Product Information

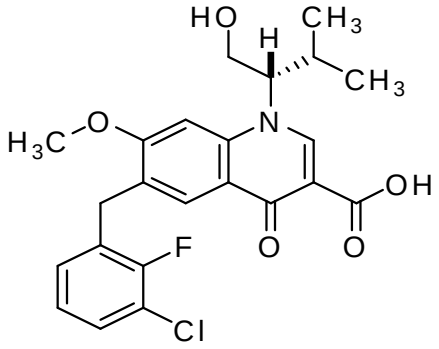
VITEKTA® (elvitegravir) tablets

NAME OF THE MEDICINE
VITEKTA (85 mg and 150 mg elvitegravir) tablets.

The active substances in VITEKTA tablets is elvitegravir.

Elvitegravir is a human immunodeficiency virus-1 (HIV-1) integrase strand transfer inhibitor (INSTI). Elvitegravir is one of the active substances in the single tablet regimen; STRIBILD®.

DESCRIPTION
The chemical name of elvitegravir is 3-quinolinecarboxylic acid, 6-[(3-chloro-2-fluorophenyl)-methyl]-1,4-dihydro-1-[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]-7-methoxy-4-oxo-. It has a molecular formula of $C_{23}H_{23}ClFNO_5$ and a molecular weight of 447.9. It has the following structural formula.



CAS registry number: 697761-98-1

Elvitegravir is a white to pale yellow solid with a solubility of less than 0.3 µg/mL in water at 20 °C. The partition coefficient (logp) for elvitegravir is 4.5 and the pKa is 6.6

VITEKTA tablets contain the following ingredients as <u>excipients:</u>
Tablet core: croscarmellose sodium, hydroxypropylcellulose, lactose monohydrate, magnesium stearate cellulose-microcrystalline, sodium lauryl sulfate.
Film-coating: indigo carmine (FD&C blue #2) aluminum lake, macrogol 3350, polyvinyl alcohol, purified talc titanium dioxide, iron oxide yellow

Each VITEKTA tablet is film-coated and green in colour. The 85 mg tablet is pentagon-shaped debossed with 'GSI' on one side and the number "85" on the other side. The 150 mg tablet is

triangle-shaped debossed with 'GSI' on one side and the number "150" on the other side. The tablets are supplied in bottles with child resistant closures.

PHARMACOLOGY

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

Mechanism of action

Elvitegravir is a 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 antiviral activity of elvitegravir with antiretroviral drugs in two-drug combination studies was additive to synergistic when combined with NRTIs (abacavir, didanosine, emtricitabine, 3TC, d4T, tenofovir, or AZT); NNRTIs (efavirenz, etravirine, or nevirapine); protease inhibitors (amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, or tipranavir); the integrase strand transfer inhibitor raltegravir; the fusion inhibitor enfuvirtide, or the CCR5 co-receptor antagonist, maraviroc. No antagonism was observed for these combinations.

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

Drug Resistance

In Cell Culture:

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

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

In Clinical Studies:

In an analysis of treatment-failure patients in Study GS-US-183-0145 through Week 96, development of one or more primary elvitegravir resistance-associated substitutions was observed in 23 of the 86 patients with evaluable genotypic data from paired baseline and VITEKTA treatment-failure isolates (23/351 elvitegravir-treated patients, 6.6%). Similar rates of

resistance development occurred among patients treated with raltegravir (26/351 raltegravir-treated patients, 7.4%). The most common substitutions that emerged in the VITEKTA-treated patients 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 VITEKTA-treated patients who developed resistance substitutions, 14/20 (70%) patients had HIV-1 isolates with reduced susceptibility to elvitegravir and 12/20 (60%) had reduced susceptibility to raltegravir.

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 mutations. Viruses expressing the T66I/A mutations maintain susceptibility to raltegravir, while most other patterns including E92Q/G, Q148R and N155H showed reduced susceptibility to raltegravir. Raltegravir resistant viruses expressing most primary raltegravir mutations, including Q148H/K/R and N155H, show cross-resistance to elvitegravir, with the exception of Y143 substitutions.

Pharmacodynamics

Effects on Electrocardiogram
In a thorough QT/QTc study in 126 healthy subjects, elvitegravir at a therapeutic dose, or at a supratherapeutic dose approximately 2-fold the recommended therapeutic dose, did not affect the QT/QTc interval and did not prolong the PR interval.

Pharmacokinetics

Absorption
Following oral administration of boosted VITEKTA with food in HIV-1 infected patients, peak plasma concentrations were observed 3-4 hours post-dose for elvitegravir. The steady-state mean C_{max}, $AUC_{tau,}$ and C_{trough} (mean ± SD) following multiple doses of boosted VITEKTA in HIV-1 infected patients, respectively, were 1.4 ± 0.39 µg/mL, 18 ± 6.8 µg•hr/mL, and 0.38 ± 0.22 µg/mL for elvitegravir, with an inhibitory quotient of ~ 8.5 (ratio of C_{trough}: protein binding-adjusted IC95 for wild-type HIV-1 virus).

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

Metabolism
Elvitegravir undergoes primarily oxidative metabolism via CYP3A, and is secondarily glucuronidated via UGT1A1/3 enzymes. Following oral administration of boosted [^{14}C]elvitegravir, elvitegravir was the predominant species in plasma, representing ~ 94% of the circulating radioactivity. Aromatic and aliphatic hydroxylation or glucuronidation metabolites are present in very low levels, display considerably lower anti-HIV activity and do not contribute to the overall antiviral activity of elvitegravir.

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

Effect of food
Relative to fasting conditions, the administration of boosted elvitegravir as STRIBILD with a light meal (~373 kcal, 20% fat) or high-fat meal (~800 kcal, 50% fat) resulted in increased exposures of elvitegravir. The C_{max} and AUC of elvitegravir increased 22% and 34% with a light meal, while increasing to 56% and 87% with a high-fat meal, respectively.

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

Age, Gender and Ethnicity
No clinically relevant pharmacokinetic differences due to ethnicity have been identified for boosted elvitegravir (see PRECAUTIONS).

The pharmacokinetics of elvitegravir in paediatric patients have not been established. Pharmacokinetics of elvitegravir have not been fully evaluated in the elderly (65 years of age and older).

No clinically relevant pharmacokinetic differences have been observed between men and women for boosted elvitegravir

Patients with Impaired Renal Function
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.

Patients with Hepatic Impairment
Elvitegravir is primarily metabolized 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 dosage 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.

Assessment of Drug Interactions

The drug interaction studies described were conducted with VITEKTA coadministered with ritonavir.

Elvitegravir is primarily metabolized by cytochrome CYP3A, and drugs that induce CYP3A may result in decreased plasma concentrations of elvitegravir and reduce the therapeutic effect of VITEKTA.

In drug interaction studies conducted with boosted elvitegravir, there was no clinically significant interaction observed between elvitegravir and abacavir, emtricitabine, etravirine, famotidine, fosamprenavir, omeprazole, stavudine, tenofovir disoproxil fumarate, or zidovudine. The effects of coadministered drugs on the exposure of elvitegravir are shown in Table 1. The effects of elvitegravir on the exposure of coadministered drugs are shown in Table 2.

Table 1. Drug Interactions: Changes in Pharmacokinetic Parameters for Elvitegravir in the Presence of the Coadministered Drug[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose (mg)	Ritonavir Booster Dose	N	% Change of Boosted Elvitegravir Pharmacokinetic Parameters[b,c] (90% CI)		
					C_{max}	AUC	C_{min}
Antacids	20 mL single dose given ± 2 hours or ± 4 hours from elvitegravir administration	50 once daily	100 once daily	39	Û	Û	Û
	20 mL single dose simultaneously administered with elvitegravir	50 once daily	100 once daily	13	¯47 (¯53 to ¯40)	¯45 (¯50 to ¯40)	¯41 (¯48 to ¯33)
Atazanavir	300 once daily	200 once daily	100 once daily	33	- 85 (- 69 to - 103)	- 100 (- 85 to - 116)	- 188 (- 153 to - 227)
	300 once daily	85 once daily	100 once daily	20	Û [d]	Û [d]	- 38[d] (- 18 to - 61)
Darunavir	600 twice daily	125 once daily	100 twice daily	21	Û	Û	Û
Didanosine	400 single dose	200 once daily	100 once daily	32	Û	Û	Û
Ketoconazole	200 twice daily	150 once daily	100 once daily	18	Û	- 48 (- 36 to - 62)	- 67 (- 48 to - 88)
Lopinavir/ ritonavir	400/100 twice daily	125 once daily	NA	14	- 52 (- 29 to - 79)	- 75 (- 50 to - 105)	- 138 (- 81 to - 213)
Maraviroc	150 twice daily	150 once daily	100 once daily	17	Û	Û	Û
Rifabutin	150 once every other day	300 once daily	100 once daily	19	Û	Û	Û
Rosuvastatin	10 single dose	150 single dose	NA[e]	10	Û [f]	Û [f]	Û [f]
Tipranavir	500 twice daily	200 once daily	200 twice daily	26	Û	Û	Û

a. All interaction studies conducted in healthy volunteers
b. - = Increase; ¯ = Decrease; Û = No Effect; NA = Not Applicable
c. The pharmacokinetic parameters of elvitegravir were compared with elvitegravir coadministered with ritonavir 100 mg once daily unless specified otherwise.
d. Comparison based on elvitegravir/ritonavir 150/100 mg once daily.
e. Study was conducted in the presence of 150 mg cobicistat.
f. Comparison based on elvitegravir/cobicistat 150/150 mg once daily.

Table 2. Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered

Drug in the Presence of Elvitegravir[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose (mg)	Ritonavir Booster Dose	N	% Change of Boosted Coadministered Drug Pharmacokinetic Parameters[b,c] (90% CI)		
					C_{max}	AUC	C_{min}
Atazanavir	300 once daily	200 once daily	100 once daily	33	Û	Û	¯35 (¯41 to ¯27)
	300 once daily	85 once daily	100 once daily	20	Û	Û	Û
Darunavir	600 twice daily	125 once daily	100 twice daily	22	Û	Û	¯17 (¯26 to ¯7)
Didanosine	400 single dose	200 once daily	100 once daily	32	¯16 (¯33 to - 5)	¯14 (¯25 to ¯1)	NC
Lopinavir/ritonavir	400/100 twice daily	125 once daily	NA	13	Û	Û	¯8 (¯21 to - 8)
Maraviroc	150 twice daily	150 once daily	100 once daily	11	- 114 (- 71 to - 169)	- 186 (- 133 to - 251)	- 323 (- 247 to - 416)
Rifabutin	150 once every other day	300 once daily	100 once daily	18	Û [d]	Û [d]	Û [d]
25-O-desacetyl-rifabutin					- 440[d] (- 366 to - 525)	- 851[d] (- 710 to - 1018)	- 1836[d] (- 1485 to - 2265)
Rosuvastatin	10 single dose	150 single dose	NA [e]	10	- 89 (- 48 to - 142)	- 38 (- 14 to - 67)	- 43 (- 8 to - 89)
Tipranavir	500 twice daily	200 once daily	200 twice daily	26	Û	Û	¯11 (¯23 to - 2)

a. All interaction studies conducted in healthy volunteers
b. - = Increase; ¯ = Decrease; Û = No Effect; NA = Not Applicable; NC = Not Calculated
c. The pharmacokinetic parameters of the protease inhibitors presented in this table were assessed in the presence of ritonavir.
d. Comparison based on rifabutin 300 mg once daily. Total antimycobacterial activity was increased by 50%.
e. Study was conducted in the presence of 150 mg cobicistat.

CLINICAL TRIALS

The efficacy of VITEKTA is primarily based on the analyses through 96 weeks from one randomized, double-blind, active-controlled study, Study 0145, in treatment experienced, HIV-1 infected patients (N=702).

In Study 0145, patients were randomized in a 1:1 ratio to receive either VITEKTA (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 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).

The mean age of patients was 45 years (range 19-78), 82% were male, 62% were White, and 34% were Black. The mean baseline plasma HIV-1 RNA was 4.3 $\log_{10}$ copies/mL (range 1.7–6.6). The mean duration of prior HIV-1 treatment was 9.4 years. The mean baseline CD4+ cell count was 262 cells/mm^3 (range 1–1497) and 45% had CD4+ cell counts ≤200 cells/mm^3. Twenty-six percent of patients had baseline viral loads >100,000 copies/mL. Baseline genotypic sensitivity scores are presented in Table 3.

Table 3. Baseline Genotypic Sensitivity Scores for Study 0145

	VITEKTA + BR (N=351)	**Raltegravir + BR (N=351)**
Baseline Genotypic Sensitivity Score[a]		
0	1%	<1%
1	14%	15%
2	81%	83%
3	3%	2%

a. Genotypic Sensitivity Score is calculated by summing up the drug susceptibility scores (1=sensitive; 0=resistance or reduced susceptibility) for all drugs in the baseline background regimen.

Treatment outcomes through 96 weeks are presented in Table 4.

Table 4. Virologic Outcome of Randomized Treatment of Study 0145 at Week 48 and Week 96

	Week 48		Week 96	
	VITEKTA+ BR (N=351)	**Raltegravir + BR (N=351)**	**VITEKTA + BR (N=351)**	**Raltegravir + BR (N=351)**
Virologic Success HIV-1 RNA < 50 copies/mL	60%	58%	52%	53%
Treatment Difference[b]	2.2% (95% CI = -5.0%, 9.3%)		-0.5% (95% CI = -7.9%, 6.8%)	
Virologic Failure[c]	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[d]	2%	5%	3%	7%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[e]	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 Treatment difference was stratified by baseline HIV-1 RNA (≤100,0000 copies/mL or > 100,000 copies/mL) and the class of second agent

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

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

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

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

Among patients with a genotypic sensitivity score of ≤1, 76% and 69% had HIV-1 RNA <50 copies/mL in the VITEKTA and raltegravir treatment arms, respectively. Among subjects with a

genotypic sensitivity score >1, 57% and 56% had HIV-1 RNA <50 copies/mL in the VITEKTA and raltegravir treatment arms, respectively.

In Study 0145, the mean increase from baseline in CD4+ cell count at Week 96 was 205 cells/mm^3 in the VITEKTA-treated patients and 198 cells/mm in the raltegravir-treated patients.

INDICATIONS

VITEKTA is indicated for the treatment of HIV-1 infection in antiretroviral treatment-experienced adults and adolescents when co-administered with a ritonavir-boosted protease inhibitor and other antiretroviral therapy.

CONTRAINDICATIONS

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

VITEKTA should not be used in combination with the single tablet regimen STRIBILD since elvitegravir is a component of STRIBILD.

PRECAUTIONS

General

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 should be advised that antiretroviral therapies, including VITEKTA have not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions must continue to be used. Patients should also be informed that VITEKTA is not a cure for HIV infection.

Drug Interactions

Elvitegravir is primarily metabolized by CYP3A. Drugs that induce CYP3A activity are expected to decrease the plasma concentrations of elvitegravir, which may lead to loss of therapeutic effect of VITEKTA and possible development of resistance.

Ritonavir-boosted protease inhibitors that are coadministered with VITEKTA may increase the plasma concentrations of concomitant drugs that are primarily metabolized by CYP3A as ritonavir is a strong CYP3A inhibitor. Higher plasma concentrations of concomitant drugs can result in increased or prolonged therapeutic or adverse effects, potentially leading to severe, life-threatening events.

Due to the need for coadministration of VITEKTA with a ritonavir-boosted protease inhibitor, prescribers should consult the complete prescribing information of the coadministered protease

inhibitor and ritonavir for a description of contraindicated drugs and other significant drug-drug interactions that may cause potentially life-threatening adverse events or loss of therapeutic effect and possible development of resistance.

Use with Other Antiretroviral Products
VITEKTA should only be used in combination with a ritonavir-boosted protease inhibitor. VITEKTA should not be used with a cobicistat-boosted protease inhibitor as dosing recommendations for such combination have not been established and may result in suboptimal plasma concentrations of VITEKTA and/or protease inhibitor leading to loss of therapeutic effect and development of resistance.

Immune Reconstitution Syndrome
Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of antiretroviral therapy. Relevant examples 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 have also been reported to occur in the setting of immune reconstitution; however, the reported time to onset is more variable, and these events can occur many months after initiation of treatment.

Resistance/Cross-Resistance
VITEKTA has a relatively low genetic barrier to resistance when used as part of a suboptimal regimen. Therefore, wherever 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 virological failure and the development of resistance.

Elvitegravir-resistant viruses show cross-resistance to the integrase strand transfer inhibitor raltegravir in most cases, with the exception of the T66I/A substitution. Raltegravir resistant viruses expressing most primary raltegravir mutations, including Q148H/K/R and N155H, showed cross-resistance to elvitegravir, with the exception of Y143 substitutions.

Effects on Fertility
Elvitegravir did not affect fertility in male and female rats at doses which achieved approximately 21- and 39- fold higher exposures (AUC), respectively, than in humans with the therapeutic 150 mg daily dose.

Fertility was normal in the offspring of rats exposed daily from before birth (*in utero*) through sexual maturity at daily exposures (AUC) of approximately 23-fold higher than human exposures at the recommended 150 mg daily dose.

Use in Pregnancy
Pregnancy Category B2.

There are no adequate and well controlled clinical studies of VITEKTA in pregnant women. Because animal reproductive studies are not always predictive of human response, VITEKTA should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Foetal development was unaffected by oral treatment of rats and rabbits during the period of organogenesis. Doses used in the rat achieved drug exposures (AUC) that were up to 29 fold higher than in humans receiving the 150 mg dose. Drug exposures in the rabbit were low (up to 02 times the human value).

Use in Lactation
Studies in rats have demonstrated that elvitegravir is secreted into milk.

It is not known whether elvitegravir is secreted in human milk. Because of the potential for both HIV transmission and for serious adverse events in nursing infants, mothers should be instructed not to breast feed if they are receiving VITEKTA.

Paediatric Use
Safety and effectiveness of VITEKTA in children less than 18 years of age have not been established.

Use in the Elderly
Clinical studies of VITEKTA did not contain sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. Caution should be exercised when prescribing VITEKTA to the elderly, keeping in mind the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Effects on Laboratory Tests
There are no known interactions of VITEKTA with any laboratory tests.

Genotoxicity
Elvitegravir was not genotoxic in the reverse mutation bacterial test (Ames test) and the rat micronucleus assay. In an *in vitro* chromosomal aberration test, elvitegravir was negative with metabolic activation; however, an equivocal response was observed without activation.

Carcinogenicity
In long-term carcinogenicity studies of elvitegravir, no drug-related increases in tumor incidence were found in mice at doses up to 2000 mg/kg/day alone or in combination with 25 mg/kg/day ritonavir (3 and 18 times, respectively, the human systemic exposure at the therapeutic 150 mg daily dose, or in rats at doses up to 2000 mg/kg/day (16 times in males and 35 times in females the human systemic exposure at the therapeutic daily dose).

INTERACTIONS WITH OTHER MEDICINES

Effect of Concomitant Drugs on the Pharmacokinetics of Elvitegravir
Elvitegravir is primarily metabolised by CYP3A. Drugs that induce CYP3A activity would be expected to increase the clearance of elvitegravir, as well as ritonavir and the coadministered protease inhibitor. This may result in decreased plasma concentration of elvitegravir and/or protease inhibitor and lead to loss of therapeutic effect and possible development of resistance.

Ritonavir-boosted protease inhibitors that are coadministered with VITEKTA may increase the plasma concentrations of concomitant drugs that are primarily metabolized by CYP3A as ritonavir is a strong CYP3A inhibitor. Higher plasma concentrations of concomitant drugs can result in increased or prolonged therapeutic or adverse effects, potentially leading to severe, life-threatening events.

Established and Other Potentially Significant Interactions

Table 5 provides dosing recommendations as a result of drug interactions with VITEKTA. These recommendations are based on either drug interactions studies or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of therapeutic effect.

For additional drug-drug interactions with ritonavir-boosted protease inhibitors, consult the prescribing information of the coadministered protease inhibitor when using VITEKTA as the drug-drug interactions may differ.

Table 5. Established and Other Potentially Significant[a] Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Antiretroviral Agents: Protease Inhibitors (PI) c		
Atazanavir	« atazanavir - elvitegravir	Atazanavir/ritonavir has been shown to significantly increase the plasma concentrations of VITEKTA. When used in combination with atazanavir, the dose of VITEKTA should be 85 mg once daily. The recommended dose of atazanavir is 300 mg with ritonavir 100 mg once daily. There are no data available to make dosing recommendations for coadministration with other doses of atazanavir.
Darunavir	« darunavir « elvitegravir	No dose adjustment is required when VITEKTA is used in combination with darunavir/ritonavir 600/100 mg twice daily. There are no data available to make dosing recommendations for coadministration with other doses of darunavir.
Fosamprenavir	« fosamprenavir « elvitegravir	No dose adjustment is required when VITEKTA is used in combination with fosamprenavir/ritonavir 700/100 mg twice daily. There are no data available to make dosing recommendations for coadministration with other doses of fosamprenavir.
Lopinavir/ritonavir	« lopinavir - elvitegravir	Lopinavir/ritonavir has been shown to significantly increase the plasma concentrations of elvitegravir. When used in combination with lopinavir/ritonavir, the dose of VITEKTA should be 85 mg once daily. The recommended dose of lopinavir/ritonavir is 400/100 mg twice daily. There are no data available to make dosing recommendations for coadministration with other doses of lopinavir/ritonavir.
Tipranavir	« tipranavir « elvitegravir	No dose adjustment is required when VITEKTA is used in combination with tipranavir/ritonavir.
Other Protease Inhibitors (with or without ritonavir)	Effect is unknown	There are no data available to make dosing recommendations for coadministration with other protease inhibitors.
Antiretroviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
Didanosine	« didanosine « elvitegravir	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).
Other NRTIs abacavir emtricitabine stavudine tenofovir disoproxil fumarate zidovudine	« NRTIs « elvitegravir	No dose adjustment is required when VITEKTA is used in combination with other NRTIs.

Antiretroviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Efavirenz	¯ elvitegravir	Coadministration of efavirenz and VITEKTA is expected to decrease elvitegravir plasma concentration which may result in loss of therapeutic effect and development of resistance. Such coadministration is not recommended.
Etravirine	« elvitegravir	No dose adjustment of VITEKTA is required when coadministered with etravirine. When etravirine is used concomitantly with VITEKTA in combination with a ritonavir-boosted protease inhibitor, consult the etravirine prescribing information for etravirine dosing recommendation.
Nevirapine	¯ elvitegravir	Coadministration of nevirapine and VITEKTA is expected to decrease elvitegravir plasma concentration which may result in loss of therapeutic effect and development of resistance. Such coadministration is not recommended.
Rilpivirine	« elvitegravir	Coadministration of VITEKTA and rilpivirine is not expected to change elvitegravir plasma concentrations, therefore no dose adjustment of VITEKTA is required. When rilpivirine is used concomitantly with VITEKTA in combination with a ritonavir-boosted protease inhibitor, consult the rilpivirine prescribing information for rilpivirine dosing recommendation.
Antiretroviral Agents: CCR5 Antagonists		
Maraviroc	« elvitegravir - maraviroc	No dose adjustment of VITEKTA is required when coadministered with maraviroc. When maraviroc is used concomitantly with VITEKTA in combination with a ritonavir-boosted protease inhibitor, consult the maraviroc prescribing information for maraviroc dosing recommendation.
Other Agents:		
Acid Reducing Agents: antacids	¯ elvitegravir	Elvitegravir plasma concentrations are lower with antacids due to local complexation in the GI tract and not to changes in gastric pH. It is recommended to separate VITEKTA and antacid administration by at least 2 hours.
Analeptics: modafinil	¯ elvitegravir	Coadministration of modafinil, a CYP3A inducer, may decrease elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Alternative analeptics should be considered.
Anticonvulsants: carbamazepine oxcarbazepine phenobarbital phenytoin	¯ elvitegravir	Coadministration of phenobarbital, phenytoin, carbamazepine, and oxcarbazepine, CYP3A inducers, may decrease elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Alternative anticonvulsants should be considered.
Antifungals: ketoconazole	- elvitegravir - ketoconazole	No dose adjustment of VITEKTA is required when coadministered with ketoconazole. Concentrations of ketoconazole may increase when used concomitantly with VITEKTA in combination with ritonavir-boosted protease inhibitors, the maximum daily dose of ketoconazole should not exceed 200 mg per day. Consult the prescribing information of coadministered protease inhibitors for any additional dosing recommendation for ketoconazole.
Antimycobacterial: rifabutin	- rifabutin - 25-*O*-desacetylrifabutin ¯ elvitegravir	When rifabutin, a potent CYP3A inducer, is used concomitantly with VITEKTA in combination with a ritonavir-boosted protease inhibitor, dose reduction of rifabutin by at least 75% of the usual dose of 300 mg/day (e.g. 150 mg every other day or 3 times per week) is recommended. Increased monitoring for rifabutin-associated adverse events is warranted.

rifampin rifapentine	¯ elvitegravir	Consult the prescribing information of coadministered protease inhibitors for any additional dosing recommendation for rifabutin. No dose adjustment of VITEKTA is required when coadministered with reduced dose of rifabutin. Coadministration of rifampin or rifapentine, potent CYP3A inducers, with VITEKTA may lead to decreased elvitegravir exposures, which may result in loss of therapeutic effect and development of resistance. Coadministration is not recommended.
Systemic Corticosteroids: dexamethasone	¯ elvitegravir	Coadministration of dexamethasone, a CYP3A inducer, may decrease elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Alternative corticosteroids should be considered.
Endothelin Receptor Antagonists: bosentan	- bosentan ¯ elvitegravir	Coadministration of bosentan with VITEKTA may lead to decreased elvitegravir exposures and loss of therapeutic effect and development of resistance. Coadministration is not recommended.
H_2-Receptor antagonists: famotidine	« elvitegravir	No dose adjustment of VITEKTA is required when coadministered with famotidine. When famotidine is used concomitantly with VITEKTA in combination with a ritonavir-boosted protease inhibitor, consult the prescribing information of coadministered protease inhibitor for dosing recommendation for the protease inhibitor and famotidine.
HMG-CoA Reductase Inhibitors: atorvastatin pravastatin rosuvastatin	« elvitegravir - rosuvastatin	No dose adjustment of VITEKTA is required when coadministered with rosuvastatin. Coadministration of VITEKTA and atorvastatin and pravastatin are not expected to change elvitegravir plasma concentrations, therefore no dose adjustment of VITEKTA is required. When atorvastatin, pravastatin, or rosuvastatin is used concomitantly with VITEKTA in combination with a ritonavir-boosted protease inhibitor, consult the prescribing information of coadministered protease inhibitor for dosing recommendation for the statin.
Herbal Products: St. John's wort (*Hypericum perforatum*)	¯ elvitegravir	Coadministration of St. John's wort, a potent CYP3A inducer, may decrease elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance. VITEKTA should not be coadministered with St. John's wort.
Hormonal Contraceptives: norgestimate/ethinyl estradiol	- norgestimate ¯ ethinyl estradiol « elvitegravir	Plasma concentration of ethinyl estradiol may be decreased when used concomitantly with VITEKTA in combination with ritonavir-boosted protease inhibitors. Alternative methods of nonhormonal contraception are recommended.
Proton-pump Inhibitors: omeprazole	« elvitegravir	No dose adjustment of VITEKTA is required when coadministered with omeprazole. When omeprazole is used concomitantly with VITEKTA in combination with a ritonavir-boosted protease inhibitor, consult the prescribing information of coadministered protease inhibitor for dosing recommendation for the protease inhibitor and omeprazole.

a. This table is not all inclusive.
b. - = increase, ¯ = decrease, « = no change
c. Protease inhibitors were coadministered with ritonavir.

The table is not all-inclusive (see Tables 1 and 2):

Effects on ability to drive and use machines

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

ADVERSE EFFECTS

CLINICAL TRIALS

The safety assessment of VITEKTA is primarily based on data from a controlled clinical study (GS-US-183-0145) in which 712 HIV-1 infected, antiretroviral treatment-experienced adults received VITEKTA(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 for at least 96 weeks.

The proportion of patients receiving VITEKTA who discontinued study treatment due to adverse events, regardless of severity, was 3.1%. The most common adverse reaction (incidence greater than or equal to 10% Grade 2-4) occurring in patients receiving VITEKTA in Study 0145 was diarrhoea. See also Table 6 for the frequency of adverse reactions (Grade 2-4) occurring in at least 3% of patients in any treatment group in Study 0145.

Table 6 Selected Treatment-Emergent Adverse Drug Reactions (Grades 2-4) Reported in ≥ 3% of Patients in Either Treatment Group in Study 0145 (Week 96 analysis)

	VITEKTA	Raltegravir
	N=354	N=358
GASTROINTESTINAL DISORDERS		
Diarrhoea	13%	8%
Nausea	4%	3%
Abdominal Pain	3%	3%
Vomiting	3%	3%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Back pain	6%	4%
Arthralgia	5%	3%
Pain in extremity	4%	4%
NERVOUS SYSTEM DISORDERS		
Headache	4%	2%
PSYCHIATRIC DISORDERS		
Depression	6%	6%

a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drugs

Treatment-emergent adverse drug reactions of at least moderate intensity (≥ Grade 2) that occurred in less than 3% of patients treated with VITEKTA in Study 145 include dyspepsia, fatigue, insomnia rash, and suicidal ideation and suicide attempt in patients with pre-existing history of depression or psychiatric illness.

Laboratory Abnormalities: The frequency of treatment-emergent laboratory abnormalities (Grade 3-4) occurring in at least 5% of patients in either treatment group in Study 0145 are presented in Table 7.

Table 7: Laboratory Abnormalities (Grades 3-4) Reported in ≥ 5% of Patients in Either Treatment Group in Study 0145 (Week 96 analysis)

	VITEKTA	Raltegravir
Laboratory Parameter Abnormality	N=354	N=358
ALT (>5.0 x ULN)	2%	5%
AST (>5.0 x ULN)	2%	6%
Total Bilirubin (>2.5 x ULN)	6%	9%
GGT (>5.0 x ULN)	3%	7%
Amylase [a] (>2.0 x ULN)	6%	6%
Total Cholesterol (> 300 mg/dL)	5%	5%
Creatine Kinase (³ 10.0 x ULN)	6%	4%
Urine RBC (Hematuria) (> 75 RBC/HPF)	6%	7%

[a] For patients with serum amylase > 1.5 x upper limit of normal, lipase test was also performed. The frequency of increased lipase (Grade 3-4) occurring in VITEKTA (n=66) and raltegravir (n=58) treatment groups was 14% and 7%, respectively.

DOSAGE AND ADMINISTRATION

The recommended dose of VITEKTA tablets is 150 mg once daily taken orally with food.
If VITEKTA is used in combination with atazanavir/ritonavir or lopinavir/ritonavir, the dose of VITEKTA should be decreased to 85 mg once daily taken orally with food.

VITEKTA must be administered in combination with a ritonavir-boosted protease inhibitor (see Table 8 for the differing dosage for each protease inhibitor). The dosing regimens presented in Table 8 have been studied in a controlled clinical study and are the recommended regimens for use of VITEKTA in combination with a ritonavir-boosted protease inhibitor. For additional dosing instructions for these protease inhibitors, refer to their respective prescribing information.

Table 8. Recommended Dosing Regimens

Dose of VITEKTA	Dose of Coadministered Ritonavir-Boosted Protease Inhibitor
85 mg once daily	atazanavir/ritonavir 300/100 mg once daily
	lopinavir/ritonavir 400/100 mg twice daily
150 mg once daily	darunavir/ritonavir 600/100 mg twice daily
	fosamprenavir/ritonavir 700/100 mg twice daily
	tipranavir/ritonavir 500/200 mg twice daily

There are no data to recommend the use of VITEKTA with dosing regimens or HIV-1 protease inhibitors other than those presented in Table 8.

Renal impairment: No clinically relevant differences in elvitegravir pharmacokinetics were observed between patients with severe renal impairment and healthy patients. No dose adjustment of VITEKTA is required for patients with renal impairment (see PHARMACOLOGY).

Hepatic impairment: No clinically relevant differences in elvitegravir pharmacokinetics were observed between patients with moderate heaptic impairment and healthy patients. No dose adjustment of VITEKTA is required in patients with mild or moderate hepatic impairment. . The effect of severe hepatic impairment on the pharmacokinetics of elvitegravir has not been studied. (see PHARMACOLOGY).

OVERDOSAGE

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

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia) and 0800 764 766 (New Zealand).

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

PRESENTATION AND STORAGE CONDITIONS

VITEKTA is available as tablets. The 85 mg tablet contains 85 mg elvitegravir and are green, pentagon shaped, film coated with 'GSI' on one side and "85" on the other side. The 150 mg tablet contains 150 mg elvitegravir and are green, triangle shaped, film-coated, debossed with "GSI" on one side and "150" on the other side.

VITEKTA is supplied in high density polyethylene (HDPE) bottles containing 30 tablets and is closed with a child resistant closure.

VITEKTA should be stored below 25 °C.

NAME AND ADDRESS OF THE SPONSOR

Gilead Sciences Pty Ltd
Level 6, 417 St Kilda Road
Melbourne, Victoria 3004

POISON SCHEDULE OF THE DRUG

S4

DATE OF FIRST INCLUSION ON ARTG:

23 October 2013

Attachment 1: Product information for AusPAR Elvitegravir Vitekta Gilead Sciences Pty Ltd PM-2012-02159-3-2 Final 16 December 2013. This Product Information was approved at the time this AusPAR was published.