inhibitors.	No dose adjustment is required when Vitekta is co-administered with atorvastatin, fluvastatin, pitavastatin or pravastatin.
ORAL CONTRACEPTIVES		
Norgestimate (0.180/0.215 mg once daily) Ethinylestradiol (0.025 mg once daily) Elvitegravir (150 mg once daily) Cobicistat (150 mg once daily)[1]	Norgestimate: AUC: ↑ 126% C_{max}: ↑ 108% C_{min}: ↑ 167% Ethinylestradiol: AUC: ↓ 25% C_{max}: ↔ C_{min}: ↓ 44% Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔	Caution should be exercised when co-administering Vitekta and a hormonal contraceptive. The hormonal contraceptive should contain at least 30 µg ethinylestradiol and contain norgestimate as the progestagen or patients should use an alternative reliable method of contraception (see sections 4.4 and 4.6). The long-term effects of substantial increases in progesterone exposure are unknown. Co-administration of elvitegravir with oral contraceptives containing progestagens other than norgestimate has not been studied and therefore should be avoided.
PROTON PUMP INHIBITORS		
Omeprazole (40 mg once daily) Elvitegravir (50 mg once daily Ritonavir (100 mg once daily)	Elvitegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↔	No dose adjustment is required when Vitekta is co-administered with omeprazole.

[1] This study was conducted using the fixed dose combination tablet elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / contraception in males and females
The use of Vitekta must be accompanied by the use of effective contraception (see sections 4.4 and 4.5).

Pregnancy
There are no or limited clinical data with elvitegravir in pregnant women.

Animal studies do not indicate direct or indirect harmful effects of elvitegravir with respect to reproductive toxicity. However, the maximum exposures evaluated in the rabbit were not in excess of those achieved therapeutically (see section 5.3).

Vitekta should not be used during pregnancy unless the clinical condition of the woman requires treatment with elvitegravir.

Breast-feeding
It is unknown whether elvitegravir/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in rats have shown excretion of elvitegravir in milk. A risk to

the newborns/infants cannot be excluded. Therefore, Vitekta should not be used during breast-feeding.

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

Fertility
No human data on the effect of elvitegravir on fertility are available. Animal studies do not indicate harmful effects of elvitegravir on fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
Assessment of adverse reactions is based on data from a controlled clinical study (GS-US-183-0145) in which 712 HIV-1 infected, antiretroviral treatment-experienced adults received elvitegravir (n = 354) or raltegravir (n = 358) each administered with a background regimen consisting of a fully active ritonavir-boosted protease inhibitor and other antiretroviral agents. Of these 712 patients, 543 (269 elvitegravir and 274 raltegravir) and 439 (224 elvitegravir and 215 raltegravir) received at least 48 and 96 weeks of treatment, respectively.

The most frequently reported adverse reactions to elvitegravir were diarrhoea (7.1%) and nausea (4.0%) (see Table 3).

Tabulated summary of adverse reactions
Adverse reactions to elvitegravir from clinical study experience are listed in Table 3 below, by body system organ class and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as common (≥ 1/100 to < 1/10) or uncommon (≥ 1/1,000 to < 1/100).

Table 3: Tabulated summary of adverse reactions to elvitegravir based on experience for 96 weeks from clinical study GS-US-183-0145

Frequency	Adverse reaction
Psychiatric disorders:	
Uncommon	suicidal ideation and suicide attempt (in patients with a pre-existing history of depression or psychiatric illness), depression, insomnia
Nervous system disorders:	
Common	headache
Uncommon	dizziness, paraesthesia, somnolence, dysgeusia
Gastrointestinal disorders:	
Common	abdominal pain, diarrhoea, vomiting, nausea
Uncommon	dyspepsia, abdominal distension, flatulence
Skin and subcutaneous tissue disorders:	
Common	rash
General disorders and administration site conditions:	
Common	fatigue

Description of selected adverse reactions

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

Immune Reactivation Syndrome
In HIV infected patients with severe immune deficiency at the time of initiation of CART, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

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

Diarrhoea
In study GS-US-183-0145, diarrhoea was reported as an adverse reaction in 7.1% of subjects in the elvitegravir group and in 5.3% of subjects in the raltegravir group. In these subjects, diarrhoea was mild to moderate in severity and did not result in discontinuation of study drug.

Paediatric population
No data are available for children below 18 years of age. Vitekta is not recommended in this population (see section 4.2).

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

4.9 Overdose

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

There is no specific antidote for overdose with elvitegravir. As elvitegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, other antivirals, ATC code: J05AX11.

Mechanism of action and pharmacodynamic effects
Elvitegravir is an HIV-1 integrase strand transfer inhibitor (INSTI). Integrase is an HIV-1 encoded enzyme that is required for viral replication. Inhibition of integrase prevents the integration of HIV-1 DNA into host genomic DNA, blocking the formation of the HIV-1 provirus and propagation of the viral infection. Elvitegravir does not inhibit human topoisomerases I or II.

Antiviral activity *in vitro*
The antiviral activity of elvitegravir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cells, monocyte/macrophage cells, and peripheral blood lymphocytes and the 50% effective concentration (EC_{50}) values were in the range of 0.02 to 1.7 nM. Elvitegravir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values ranged from 0.1 to 1.3 nM) and activity against HIV-2 (EC_{50} of 0.53 nM). The *in vitro* antiviral activity of elvitegravir when combined with antiretroviral drugs from the nucleos(t)ide reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI),

integrase strand transfer inhibitor, fusion inhibitor, or CCR5 co-receptor antagonist classes showed no antagonism.

Elvitegravir did not show inhibition of replication of HBV or HCV *in vitro*.

Resistance

In cell culture

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

Cross resistance

Elvitegravir-resistant viruses show varying degrees of cross-resistance to the integrase strand transfer inhibitor raltegravir depending on the type and number of substitutions. Viruses expressing the T66I/A substitutions maintain susceptibility to raltegravir, while most other patterns of elvitegravir-associated substitutions are associated with reduced susceptibility to raltegravir. With the exception of Y143C/R/H, HIV-1 with the primary raltegravir-associated substitutions T66K, Q148H/K/R, or N155H in integrase is associated with reduced susceptibility to elvitegravir.

In treatment-experienced patients

In an analysis of HIV-1 isolates from treatment-failure subjects in study GS-US-183-0145 through week 96, the development of one or more primary elvitegravir resistance associated substitutions was observed in 23 of the 86 subjects with evaluable genotypic data from paired baseline and elvitegravir treatment-failure isolates (23/351 elvitegravir-treated subjects, 6.6%). Similar rates of raltegravir resistance development occurred in the HIV-1 from subjects treated with raltegravir (26/351 raltegravir-treated subjects, 7.4%). The most common substitutions that emerged in HIV-1 isolates from elvitegravir-treated subjects were T66I/A (n = 8), E92Q/G (n = 7), T97A (n = 4), S147G (n = 4), Q148R (n = 4), and N155H (n = 5) in integrase. In phenotypic analyses of HIV-1 isolates with resistance substitutions from elvitegravir-treated subjects, 14/20 (70%) had reduced susceptibility to elvitegravir and 12/20 (60%) had reduced susceptibility to raltegravir.

Clinical experience

In treatment-experienced HIV-1 infected patients

The efficacy of elvitegravir is primarily based on the analyses through 96 weeks from one randomised, double-blind, active-controlled study, study GS-US-183-0145, in treatment-experienced, HIV-1 infected patients (n = 702).

In study GS-US-183-0145, patients were randomised in a 1:1 ratio to receive either elvitegravir (150 mg or 85 mg) once daily or raltegravir 400 mg twice daily, each administered with a background regimen (BR) containing a fully-active ritonavir-boosted protease inhibitor (either atazanavir, darunavir, fosamprenavir, lopinavir or tipranavir) and a second agent. The BR was selected by the investigator based on genotypic/phenotypic resistance testing and prior antiretroviral treatment history. Randomisation was stratified by screening HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) and the class of the second agent (NRTI or other classes). Virologic response rate was evaluated in both treatment arms. Virologic response was defined as achieving an undetectable viral load (HIV-1 RNA < 50 copies/mL).

Baseline characteristics and treatment outcomes through 96 weeks for study GS-US-183-0145 are presented in Tables 4 and 5 respectively.

Table 4: Demographic and baseline disease characteristics of antiretroviral treatment-experienced HIV-1 infected adult subjects in study GS-US-183-0145

	Elvitegravir + background regimen n = 351	Raltegravir + background regimen n = 351
Demographic characteristics		
Median age, years (min-max)	44 (20-78)	45 (19-74)
Sex		
Male	83.2%	80.9%
Female	16.8%	19.1%
Ethnicity		
White	60.1%	64.4%
Black/African American	35.6%	32.2%
Asian	2.6%	1.4%
Other	1.7%	2.0%
Baseline disease characteristics		
Median baseline plasma HIV-1 RNA (range) log_{10} copies/mL	4.35 (1.69-6.63)	4.42 (1.69-6.10)
Percentage of subjects with viral load > 100,000 copies/mL	25.6	25.6
Median baseline CD4+ cell count (range), cells/mm^3	227.0 (2.0-1,374.0)	215.0 (1.0-1,497.0)
Percentage of subjects with CD4+ cell counts ≤ 200 cells/mm^3	44.4	44.9
Baseline genotypic sensitivity score[a]		
0	1%	< 1%
1	14%	15%
2	81%	83%
3	3%	2%

a Genotypic sensitivity scores are calculated by summing up drug susceptibility values (1 = sensitive; 0 = reduced susceptibility) on all drugs in the baseline background regimen.

Table 5: Virologic outcome of randomised treatment of study GS-US-183-0145 at week 48 and week 96 (snapshot analysis)[a]

	Week 48		Week 96	
	Elvitegravir + background regimen n = 351	**Raltegravir + background regimen n = 351**	**Elvitegravir + background regimen n = 351**	**Raltegravir + background regimen n = 351**
Virologic success HIV-1 RNA < 50 copies/mL	60%	58%	52%	53%
Treatment difference	2.2% (95% CI = -5.0%, 9.3%)		-0.5% (95% CI = -7.9%, 6.8%)	
Virologic failure[b]	33%	32%	36%	31%
No virologic data at week 48 or week 96 window	7%	11%	12%	16%
Discontinued study drug due to AE or death[c]	2%	5%	3%	7%
Discontinued study drug	4%	5%	8%	9%

	Week 48		Week 96	
	Elvitegravir + background regimen n = 351	**Raltegravir + background regimen n = 351**	**Elvitegravir + background regimen n = 351**	**Raltegravir + background regimen n = 351**
due to other reasons and last available HIV-1 RNA < 50 copies/mL[d]				
Missing data during window but on study drug	1%	1%	1%	1%

a Week 48 window is between day 309 and 364 (inclusive), week 96 window is between day 645 and 700 (inclusive)
b Includes subjects who had ≥ 50 copies/mL in the week 48 or week 96 window, subjects who discontinued early due to lack or loss of efficacy, subjects who had a viral load ≥ 50 copies/mL at time of change in background regimen, subjects who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral load of ≥ 50 copies/mL.
c Includes patients who discontinued due to an AE or death at any time point from day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
d Includes subjects who discontinued for reasons other than an AE, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

Elvitegravir was non-inferior in achieving HIV-1 RNA < 50 copies/mL when compared to raltegravir.

Among subjects with a genotypic sensitivity score of ≤ 1, 76% and 69% had HIV-1 RNA < 50 copies/mL at week 48 in the elvitegravir and raltegravir treatment arms, respectively. Among subjects with a genotypic sensitivity score > 1, 57% and 56% had HIV-1 RNA < 50 copies/mL at week 48 in the elvitegravir and raltegravir treatment arms, respectively.

In study GS-US-183-0145, the mean increase from baseline in CD4+ cell count at week 96 was 205 cells/mm^3 in the elvitegravir-treated patients and 198 cells/mm^3 in the raltegravir-treated patients.

In study GS-US-183-0145, subgroup analyses by co-administered protease inhibitor showed similar rates of virologic success for elvitegravir and raltegravir within each protease inhibitor subgroup at weeks 48 and 96 (HIV-1 RNA < 50 copies/mL) (Table 6).

Table 6: Virologic success by co-administered protease inhibitor in study GS-US-183-0145 at week 48 and week 96 (snapshot analysis)

			Elvitegravir *versus* raltegravir
HIV-1 RNA < 50 copies/mL, n/N (%)	**Elvitegravir (N = 351)**	**Raltegravir (N = 351)**	**Difference in percentages (95% CI)[a]**
Virologic success at week 48			
Darunavir/ritonavir	126/202 (62.4%)	122/207 (58.9%)	3.4% (-6.0% to 12.9%)
Lopinavir/ritonavir	39/68 (57.4%)	37/68 (54.4%)	2.9% (-13.7% to 19.6%)
Atazanavir/ritonavir	34/61 (55.7%)	28/51 (54.9%)	0.8% (-17.7% to 19.3%)
Fosamprenavir/ritonavir	8/14 (57.1%)	10/18 (55.6%)	1.6% (-33.0% to 36.2%)
Tipranavir/ritonavir	3/6 (50.0%)	5/7 (71.4%)	-21.4% (-73.6% to 30.7%)
Virologic success at week 96			
Darunavir/ritonavir	105/202 (52.0%)	112/207 (54.1%)	-2.1% (-11.8% to 7.5%)
Lopinavir/ritonavir	36/68 (52.9%)	37/68 (54.4%)	-1.5% (-18.2% to 15.3%)
Atazanavir/ritonavir	33/61 (54.1%)	23/51 (45.1%)	9.0% (-9.5% to 27.5%)
Fosamprenavir/ritonavir	7/14 (50.0%)	11/18 (61.1%)	-11.1% (-45.7% to 23.4%)
Tipranavir/ritonavir	3/6 (50.0%)	3/7 (42.9%)	7.1% (-47.1% to 61.4%)

a The difference in proportions and its 95% CIs between randomised treatment groups is based on normal approximation.

Although limited by the small number of female subjects in study GS-US-183-0145, subgroup analysis by gender showed that the rates of virologic success in female subjects at weeks 48 and 96 (HIV-1 RNA < 50 copies/mL) were numerically lower in the elvitegravir treatment arm than in the raltegravir treatment arm. Virologic success rates at week 48 for elvitegravir and raltegravir were 47.5% (28/59) and 62.7% (42/67) (difference: -12.3% [95% CI: -30.1% to 5.5%]), respectively, for female subjects, and 62.3% (182/292) and 56.3% (160/284) (difference: 5.3% [95% CI: -2.5% to 13.2%]), respectively, for male subjects. Virologic success rates at week 96 for elvitegravir and raltegravir were 39.0% (23/59) and 52.2% (35/67) (difference: -8.4% [95% CI: -26.1% to 9.2%]), respectively, for female subjects, and 55.1% (161/292) and 53.2% (151/284) (difference: 1.5% [95% CI: -6.5% to 9.6%]), respectively, for male subjects.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with elvitegravir in one or more subsets of the paediatric population in the treatment of HIV-1 infection (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Following oral administration of ritonavir-boosted elvitegravir with food in HIV-1 infected subjects, elvitegravir peak plasma concentrations were observed 4 hours post-dose. The steady-state mean C_{max}, AUC_{tau}, and C_{trough} (mean ± SD) following multiple doses of elvitegravir plus a ritonavir-boosted protease inhibitor (150 mg elvitegravir with darunavir or fosamprenavir; 85 mg elvitegravir with atazanavir or lopinavir) in HIV-1 infected subjects were 1.4 ± 0.39 µg/mL, 18 ± 6.8 µg•h/mL, and 0.38 ± 0.22 µg/mL for elvitegravir, respectively. The absolute oral bioavailability has not been determined.

Relative to fasting conditions, the administration of boosted elvitegravir as the fixed-dose combination 150 mg elvitegravir/150 mg cobicistat/200 mg emtricitabine/245 mg tenofovir disoproxil with a light meal (approximately 373 kcal, 20% fat) or high-fat meal (approximately 800 kcal, 50% fat) resulted in increased exposures of elvitegravir. The C_{max} and AUC_{tau} of elvitegravir increased 22% and 36% with a light meal, while increasing 56% and 91% with a high-fat meal, respectively.

Distribution
Elvitegravir is 98-99% bound to human plasma proteins and the binding is independent of drug concentration over the range of 1.0 ng/mL to 1.6 µg/mL. The mean plasma to blood drug concentration ratio is 1.37.

Biotransformation
Elvitegravir undergoes oxidative metabolism by CYP3A (major route), and glucuronidation via UGT1A1/3 enzymes (minor route).

Ritonavir inhibits CYP3A, thereby substantially increasing the plasma concentrations of elvitegravir. Administration of once-daily ritonavir (20-200 mg) results in an increased elvitegravir exposure following repeat once-daily administration, with elvitegravir exposure reaching a plateau with approximately 100 mg of ritonavir. Further increases in ritonavir dose do not result in further increases in elvitegravir exposure. Vitekta is indicated for use only when co-administered with ritonavir as a boosting agent.

Mean steady-state exposure (AUC_{tau}) of unboosted elvitegravir is ~ 20% lower after multiple dosing *versus* a single dose, indicating modest autoinduction of its metabolism. Upon boosting with ritonavir (100 mg), net inhibition of elvitegravir metabolism is observed with significantly increased systemic exposures (20-fold higher AUC), high trough concentrations, and longer median elimination half-life (9.5 *versus* 3.5 hours).

Following oral administration of a single dose of ritonavir-boosted [^{14}C]elvitegravir, elvitegravir was the predominant species in plasma, representing approximately 94% and 61% of the circulating radioactivity at 32 and 48 hours, respectively. Metabolites produced by aromatic and aliphatic hydroxylation or glucuronidation are present in very low levels and do not contribute to the overall antiviral activity of elvitegravir.

Elimination
Following oral administration of ritonavir-boosted [^{14}C]elvitegravir, 94.8% of the dose was recovered in faeces, consistent with the hepatobiliary elimination of elvitegravir; 6.7% of the administered dose was recovered in urine as metabolites. The median terminal plasma half-life of ritonavir-boosted elvitegravir is approximately 8.7 to 13.7 hours.

Linearity/non-linearity
Elvitegravir plasma exposures are non-linear and less than dose-proportional, likely due to solubility-limited absorption.

Elderly
Pharmacokinetics of elvitegravir have not been fully evaluated in the elderly (over 65 years of age).

Gender
No clinically relevant pharmacokinetic differences due to gender have been identified for boosted elvitegravir.

Ethnicity
No clinically relevant pharmacokinetic differences due to ethnicity have been identified for boosted elvitegravir.

Paediatric population
The pharmacokinetics of elvitegravir in paediatric subjects have not been established.

Renal impairment
A study of the pharmacokinetics of boosted elvitegravir was performed in non HIV-1 infected subjects with severe renal impairment (estimated creatinine clearance below 30 mL/min). No clinically relevant differences in elvitegravir pharmacokinetics were observed between subjects with severe renal impairment and healthy subjects. No dose adjustment of Vitekta is required for patients with renal impairment.

Hepatic impairment
Elvitegravir is primarily metabolised and eliminated by the liver. A study of the pharmacokinetics of boosted elvitegravir was performed in non-HIV-1 infected subjects with moderate hepatic impairment (Child-Pugh Class B). No clinically relevant differences in elvitegravir pharmacokinetics were observed between subjects with moderate impairment and healthy subjects. No dose adjustment of Vitekta is necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of elvitegravir has not been studied.

Hepatitis B and/or hepatitis C virus co-infection
Limited data from population pharmacokinetic analysis (n = 56) indicated that hepatitis B and/or C virus infection had no clinically relevant effect on the exposure of boosted elvitegravir.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. The maximum doses of elvitegravir tested in the development toxicity studies in rats and rabbits corresponded to exposures that are approximately 29-fold and 0.2-fold the human therapeutic exposure, respectively.

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.

Elvitegravir did not show any carcinogenic potential in long-term oral carcinogenicity studies in mice and rats.

The active substance elvitegravir is persistent in the environment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Croscarmellose sodium
Hydroxypropyl cellulose
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose
Sodium lauryl sulfate

Film-coating
Indigo carmine aluminium lake (E132)
Macrogol 3350 (E1521)
Polyvinyl alcohol (partially hydrolysed) (E1203)
Talc (E553B)
Titanium dioxide (E171)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with a child-resistant closure containing 30 film-coated tablets.

Pack size: 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. MARKETING AUTHORISATION HOLDER

Gilead Sciences International Limited
Cambridge
CB21 6GT
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/883/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 November 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Gilead Sciences Ireland UC
IDA Business & Technology Park
Carrigtohill
County Cork
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

BOTTLE AND CARTON LABELLING

1. NAME OF THE MEDICINAL PRODUCT

Vitekta 85 mg film-coated tablets
Elvitegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 85 mg of elvitegravir.

3. LIST OF EXCIPIENTS

Contains lactose, see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets.
30 tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Intl Ltd
Cambridge
CB21 6GT
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/883/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vitekta 85 mg [Outer packaging only]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

BOTTLE AND CARTON LABELLING

1. NAME OF THE MEDICINAL PRODUCT

Vitekta 150 mg film-coated tablets
Elvitegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg of elvitegravir.

3. LIST OF EXCIPIENTS

Contains lactose, see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets.
30 tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Intl Ltd
Cambridge
CB21 6GT
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/883/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vitekta 150 mg [Outer packaging only]

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Vitekta 85 mg film-coated tablets
Elvitegravir

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Vitekta is and what it is used for

Vitekta contains the active substance elvitegravir.

Vitekta is a **treatment for human immunodeficiency virus (HIV) infection** in adults aged 18 years and over.

Vitekta must always be taken with certain other HIV medicines. See section 3, *How to take Vitekta*.

The HIV virus produces an enzyme called HIV integrase. This enzyme helps the virus to multiply in the cells in your body. Vitekta stops this enzyme working and reduces the amount of HIV in your body. This will improve your immune system and reduce the risk of developing illnesses linked to HIV infection.

This medicine is not a cure for HIV infection. While taking Vitekta you may still develop infections or other illnesses associated with HIV infection.

2. What you need to know before you take Vitekta

Do not take Vitekta

- **if you are allergic to elvitegravir** or any of the other ingredients of this medicine (listed in section 6 of this leaflet).

- **if you are taking one of these medicines:**
  - **carbamazepine, phenobarbital, phenytoin,** used to treat epilepsy and prevent seizures
  - **rifampicin,** used to prevent and treat tuberculosis and other infections
  - **St. John's wort** (*Hypericum perforatum*), a herbal remedy used for depression and anxiety, or products that contain it

→ If any of these applies to you, do not take Vitekta and tell your doctor immediately.

Warnings and precautions

Your treatment with Vitekta should only be started by a doctor who is experienced in treating HIV infection.

You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your doctor the precautions needed to avoid infecting other people. This medicine is not a cure for HIV infection. While taking Vitekta you may still develop infections or other illnesses associated with HIV infection.

Talk to your doctor before taking Vitekta:

- **If you have liver problems or a history of liver disease, including hepatitis.** Patients with liver disease including chronic hepatitis B or C, who are treated with antiretrovirals, have a higher risk of severe and potentially fatal liver complications. If you have hepatitis B infection, your doctor will carefully consider the best treatment for you.

→ If any of these applies to you, talk to your doctor before taking Vitekta.

While you are taking Vitekta

Look out for the following:

- **any signs of inflammation or infection**

- **bone problems**

→ If you notice any of these symptoms, tell your doctor immediately. For more information see section 4 of this leaflet.

Children and adolescents

- **Do not give this medicine to children** and adolescents under 18 years of age. The use of Vitekta in children and adolescents has not yet been studied.

Other medicines and Vitekta

Tell your doctor or pharmacist if you are taking, plan to take, or have recently taken any other medicines. This includes medicines and herbal products obtained without a prescription. Vitekta may interact with other medicines which can affect the amounts of Vitekta or other medicines in your blood. This may stop your medicines from working properly, or may make any side effects worse.

Medicines that should never be taken with Vitekta:
- **carbamazepine, phenobarbital, phenytoin,** used to treat epilepsy and prevent seizures
- **rifampicin,** used to prevent and treat tuberculosis and other infections
- **St. John's wort** (*Hypericum perforatum*), a herbal remedy used for depression and anxiety, or products that contain it

Other medicines used in treating HIV infection:
You should not take Vitekta with other medicines containing:
- **cobicistat**
- **elvitegravir**

Talk to your doctor if you are taking:
- **efavirenz**
- **nevirapine**
- **didanosine** (see also section 3 of this leaflet)

→ **Tell your doctor** if you are taking any of these HIV medicines.

Other types of medicine:
Talk to your doctor if you are taking:
- **rifabutin,** used to treat bacterial infections including tuberculosis
- **warfarin,** used to thin the blood
- **contraceptive pill,** used to prevent pregnancy
- **bosentan,** used to treat pulmonary arterial hypertension
- **antacids,** used to treat heartburn or acid reflux, such as aluminium/magnesium hydroxide or calcium carbonate (see also section 3 of this leaflet)
- **multivitamins,** used to supplement your diet (see also section 3 of this leaflet).

→ **Tell your doctor** if any of these apply to you.

→ **Tell your doctor if you are taking these or any other medicines.** Do not stop your treatment without contacting your doctor.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

- **Women must not get pregnant** while taking Vitekta.
- Use effective contraception while taking Vitekta.
- **Tell your doctor immediately if you become pregnant.** If you are pregnant, you should not take Vitekta unless you and your doctor decide it is clearly needed. Your doctor will discuss the potential benefits and risks of taking Vitekta to you and your child.

Do not breast-feed during treatment with Vitekta: It is not known if the active substance in this medicine can pass into human breast milk. If you are a woman with HIV it is recommended that you do not breast-feed to avoid passing the virus to the baby in breast milk.

Vitekta contains lactose

Tell your doctor if you are lactose intolerant or intolerant to other sugars. Vitekta contains lactose. If you are lactose-intolerant, or if you have been told that you have an intolerance to other sugars, talk to your doctor before taking this medicine.

3. How to take Vitekta

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. This is to make sure that your medicine is fully effective, and to reduce the risk of developing resistance to the treatment. Do not change the dose unless your doctor tells you to.

You must always take Vitekta with one of the following combinations of medicines:

- atazanavir and ritonavir
- darunavir and ritonavir

- fosamprenavir and ritonavir
- lopinavir/ritonavir

A dose of 85 mg is recommended:
If you are taking Vitekta with:
- atazanavir and ritonavir
- lopinavir/ritonavir

In these combinations the dose is one 85 mg tablet each day, with food. Do not chew, crush or split the tablet. Take the 85 mg tablet at the same time as atazanavir and ritonavir, or at the same time as the first dose of lopinavir/ritonavir.

A dose of 150 mg is recommended:
If you are taking Vitekta with:
- darunavir and ritonavir
- fosamprenavir and ritonavir

In these combinations the dose is one 150 mg tablet each day, with food. Do not chew, crush or split the tablet. Take the 150 mg tablet at the same time as the first dose of darunavir or fosamprenavir and ritonavir. Refer to the package leaflet for Vitekta 150 mg tablets.

If you are also taking other medicines:

If you are also taking didanosine, take it at least 1 hour before or at least 2 hours after Vitekta.

If you are also taking an antacid such as aluminium/magnesium hydroxide or calcium carbonate, or a **multivitamin supplement,** take it at least 4 hours before or at least 4 hours after Vitekta.

If you take more Vitekta than you should

If you accidentally take more than the recommended dose of Vitekta you may be at increased risk of experiencing possible side effects with this medicine (see section 4 of this leaflet).

Contact your doctor or nearest emergency department immediately for advice. Keep the tablet bottle with you so that you can easily describe what you have taken.

If you forget to take Vitekta

It is important not to miss a dose of Vitekta.

If you do miss a dose:
- **If you notice within 18 hours** of the time you usually take Vitekta, you must take the tablet as soon as possible. Always take the tablet with food. Then take the next dose as usual.
- **If you notice 18 hours or more** after the time you usually take Vitekta, then do not take the missed dose. Wait and take the next dose, with food, at your usual time.

If you vomit less than 1 hour after taking Vitekta, take another tablet with food.

Do not stop taking Vitekta

Do not stop taking Vitekta without talking to your doctor. Stopping Vitekta can seriously affect your response to future treatment. If Vitekta is stopped for any reason, speak to your doctor before you restart taking Vitekta tablets.

When your supply of Vitekta starts to run low, get more from your doctor or pharmacist. This is very important because the amount of virus may start to increase if the medicine is stopped for even a short time. The disease may then become harder to treat.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Like all medicines, this medicine can cause side effects, although not everybody gets them. When treating HIV infection, it is not always possible to tell whether some of the unwanted effects are caused by Vitekta or by other medicines that you are taking at the same time, or by the HIV infection itself.

Common side effects
(may affect 1 to 10 in every 100 patients treated)
- stomach pain
- vomiting
- rashes
- headache
- diarrhoea
- feeling sick *(nausea)*
- tiredness.

Uncommon side effects
(may affect up to 1 in every 100 patients treated)
- suicidal thoughts and suicide attempts (in patients who have had depression or mental health problems before)
- depression
- difficulty sleeping *(insomnia)*
- problems with digestion resulting in discomfort after meals *(dyspepsia)*
- feeling bloated
- wind *(flatulence)*
- dizziness
- tingling
- sleepiness
- abnormal taste.

→ If you think that you may have any of these side effects, talk to your doctor.

Other effects that may be seen during HIV treatment
The frequency of the following side effects is not known (frequency cannot be estimated from the available data):

Any signs of inflammation or infection. If you have advanced HIV infection (AIDS) and have an infection, you may develop symptoms of infection and inflammation or worsening of the symptoms of an existing infection once treatment with Vitekta is started. These symptoms may indicate that your body's improved immune system is fighting infection. Look out for signs of inflammation or infection soon after you start taking Vitekta. If you notice signs of inflammation or infection, **tell your doctor at once.** In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the

hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

- **Bone problems.** Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are:
  - joint stiffness
  - joint aches and pains (especially of the hip, knee and shoulder)
  - difficulty with movement.

  If you notice any of these symptoms, **tell your doctor.**

Reporting of side effects

→ **If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.** You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Vitekta

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle and carton after {EXP}. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Vitekta contains

The active substance is elvitegravir. Each film-coated tablet contains 85 mg elvitegravir.

The other ingredients are

Tablet core:
Croscarmellose sodium, hydroxypropyl cellulose, lactose (as monohydrate), magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate.

Film coating:
Indigo carmine aluminium lake (E132), macrogol 3350 (E1521), polyvinyl alcohol (partially hydrolysed) (E1203), talc (E553B), titanium dioxide (E171), iron oxide yellow (E172).

What Vitekta looks like and contents of the pack

Vitekta film-coated tablets are green, pentagon-shaped tablets, debossed on one side with "GSI" and "85" on the other side of the tablet.

The following pack size is available: outer cartons containing 1 bottle of 30 film-coated tablets.

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Manufacturer
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This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Package leaflet: Information for the patient

Vitekta 150 mg film-coated tablets
Elvitegravir

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Vitekta is and what it is used for

Vitekta contains the active substance elvitegravir.

Vitekta is a **treatment for human immunodeficiency virus (HIV) infection** in adults aged 18 years and over.

Vitekta must always be taken with certain other HIV medicines. See section 3, *How to take Vitekta*.

The HIV virus produces an enzyme called HIV integrase. This enzyme helps the virus to multiply in the cells in your body. Vitekta stops this enzyme working and reduces the amount of HIV in your body. This will improve your immune system and reduce the risk of developing illnesses linked to HIV infection.

This medicine is not a cure for HIV infection. While taking Vitekta you may still develop infections or other illnesses associated with HIV infection.

2. What you need to know before you take Vitekta

Do not take Vitekta

- **if you are allergic to elvitegravir** or any of the other ingredients of this medicine (listed in section 6 of this leaflet).

- **if you are taking one of these medicines:**
  - **carbamazepine, phenobarbital, phenytoin,** used to treat epilepsy and prevent seizures
  - **rifampicin,** used to prevent and treat tuberculosis and other infections
  - **St. John's wort** (*Hypericum perforatum*), a herbal remedy used for depression and anxiety, or products that contain it

→ If any of these applies to you, do not take Vitekta and tell your doctor immediately.

Warnings and precautions

Your treatment with Vitekta should only be started by a doctor who is experienced in treating HIV infection.

You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your doctor the precautions needed to avoid infecting other people. This medicine is not a cure for HIV infection. While taking Vitekta you may still develop infections or other illnesses associated with HIV infection.

Talk to your doctor before taking Vitekta:

- **If you have liver problems or a history of liver disease, including hepatitis.** Patients with liver disease including chronic hepatitis B or C, who are treated with antiretrovirals, have a higher risk of severe and potentially fatal liver complications. If you have hepatitis B infection, your doctor will carefully consider the best treatment for you.

→ If any of these applies to you, talk to your doctor before taking Vitekta.

While you are taking Vitekta

Look out for the following:

- **any signs of inflammation or infection**

- **bone problems**

→ If you notice any of these symptoms, tell your doctor immediately. For more information see section 4 of this leaflet.

Children and adolescents

- **Do not give this medicine to children** and adolescents under 18 years of age. The use of Vitekta in children and adolescents has not yet been studied.

Other medicines and Vitekta

Tell your doctor or pharmacist if you are taking, plan to take, or have recently taken any other medicines. This includes medicines and herbal products obtained without a prescription. Vitekta may interact with other medicines which can affect the amounts of Vitekta or other medicines in your blood. This may stop your medicines from working properly, or may make any side effects worse.

Medicines that should never be taken with Vitekta:
- **carbamazepine, phenobarbital, phenytoin,** used to treat epilepsy and prevent seizures
- **rifampicin,** used to prevent and treat tuberculosis and other infections
- **St. John's wort** (*Hypericum perforatum*), a herbal remedy used for depression and anxiety, or products that contain it

Other medicines used in treating HIV infection:
You should not take Vitekta with other medicines containing:
- **cobicistat**
- **elvitegravir**

Talk to your doctor if you are taking:
- **efavirenz**
- **nevirapine**
- **didanosine** (see also section 3 of this leaflet)

→ **Tell your doctor** if you are taking any of these HIV medicines.

Other types of medicine:
Talk to your doctor if you are taking:
- **rifabutin,** used to treat bacterial infections including tuberculosis
- **warfarin,** used to thin the blood
- **contraceptive pill,** used to prevent pregnancy
- **bosentan,** used to treat pulmonary arterial hypertension
- **antacids,** used to treat heartburn or acid reflux, such as aluminium/magnesium hydroxide or calcium carbonate (see also section 3 of this leaflet)
- **multivitamins,** used to supplement your diet (see also section 3 of this leaflet).

→ **Tell your doctor** if any of these apply to you.

→ **Tell your doctor if you are taking these or any other medicines.** Do not stop your treatment without contacting your doctor.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

- **Women must not get pregnant** while taking Vitekta.
- Use effective contraception while taking Vitekta.
- **Tell your doctor immediately if you become pregnant.** If you are pregnant, you should not take Vitekta unless you and your doctor decide it is clearly needed. Your doctor will discuss the potential benefits and risks of taking Vitekta to you and your child.

Do not breast-feed during treatment with Vitekta: It is not known if the active substance in this medicine can pass into human breast milk. If you are a woman with HIV it is recommended that you do not breast-feed to avoid passing the virus to the baby in breast milk.

Vitekta contains lactose

Tell your doctor if you are lactose intolerant or intolerant to other sugars. Vitekta contains lactose. If you are lactose-intolerant, or if you have been told that you have an intolerance to other sugars, talk to your doctor before taking this medicine.

3. How to take Vitekta

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. This is to make sure that your medicine is fully effective, and to reduce the risk of developing resistance to the treatment. Do not change the dose unless your doctor tells you to.

You must always take Vitekta with one of the following combinations of medicines:

- atazanavir and ritonavir
- darunavir and ritonavir

- fosamprenavir and ritonavir
- lopinavir/ritonavir

A dose of 150 mg is recommended:
If you are taking Vitekta with:
- darunavir and ritonavir
- fosamprenavir and ritonavir

In these combinations the dose is one 150 mg tablet each day, with food. Do not chew, crush or split the tablet. Take the 150 mg tablet at the same time as the first dose of darunavir or fosamprenavir and ritonavir.

A dose of 85 mg is recommended:
If you are taking Vitekta with:
- atazanavir and ritonavir
- lopinavir/ritonavir

In these combinations the dose is one 85 mg tablet each day, with food. Do not chew, crush or split the tablet. Take the 85 mg tablet at the same time as atazanavir and ritonavir or at the same time as the first dose of lopinavir/ritonavir. Refer to the package leaflet for Vitekta 85 mg tablets.

If you are also taking other medicines:

If you are also taking didanosine, take it at least 1 hour before or at least 2 hours after Vitekta.

If you are also taking an antacid such as aluminium/magnesium hydroxide or calcium carbonate, or a **multivitamin supplement,** take it at least 4 hours before or at least 4 hours after Vitekta.

If you take more Vitekta than you should

If you accidentally take more than the recommended dose of Vitekta you may be at increased risk of experiencing possible side effects with this medicine (see section 4 of this leaflet).

Contact your doctor or nearest emergency department immediately for advice. Keep the tablet bottle with you so that you can easily describe what you have taken.

If you forget to take Vitekta

It is important not to miss a dose of Vitekta.

If you do miss a dose:
- **If you notice within 18 hours** of the time you usually take Vitekta, you must take the tablet as soon as possible. Always take the tablet with food. Then take the next dose as usual.
- **If you notice 18 hours or more** after the time you usually take Vitekta, then do not take the missed dose. Wait and take the next dose, with food, at your usual time.

If you vomit less than 1 hour after taking Vitekta, take another tablet with food.

Do not stop taking Vitekta

Do not stop taking Vitekta without talking to your doctor. Stopping Vitekta can seriously affect your response to future treatment. If Vitekta is stopped for any reason, speak to your doctor before you restart taking Vitekta tablets.

When your supply of Vitekta starts to run low, get more from your doctor or pharmacist. This is very important because the amount of virus may start to increase if the medicine is stopped for even a short time. The disease may then become harder to treat.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Like all medicines, this medicine can cause side effects, although not everybody gets them. When treating HIV infection, it is not always possible to tell whether some of the unwanted effects are caused by Vitekta or by other medicines that you are taking at the same time, or by the HIV infection itself.

Common side effects
(may affect 1 to 10 in every 100 patients treated)
- stomach pain
- vomiting
- rashes
- headache
- diarrhoea
- feeling sick *(nausea)*
- tiredness.

Uncommon side effects
(may affect up to 1 in every 100 patients treated)
- suicidal thoughts and suicide attempts (in patients who have had depression or mental health problems before)
- depression
- difficulty sleeping *(insomnia)*
- problems with digestion resulting in discomfort after meals *(dyspepsia)*
- feeling bloated
- wind *(flatulence)*
- dizziness
- tingling
- sleepiness
- abnormal taste.

→ If you think that you may have any of these side effects, talk to your doctor.

Other effects that may be seen during HIV treatment
The frequency of the following side effects is not known (frequency cannot be estimated from the available data):

Any signs of inflammation or infection. If you have advanced HIV infection (AIDS) and have an infection, you may develop symptoms of infection and inflammation or worsening of the symptoms of an existing infection once treatment with Vitekta is started. These symptoms may indicate that your body's improved immune system is fighting infection. Look out for signs of inflammation or infection soon after you start taking Vitekta. If you notice signs of inflammation or infection, **tell your doctor at once.** In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the

hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

- **Bone problems.** Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are:
  - joint stiffness
  - joint aches and pains (especially of the hip, knee and shoulder)
  - difficulty with movement.

  If you notice any of these symptoms, **tell your doctor.**

Reporting of side effects

→ **If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.** You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Vitekta

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle and carton after {EXP}. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Vitekta contains

The active substance is elvitegravir. Each film-coated tablet contains 150 mg elvitegravir.

The other ingredients are

Tablet core:
Croscarmellose sodium, hydroxypropyl cellulose, lactose (as monohydrate), magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate.

Film coating:
Indigo carmine aluminium lake (E132), macrogol 3350 (E1521), polyvinyl alcohol (partially hydrolysed) (E1203), talc (E553B), titanium dioxide (E171), iron oxide yellow (E172).

What Vitekta looks like and contents of the pack

Vitekta film-coated tablets are green, triangle-shaped tablets, debossed on one side with "GSI" and "150" on the other side of the tablet.

The following pack size is available: outer cartons containing 1 bottle of 30 film-coated tablets.

Marketing Authorisation Holder
Gilead Sciences International Limited
Cambridge
CB21 6GT
United Kingdom

Manufacturer
Gilead Sciences Ireland UC
IDA Business & Technology Park
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