Product Monograph

PrVITEKTA™

(Elvitegravir Tablets)

85 and 150 mg

Antiretroviral Agent

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TABLE OF CONTENTS

PART I. HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet/ Elvitegravir 85 and 150 mg	Lactose monohydrate *For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

INDICATIONS AND CLINICAL USE

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 antiretroviral treatment-experienced adults *(18 years of age or older).*

This indication is primarily based on 48-week efficacy data and 96-week safety data from one randomised, double-blind, active-controlled study (GS-US-183-0145), in treatment-experienced, HIV-1 infected patients (n = 702). An additional efficacy analysis through 96 weeks was also conducted. In this study, VITEKTA was administered with ritonavir-boosted protease inhibitors (atazanavir, lopinavir, darunavir, fosamprenavir or tipranavir). No data on administration with other protease inhibitors is available.

Geriatrics (≥65 years of age):

Clinical studies of VITEKTA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from adult subjects < 65 years of age.

Pediatrics (<18 years of age):

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

CONTRAINDICATIONS

VITEKTA is contraindicated in patients with known hypersensitivity to any of the components of the product. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

WARNINGS AND PRECAUTIONS

General

Elvitegravir is primarily metabolised by CYP3A. Medicinal products 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 (see **DRUG INTERACTIONS: Drug-Drug Interactions**).

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 combinations have not been established and may result in suboptimal plasma concentrations of VITEKTA and/or the protease inhibitor leading to loss of therapeutic effect and possible development of resistance. The Product Monographs of ritonavir and the co-administered medicinal products must be consulted.

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

Due to the need for co-administration of VITEKTA with a ritonavir-boosted protease inhibitor, prescribers should consult the Product Monographs 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 events or loss of therapeutic effect and possible development of resistance.

VITEKTA has not been studied with any protease inhibitors other than atazanavir, lopinavir, darunavir, fosamprenavir and tipranavir. No data on administration is available for other protease inhibitors (see **DOSAGE AND ADMINISTRATION**).

VITEKTA should not be used in combination with the fixed-dose combination product STRIBILD® (Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate) since elvitegravir is a component of STRIBILD.

Carcinogenesis, Mutagenesis, Impairment of Fertility

See **TOXICOLOGY** section.

Immune

Immune Reconstitution:

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. During the initial phase of combination antiretroviral treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infections,

cytomegalovirus, *Pneumocystis jiroveci* pneumonia (PCP), and tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.

Musculoskeletal

Mostly asymptomatic Grade 3-4 creatine kinase laboratory abnormalities were observed in patients treated with VITEKTA (see **ADVERSE REACTIONS**). One case of myopathy, without elevation in creatine kinase, has been reported in clinical trials with uncertain causal relationship to VITEKTA. VITEKTA should be used with caution in patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medications known to cause these conditions.

Resistance/Cross-Resistance

VITEKTA has a relatively low genetic barrier to resistance when used as part of a suboptimal regimen. 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 virological failure and the development of resistance (see **VIROLOGY**).

Special Populations

Hepatitis B and/or C coinfection:

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. VITEKTA should not be administered in patients with severe hepatic impairment (see **ADVERSE REACTIONS**).

Women:

No clinically relevant pharmacokinetic differences due to gender have been identified for ritonavir-boosted VITEKTA. In a Phase 3 study, the virologic success rate at Week 48 in the VITEKTA group was numerically lower in females than males. However the number of women in the VITEKTA group is insufficient to determine whether they respond differently than men (see **CLINICAL TRIALS**, **Study Results**).

Pregnant Women:

VITEKTA has not been studied in pregnant women. VITEKTA should not be used in pregnant women unless the potential benefits outweigh the potential risks to the fetus (see **TOXICOLOGY**).

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to ART (antiretroviral therapy) including VITEKTA, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients, http://www.apregistry.com; Telephone: (800) 258–4263; Fax: (800) 800-1052.

Nursing Women:

HIV-1 infected mothers should not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that elvitegravir is secreted in milk. It is not known whether elvitegravir is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving VITEKTA**.

Pediatrics (<18 years of age): Safety and effectiveness in children less than 18 years of age have not been established.

Geriatrics (>65 years of age): Clinical studies of VITEKTA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than adult subjects < 65 years of age. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Drug Reaction Overview

The safety assessment of VITEKTA is primarily based on data from a Phase 3 randomized, double-blind clinical trial, Study 145, 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.

See Table 1 for the frequency of adverse reactions (all grades) occurring in at least 2% of subjects in any treatment group in Study 145. The most common adverse reactions (incidence greater than or equal to 2%) occurring in subjects receiving VITEKTA in Study 145, attributed to study drug were diarrhea, nausea and headache.

Table 1. Treatment-Emergent Adverse Drug Reactions[a] (All Grades) Reported in ≥ 2% of Subjects in Either Treatment Group in Study 145 (Week 96 analysis)

	VITEKTA	Raltegravir
	N=354	N=358
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Lymphadenopathy	3%	3%
Anaemia	2%	1%
GASTROINTESTINAL DISORDERS		
Diarrhoea	34%	22%
Nausea	12%	11%
Vomiting	6%	8%
Abdominal Pain	6%	6%
Constipation	3%	3%
Haemorrhoids	3%	3%
Flatulence	3%	3%
Abdominal Distension	3%	3%
Dyspepsia	3%	3%
Gastrooesophageal Reflux Disease	3%	2%
Abdominal Discomfort	3%	1%
Abdominal Pain Upper	3%	2%
Gastritis	2%	3%
Toothache	1%	3%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue	10%	7%
Pyrexia	4%	6%
Oedema Peripheral	5%	3%
Influenza Like Illness	3%	4%
Chest Pain	2%	3%
Pain	2%	2%
IMMUNE SYSTEM DISORDERS		
Seasonal Allergy	2%	3%
INFECTIONS AND INFESTATIONS		
Upper Respiratory Tract Infection	19%	16%
Bronchitis	10%	10%
Nasopharyngitis	9%	8%
Urinary Tract Infection	7%	10%
Sinusitis	8%	8%
Pneumonia	5%	3%
Anogenital Warts	4%	3%

	VITEKTA	Raltegravir
Folliculitis	5%	2%
Onychomycosis	4%	3%
Influenza	4%	3%
Oral Candidiasis	3%	3%
Herpes Zoster	3%	3%
Gastroenteritis	4%	2%
Cellulitis	3%	3%
Oral Herpes	4%	2%
Pharyngitis	3%	3%
Tinea Pedis	3%	2%
Viral Infection	2%	3%
Syphilis	3%	2%
Respiratory Tract Infection	3%	2%
Herpes Simplex	3%	1%
Tooth Abscess	1%	2%
Tinea Cruris	2%	1%
Ear Infection	< 1%	2%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Arthropod Bite	3%	1%
Contusion	2%	1%
Muscle Strain	2%	1%
INVESTIGATIONS		
Blood Triglycerides Increased	3%	3%
Lymph Node Palpable	4%	2%
Weight Decreased	3%	3%
Blood Cholesterol Increased	2%	3%
METABOLISM AND NUTRITION DISORDERS		
Hypercholesterolaemia	3%	5%
Hypertriglyceridaemia	5%	4%
Decreased Appetite	3%	2%
Hyperlipidaemia	3%	2%
Vitamin D Deficiency	3%	1%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Back Pain	11%	10%
Arthralgia	8%	7%
Pain in Extremity	7%	7%
Muscle Spasms	5%	3%
Myalgia	3%	3%
Musculoskeletal Pain	3%	3%

	VITEKTA	Raltegravir
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
Skin Papilloma	3%	2%
NERVOUS SYSTEM DISORDERS		
Headache	13%	10%
Dizziness	2%	5%
Paraesthesia	3%	1%
Hypoaesthesia	3%	1%
PSYCHIATRIC DISORDERS		
Depression	8%	9%
Insomnia	6%	6%
Anxiety	5%	3%
RENAL AND URINARY DISORDERS		
Dysuria	4%	3%
Haematuria	2%	3%
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
Erectile Dysfunction	4%	2%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Cough	10%	13%
Nasal Congestion	4%	4%
Oropharyngeal Pain	4%	3%
Rhinitis Allergic	4%	2%
Dyspnoea	4%	2%
Asthma	2%	3%
Rhinorrhoea	1%	2%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Rash	7%	8%
Pruritus	4%	2%
Dermatitis	1%	3%
Dry Skin	2%	1%
VASCULAR DISORDERS		
Hypertension	4%	6%

a Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of causality.

Selected treatment-emergent adverse drug reactions of at least moderate intensity (≥ Grade 2) that occurred in less than 2% of subjects treated with VITEKTA in Study 145 include abdominal pain, fatigue, gastroesophageal reflux disease, headache, insomnia, nausea, oedema peripheral, rash maculo-papular and vomiting. Suicidal ideation and suicide attempt occurred in less than 1% of patients receiving VITEKTA, all of whom had a pre-existing history of depression or psychiatric illness.

Laboratory Abnormalities: The frequency of treatment-emergent laboratory abnormalities (Grade 2-4) occurring in at least 2% of subjects in either treatment group in Study 145 are presented in Table 2.

Table 2. Laboratory Abnormalities (Grades 2-4) Reported in ≥ 2% of Subjects in Either Treatment Group in Study 145 (Week 96 analysis)

	VITEKTA	Raltegravir
Laboratory Parameter Abnormality	**N=354**	**N=358**
Albumin (< 3.0 g/dL)	6%	6%
ALT (> 2.5 × ULN)	7%	13%
AST (> 2.5 × ULN)	9%	11%
GGT (> 2.5 × ULN)	7%	13%
Creatine (> 2.0 mg/dL)	3%	2%
Creatine Kinase (≥ 6.0 x ULN)	8%	7%
Hematuria (> 10 RBC/HPF)	13%	14%
Hemoglobin (< 8.5 g/dL)	2%	2%
Neutrophils (< 1000/mm^3)	9%	7%
Phosphate (< 2.0 mg/dL)	5%	5%
Platelets (< 100,000/mm^3)	2%	4%
Serum Amylase[a] (> 1.5 × ULN)	14%	13%
Serum Bicarbonate (< 16.0 mEq/L)	2%	3%
Serum Glucose (> 160 mg/dL)	13%	11%
Serum Potassium (< 3.0 mEq/L)	2%	1%
Serum Sodium (< 130 mEq/L)	2%	1%
Total Bilirubin (> 1.5 × ULN)	15%	14%
Total Cholesterol (> 239 mg/dL)	22%	20%
Triglycerides (> 500 mg/dL)	11%	9%
Uric Acid (> 10 mg/dL)	6%	5%
Urine Glucose (+3 or +4)	7%	6%
Urine Protein (+2. +3, or +4)	11%	14%

a For subjects with serum amylase > 1.5 x upper limit of normal, lipase test was also performed. The frequency of increased lipase (Grade 2-4) occurring in VITEKTA and raltegravir treatment groups was 29% (19/66) and 22% (13/58), respectively.

Patients with co-existing Conditions

Patients coinfected with hepatitis B and/or hepatitis C virus
In Study 145, 60 patients treated with VITEKTA and 67 patients treated with raltegravir, each with ritonavir boosted protease inhibitor and an active third agent, were seropositive for hepatitis B and/or C at study entry. Within the VITEKTA group, no difference in the overall safety profile was noted between seropositive and seronegative patients; increased frequency of liver laboratory abnormalities in seropositive patients is consistent with the underlying viral hepatitis infection.

Patients at risk of musculoskeletal events
In Study 145, mostly asymptomatic Grade 3-4 creatine kinase laboratory abnormalities were observed in patients treated with VITEKTA. One case of myopathy, without elevation in creatine kinase, has been reported in clinical trials with uncertain causal relationship to VITEKTA. VITEKTA should be used with caution in patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medications known to cause these conditions.

DRUG INTERACTIONS

Serious Drug Interactions

Elvitegravir is metabolized by CYP3A. Drugs that induce CYP3A activity may decrease plasma concentrations of VITEKTA, which may lead to loss of therapeutic effect of and possible development of resistance (see **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS**, **Table 3 – Established and Other Potentially Significant Drug Interactions**).

Drug-Drug Interactions

Effect of Concomitant Drugs on the Pharmacokinetics of Elvitegravir

Elvitegravir is metabolized 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 concentrations of elvitegravir and/or protease inhibitor and lead to loss of therapeutic effect and possible resistance (see **WARNINGS AND PRECAUTIONS**).

Established and Other Potentially Significant Drug Interactions

Atazanavir/ritonavir and lopinavir/ritonavir have been shown to significantly increase the plasma concentrations of VITEKTA. When used in combination with atazanavir/ritonavir and lopinavir/ritonavir, the dose of VITEKTA should be decreased to 85 mg once daily (see **DOSAGE AND ADMINISTRATION)**.

Table 3 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. The table includes potentially significant interactions, but is not all inclusive (see **DRUG INTERACTIONS: Assessment of Drug Interactions, Table 4 - Table 5**).

For additional drug-drug interactions with ritonavir-boosted protease inhibitors, consult the Product Monographs of the coadministered protease inhibitor and ritonavir when using VITEKTA.

Table 3. Established and Other Potentially Significant[a] Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

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 (see **DOSAGE and ADMINISTRATION**). 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 (see **DOSAGE and ADMINISTRATION**). 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 (see **DOSAGE and ADMINISTRATION**). 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 is 400/100 mg twice daily (see **DOSAGE and ADMINISTRATION**). 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 (see **DOSAGE and ADMINISTRATION**).
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).

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
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	Such coadministration is not recommended. Coadministration of efavirenz and VITEKTA is expected to decrease elvitegravir plasma concentration which may result in loss of therapeutic effect and development of resistance.
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 Product Monograph for dosing recommendation.
nevirapine	↓ elvitegravir	Such coadministration is not recommended. Coadministration of nevirapine and VITEKTA is expected to decrease elvitegravir plasma concentration which may result in loss of therapeutic effect and development of resistance.
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 Product Monograph for 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 Product Monograph for 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.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
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, or oxcarbazepine, CYP3A inducers, with VITEKTA 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 a ritonavir-boosted protease inhibitor, the maximum daily dose of ketoconazole should not exceed 200 mg per day. Consult the Product Monographs of the coadministered protease inhibitor and ketoconazole 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. Consult the Product Monographs of the coadministered protease inhibitor and rifabutin for any additional dosing recommendation for rifabutin. No dose adjustment of VITEKTA is required when coadministered with reduced dose of rifabutin.
rifampin rifapentine*	↓ elvitegravir	Coadministration is not recommended. 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.
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 is not recommended. Coadministration of bosentan with VITEKTA may lead to decreased elvitegravir exposures and loss of therapeutic effect and development of resistance.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
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 Product Monographs of the coadministered protease inhibitor and famotidine for dosing recommendation for the protease inhibitor and famotidine.
HCV Protease Inhibitors: boceprevir telaprevir	↓ boceprevir ↓ telaprevir ↑ or ↓ HIV protease inhibitors	Coadministration with telaprevir or boceprevir is not recommended since VITEKTA must be administered with a ritonavir-boosted protease inhibitor. Coadministration of boceprevir or telaprevir with ritonavir-boosted HIV protease inhibitors resulted in reduced plasma concentrations of the HCV medication, and may increase or decrease the plasma concentrations of the protease inhibitor. This may result in loss of therapeutic effect and development of resistance.
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 Product Monographs of the coadministered protease inhibitor and the statin for dosing recommendation for the statin.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
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. The effects of increases in the concentration of the progestational component norgestimate are not fully known and can include increased risk of insulin resistance, dyslipedemia, acne and venous thrombosis. The potential unknown risks and benefits associated with coadministration of norgestimate/ethinyl estradiol with VITEKTA should be considered, particularly in women who have risk factors for these events. Coadministration of VITEKTA with oral contraceptives containing progestagens other than norgestimate or other hormonal contraceptives (e.g. contraceptive patch, contraceptive vaginal ring), has not been studied; therefore alternative non-hormonal methods of contraception should be considered.
Narcotic Analgesics: Methadone	⇔ R-methadone ⇔ S-methadone	Methadone exposures are unaffected upon coadministration with elvitegravir. No dose adjustment of methadone is required upon coadministration with VITEKTA.
Buprenorphine/naloxone	↑ buprenorphine ↑ norbuprenorphine ↓ naloxone	Concentrations of buprenorphine and norbuprenorphine are modestly increased and concentrations of naloxone are modestly decreased when coadministered with elvitegravir, with no changes on opioid pharmacodynamics. Accordingly, the observed concentration changes are not considered clinically relevant and no dose adjustment of buprenorphine/naloxone is required upon coadministration with VITEKTA.
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 Product Monographs of the coadministered protease inhibitor and omeprazole 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.

* Not marketed in Canada

Assessment of Drug Interactions

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

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 4. The effects of elvitegravir on the exposure of coadministered drugs are shown in Table 5. For information regarding clinical recommendations, see **DRUG INTERACTIONS, Table 3 – Established and Other Potentially Significant Drug Interactions**.

Table 4. Drug Interactions: Changes in Pharmacokinetic Parameters for Elvitegravir in the Presence of the Coadministered Drug[a]

Co-administered Drug	Dose of Co-administered 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	⇔	⇔	⇔
	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	⇔[d]	⇔[d]	↑38[d] (↑18 to ↑61)
Darunavir	600 twice daily	125 once daily	100 twice daily	21	⇔	⇔	⇔
Didanosine	400 single dose	200 once daily	100 once daily	32	⇔	⇔	⇔
Ketoconazole	200 twice daily	150 once daily	100 once daily	18	⇔	↑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	⇔	⇔	⇔
Rifabutin	150 once every other day	300 once daily	100 once daily	19	⇔	⇔	⇔
Rosuvastatin	10 single dose	150 single dose	NA[e]	10	⇔[f]	⇔[f]	⇔[f]
Tipranavir	500 twice daily	200 once daily	200 twice daily	26	⇔	⇔	⇔

a All interaction studies conducted in healthy volunteers

b ↑ = Increase; ↓ = Decrease; ⇔ = 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 cobicistat 150 mg once daily.

f Comparison based on elvitegravir/cobicistat 150/150 mg once daily.

Table 5. Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Elvitegravir[a]

Co-administered Drug	Dose of Co-administered 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	⇔	⇔	↓35 (↓41 to ↓27)
	300 once daily	85 once daily	100 once daily	20	⇔	⇔	⇔
Darunavir	600 twice daily	125 once daily	100 twice daily	22	⇔	⇔	↓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	⇔	⇔	↓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	⇔[d]	⇔[d]	⇔[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	⇔	⇔	↓11 (↓23 to ↑2)

a All interaction studies conducted in healthy volunteers

b ↑ = Increase; ↓ = Decrease; ⇔ = 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 cobicistat 150 mg once daily.

Drug-Food Interactions

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 56% and 91% with a high-fat meal, respectively

Drug-Herb Interactions

Coadministration of St. John's wort (*Hypericum perforatum*), 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.

Drug-Laboratory Interactions

Interactions of VITEKTA with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

The recommended oral dose of VITEKTA tablets is 150 mg once daily with food.

VITEKTA must be administered in combination with a ritonavir-boosted protease inhibitor. The dosing regimens presented in Table 6 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 Product Monographs.

If VITEKTA is used in combination with atazanavir/ritonavir or lopinavir/ritonavir, the dose of VITEKTA should be decreased to 85 mg once daily with food (see **DRUG INTERACTIONS: Drug-Drug Interactions**).

Table 6. 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 6.

Geriatrics (≥65 years of age)

Insufficient data are available on which to make a dose recommendation for patients over 65 years of age.

Pediatrics (<18 years of age)

VITEKTA is not indicated for use in pediatric patients < 18 years of age.

Dose Adjustment for Renal Impairment

No dose adjustment of VITEKTA is required for patients with renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY: Renal Insufficiency**).

Dose Adjustment for 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). VITEKTA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) (see **ACTION AND CLINICAL PHARMACOLOGY: Hepatic Insufficiency**).

Missed Dose

If the patient misses a dose of VITEKTA, the missed dose should be taken as soon as possible with food unless it is almost time for the next dose. Do not double the next dose. The patient should then take their next scheduled dose of VITEKTA at its regular time with the ritonavir-boosted protease inhibitor.

OVERDOSAGE

For management of a suspected drug overdose, please contact your regional Poison Control Centre.

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. Although no data are available, administration of activated charcoal may be used to aid in removal of unabsorbed drug.

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

The Product Monographs of the co-administered protese inhibitor and ritonavir should also be consulted.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

Pharmacodynamics

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, lamivudine, stavudine, tenofovir, or zidovudine); NNRTIs (efavirenz, etravirine, or nevirapine); PIs (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.

Effects on Electrocardiogram:

In a thorough QT/QTc study in 126 healthy subjects, ritonavir-boosted 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 subjects, peak plasma concentrations were observed 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 IC_{95} for wild-type HIV-1 virus).

Distribution:

Elvitegravir is 98-99% bound to human plasma proteins and the 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 is 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 feces, 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.

Linearity/Non-linearity:

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

Special Populations and Conditions

Pediatrics:

VITEKTA is not recommended for pediatric administration. The pharmacokinetics of elvitegravir in pediatric subjects (< 18 years) have not been established.

Geriatrics:

Pharmacokinetics of cobicistat have not been fully evaluated in the elderly (≥ 65 years).

Race:

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

Gender:

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

Hepatic Insufficiency:

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.

Renal Insufficiency:

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.

Hepatitis B and/or Hepatitis C Virus Coinfection:

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.

STORAGE AND STABILITY

Store at room temperature 15–30 °C (59–86 °F).

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

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

VITEKTA is available as tablets. Each tablet contains 85 or 150 mg of elvitegravir as the active ingredient. The tablets also include the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, sodium lauryl sulfate, croscarmellose sodium,

hydroxypropyl cellulose, and magnesium stearate. The tablets are film-coated with indigo carmine (FD&C blue #2) aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and yellow iron oxide. VITEKTA 85 mg tablets are 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. VITEKTA 150 mg tablets are green, triangle-shaped, film-coated tablet of dimensions 10.9 mm x 10.5 mm, debossed with "GSI" on one side of the tablet and "150" on the other side of the tablet. Each bottle contains 30 tablets and is closed with a child-resistant closure.

PART II. SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Elvitegravir is a HIV-1 integrase strand transfer inhibitor.

Drug Substance

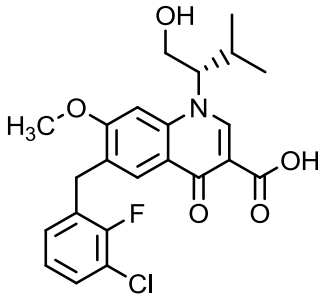
Common Name: elvitegravir (USAN)

Chemical Name: 3-quinolinecarboxylic acid, 6-[(3-chloro-2-fluorophenyl)methyl]-1,4-dihydro-1-[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]-7-methoxy-4-oxo-

Empirical Formula: $C_{23}H_{23}ClFNO_5$

Molecular Weight: 477.9

Structural Formula:



Physicochemical Properties:

Description: Elvitegravir is a white to pale yellow powder.

Solubility: The solubility is approximately 0.0003 mg/mL in water at 20 °C. The partition coefficient (log P) cannot be determined due to its low solubility in aqueous media and the pKa is 6.6 (carboxylic acid).

CLINICAL TRIALS

Study Demographics and Trial Design

Description of Clinical Studies

The efficacy of VITEKTA is primarily based on the analyses through 96 weeks from one randomized, double-blind, active-controlled study, Study 145, in treatment experienced, HIV-1 infected patients (N=702).

In Study 145, 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. Randomization 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 and defined as achieving an undetectable viral load (< 50 HIV-1 RNA copies/mL).

Baseline characteristics for Study 145 are presented in Table 7.

Table 7. Demographic and Baseline Disease Characteristics of Antiretroviral Treatment-experienced HIV-1 Infected Adult Subjects in Study 145

	VITEKTA + BR (N=351)	**Raltegravir + BR (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%
Baseline disease characteristics		
Median baseline plasma HIV-1 RNA (min-max) $\log_{10}$ 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 (min-max), 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		

	VITEKTA + BR (N=351)	Raltegravir + BR (N=351)
score[a]		
0	1%	1%
1	14%	15%
2	81%	83%
3	3%	2%
Baseline Hepatitis B coinfection		
Indeterminate	< 1%	0%
Negative	95%	97%
Positive	5%	3%
Baseline Hepatitis C coinfection		
Indeterminate	< 1%	< 1%
Negative	87%	84%
Positive	13%	16%

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.

Study Results

Treatment outcomes through 48-weeks (primary efficacy endpoint) and 96-weeks are presented in Table 8, and in Table 9 by Genotypic Sensitivity Score.

Table 8. Virologic Outcome of Randomized Treatment of Study 145 at Week 48 and Week 96[a]

	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	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 the time of change in background regimen, subjects 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.

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

d Includes subjects 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.

Table 9. Virologic Outcomes by Baseline Genotypic Sensitivity Score at Week 48 and Week 96[a]

	Week 48				**Week 96**			
	Baseline GSS ≤1		**Baseline GSS >1**		**Baseline GSS ≤1**		**Baseline GSS >1**	
	EVG + BR (N=54)	**RAL + BR** (N=54)	**EVG + BR** (N=54)	**RAL + BR** (N=54)	**EVG + BR** (N=54)	**RAL + BR** (N=54)	**EVG + BR** (N=54)	**RAL + BR** (N=54)
Virologic Success HIV-1 RNA < 50 copies/mL	76%	69%	57%	56%	70%	67%	49%	51%
Treatment Difference	9.5% (95% CI: -7.9%, 26.8%)		1.0% (95% CI: -6.8%, 8.8%)		4.8% (95% CI: -12.9%, 22.6%)		-1.5% (95% CI: -9.5%, 6.5%)	
Virologic Failure[b]	24%	17%	34%	35%	28%	13%	37%	34%
No Virologic Data at Week 48 or Week 96 Window	0	15%	9%	10%	2%	20%	14%	15%
Discontinued Study Drug Due to AE or Death[c]	0	9%	3%	4%	0	13%	3%	6%
Discontinued Study Drug Due to Other Reasons and Last	0	6%	5%	5%	2%	7%	9%	8%

Available HIV-1 RNA < 50 copies/mL[d]								
Missing Data During Window but on Study Drug	0	0	1%	1%	0	0	1%	1%

GSS: Genotypic sensitivity score; RAL: Raltegravir; EVG: Elvitegravir

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 the time of change in background regimen, subjects 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.

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

d Includes subjects 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.

In Study 145, 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^3 in the raltegravir-treated patients.

In Study 145, among female subjects, the virologic success rates at Week 48 in the VITEKTA group was numerically lower than in the raltegravir group (47.5% [28/59] and 62.7% [42/67], respectively); the treatment difference was -12.3% (95% CI: -30.1% to 5.5%). Among male subjects, the virologic success rates at Week 48 in the VITEKTA group and in the raltegravir group was 62.3% (182/292) and 56.3% (160/284), respectively; the treatment difference was 5.3% (95% CI: -2.5% to 13.2%). The low virologic success rate among female subjects in the VITEKTA group may be attributable to the high rate of discontinuation due to reasons other than lack of efficacy, adverse event, or death. The rate of study drug discontinuation due to reasons other than lack of efficacy, adverse event, or death was high in female subjects in the VITEKTA group (23.7% [14/59]).

DETAILED PHARMACOLOGY

Mechanism of Action

See **ACTION AND CLINICAL PHARMACOLOGY: Mechanism of Action.**

VIROLOGY (MICROBIOLOGY)

Antiviral Activity

See **ACTION AND CLINICAL PHARMACOLOGY: Antiviral Activity *In Vitro***.

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 mutations T66I, E92Q, and Q148R. Additional integrase mutations 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 Treatment-Experienced Patients

In an analysis of treatment-failure subjects in Study 145 through Week 96, 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 VITEKTA treatment-failure isolates (23/351 elvitegravir-treated subjects, 6.6%). Similar rates of resistance development occurred among subjects treated with raltegravir (26/351 raltegravir-treated subjects, 7.4%). The most common substitutions that emerged in the 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 elvitegravir-treated subjects who developed resistance substitutions, 14/20 (70%) subjects had HIV-1 isolates with reduced susceptibility to elvitegravir and 12/20 (60%) had reduced susceptibility to raltegravir.

Cross-resistance

Cross-resistance has been observed among INSTIs. Among the 23 subjects who developed genotypic resistance to elvitegravir with evidence of emerging primary elvitegravir resistance-associated substitutions in Study 145, 12/21 (57%) subjects with evaluable drug susceptibility data had HIV-1 with reduced susceptibility to raltegravir (greater than 1.5-fold, above the biological cutoff for raltegravir).

Elvitegravir-resistant viruses showed varying degrees of cross-resistance in cell culture to raltegravir in the INSTI class depending on the type and number of substitutions in HIV-1 integrase. Of the primary elvitegravir resistance-associated substitutions tested (T66A/I/K, E92G/Q, T97A, S147G, Q148H/K/R, and N155H), all but three (T66I, E92G, and S147G) conferred greater than 1.5-fold reduced susceptibility to raltegravir when introduced individually into a wild-type virus by site-directed mutagenesis. Of the primary raltegravir resistance-associated substitutions tested (Y143C/H/R, Q148H/K/R, and N155H), all but one (Y143H) conferred greater than 2.5-fold reductions in susceptibility to elvitegravir (above the biological cutoff for elvitegravir).

TOXICOLOGY

General

The nonclinical safety profile of elvitegravir has been studied in mice, rats, rabbits and dogs. Elvitegravir has demonstrated minimal acute toxicity after oral dosing to rats and dogs (lethal dose > 2000 mg/kg and > 1000 mg/kg in rats and dogs, respectively). There were no significant adverse effects in mice treated for 13 weeks at doses up to 2000 mg/kg/day. No adverse target organ toxicity has been observed in studies up to 26 weeks in rats and 39 weeks in dogs at dose levels up to 2000 mg/kg/day and 100 mg/kg/day, respectively. Two nonadverse findings, not considered clinically relevant, were observed in rats and dogs. Lipid-like vacuoles were observed in the lamina propria, mainly in the upper small intestine (duodenum and/or jejunum) in rats and dogs, but there were no toxic or reactive changes associated with these vacuoles. Increased cecal weight and dilatation with whitish loose contents in rats were not accompanied by histopathologic changes or adverse clinical observations. The NOAELs for elvitegravir are considered to be 2000 mg/kg/day for mice and rats, and 100 mg/kg/day for dogs – the highest doses evaluated in the 13-week, 26-week, and 39-week repeat-dose studies, respectively.

Carcinogenesis

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 (4 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 (25 times the human systemic exposure at the therapeutic daily dose).

Mutagenesis

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.

Reproductive Toxicology

Reproductive studies were conducted in rats and rabbits. Animal studies do not indicate direct or indirect harmful effects of elvitegravir with respect to pregnancy, fetal development, parturition or postnatal development. There were no effects on mating or fertility parameters.

Studies in animals have shown no evidence of teratogenicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with elvitegravir during pregnancy, there were no toxicologically significant effects on developmental endpoints. The exposures at the embryo-fetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 29 and 0.2 times higher than the exposure in humans at the recommended daily dose of 150 mg.

Elvitegravir did not affect fertility in male and female rats at approximately 21- and 38-fold higher exposures (AUC), respectively, than in humans at 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 22-fold higher than human exposures at the recommended 150 mg daily dose.

REFERENCES

1. Molina JM, Lamarca A, Andrade-Villanueva J, Clotet B, Clumeck N, Liu YP, Zhong L, Margot N, Cheng AK, Chuck SL. Efficacy and safety of once daily elvitegravir versus twice daily raltegravir in treatment-experienced patients with HIV-1 receiving a ritonavir-boosted protease inhibitor: randomised, double-blind, phase 3, non-inferiority study. *Lancet Infect Dis* 2012;12:27-35.

2. Elion R, Molina JM, López, JR, Cooper D, Maggiolo F, Wilkins E, Conway B, Liu YP, Margot N, Rhee M, Chuck SL, Szwarcberg J. A Randomized Phase 3 Study Comparing Once-Daily Elvitegravir to Twice-Daily Raltegravir in Treatment-Experienced Subjects with HIV-1 infection: 96-Week Results. *JAIDS*; Forthcoming 2013.

PART III. CONSUMER INFORMATION

Pr VITEKTA™
(Elvitegravir Tablets)

This leaflet is Part III of a three part "Product Monograph" published when VITEKTA was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about VITEKTA. Contact your doctor or pharmacist if you have any questions about the drug.

Part III of the Product Monographs of the co-administered anti-HIV medicines should also be consulted.

ABOUT THIS MEDICATION

What the medication is used for:
VITEKTA contains the active substance elvitegravir.

VITEKTA is a prescription medicine used in the treatment of Human Immunodeficiency Virus-1 (HIV) infection in adults.

VITEKTA must be taken with other anti-HIV medicines, including **one** of the following:

- atazanavir (REYATAZ®) with ritonavir (NORVIR®);
- darunavir (PREZISTA®) with ritonavir (NORVIR®);
- fosamprenavir (TELZIR ®) with ritonavir (NORVIR®);
- lopinavir/ritonavir (KALETRA®); or
- tipranavir (APTIVUS®) with ritonavir (NORVIR®).

Your doctor will tell you which of these medicines to take with VITEKTA.

The safety and effect of VITEKTA has not been established in children under age 18.

What it does:
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 the blood (viral load).

HIV infection destroys CD4 (T) cells, which are important to the immune system. The immune system helps fight infection. After a large number of T cells are destroyed, acquired immune deficiency syndrome (AIDS) develops.

VITEKTA may help increase the count of CD4+ (T) white blood cells that help fight off other infections. Lowering the amount of HIV in the blood and increasing the CD4+ (T) lowers the chance of deaths or getting infections that happen when your immune system is weak (opportunistic infections).

VITEKTA does not cure HIV infection or AIDS. The long-term effects of VITEKTA are not known at this time. People taking VITEKTA may still get opportunistic infections or other conditions that happen with HIV infection. Opportunistic infections are infections that develop because the immune system is weak. Some of these conditions are pneumonia, herpes virus infections, and *Mycobacterium avium* complex (MAC) infections. **It is very important that you see your doctor regularly while taking VITEKTA.**

VITEKTA has not been shown to reduce the risk of passing HIV to others through sexual contact or blood contamination. Continue to practice safe sex. Use latex or polyurethane condoms to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood. Do not re-use or share needles.

When it should not be used:
Do not take VITEKTA if:
- you are allergic to VITEKTA or any of its ingredients. The medicinal ingredient is elvitegravir **(**see: **What the important nonmedicinal ingredients in VITEKTA are).**

What the medicinal ingredients are:
elvitegravir
What the important nonmedicinal ingredients are:
lactose monohydrate, microcrystalline cellulose, sodium lauryl sulfate, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The tablets are film-coated with a coating material containing indigo carmine (FD&C blue #2) aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and yellow iron oxide.

What dosage forms it comes in:

VITEKTA is available as tablets. VITEKTA tablets are for oral administration. Each tablet contains 85 or 150 mg of elvitegravir as active ingredient. VITEKTA 85 mg tablets are 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. VITEKTA 150 mg tablets are green, triangle-shaped, film-coated tablet of dimensions 10.9 mm x 10.5 mm, debossed with "GSI" on one side of the tablet and "150" on the other side of the tablet. Each bottle contains 30 tablets and is closed with a child-resistant closure.

WARNINGS AND PRECAUTIONS

BEFORE you use VITEKTA (elvitegravir) talk to your doctor or pharmacist:

If you are pregnant or plan to become pregnant: It is not known if VITEKTA can harm your unborn child.

Pregnancy Registry: There is a pregnancy registry for women who take antiviral medicines during pregnancy. This registry collects information about your health and your baby's health. If you become pregnant while taking VITEKTA, talk with your doctor about taking part in this registry.

***If you are breast-feeding or plan to breast-feed*:** Do not breast-feed if you have HIV because of the chance of passing the HIV virus to your baby. It is not known if VITEKTA can pass through your breast milk and harm your baby. If you are a woman who has or will have a baby, talk with your doctor about the best way to feed your baby.

If you have other medical conditions: Let your doctor know if you have other medical conditions, especially liver problems (including hepatitis B or C virus infection).

If you are taking other medicines: VITEKTA may change the effect of other medicines and may cause side effects that can be serious or life-threatening. Other medicines can make the amount of VITEKTA in your body too low to help control your HIV infection and the virus in your body may become resistant to VITEKTA. For some medicines, your healthcare provider may need to change the amount of medicine you take or monitor your therapy more closely. As well, some medicines can interact when taken together, including prescription and non-prescription medicines, herbal products and dietary supplements (see **INTERACTIONS WITH THIS MEDICATION**).

INTERACTIONS WITH THIS MEDICATION

If you are taking VITEKTA, you should not take:

- Cobicistat TYBOST™-boosted protease inhibitors.
- Other medicines that contain elvitegravir (STRIBILD®).

Also tell your doctor if you take:

- An antacid medicine that contains aluminum, magnesium hydroxide, or calcium carbonate. Take antacids at least 2 hours before or after you take VITEKTA.
- Didanosine (VIDEX®, VIDEX EC®). Take didanosine at least 1 hour before or 2 hours after VITEKTA.
- efavirenz, nevirapine, teleprevir, boceprevir
- anticonvulsants (e.g. cabamazepine (Tegretol®), phenobarbital, phenytoin (Dilantin®)
- hormonal contraceptives (e.g. norgestimate/ethinyl estradiol)
- antimycobacterial (rifampin (Rifadin®, Rifamate®*, Rifater®, Rofact®), rifabutin)
- dexamethasone, modafinil, bosentan
- St. John's Wort (*Hypericum perforatum*)

These are not all the medicines that may cause problems if you take VITEKTA. Be sure to tell your doctor about all the medicines you take.

Keep a complete list of all the prescription and nonprescription medicines as well as any herbal medicines that you are taking, how much you take and how often you take them. Make a new list when medicines or herbal medicines are added or stopped, or if the dose changes. Give copies of this list to all your doctors and pharmacists **every** time you visit them or fill a prescription. This will give your doctor a complete picture of the medicines you use. Then he or she can decide the best approach for the situation.

PROPER USE OF THIS MEDICATION

Together with your doctor, you need to decide whether VITEKTA is right for you.

Stay under a doctor's care when taking VITEKTA. Do not change your treatment or stop treatment without first talking with your doctor.

Take VITEKTA every day exactly as your doctor prescribed it. Follow the directions from your doctor,

exactly as written on the label. Set up a dosing schedule and follow it carefully.

When your VITEKTA supply starts to run low, get more from your doctor or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. If VITEKTA is not taken regularly, as prescribed, the virus may develop resistance to VITEKTA and become harder to treat.

Only take medicine that has been prescribed specifically for you. Do not give VITEKTA to others or take medicine prescribed for someone else.

Do not use if seal over bottle opening is broken or missing.

Usual Adult Dose:

VITEKTA is not indicated for use in pediatric patients < 18 years of age.

You must always take VITEKTA with **one** of the following:

— Atazanavir (REYATAZ®) and ritonavir (NORVIR®)
— Darunavir (PREZISTA®) and ritonavir
— Fosamprenavir (TELZIR ®) and ritonavir
— Lopinavir/ritonavir (KALETRA®)
— Tipranvir (APTIVUS®) and ritonavir

- If you are taking VITEKTA with atazanavir (REYATAZ®) and ritonavir (NORVIR®) or lopinavir/ritonavir (KALETRA®), the recommended dose of VITEKTA is one 85 mg tablet orally (by mouth) once a day.
- If you are taking VITEKTA with darunavir (PREZISTA®) and ritonavir (NORVIR®) , fosamprenavir (TELZIR ®) and ritonavir or tipranavir (APTIVUS®) and ritonavir, the recommended dose of VITEKTA is one 150 mg tablet orally (by mouth) once a day.
- Swallow with plenty of water.
- Take VITEKTA with food. Taking VITEKTA with food helps get the right amount of medicine in your body.

Overdosage:

In case of drug overdose, contact your healthcare practitioner (e.g. doctor), hospital emergency department or regional poison control centre, even if there are no symptoms.

Missed Dose:

It is important that you do not miss any doses. If you miss a dose of VITEKTA, take the missed dose as soon as possible with food. Then take your next dose as usual with your other HIV medicines. If it is almost time for your next dose of VITEKTA, do not take the missed dose. Wait and take your next dose with food at your usual time with your other HIV medicines. **Do not** take a double dose to make up for a missed dose. Call your doctor or pharmacist if you are not sure what to do.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects of VITEKTA are:

- Diarrhea
- nausea
- vomiting
- headache
- abdominal pain
- tiredness muscle and joint pain
- back pain

Additional side effects may include:

- back pain
- depression
- trouble sleeping
- rash

Changes in your immune system (Immune Reconstitution Syndrome) can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time, or you could develop an autoimmune disease in which your immune system reacts against your own body (e.g. Grave's disease (which affects the thyroid gland), Guillain-Barre syndrome (which affects the nervous system) or polymyositis (which affects the muscles) and it may develop at any time, sometimes months later after the start of HIV therapy). Sometimes symptoms can be severe, so if you develop high temperature (fever), joint or muscle pain, redness, rash, swelling or fatigue, or any new symptoms, contact your doctor right away.

For more information on the side effects of of the co-administered anti-HIV medicines see the Consumer Information Leaflets for these products.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are **not** all the possible side effects of VITEKTA. If you have questions about side effects, ask your doctor, nurse, or pharmacist. You should report any new or continuing symptoms to your doctor right away. Your doctor may be able to help you manage these side effects.

HOW TO STORE IT

- Keep VITEKTA and all other medications out of reach of children.
- VITEKTA should be stored at 15–30 °C (59–86 °F). It should remain stable until the expiration date printed on the label.
- Do not keep your medicine in places that are too hot or cold.
- Do not keep medicine that is out of date or that you no longer need. If you throw any medicines away make sure that children will not find them.
- Keep VITEKTA in its original container and keep the container tightly closed.

REPORTING SUSPECTED SIDE EFFECTS
You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the Medeffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, please contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at: www.gilead.ca or by contacting the sponsor, Gilead Sciences Canada, Inc., at: 1-866-207-4267

This leaflet was prepared by Gilead Sciences, Inc.

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