PRODUCT MONOGRAPH

PrSYMTUZA™

darunavir*/cobicistat/emtricitabine/tenofovir alafenamide**

film-coated tablets (800 mg/150 mg/200 mg/10 mg)
*as 867 mg darunavir ethanolate
**as 11.2 mg tenofovir alafenamide hemifumarate

Antiretroviral Agent

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Pharmaceutical Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	film-coated tablet 800 mg darunavir*/ 150 mg cobicistat/ 200 mg emtricitabine/ 10 mg tenofovir alafenamide** *as 867 mg darunavir ethanolate **as 11.2 mg tenofovir alafenamide hemifumarate	*For a complete listing see* **DOSAGE FORMS, COMPOSITION AND PACKAGING** *section.*

INDICATIONS AND CLINICAL USE

SYMTUZA™ (darunavir/cobicistat/emtricitabine/tenofovir alafenamide) is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg) and with no known mutations associated with resistance to the individual components of SYMTUZA™.

For a description of the clinical data and dosing in support of this indication, refer to **CLINICAL TRIALS** and **DOSAGE AND ADMINISTRATION**.

Pediatrics (≥12 and < 18 years of age)
The safety and efficacy of SYMTUZA™ in children younger than 12 years or weighing less than 40 kg have not been established. (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Geriatrics (≥ 65 years of age)
Limited information is available on the use of SYMTUZA™ in patients aged 65 and over). (see **WARNINGS AND PRECAUTIONS**, **DOSAGE AND ADMINISTRATION,** and **ACTION AND CLINICAL PHARMACOLOGY**). Therefore, SYMTUZA™ should be used with caution in elderly patients.

CONTRAINDICATIONS

SYMTUZA™ is contraindicated in patients who are hypersensitive to darunavir, cobicistat, emtricitabine, tenofovir alafenamide, or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

SYMTUZA™ is contraindicated in patients with severe (Child-Pugh Class C) hepatic insufficiency.

Darunavir and cobicistat are both inhibitors of the cytochrome P450 3A (CYP3A) isoform. Administration of SYMTUZA™ is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index). Darunavir and cobicistat are both substrates of the cytochrome P450 3A (CYP3A) isoform. Co-administration of SYMTUZA™ is contraindicated with potent CYP3A inducers as it may lead to lower exposures of darunavir and cobicistat and potential loss of efficacy of darunavir and development of resistance. Drugs that are contraindicated with SYMTUZA™ are listed in Table 1 (also see **DRUG INTERACTIONS**, **Drug-Drug Interactions**, Table 6).

Table 1: Drugs that are Contraindicated with SYMTUZA™

Drug Class	Drugs within Class that are Contraindicated with SYMTUZA™
Alpha 1-Adrenoreceptor Antagonist	Alfuzosin
Antiarrhythmics	amiodarone, bepridil[1], dronedarone, lidocaine (systemic), quinidine
Anti-coagulants	apixaban, rivaroxaban
Anti-convulsants	carbamezepine, phenobarbital, phenytoin
Anti-gout	colchicine (in patients with renal and/or hepatic impairment)
Antihistamines	astemizole[1], terfenadine[1]
Antimycobacterial	rifampin
Ergot Derivatives	dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI Motility Agents	cisapride[1]
Hepatitis C Virus Direct-Acting Antivirals	elbasvir/grazoprevir
Herbal Products	St. John's wort (*Hypericum perforatum*)
HMG-CoA Reductase Inhibitors	lovastatin, simvastatin
Other Lipid Modifying Agents:	lomitapide
Inhaled Beta Agonist	salmeterol
Neuroleptics	lurasidone, pimozide
PDE-5 Inhibitor	sildenafil (for treatment of pulmonary arterial hypertension)
Platelet Aggregation Inhibitor	ticagrelor
Sedatives/Hypnotics	orally administered midazolam, triazolam

[1] Not marketed in Canada.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Post-treatment Exacerbation of Hepatitis

SYMTUZA™ is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of SYMTUZA™ have not been established in patients coinfected with HIV-1 and HBV. Discontinuation of SYMTUZA™ therapy in patients coinfected with HIV-1 and HBV may be associated with severe acute exacerbations of hepatitis due to the emtricitabine or tenofovir alafenamide components of SYMTUZA™. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue SYMTUZA™. If appropriate, initiation of antihepatitis B therapy may be warranted (see W**ARNINGS AND PRECAUTIONS, Special Populations**).

General

Patients with HIV-1 harboring mutations

SYMTUZA™ should not be used in antiretroviral-experienced patients with HIV-1 harboring any darunavir resistance-associated mutations (such as V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V) in HIV-1 protease or the K65R mutation in HIV-1 reverse transcriptase (see **MICROBIOLOGY**), or with suspected darunavir or tenofovir resistance, in virologically suppressed patients if no genotype is available.

Interactions with medicinal products

SYMTUZA™ can cause and/or is subject to drug interactions which may be life-threatening or result in lack of efficacy (see **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, General** and **DRUG INTERACTIONS**).

SYMTUZA™ should not be coadministered with products containing any of the same components, darunavir, cobicistat, emtricitabine or tenofovir alafenamide (PREZISTA®, PREZCOBIX®, TYBOST®, STRIBILD®, ATRIPLA®, COMPLERA®, DESCOVY®, EMTRIVA®, GENVOYA®, ODEFSEY™, TRUVADA®, VEMLIDY™); or with products containing lamivudine (3TC®, COMBIVIR®, TRIUMEQ® and TRIZIVIR®) or tenofovir disoproxil fumarate (ATRIPLA®, COMPLERA®, TRUVADA®, VIREAD®); SYMTUZA™ should not be administered concurrently with ritonavir or ritonavir containing products or regimens (HOLKIRA™ PAK, KALETRA®, NORVIR®) due to similar effects of cobicistat and ritonavir on CYP3A. SYMTUZA™ should not be administered with adefovir dipivoxil (HEPSERA®). SYMTUZA™ should not be used in combination with another antiretroviral that requires pharmacokinetic boosting with ritonavir or cobicistat (REYATAZ®, INVIRASE®, KALETRA®, CRIXIVAN®).

Due to inhibition of CYP3A by SYMTUZA™, co-administration of SYMTUZA™ with quetiapine may results in increased quetiapine concentrations. Serious and life-threatening quetiapine-related adverse reactions have been reported with CYP3A inhibitors. SYMTUZA™ should not be used in combination with quetiapine (see **DRUG INTERACTIONS**). Monitoring and dose reductions may be required if necessary.

Carcinogenesis and Mutagenesis

Darunavir was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays including bacterial reverse mutation (Ames), chromosomal aberration in human lymphocytes and *in vivo* micronucleus test in mice (see **TOXICOLOGY, Carcinogenesis and Mutagenesis**).

Refer to **TOXICOLOGY, Carcinogenesis and Mutagenesis** for information regarding cobicistat, emtricitabine and tenofovir alafenamide.

Endocrine and Metabolism

Diabetes Mellitus/Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor (PI) therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued PI therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and causal relationships between PI therapy and these events have not been established.

Serum Lipids and Blood Glucose

Serum lipid and blood glucose levels may increase during antiretroviral therapy. Disease control and life style changes may also be contributing factors. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders and blood glucose elevations should be managed as clinically appropriate. See **DRUG INTERACTIONS,** Table 6 and Table 7 for information on potential drug interactions with SYMTUZA™ and HMG-CoA reductase inhibitors /other lipid modifying agents.

Hematologic

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship between protease inhibitor therapy and these events has not been established; however, the frequency of bleeding episodes should be closely monitored in patients on SYMTUZA™

Hepatic/Biliary/Pancreatic

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including emtricitabine (FTC), a component of SYMTUZA™, and tenofavir disoproxil fumarate (TDF), another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with SYMTUZA™ should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or

pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Hepatic Impairment

SYMTUZA™ has not been investigated in patients with hepatic impairment. However, there are pharmacokinetic data for the components of SYMTUZA™. (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency**).

SYMTUZA™ is contraindicated in patients with severe hepatic insufficiency (Child-Pugh Class C) (see **CONTRAINDICATIONS**). Patients with mild or moderate hepatic impairment (Child-Pugh Class A or B, respectively) should be closely monitored.

The safety and efficacy of SYMTUZA™ have not been studied specifically in patients with underlying liver disorders. Patients with chronic hepatitis B or C and treated with antiretroviral therapy (ART) are at increased risk for severe and potentially fatal hepatic adverse events (see **WARNINGS AND PRECAUTIONS, Special Populations**).

Hepatotoxicity

In patients receiving darunavir, cases of drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported in 0.5% of patients.

Post-marketing cases of clinical hepatitis and hepatic decompensation, including some fatalities have been reported. These have generally occurred in patients with advanced HIV disease taking multiple concomitant medications, having co-morbidities including hepatitis B or C co-infection, and/or developing immune reconstitution inflammatory syndrome. A causal relationship with darunavir/ritonavir therapy has not been established.

Patients with pre-existing liver dysfunction including chronic hepatitis B or C have an increased frequency of liver function abnormalities during combination antiretroviral therapy. They should be monitored according to standard practice.

Appropriate monitoring should be conducted prior to initiating therapy with SYMTUZA™ and increased monitoring should be considered in patients with elevated baseline transaminase levels, active hepatitis B and/or C and in patients with underlying liver disease, especially during the first several months of SYMTUZA™ treatment.

Evidence of new or worsening liver dysfunction (including clinically significant elevation of liver enzymes and/or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness and hepatomegaly) in patients on SYMTUZA™, should prompt consideration to interrupt or discontinue treatment.

Pancreatic

Caution should be exercised in the use of SYMTUZA™ in patients with a history of pancreatitis or risk factors for the development of pancreatitis. Pancreatitis has been observed in patients receiving darunavir/ritonavir therapy and those receiving nucleoside analogues, including those who developed marked triglyceride elevations. Although a causal relationship to darunavir has

not been established, marked triglyceride elevation is a risk factor for development of pancreatitis (see **WARNINGS AND PRECAUTIONS**, **Endocrine and Metabolism, Serum Lipids and Blood Glucose**). Patients with advanced HIV disease may be at risk of elevated triglycerides and pancreatitis, and patients with a history of pancreatitis may be at increased risk for recurrence during SYMTUZA™ therapy. Therapy should be suspended in patients with suspected pancreatitis.

Immune

Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome has been reported in patients treated with combination ART, including emtricitabine, a component of SYMTUZA™. During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection (MAC), cytomegalovirus (CMV), *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis (TB)), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis and Guillain-Barré 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

Bone Effects of Tenofovir Alafenamide

Tenofovir alafenamide and tenofovir have been shown to be associated with decreases in bone mineral density (BMD) in animal toxicology studies and in human clinical trials. Refer to DESCOVY Product Monograph for further information.

The effects of tenofovir alafenamide-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown.

In a pooled analysis of two Phase 3 clinical studies in HIV-1 infected ART treatment-naïve adults who received FTC+TAF in combination with elvitegravir (EVG) and COBI as a fixed dose combination (FDC) tablet, the percentage of patients who had more than a 3% decrease from baseline in hip and spine BMD at Week 48 was 17% and 27%, respectively, and at Week 96 was 23% and 26%, respectively.

The effects of TAF-associated changes in BMD on long-term bone health and future fracture risk are unknown.

Renal

Effects on Serum Creatinine

Cobicistat has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function (see **ADVERSE REACTIONS, Decrease estimated creatinine clearance**). This effect should be considered

when interpreting changes in creatinine clearance in patients initiating SYMTUZA™ particularly when co-administered with a drug that has dosing adjustment recommendations guided by estimated creatinine clearance. Dosing recommendations are not available for drugs that require dosing adjustment for renal impairment with the use of cobicistat (see **DOSAGE AND ADMINISTRATION**, **Recommended Dose and Dosage Adjustment, Renal Impairment**). Consider alternative medications that do not require dosing adjustments.

Although cobicistat may cause modest increases in serum creatinine and modest declines in estimated creatinine clearance without affecting renal glomerular function, patients who experience a confirmed increase in serum creatinine of greater than 0.4 mg per dL from baseline should be closely monitored for renal safety including measuring serum phosphorus, urine glucose, and urine protein.

Renal Impairment

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir prodrugs in both animal toxicology studies and human trials.

A potential risk of nephrotoxicity resulting from chronic exposure to low levels of tenofovir due to dosing with tenofovir alafenamide cannot be excluded. Patients taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents including non-steroidal anti-inflammatory drugs are at increased risk of developing renal-related adverse reactions.

Sensitivity

Darunavir contains a sulfonamide moiety. SYMTUZA™ should be used with caution in patients with a known sulfonamide allergy. The potential for cross-sensitivity between drugs in the sulfonamide class and darunavir is unknown. In clinical studies with darunavir/ritonavir, the incidence and severity of rash was similar in patients with or without a history of sulphonamide allergy.

Severe Skin Reactions

In patients receiving darunavir, severe skin reactions may occur. During the clinical development program (n=3,063), where darunavir was co-administered with low dose ritonavir, severe skin reactions, which may be accompanied by fever and/or elevations of transaminases, have been reported in 0.4% of patients. Stevens-Johnson Syndrome was rarely (< 0.1%) reported; and during post-marketing experience toxic epidermal necrolysis, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) and acute generalized exanthematous pustulosis have been reported very rarely (< 0.01%). Discontinue SYMTUZA™ immediately if signs or symptoms of severe skin reactions develop. These can include but are not limited to severe rash or rash accompanied with fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis and/or eosinophilia.

Special Populations

Pregnant Women

There are no human data on the use of SYMTUZA™ during pregnancy. SYMTUZA™ is not recommended for use during pregnancy because of substantially lower exposures of darunavir and cobicistat during pregnancy. SYMTUZA™ should not be initiated in pregnant women. An alternative regimen is recommended for women who become pregnant during therapy with SYMTUZA™.

Darunavir/cobicistat in combination with a background regimen was evaluated in a clinical trial of 7 pregnant women during the second and third trimesters, and postpartum (6-12 weeks). The pharmacokinetic data demonstrate that exposure to darunavir boosted with cobicistat was substantially lower during pregnancy compared with postpartum (see **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions, Pregnancy**).

There are no clinical data on the virologic response when SYMTUZA™ is initiated during pregnancy.

In the embryo-fetal development study in rats, administration of tenofovir alafenamide was associated with reduced fetal body weight and delayed ossification rate at ≥100 mg/kg. The no-observed-adverse-effect-level (NOAEL) for embryo-fetal development was 25 mg/kg (approximately 10 times the clinical tenofovir exposure based on AUC).

In the embryo-fetal toxicity study in pregnant rabbits, administration of tenofovir alafenamide resulted in significantly increased number of litters with minor external and visceral anomalies at 100 mg/kg (approximately 90 times the clinical tenofovir exposure based on AUC). The NOAEL for embryo-fetal development was 30 mg/kg/day (approximately 17 times the clinical tenofovir exposure based on AUC).

In the peri- and postnatal development study, administration of tenofovir disoproxil fumarate, another prodrug of tenofovir, to pregnant rats resulted in increased peri/postparturn pup mortality, reduced pup survival, reduced pup body weights, reduced survival of F1 generation, reduced body weight/food consumption of F1 generation and delayed sexual maturation of F1 generation at ≥400 mg/kg (approximately 90 times the clinical tenofovir exposure based on AUC). The NOAEL for these effects was 150 mg/kg (approximately 25 times the clinical tenofovir exposure based on AUC). These results are considered relevant to tenofovir alafenamide.

Antiretroviral Pregnancy Registry: *To monitor maternal-fetal outcomes of pregnant women exposed to SYMTUZA™, an Antiretroviral Pregnancy Registry has been established. Healthcare professionals are encouraged to register patients*
http://www.apregistry.com
Telephone: 1-800-258-4263
Fax: 1-800- 800-1052.

Nursing Women

HIV-infected mothers should not breast-feed their infants to avoid risking postnatal transmission of HIV.

Emtricitabine is excreted in human milk. It is not known whether darunavir, cobicistat, tenofovir alafenamide or their metabolites are excreted in human milk. Animal studies have demonstrated that darunavir, cobicistat, and tenofovir are excreted in milk.

In humans, samples of breast milk obtained from five HIV-1 infected mothers show that emtricitabine is secreted in human milk at estimated neonatal concentrations 3 to 12 times higher than the emtricitabine IC_{50} but 3 to 12 times lower than the C_{min} achieved from oral administration of emtricitabine. Breastfeeding infants whose mothers are being treated with emtricitabine may be at risk for developing viral resistance to emtricitabine. Other emtricitabine-associated risks in infants breastfed by mothers being treated with emtricitabine are unknown.

Tenofovir-associated risks, including the risk of developing viral resistance to tenofovir, in infants breastfed by mothers being treated with tenofovir alafenamide are unknown.

There is insufficient information on the effects of cobicistat, emtricitabine, and tenofovir in newborns/infants, and children below 3 years of age should not be exposed to darunavir (see **TOXICOLOGY, Reproductive and Developmental Toxicity**). Therefore, SYMTUZA™ should not be used during breast-feeding. Because of both the potential for HIV transmission and the potential for serious adverse events in nursing infants, mothers should be instructed not to breast-feed if they are receiving SYMTUZA™ (see **TOXICOLOGY**, **Reproductive and Developmental Toxicity**).

Fertility

There was no effect on mating or fertility with darunavir, cobicistat, emtricitabine, or tenofovir alafenamide treatment in animals (see **TOXICOLOGY, Reproductive and Developmental Toxicity**). No effect on reproduction or fertility is expected with SYMTUZA™.

Pediatrics (≥12 and< 18 years of age)

Safety and efficacy of SYMTUZA™ in children younger than 12 years or weighing <40 kg have not been established.

Geriatrics (≥ 65 years of age)

Limited information is available on the use of SYMTUZA™ in patients aged 65 and over. (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Elderly)**.

In general, caution should be exercised in the administration and monitoring of SYMTUZA™ in elderly patients, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy.

Patients co-infected with HIV and hepatitis B (HBV) or C (HCV) virus

Patients with chronic hepatitis B or C treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. It is recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B virus (HBV) before initiating ART.

The safety and efficacy of SYMTUZA™ in patients co-infected with HIV-1 and HBV and/or HCV have not been established.

Severe acute exacerbations of hepatitis B (and association with liver decompensation and liver failure in some patients), may occur in patients coinfected with HBV and HIV-1 after discontinuation of emtricitabine and tenofovir alafenamide, two of the components of SYMTUZA™.

Hepatic function should be closely monitored with both clinical and laboratory follow-up for at least several months in patients who discontinue SYMTUZA™ and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure. Therefore, in these patients, discontinuation of treatment without initiation of alternative anti-hepatitis B therapy is not recommended.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The overall safety profile of SYMTUZA™ is based on a randomized, double-blinded, comparative Phase 2 trial, GS-US-299-0102, and on all available clinical trial and post marketing data of its components. As SYMTUZA™ contains darunavir, cobicistat, emtricitabine, and tenofovir alafenamide, the adverse reactions associated with each of the individual compounds may be expected.

The following adverse drug reactions are discussed in other sections of the product monograph:

- Lactic Acidosis/Severe Hepatomegaly with Steatosis (See **WARNINGS AND PRECAUTIONS, Lactic Acidosis/Severe Hepatomegaly with Steatosis**)
- Severe Acute Exacerbations of Hepatitis B (see **Serious Warnings and Precautions**, **WARNINGS AND PRECAUTIONS, Special Populations, Patients co-infected with HIV and hepatitis B (HBV) or C (HCV) virus**)
- Immune Reconstitution Inflammatory Syndrome (see **WARNINGS AND PRECAUTIONS**)

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 Reactions in Trials with Darunavir/Cobicistat/Emtricitabine/Tenofovir disoproxil fumarate 800/150/200/10 mg q.d.

In clinical study GS US-299-0102, 153 HIV-1 infected treatment-naïve adult patients received either SYMTUZA™ (N=103) or cobicistat (COBI)-boosted darunavir (DRV) (single agents) plus emtricitabine/tenofovir disoproxil fumarate (FTC/TDF fixed-dose combination) (N=50) once daily for at least 48 weeks. The median exposure in 103 patients treated with SYMTUZA™ was 68 weeks. The majority of the adverse reactions reported during treatment with SYMTUZA™ were mild in severity. The most frequent (≥5%) adverse reaction to SYMTUZA™ that was moderate to severe (Grade 2-4) was diarrhea. Grade 3 adverse reactions were drug hypersensitivity and rash (incidence 1%); no Grade 4 adverse reactions were reported. 1% of the patients discontinued treatment due to adverse reactions. An overview of adverse reactions of at least Grade 2 severity reported in GS US-299-0102 is presented in Table 2 below.

Table 2: Adverse Reactions at Least Grade 2 Severity in GS-US-299-0102

System Organ Class Adverse Reaction	**SYMTUZA™** N=103	**DRV+COBI+FTC/TDF** N=50
Gastrointestinal disorders		
Diarrhea	5.8%	8.0%
Nausea	1.9%	2.0%
Abdominal pain	1.0%	6.0%
Vomiting	1.0%	2.0%
Dyspepsia	1.0%	0
General disorders and administration site conditions		
Fatigue	2.9%	2.0%
Immune system disorders		
(Drug) hypersensitivity	1.0%	0
Musculoskeletal and connective tissue disorders		
Myalgia	1.9%	0
Nervous system disorders		
Headache	1.0%	2.0%
Skin and subcutaneous tissue disorders		
Rash	3.9%	4.0%
Pruritus	1.0%	0

Additional adverse reactions of Grade 2-4 severity that were reported for SYMTUZA™ components in other trials are presented in Table 3.

Table 3: Additional Adverse Reactions at Least Grade 2 Severity Reported for SYMTUZA™ Components	
System Organ Class Adverse Reaction	
Gastrointestinal disorders	
Abdominal distension	2.0%
Flatulence	1.0%
Acute pancreatitis	0.6%
General disorders and administration site conditions	
Asthenia	0.9%
Hepatobiliary disorders	
Acute hepatitis	0.3%
Immune system disorders	
Immune reconstitution syndrome	0.3%
Metabolism and nutrition disorders	
Anorexia	1.5%
Diabetes mellitus	0.6%
Musculoskeletal and connective tissue disorders	
Osteonecrosis	0.3%
Psychiatric disorders	
Abnormal dreams	0.3%
Reproductive system and breast disorders	
Gynecomastia	0.3%
Skin and subcutaneous tissue disorders	
Urticaria	1.2%
Lipodystrophy	0.9%
Angioedema	0.6%
Stevens-Johnson syndrome	0.3%

Note: The incidence is based on Grade 2-4 adverse reactions reported in (1) GS-US-216-0130 (DRV/COBI, 48 week analysis, N=313), (2) ARTEMIS trial (DRV/rtv qd, 192 week analysis, N=343), or (3) TITAN trial (DRV/rtv bid, 96 week analysis, N=298).

Adverse Reactions from Clinical Trials of the Components of SYMTUZA™

For information on the safety profile of EMTRIVA, TYBOST™, PREZISTA®, PREZCOBIX® and DESCOVY® consult the Product Monograph for each of these products.

Abnormal Clinical Chemistry Findings

Serum Lipids

In Study GS-US-299-0102, increases from baseline were observed for fasting total cholesterol, fasting direct LDL cholesterol, fasting HDL cholesterol, and fasting triglycerides at Week 48 for each treatment group, with the median increase from baseline being greater in the SYMTUZA™ group compared with the DRV+COBI+FTC/TDF.

A similar percentage of subjects in each treatment group received concomitant lipid-modifying agents (SYMTUZA™ 14.6%, 15 subjects; DRV+COBI+FTC/TDF 14.0%, 7 subjects). In the SYMTUZA™ group, 10 of the 15 subjects were continuing treatment from baseline, while 5 initiated treatment during the study. In the DRV+COBI+FTC/TDF group, 3 subjects were continuing treatment from baseline, and 4 subjects initiated treatment during the study. Changes from baseline in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, and total cholesterol to HDL ratio are presented in Table 4.

Table 4: Lipid Values, Mean Change from Baseline, Reported in Patients Receiving SYMTUZA™ or DRV+COBI+FTC/TDF in Study GS-US-299-0102

	SYMTUZA™ (N = 103)		DRV+COBI+FTC/TDF (N = 50)	
	Baseline	Change[a] at Week 48	Baseline	Change[a] at Week 48
	n=77[c]		n=45[d]	
Total Cholesterol (fasted) mmol/L	4.09	+1.01	4.31	+0.33
HDL-cholesterol (fasted) mmol/L	1.11	+0.18	1.18	+0.05
LDL-cholesterol (fasted) mmol/L	2.52	+0.80	2.77	+0.22
Triglycerides (fasted) mmol/L	1.46	+0.43	1.29	+0.36
Total Cholesterol to HDL ratio	4.21	0.39	3.83	0.15

a. Subjects on lipid lowering agents (i.e. lipid modifying agents, excluding omega-3 fatty acids and fish oil given for general health) at screening/baseline were excluded from the analysis (8 on SYMTUZA™, 1 on DRV+COBI+FTC/TDF). Subjects initiating a lipid-lowering agent post-baseline (5 on SYMTUZA™, 4 on DRV+COBI+FTC/TDF) had their last fasted on-treatment value (prior to starting the agent) carried forward.

b. The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 48 values (the baseline mean is calculated only in subjects having value at Week 48)

c. n=77 for all tests.

d. n=45 for all tests.

Laboratory abnormalities, Grade 2-4, reported in study GS US-299-0102 and considered adverse reactions are shown in Table 5.

Table 5: Laboratory Abnormalities, Grade 2-4, Considered Adverse Reactions in GS-US-299-0102

Laboratory Parameter Grade	Limit	SYMTUZA™ N=102 %*	DRV+COBI+FTC/TDF N=50 %*
Amylase			
Grade 2	>1.5 to ≤2.0 x ULN	1%	10%
Grade 3	>2.0 to ≤5.0 x ULN	0	2%
Grade 4	>5.0 x ULN	1%	0
Lipase			
Grade 2	>1.5 to ≤3.0 x ULN	0	22.2%
Creatinine			
Grade 2	1.4 to 1.8 x ULN	0	2%
Triglycerides, fasting			
Grade 2	5.65-8.48 mmol/L	2%	2%
Grade 3	8.49-13.56 mmol/L	3%	0
Grade 4	>13.56 mmol/L	1%	2%
Total Cholesterol, fasting			
Grade 2	240-300 mg/dL	15.2%	12.2%
Grade 3	>300 mg/dL	4%	2%
LDL Cholesterol, fasting			
Grade 2	4.13-4.9 mmol/L	19.2%	10.2%

Table 5: Laboratory Abnormalities, Grade 2-4, Considered Adverse Reactions in GS-US-299-0102			
Grade 3	>4.9 mmol/L	5.1%	8.2%
Hyperglycemia			
Grade 2	6.95-13.88 mmol/L	19.6%	18%
Grade 3	13.89-27.75 mmol/L	2%	0
Grade 4	>27.75 mmol/L	1%	0
Alanine Aminotransferase			
Grade 2	>2.5 to ≤5.0 x ULN	2.9%	4%
Grade 3	>5.0 to ≤10.0 x ULN	1%	0
Aspartate Aminotransferase			
Grade 2	>2.5 to ≤5.0 x ULN	2.9%	4%
Grade 3	>5.0 to ≤10.0 x ULN	0	2%
Grade 4	>10.0 x ULN	1%	2%

Note: no Grade 2-4 abnormalities were reported for Alkaline Phosphatase
N=total number of subjects with data
* The number of subjects with data can vary per laboratory parameter, but the % reflects the true percentage of observed abnormalities.

Rash

Rash is a common adverse reaction in patients treated with darunavir. Rash was mostly mild to moderate, often occurring within the first four weeks of treatment and resolving with continued dosing. The discontinuation rate due to rash in patients using darunavir is ≤2.2%. In the comparative Phase 2 trial investigating SYMTUZA™ as a single tablet regimen, 11.7% of patients receiving SYMTUZA™ (N=103) experienced rash (most of which were grade 1), of which 1% of patients discontinued treatment due to grade 3 hypersensitivity and rash.

Decrease estimated creatinine clearance

Cobicistat increases serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function as assessed, for instance, by using Cystatin C (Cyst C) as filtration marker.

In the Phase 2 trial of SYMTUZA™ in treatment-naïve patients, increases in serum creatinine and decreases in $eGFR_{CG}$ occurred at the first on-treatment assessment (Week 2) and remained stable through 48 weeks. At Week 48, changes from baseline were smaller with darunavir/ cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) than with darunavir+cobicistat+ emtricitabine/tenofovir disoproxil fumarate (D+C+F/TDF). The median change in $eGFR_{CG}$ was 2.9 mL/min with D/C/F/TAF and -10.6 mL/min with D+C+F/TDF (p=0.017). Using Cyst C as filtration marker, the median changes in estimated glomerular filtration rate calculated using the CKD-EPI ($eGFR_{CKD-EPI}$ Cyst C) formula were respectively 6.7 mL/min/1.73m² and 0.3 mL/min/1.73m² (p=0.029).

Clinical Trials in Pediatric Patients (12 to <18 years of age)

The safety of SYMTUZA™ in pediatric patients has not been investigated. However, the safety of SYMTUZA™ components was evaluated through the clinical studies TMC114-C230 (N=12) for darunavir with ritonavir and GS-US-292-0106 (N=50) for a fixed-dose combination containing elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide. Data from these studies showed that the overall safety profile in adolescent patients aged 12 to <18 years and weighing at least 40 kg was similar to that observed in the adult population.

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

Limited information is available on the use of SYMTUZA™ components in patients co-infected with hepatitis B and/or C virus. Among 1968 treatment-experienced patients receiving darunavir co-administered with ritonavir twice daily, 236 patients were co-infected with hepatitis B or C. In co-infected patients, the incidence of adverse events and clinical chemistry abnormalities was not higher than in patients who were not co-infected, except for increased hepatic enzymes. The safety of emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet was evaluated in approximately 70 HIV/HBV co-infected patients receiving treatment for HIV in an open-label clinical study (GS US-292-1249). Based on this limited experience, the safety profile of emtricitabine and tenofovir alafenamide in patients with HIV/HBV co-infection appears to be similar to that in patients with HIV-1 monoinfection.

Post-Market Adverse Drug Reactions

In addition to adverse events identified in clinical trials, the following post-marketing events have been reported voluntarily during post-approval use of darunavir and/or cobicistat and emtricitabine. These events have been included due to their seriousness, frequency of reporting, potential causal association with treatment, or a combination of these factors. Because they are reported spontaneously from a population of unknown size, estimates of incidence cannot be made.

Darunavir/Cobicistat:

Blood and Lymphatic System Disorders: anemia, pancytopenia, thrombocytopenia and neutropenia

Cardiac Disorders: bradycardia, myocarditis

Eye Disorders: eye swelling, uveitis, maculopathy, blurred vision

Gastrointestinal Disorders: pancreatitis relapsing, rectal hemorrhage, gastritis

Hepatobiliary Disorders: bile duct obstruction, hepatic cirrhosis, hepatic failure, hepatotoxicity, jaundice

Infections and Infestations: clostridial infection, cryptosporidiosis infection, cytomegalovirus encephalitis, hepatitis B, esophageal candidiasis, progressive multifocal leukoencephalopathy, sepsis

Investigations: blood alkaline phosphatase increased, blood bilirubin increased, abnormal liver function test

Injury, Poisoning and Procedural Complications: drug toxicity

Metabolism and Nutrition Disorders: dehydration, hyperkalemia, metabolic acidosis

Musculoskeletal and Connective Tissue Disorders: increased creatine phosphokinase (CPK), myositis, rhabdomyolysis, sensation of heaviness, arthritis, bone pain, pain in extremities, arthropathy

Neoplasms Benign, Malignant and Unspecified: diffuse large B-cell neoplasm, malignant hepatic neoplasm, lymphoma

Nervous System Disorders: altered state of consciousness, cerebrovascular accident, dizziness, facial palsy, grand mal convulsion, ischemic cerebral infarction, nervous system disorder, neuromyopathy, petit mal epilepsy

Psychiatric Disorders: completed suicide, anxiety, depression

Renal and Urinary Disorders: acute renal failure, hematuria, renal tubular necrosis, creatinine renal decreased, GFR decreased, renal failure, proteinuria

Respiratory, Thoracic and Mediastinal Disorders: acute respiratory distress syndrome, pharyngeal lesion, pneumothorax, respiratory failure, pulmonary edema, epistaxis

Skin and Subcutaneous Tissue Disorders: angioedema, swelling face, toxic epidermal necrolysis, urticaria, acute generalized exanthematous pustulosis, DRESS (Drug Rash with Eosinophilia and Systemic Symptoms)

Emtricitabine:
Blood and lymphatic system disorders: thrombocytopenia

Gastrointestinal disorders: pancreatitis

General disorders and administrative site conditions: pyrexia

Metabolism and nutrition disorders: lactic acidosis

For information on the safety profile of EMTRIVA, TYBOST™, PREZISTA®, PREZCOBIX® and DESCOVY® consult the Product Monograph for each of these products.

DRUG INTERACTIONS

Serious Drug Interactions

- Darunavir and cobicistat are both inhibitors of the cytochrome P450 3A (CYP3A) isoform. SYMTUZA™ should not be co-administered with medicinal products that are highly dependent on CYP3A for clearance, and for which increased plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index). These medicinal products include alfuzosin, amiodarone, apixaban, astemizole, bepridil, cisapride, colchicine (in patients with renal and/or hepatic impairment), dronedarone, elbasvir/grazoprevir, the ergot alkaloids (e.g., ergotamine, dihydroergotamine, ergonovine, and methylergonovine), lidocaine (systemic), lomitapide, lovastatin, lurasidone, oral midazolam, pimozide, quinidine, rivaroxaban, salmeterol, sildenafil (when used for the treatment of pulmonary arterial hypertension), simvastatin, terfenadine, ticagrelor and triazolam (see **CONTRAINDICATIONS**).
- Rifampin and St John's Wort (*Hypericum perforatum*), carbamezepine, phenytoin and phenobarbital are potent inducers of CYP450 metabolism. SYMTUZA™ should not be used in combination with these products as this may cause significant decreases in darunavir plasma concentrations. This may result in a loss of therapeutic effect of SYMTUZA™ and development of resistance (see **CONTRAINDICATIONS**).

Overview

SYMTUZA™ can cause and/or is subject to drug interactions which may be life-threatening or result in lack of efficacy (see **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, General** and **Drug-Drug Interactions**).

No drug interaction studies have been performed using SYMTUZA™. Interactions that may occur with SYMTUZA™ are determined by interactions that have been identified with any of its components.

Darunavir and cobicistat

Darunavir is an inhibitor of the cytochrome P450 isoform CYP3A. Cobicistat is a weak inhibitor of CYP2D6 and strong inhibitor of CYP3A. Cobicistat is not expected to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9 or CYP2C19. Cobicistat is not expected to induce CYP1A2, CYP3A4, CYP2C9, CYP2C19, uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), or multidrug resistance protein 1 (MDR1). The transporters cobicistat inhibits include p-glycoprotein (P-gp), BCRP, MATE1, OATP1B1 and OATP1B3. Thus, co-administration of SYMTUZA™ with drugs that are primarily metabolized by CYP3A, or CYP2D6, or are substrates of P-gp, BCRP, MATE1, OATP1B1, or OATP1B3 may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse events (see **CONTRAINDICATIONS** and **Drug-Drug Interactions**, Table 6 and Table 7).

Darunavir and cobicistat are metabolized by CYP3A. Drugs that induce CYP3A activity would be expected to lower plasma concentrations of darunavir and cobicistat. Co-administration with strong inducers of CYP3A could potentially lead to loss of efficacy of darunavir and possible development of resistance (see **CONTRAINDICATIONS** and **Drug-Drug Interactions**, Table 6 and Table 7). Co-administration of SYMTUZA™ and other medicinal products that inhibit CYP3A may increase plasma concentrations of darunavir and cobicistat.

SYMTUZA™ should not be used in combination with another antiretroviral that requires pharmacokinetic boosting (e.g. atazanavir, indinavir, lopinavir, saquinavir). SYMTUZA™ should not be used in combination with the individual components of SYMTUZA™ (darunavir, cobicistat, emtricitabine or tenofovir alafenamide; or with products containing lamivudine or tenofovir disoproxil fumarate; and SYMTUZA™ should not be administered with adefovir dipivoxil (see **WARNINGS AND PRECAUTIONS, General**).

Emtricitabine

In vitro and clinical pharmacokinetic drug-drug interaction studies have shown that the potential for CYP-mediated interactions involving emtricitabine with other medicinal products is low.

Emtricitabine is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No drug-drug interactions due to competition for renal excretion have been observed; however, coadministration of emtricitabine with drugs that are eliminated by active tubular secretion may increase concentrations of emtricitabine, and/or the coadministered drug.

Drugs that decrease renal function may increase concentrations of emtricitabine.

In drug interaction studies conducted with emtricitabine and with tenofovir disoproxil fumarate, coadministration of emtricitabine and famciclovir had no effect on the C_{max} or AUC of either drug.

Tenofovir alafenamide

Tenofovir alafenamide, a component of SYMTUZA™, is transported by P-glycoprotein (P-gp). Drugs that strongly affect P-gp activity may lead to changes in tenofovir alafenamide absorption (see Table 6 and Table 7). Drugs that induce P-gp activity are expected to decrease the absorption of tenofovir alafenamide, resulting in decreased plasma concentration of tenofovir alafenamide, which may lead to loss of therapeutic effect of SYMTUZA™ and development of resistance.

Coadministration of SYMTUZA™ with other drugs that inhibit P-gp may increase the absorption and plasma concentration of tenofovir alafenamide.

Coadministration of SYMTUZA™ with drugs that inhibit the lysosomal carboxypeptidase cathepsin A may decrease metabolism of tenofovir alafenamide to tenofovir in target cells, which may lead to reduced therapeutic effect of SYMTUZA™ and development of resistance.

Tenofovir alafenamide (TAF) is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 *in vitro*. It is not an inhibitor or inducer of CYP3A *in vivo*.

Expected interactions between SYMTUZA™ with potential concomitant drugs are listed in Table 6 and Table 7) below and are based on studies conducted with the components of SYMTUZA™, as individual agents or in combination, or are predicted interactions. It should be noted that the interaction profile of darunavir depends on whether ritonavir or cobicistat was used as pharmacokinetic enhancer; refer to the prescribing information for PREZCOBIX®, and DESCOVY™ for further information.

SYMTUZA™ is a complete antiretroviral treatment regimen. Therefore, information regarding drug interactions with other antiretroviral products is not provided.

Drug-Drug Interactions

Drugs that are contraindicated for co-administration with SYMTUZA™ are included in Table 6. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

Table 6: Drugs that are CONTRAINDICATED with SYMTUZA™

Drug Class: Drug Name	Clinical Comment
Alpha 1-Adrenoreceptor Antagonists: alfuzosin	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as hypotension.
Antiarrhythmics: amiodarone bepridil[1] dronedarone lidocaine (systemic) quinidine	CONTRAINDICATED: Concentrations of amiodarone, bepredil, dronedarone, lidocaine (systemic), and quinidine may be increased (inhibition of CYP3A and/or CYP2D6) when co-administered with SYMTUZA™.
Direct Oral Anticoagulants (DOACs): apixaban rivaroxaban	CONTRAINDICATED: DOACs are primarily metabolized by CYP3A4 and/or transported by P-gp. Co-administration with SYMTUZA™ may result in increased plasma concentrations of the DOAC, which may lead to an increased bleeding risk. Concentrations of apixaban or rivaroxaban may be increased when co-administered with SYMTUZA™ (affected by both CYP3A and P glycoprotein).
Anti-convulsants carbamezepine phenobarbital phenytoin	CONTRAINDICATED: Co-administration of SYMTUZA™ with carbamazepine, phenobarbital, or phenytoin (which are CYP3A and P-gp inducers) decreases plasma concentrations of darunavir, cobicistat, and tenofovir alafenamide which may result in loss of therapeutic effect and development of resistance.
Anti-gout: colchicine	Concomitant use of SYMTUZA™ with colchicine may increase concentrations of colchicine (inhibition of CYP3A). Refer to colchicine product information for dosing recommendations. CONTRAINDICATED: Patients with renal or hepatic impairment should not be given colchicine with SYMTUZA™.
Antihistamines: astemizole[1] terfenadine[1]	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.

Table 6: Drugs that are CONTRAINDICATED with SYMTUZA™	
Drug Class: Drug Name	**Clinical Comment**
Antimycobacterials: rifampin	CONTRAINDICATED: Rifampin is a potent inducer of CYP450 metabolism. SYMTUZA™ should not be used in combination with rifampin, as this may cause significant decreases in darunavir, cobicistat and/or tenofovir alafenamide plasma concentrations. This may result in loss of therapeutic effect of SYMTUZA™ and development of resistance.
Ergot Derivatives: dihydroergotamine ergonovine ergotamine methylergonovine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Gastrointestinal Motility Agents: cisapride[1]	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Hepatitis C Virus Direct-Acting Antivirals: elbasvir/grazoprevir	CONTRAINDICATED: Concomitant use of elbasvir/grazoprevir and SYMTUZA™ may increase the exposure to grazoprevir (inhibition of OATPB1 and CYP3A).
Herbal Products: St. John's wort (*Hypericum perforatum*)	CONTRAINDICATED: SYMTUZA™ should not be used concomitantly with products containing St. John's wort (*Hypericum perforatum)* because co-administration may cause significant decreases in darunavir, cobicistat and/or tenofovir alafenamide plasma concentrations (induction of CYP3A or P-gp). This may result in loss of therapeutic effect and development of resistance.
HMG-CoA Reductase Inhibitors: lovastatin simvastatin	CONTRAINDICATED: HMG-CoA reductase inhibitors, such as lovastatin and simvastatin, which are highly dependent on CYP3A4 metabolism, are expected to have markedly increased plasma concentrations when co-administered with SYMTUZA™. Increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis. Concomitant use of SYMTUZA™ with lovastatin or simvastatin is contraindicated For information regarding atorvastatin, rosuvastatin and pravastatin see Table 7.
Other lipid modifying agents: **l**omitapide	CONTRAINDICATED: SYMTUZA™ is expected to increase the exposure of lomitapide when co-administered.
Inhaled Beta Agonist: salmeterol	CONTRAINDICATED as the combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
Neuroleptics: lurasidone pimozide	CONTRAINDICATED due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
PDE-5 In hibitors: sildenafil (for treatment of pulmonary arterial hypertension)\	CONTRAINDICATED: A safe and effective dose of the PDE-5 inhibitors for the treatment of pulmonary arterial hypertension has not been established when co-administered with SYMTUZA™. There is an increased potential for sildenafil-associated adverse events (which include visual disturbances, hypotension, prolonged erection, and syncope).

Table 6: Drugs that are CONTRAINDICATED with SYMTUZA™	
Drug Class: Drug Name	**Clinical Comment**
Platelet Aggregation Inhibitors: ticagrelor	CONTRAINDICATED: Based on theoretical considerations co-administration of SYMTUZA™ with ticagrelor may increase concentrations of the anticoagulant (CYP3A and/or P-glycoprotein inhibition). Concomitant administration of SYMTUZA™ with ticagrelor is contraindicated.
Sedatives/Hypnotics: Oral midazolam triazolam	CONTRAINDICATED due to the potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

[1] Not marketed in Canada.

Established and other potentially significant drug interactions with SYMTUZA™ are included in Table 7. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

Table 7: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction		
Concomitant Drug Class: Drug Name	**Effect on Concentration of Darunavir and/or Cobicistat or Concomitant Drug**	**Clinical Comment**
Antacids: aluminium/magnesium, hydroxide, calcium carbonate	↔ darunavir ↔ cobicistat	SYMTUZA™ and antacids can be used concomitantly without dose adjustment.
Antiarrhythmics digoxin	↑ digoxin	Co-administration of SYMTUZA™ with digoxin may increase concentrations of digoxin (inhibition of p-glycoprotein). The lowest dose of digoxin should initially be prescribed. The serum digoxin concentrations should be monitored and used for titration of digoxin dose to obtain the desired clinical effect.
disopyramide flecainide mexiletine propafenone	↑ antiarrhythmics	Co-administration of SYMTUZA™ with disopyramide, flecainide, mexiletine or propafenoe may increase concentrations of the antiarrhythmic (inhibition of CYP3A). Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when co-administered with SYMTUZA™.
Anticancer Agents: dasatinib nilotinib vinblastine vincristine	↑ anticancer agent	Co-administration of SYMTUZA™ with these anticancer agents may increase concentrations of the anticancer agent (inhibition of CYP3A), resulting in the potential for increased adverse events usually associated with these agents. Clinical monitoring is recommended when coadministering SYMTUZA™ with these anticancer agents.
everolimus		Concomitant use of everolimus and SYMTUZA™ is not recommended.

Table 7: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir and/or Cobicistat or Concomitant Drug	Clinical Comment
Direct Oral Anticoagulants (DOACs): dabigatran etexilate edoxaban	↑ dabigatran etexilate ↑ edoxaban	DOACs are primarily metabolized by CYP3A4 and/or transported by P-gp. Co-administration with SYMTUZA™ may result in increased plasma concentrations of the DOAC, which may lead to an increased bleeding risk. Clinical monitoring and/or dose adjustment is recommended when a DOAC not affected by CYP3A4 but transported by P-gp, including dabigatran and edoxaban, is co administered with SYMTUZA™. Co-administration of SYMTUZA™ with dabigatran etexilate is not recommended in subjects with severe renal impairment.
warfarin	effect on warfarin unknown	Warfarin concentrations may be affected when co-administered with SYMTUZA™. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined with SYMTUZA™.
Anticonvulsants: oxcarbazepine	↓ darunavir ↓ cobicistat ↓ tenofovir alafenamide	Co-administration of SYMTUZA™ with oxcarbazepine may decrease darunavir, cobicistat and tenofovir alafenamide concentrations (induction of CYP3A and P-gp), which may result in loss of therapeutic effect to darunavir and development of resistance. Co-administration of SYMTUZA™ with oxcarbezepine is not recommended. Alternative anticonvulsants should be considered.
clonazepam, ethosuximide	↑clonazepam ↑ethosuximide	Co-administration of SYMTUZA™with clonazepam or ethosuximide may increase concentrations of the anticonvulsant (inhibition of CYP3A). Clinical monitoring is recommended when coadministering SYMTUZA™ with these anticonvulsants.
Antidepressants: amitriptyline desipramine imipramine nortriptyline paroxetine sertraline trazodone	↑ antidepressant	Concomitant use of SYMTUZA™ and these antidepressants may increase concentrations of the antidepressant (inhibition of CYP2D6 and/or CYP3A). Clinical monitoring is recommended when co-administering SYMTUZA™ with these antidepressants and a dose adjustment of the antidepressant may be needed.
Anti-infectives ketolide or macrolide antibiotics clarithromycin erythromycin	effect on darunavir unknown ↑ cobicistat ↑ anti-infective	Co-administration of SYMTUZA™ with these antibacterials may increase concentrations of darunavir (although no darunavir increase was observed with ritonavir-boosted darunavir and clarithromycin), cobicistat or the antibacterial (inhibition of CYP3A). SYMTUZA™ and clarithromycin can be used without dose adjustment in patients with normal renal function; for patients with renal impairment, consult the prescribing information for clarithromycin for the recommended dosage.

Table 7: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir and/or Cobicistat or Concomitant Drug	Clinical Comment
Antifungals: fluconazole ketoconazole itraconazole	↑ darunavir ↑ cobicistat ↑ antifungal ↑ tenofovir alafenamide	Co-administration of SYMTUZA™ with these antifungals may increase concentrations of darunavir, cobicistat, tenofovir alafenamide and/or the antifungal (inhibition of CYP3A and/or P-glycoprotein). Clinical monitoring is recommended when coadministering SYMTUZA™ with these antifungals. When co-administration is required, the daily dose of ketoconazole or itraconazole should not exceed 200 mg.
posaconazole		Clinical monitoring is recommended when co administering SYMTUZA™ with posaconazole.
voriconazole		Voriconazole should not be administered to patients receiving SYMTUZA™ unless an assessment of the benefit/risk ratio justifies the use of voriconazole.
Anti-gout: colchicine	↑ colchicine	Concomitant use of SYMTUZA™ with colchicine may increase concentrations of colchicine (inhibition of CYP3A). Refer to colchicine product information for dosing recommendations. **Patients with renal or hepatic impairment should not be given colchicine with SYMTUZA™.**
Antimalarials: artemether/lumefantrine	↑ artemether ↑ lumefantrine ↔ darunavir	Artemether/lumefantrine are not approved for use in Canada. Co-administration of SYMTUZA™ with artemether/lumefantrine may increase concentrations of artemether and lumefantrine (inhibition of CYP3A). The combination of SYMTUZA™ and artemether/lumefantrine can be used without dose adjustments; however, due to the expected increase in lumefantrine exposure, the combination should be used with caution.

Table 7: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir and/or Cobicistat or Concomitant Drug	Clinical Comment
Antimycobacterials: rifabutin rifapentine[1]	↓ darunavir ↓ cobicistat ↑ rifabutin ↓ tenofovir alafenamide	Co-administration of SYMTUZA™ with rifabutin may decrease darunavir, cobicistat and/or tenofovir alafenamide concentrations (induction of CYP3A and P-gp), which may result in loss of therapeutic effect and development of resistance. Rifabutin concentrations may be increased when co-administered with SYMTUZA™. Co-administration of SYMTUZA™ with rifabutin is not recommended. A dosage reduction of rifabutin by 75% of the usual dose of 300 mg/day (i.e., rifabutin 150 mg every other day) is warranted if rifabutin is co-administered with SYMTUZA™. Increased monitoring for rifabutin-related adverse events is warranted in patients receiving the combination. Co-administration of SYMTUZA™ with rifapentine may decrease darunavir, cobicistat and/or tenofovir alafenamide concentrations (induction of CYP3A), which may result in loss of therapeutic effect of darunavir and development of resistance. Co-administration of SYMTUZA™ with rifapentine is not recommended.
β-Blockers: carvedilol metoprolol timolol	↑ β-blockers	Co-administration of SYMTUZA™ and beta-blockers may increase concentrations of the beta-blocker (inhibition of CYP2D6). Clinical monitoring is recommended when co-administering SYMTUZA™ with beta-blockers and a lower dose of the beta-blocker should be considered.
Calcium Channel Blockers: amlodipine diltiazem felodipine nifedipine nicardipine verapamil	↑ calcium channel blockers	Plasma concentrations of calcium channel blockers (e.g., amlodipine, diltiazem, felodipine, nifedipine, nicardipine, verapamil) may increase when SYMTUZA™ are co-administered. Caution is warranted and clinical monitoring of patients is recommended.

Table 7: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	**Effect on Concentration of Darunavir and/or Cobicistat or Concomitant Drug**	**Clinical Comment**
Corticosteroids: Systemic dexamethasone prednisone Primarily metabolized by CYP3A, including inhaled/nasal betamethasone budesonide fluticasone mometasone, triamcinolone	↓ darunavir ↓ cobicistat ↑ corticosteroid	Systemic dexamethasone induces CYP3A4 and can thereby decrease darunavir and/or cobicistat plasma concentrations. This may result in loss of therapeutic effect of darunavir and development of resistance. Co-administration of SYMTUZA™ with (systemic) dexamethasone is not recommended. Corticosteroid concentrations may be increased when coadministered with SYMTUZA™. Concomitant use may increase the risk for development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. Clinical monitoring is recommended when co-administering SYMTUZA™ with corticosteroids. Concomitant use of inhaled corticosteroids and SYMTUZA™ may increase plasma concentrations of the corticosteroid. Alternatives should be considered, particularly for long-term use.
Endothelin Receptor Antagonists: bosentan	↓ darunavir ↓ cobicistat ↑ bosentan	Bosentan concentrations may be increased when co-administered with SYMTUZA™. Clinical monitoring is recommended when co-administering SYMTUZA™ with bosentan and a dose adjustment of bosentan may be needed.

Table 7: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir and/or Cobicistat or Concomitant Drug	Clinical Comment
Hormonal Contraceptives: drospirenone ethinyl estradiol norethindrone norgestimate	↑ drospirenone ↑ norgestimate ↓ ethinyl estradiol ↓ norethindrone	The results of an interaction trial between DRV+COBI and ethinylestradiol and drospirenone demonstrated that single dose systemic exposures to ethinylestradiol and drospirenone are decreased by 30% and increased by 58%, respectively. When SYMTUZA™ is co-administered with a drospirenone-containing product, clinical monitoring is recommended due to the potential for hyperkalemia. No data are available to make recommendations on the use of SYMTUZA™ with other hormonal contraceptives. Therefore, additional or alternative methods of non-hormonal contraception are recommended. Drug interaction data with hormonal contraceptives are available from studies using one of the active products of SYMTUZA™ together with other products; it is not known which of the products is responsible for the observed effects. The results of an interaction trial between darunavir/rtv (600/100 mg b.i.d.) and ethinyl estradiol and norethindrone demonstrated that at steady-state, systemic exposures to ethinyl estradiol and norethindrone are decreased by 44% and 14%, respectively. A drug interaction study between elvitegravir/emtricitabine/tenofovir/cobicistat, which contains cobicistat, and a norgestimate/ethinyl estradiol containing hormonal oral contraceptive resulted in decreased plasma concentrations of ethinyl estradiol and an increase in norgestimate. 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 co-administration of norgestimate/ethinyl estradiol with cobicistat should be considered, particularly in women who have risk factors for these events.
Eugeroics: modafinil	↓ darunavir ↓ cobicistat	Co-administration of SYMTUZA™ with modafinil may decrease darunavir and/or cobicistat concentrations (induction of CYP3A), which may result in loss of therapeutic effect and development of resistance. Co-administration of SYMTUZA™ and modafinil is not recommended.

Table 7: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir and/or Cobicistat or Concomitant Drug	Clinical Comment
H_2-Receptor Antagonists and Proton Pump Inhibitors: cimetidine famotidine nizatidine ranitidine esomeprazole lansoprazole omeprazole pantoprazole rabeprazole	↔ darunavir ↔ cobicistat	Based on mechanistic considerations (i.e. decreased gastric acidity) no interaction is expected when SYMTUZA™ is co-administered with H2-receptor antagonists. SYMTUZA™ can be co-administered with H2-receptor antagonists and proton pump inhibitors without dose adjustments.
Hepatitis C Virus (HCV) direct-acting antivirals: glecaprevir/pibrentasvir sofosbuvir, ledipasvir, daclatasvir	↑glecaprevir ↑pibrentasvir	Concomitant use of glecaprevir/pibrentasvir and SYMTUZA™ may increase the exposure to glecaprevir and pibrentasvir (inhibition of P-gp, BCRP and/or OATP1B1/3). Co-administration of SYMTUZA™ with glecaprevir/pibrentasvir is not recommended. Based on mechanistic considerations, no clinically relevant interaction is expected when SYMTUZA™ is co-administered with sofosbuvir, sofosbuvir/ledipasvir, or daclatasvir. SYMTUZA™ can be co-administered with sofosbuvir, sofosbuvir/ledipasvir, or daclatasvir without dose adjustment.
HMG-CoA Reductase Inhibitors: atorvastatin rosuvastatin pravastatin	↑HMG-CoA reductase inhibitors	Concomitant use of a HMG-CoA reductase inhibitor and SYMTUZA™ may increase plasma concentrations of the lipid-lowering agent (inhibition of CYP3A and/or transport), which may lead to adverse events such as myopathy. Clinical monitoring is recommended when co-administering SYMTUZA™ with HMG-CoA reductase inhibitors and a lower dose of the lipid-lowering agent should be considered. The results of an interaction trial with DRV+COBI and atorvastatin (10 mg q.d.) showed a 3.9-fold increase in exposure to atorvastatin. When administration of atorvastatin and SYMTUZA™ is desired, it is recommended to start with an atorvastatin dose of 10 mg q.d. A gradual dose increase of atorvastatin may be tailored to the clinical response. The results of an interaction trial with DRV+COBI and rosuvastatin (10 mg q.d.) showed a 1.9-fold increase in exposure to rosuvastatin. When administration of rosuvastatin and SYMTUZA™ is desired, it is recommended to start with the lowest possible dose of rosuvastatin and titrate up to the desired clinical effect while monitoring for safety. For information regarding lovastatin, simvastatin see Table 6

Table 7: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir and/or Cobicistat or Concomitant Drug	Clinical Comment
Immunosuppressants: cyclosporine everolimus tacrolimus sirolimus	↑ immunosuppressants	Plasma concentrations of cyclosporine, everolimus, tacrolimus or sirolimus may be increased when co-administered with SYMTUZA™. Co-administration with cyclosporine may result in increased plasma concentration of tenofovir alafenamide. Therapeutic concentration monitoring of the immunosuppressive agent is recommended for immunosuppressant agents when co-administered with SYMTUZA™. Concomitant use of everolimus and SYMTUZA™ is not recommended.
Narcotic Analgesics: methadone buprenorphine/naloxone	↓ methadone ↔ buprenorphine ↔naloxone ↑ norbuprenorphine	No dose adjustment of buprenorphine or methadone is required when co-administering with SYMTUZA™. However, careful clinical monitoring is recommended as the dose of buprenorphine or methadone may need to be adjusted in some patients.
meperidine	↓ meperidine	SYMTUZA™ is expected to decrease meperidine concentrations and increase normeperidine metabolite concentrations. Dosage increase and long-term use of meperidine and SYMTUZA™ are not recommended due to the increased concentrations of the metabolite normeperidine, which has both analgesic and CNS stimulant activity (e.g., seizures).
fentanyl oxycodone tramadol	↑ fentanyl ↑ oxycodone ↑ tramadol	Co-administration of SYMTUZA™ with these analgesics may increase concentrations of the analgesic (inhibition of CYP2D6 and/or CYP3A). Clinical monitoring is recommended when co-administering SYMTUZA™ with these analgesics.

Table 7: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir and/or Cobicistat or Concomitant Drug	Clinical Comment
Neuroleptics: perphenazine risperidone thioridazine	↑ neuroleptics	Co-administration of SYMTUZA™ and these neuroleptics may increase concentrations of the neuroleptic (inhibition of CYP3A or CYP2D6). Clinical monitoring is recommended when co-administering SYMTUZA™ with these neuroleptics and a lower dose of the neuroleptic should be considered.
quetiapine	↑ quetiapine	SYMTUZA™ should not be used in combination with quetiapine. Due to CYP3A inhibition by SYMTUZA™, concentrations of quetiapine are expected to increase, which can result in serious and/or life-threatening adverse reactions. *Initiation of SYMTUZA™ in patients taking quetiapine:* consider alternative antiretroviral therapy to avoid increases in quetiapine exposure. If co-administration is necessary, reduce the quetiapine dose to 1/6 of the current dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations on adverse reaction monitoring. *Initiation of quetiapine in patients taking SYMTUZA™* refer to the quetiapine prescribing information for initial dosing and titration of quetiapine.
PDE-5 Inhibitors: sildenafil tadalafil vardenafil	↑ PDE-5 inhibitors	Co-administration with SYMTUZA™ may result in an increase in PDE-5 inhibitor-associated adverse events, including hypotension, syncope, visual disturbances and priapism. <u>Use of PDE-5 inhibitors for erectile dysfunction:</u> Concomitant use of PDE-5 inhibitors, when used for the treatment of erectile dysfunction, should be done with caution. Co-administration of darunavir with sildenafil or tadalafil is expected to substantially increase the PDE-5 concentration and may result in an increase in PDE-5 inhibitor-associated adverse events including hypotension, visual changes, syncope and priapism. If concomitant use of SYMTUZA™ with sildenafil or tadalafil is required, sildenafil at a single dose not exceeding 25 mg in 48 hours or tadalafil at a single dose not exceeding 10 mg in 72 hours is recommended with increased monitoring for PDE-5 inhibitor-associated adverse events. Vardenafil should not be used with SYMTUZA™. <u>Use of PDE-5 inhibitors for pulmonary arterial hypertension (PAH):</u> Use of sildenafil is contraindicated (see Table 6). Based on theoretical considerations, co-administration of SYMTUZA™ with tadalafil may increase concentrations of tadalafil (CYP3A inhibition). Co-administration of SYMTUZA™ with tadalafil is not recommended.

Table 7: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction		
Concomitant Drug Class: Drug Name	**Effect on Concentration of Darunavir and/or Cobicistat or Concomitant Drug**	**Clinical Comment**
Sedatives/Hypnotics: buspirone clorazepate diazepam estazolam flurazepam zoldipem[1] parenterally administered midazolam	↑ sedatives/hypnotics	Co-administration of SYMTUZA™ with these sedatives/hypnotics may increase concentrations of the sedative/hypnotic (inhibition of CYP3A). Clinical monitoring is recommended when co-administering SYMTUZA™ with these sedatives/hypnotics and a lower dose of the sedatives/hypnotics should be considered. Co-administration of parenteral midazolam should be done in a setting that ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dose reduction for parenteral midazolam should be considered, especially if more than a single dose of midazolam is administered.

[1] Not marketed in Canada

Drug-Food Interactions

SYMTUZA™ should be taken with food. The type of food does not affect the exposure to SYMTUZA™.

Drug-Herb Interactions

Concomitant use of SYMTUZA™ and St. John's wort (*Hypericum perforatum*) or products containing St. John's wort is contraindicated. Co-administration of SYMTUZA™ with St. John's wort may cause significant decreases in darunavir, cobicistat, and/or tenofovir alafenamide concentrations which may result loss of therapeutic effect and development of resistance (see **Drug-Drug Interactions**, Table 6).

Interactions with other herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

SYMTUZA™ is a fixed dose combination of 800 mg of HIV protease inhibitor darunavir, 150 mg of pharmacokinetic enhancer cobicistat, 200 mg of nucleoside reverse transcriptase inhibitior emtricitabine and 10 mg nucleotide reverse transcriptase inhibitor tenofovir alafenamide.

After therapy with SYMTUZA™ has been initiated, patients should not alter the dosage or discontinue therapy without instruction of their healthcare provider. Separate pharmaceutical

forms of the components of SYMTUZA™ are available, either alone or in combination products. Therefore, if patients are unable to swallow the SYMTUZA™ tablet, require a dose modification of any of the components of SYMTUZA™, or discontinue treatment with SYMTUZA™ alternatively, the pharmaceutical forms of the individual components may be used. Please refer to the respective prescribing information for proper use of the products.

Recommended Dose and Dosage Adjustment

Adults

The recommended dose regimen is one tablet taken once daily with food. SYMTUZA™ should be taken with food. The type of food does not affect the exposure to the components of SYMTUZA™. (see **DRUG INTERACTIONS**, **Drug-Food Interactions**, and **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics,** Effects of Food on Oral Absorption). SYMTUZA™ should be swallowed whole without breaking or crushing to ensure administration of the entire dose.

Geriatric Patients

Limited information is available on the use of SYMTUZA™ in patients 65 years of age and older. Therefore, SYMTUZA™ should be used with caution in elderly patients (see **INDICATIONS AND CLINICAL USE**, **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

Pediatric Patients

In adolescent patients aged 12 years and older weighing at least 40 kg, the recommended dosage is one tablet taken once daily with food. No dose has been established for SYMTUZA™ for pediatric patients 3-11 years of age or weighing less than 40 kg. SYMTUZA™ should not be used in pediatric patients below 3 years of age. In pre-clinical studies of darunavir, toxicity and mortality was observed in juvenile rates dosed with darunavir (from 20 mg/kg to 1000 mg/kg) up to days 23 and 26 of age (see **WARNINGS AND PRECAUTIONS, ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Pediatrics** and **TOXICOLOGY, Reproductive and Developmental Toxicity**).

Pregnancy and postpartum

SYMTUZA™ is not recommended for use during pregnancy because of substantially lower exposure of darunavir and cobicistat during pregnancy.

Therapy with SYMTUZA™ should not be initiated during pregnancy, and women who become pregnant during therapy with SYMTUZA™ should be switched to an alternative regimen (see **WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women**).

Hepatic Impairment

No dose adjustment of SYMTUZA™ is required in patients with mild (Child Pugh Class A) or moderate (Child Pugh Class B) hepatic impairment (see **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics**)

SYMTUZA™ has not been studied in patients with severe hepatic impairment (Child Pugh Class C) and there are only limited data regarding the use of SYMTUZA™ components in this population. The safety and efficacy of SYMTUZA™ have not been established in patients with severe hepatic insufficiency (see **CONTRAINDICATIONS**)

Renal Impairment
No dose adjustment of SYMTUZA™ is required in patients with an estimated glomerular filtration rate accoding to Cockcroft-Gault formula for creatinine clearance ($eGFR_{CG}$) of 30 mL/min or above. SYMTUZA™ should not be initiated in patients with $eGFR_{CG}$ below 30 mL/min (see **WARNINGS AND PRECAUTIONS**, **Renal** and **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics**).

SYMTUZA™ should be discontinued in patients with $eGFR_{CG}$ that declines below 30 mL/min during treatment.

Missed Dose
If a dose of SYMTUZA™ is missed within 12 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of SYMTUZA™ with food as soon as possible. If a missed dose is noticed later than 12 hours of the time it is usually taken, it should not be taken and the patient should resume the usual dosing schedule.

OVERDOSAGE

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

Human experience of acute overdose with SYMTUZA™ is limited. If overdose occurs, the patient must be monitored for evidence of toxicity (see **ADVERSE REACTIONS**).

There is no specific antidote for overdose with SYMTUZA™. Treatment of overdose with SYMTUZA™ consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. Since darunavir and cobicistat are highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substances.

Darunavir
Single doses up to 3,200 mg of the oral solution of darunavir alone and up to 1,600 mg of the tablet formulation of darunavir co-administered with ritonavir have been administered to healthy volunteers without untoward symptomatic effects. Since darunavir is highly protein bound, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis.

Cobicistat
Limited clinical experience with cobicistat is available at doses higher than the therapeutic dose. In two studies, a single dose of cobicistat 400 mg was administered to a total of 60 healthy subjects. No severe adverse reactions were reported. The effects of higher doses are not known.

Since cobicistat is highly protein bound, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis.

Emtricitabine

Limited clinical experience is available at doses higher than the therapeutic dose of EMTRIVA. In one clinical pharmacology study, single doses of emtricitabine 1200 mg (6 times the dose in GENVOYA/DESCOVY) were administered to 11 subjects. No severe adverse reactions were reported. The effects of higher doses are not known. Emtricitabine can be removed by hemodialysis, which removes approximately 30% of the emtricitabine dose over a 3 hour dialysis period starting within 1.5 hours of emtricitabine dosing. It is not known whether emtricitabine can be removed by peritoneal dialysis.

Tenofovir Alafenamide

Limited clinical experience is available at doses higher than the therapeutic dose of tenofovir alafenamide. A single supratherapeutic dose of 125 mg tenofovir alafenamide was administered to 48 healthy subjects. No serious adverse reactions were reported. The effects of higher doses are unknown. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. It is not known whether tenofovir can be removed by peritoneal dialysis.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

SYMTUZA™ consists of the HIV protease inhibitor darunavir (DRV), the pharmacokinetic enhancer cobicistat (COBI), the nucleoside reverse transcriptase inhibitor emtricitabine (FTC), and the nucleotide reverse transcriptase inhibitor tenofovir alafenamide (TAF).

Darunavir: DRV is an inhibitor of the dimerization and of the catalytic activity of the HIV-1 protease. It selectively inhibits the cleavage of HIV-encoded Gag-Pol polyproteins in virus-infected cells, thereby preventing the formation of mature infectious virus particles. Darunavir tightly binds to the HIV-1 protease with a K_D of 4.5 x 10^{-12} M. Darunavir is not an inhibitor of any of 13 tested human cellular proteases.

Cobicistat: COBI is a selective, mechanism-based inhibitor of the CYP3A subfamily. Inhibition of CYP3A-mediated metabolism by cobicistat enhances the systemic exposure of CYP3A substrates, such as darunavir, where bioavailability is limited and half-life is shortened due to CYP3A-dependent metabolism.

Emtricitabine: FTC is a nucleoside analogue of 2'-deoxycytidine. FTC is phosphorylated by cellular enzymes to form FTC triphosphate. FTC triphosphate inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination. FTC has activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2) and hepatitis B virus. FTC triphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there was no evidence of toxicity to mitochondria *in vitro* and *in vivo*.

Tenofovir alafenamide: TAF is a phosphonamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). TAF is permeable into cells and due to increased plasma stability and intracellular activation through hydrolysis by cathepsin A, TAF is efficient in loading tenofovir in peripheral blood mononuclear cells (PBMCs) (including lymphocytes and other HIV target cells) and macrophages. Intracellular tenofovir is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination. Tenofovir has activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2). TAF displayed antiviral activity in cell culture against all HIV-1 groups. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerase-that include mitochondrial DNA polymerase γ. In the *in vitro* study, TAF did not significantly affect mitochondrial DNA in HepG2 cells.

Pharmacodynamics

Electrocardiogram (Effect on QT Interval)

Darunavir: In an open-label, randomized, placebo- and active-controlled, four-way crossover trial, 40 healthy subjects were administered supratherapeutic doses of darunavir/ritonavir 1,600/100 mg once daily and 800/100 mg twice daily for seven days.

At the mean maximum darunavir concentration of 6,599 ng/mL observed in this study, the mean increase in QTcF was 2.2 ms with a 90% two-sided confidence interval (CI) of –2.0 to 6.3 ms. When evaluating the two-sided 90% CI on the time-matched mean changes in QTcF versus placebo control, the upper bounds of both darunavir/ritonavir groups never exceeded the 10 ms boundary. In the setting of this trial, darunavir/ritonavir did not appear to prolong the QTc interval.

Cobicistat: The electrocardiographic effects of cobicistat were determined in a study of 48 healthy subjects. Cobicistat did not prolong the QTcF interval at doses of 250 mg and 400 mg, providing exposures 2- and 4-fold above the recommended therapeutic dose, respectively. A modest increase in PR interval (+9.6 msec) occurred around C_{max}, 3 to 5 hours after dosing of cobicistat 250 mg. This finding was not considered to be clinically significant.

In a human clinical study of 35 healthy subjects, echocardiograms performed at baseline and after receiving 150 mg cobicistat once daily for at least 15 days indicated no clinically significant change in left ventricular function.

Emtricitabine: The effect of FTC on the QT interval is not known.

Tenofovir alafenamide: In a thorough QT/QTc study in 48 healthy subjects, TAF at the therapeutic dose or at a supratherapeutic dose approximately 5 times the recommended therapeutic dose did not affect the QT/QTc interval and did not prolong the PR interval.

Effects on Serum Creatinine

The effect of cobicistat on serum creatinine was investigated in a Phase I study in subjects with normal renal function (eGFR ≥ 80 mL/min, N=12) and mild to moderate renal impairment

(eGFR 50-79 mL/min, N=18). A statistically significant change of estimated glomerular filtration rate calculated by Cockcroft-Gault method ($eGFR_{CG}$) from baseline was observed after 7 days of treatment with cobicistat 150 mg among subjects with normal renal function (9.9 ± 13.1 mL/min) and mild to moderate renal impairment (11.9 ± 7.0 mL/min).

An increase in serum creatinine due to cobicistat's inhibitory effect generally does not exceed 0.4 mg per dL from baseline.

These decreases in $eGFR_{CG}$ were reversible after cobicistat was discontinued. The actual glomerular filtration rate, as determined by the clearance of probe drug iohexol, was not altered from baseline following treatment of cobicistat among subjects with normal renal function and mild to moderate renal impairment, indicating cobicistat inhibits tubular secretion of creatinine, reflected as a reduction in $eGFR_{CG}$, without affecting the actual glomerular filtration rate.

Pharmacokinetics

General

The bioavailability of all components of SYMTUZA™ was comparable to that when DRV 800 mg, COBI 150 mg, and FTC/TAF 200/10 mg were co administered as separate formulations; bioequivalence was established following single-dose administration under fed conditions in healthy subjects (N=96). (see **CLINICAL TRIALS, Pivotal Comparative Bioavailability Study**).

Absorption and Bioavailability

The absolute bioavailability of a single 600 mg dose of DRV alone was approximately 37% and increased to approximately 82% in the presence of ritonavir. The absolute bioavailability of the FTC 200 mg capsule was 93%. All components were rapidly absorbed following oral administration of SYMTUZA™ in healthy subjects. Maximum plasma concentrations of DRV, COBI, FTC, and TAF were achieved at 4.00, 4.00, 2.00, and 1.50 hours after dosing, respectively.

Effects of Food on Oral Absorption

The exposure (AUC) of DRV and COBI administered as SYMTUZA™ was 34% and 29% lower, respectively, in fasted condition compared to fed condition. For FTC and TAF, exposure was comparable in fed and fasted conditions. Therefore, SYMTUZA™ should be taken with food. The type of food does not affect exposure to SYMTUZA™.

Distribution

Darunavir: DRV is approximately 95% bound to plasma proteins. Darunavir binds primarily to plasma alpha-1-acid glycoprotein (AAG).

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

Emtricitabine: *In vitro* binding of FTC to human plasma proteins was <4% and independent of concentration over the range of 0.02 to 200 mcg/mL. At peak plasma concentration, the mean

plasma to blood drug concentration ratio was ~1.0 and the mean semen to plasma drug concentration ratio was ~4.0.

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

Metabolism

Darunavir: In vitro experiments with human liver microsomes (HLMs) indicate that darunavir primarily undergoes oxidative metabolism. Darunavir is extensively metabolized by the hepatic CYP system, and almost exclusively by isozyme CYP3A4. A ^{14}C-darunavir trial in healthy volunteers showed that a majority of the radioactivity in plasma after a single 400/100 mg darunavir/ritonavir dose was due to the parent drug. At least three oxidative metabolites of darunavir have been identified in humans; all showed activity that was at least 10-fold less than the activity of darunavir against wild-type HIV.

Cobicistat: Cobicistat is metabolized via CYP3A (major) and CYP2D6 (minor)-mediated oxidation and does not undergo glucuronidation. Following oral administration of ^{14}C-cobicistat, 99% of circulating radioactivity in plasma was unchanged cobicistat. Low levels of metabolites are observed in urine and feces and do not contribute to the CYP3A inhibitory activity of cobicistat.

Emtricitabine: Emtricitabine is not significantly metabolized.

Tenofovir alafenamide: Metabolism is a major elimination pathway for TAF in humans, accounting for >80% of an oral dose. *In vitro* studies have shown that TAF is metabolized to tenofovir (major metabolite) by cathepsin A in PBMCs (including lymphocytes and other HIV target cells) and macrophages; and by carboxylesterase-1 in hepatocytes. Tenofovir alafenamide is a substrate of P-gp and BCRP transporters, and is minimally metabolized by CYP3A4. Upon coadministration with the moderate CYP3A inducer probe efavirenz, tenofovir alafenamide exposure was unaffected.

In vivo, TAF is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. In human clinical studies, a 10 mg oral dose of TAF resulted in tenofovir diphosphate concentrations >4-fold higher in PBMCs and >90% lower concentrations of tenofovir in plasma as compared to a 300 mg oral dose of tenofovir disoproxil fumarate in STRIBILD.

In vitro, TAF is not metabolized by CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or UGT1A1. Tenofovir alafenamide is a weak inhibitor of CYP3A *in vitro*. Tenofovir alafenamide is not an inhibitor or inducer of CYP3A *in vivo*.

Excretion

Darunavir: After a 400/100 mg ^{14}C-darunavir/ritonavir dose, approximately 79.5% and 13.9% of the administered dose of ^{14}C-darunavir could be retrieved in feces and urine, respectively.

Unchanged darunavir accounted for approximately 41.2% and 7.7% of the administered dose in feces and urine, respectively. The terminal elimination half-life of darunavir was approximately 11 hours when combined with cobicistat. The intravenous clearance of darunavir alone (150 mg) and in the presence of low-dose ritonavir was 32.8 L/h and 5.9 L/h, respectively. The terminal elimination half life of DRV is approximately 6 hours following administration of SYMTUZA™.

Cobicistat: Following oral administration of ^{14}C-cobicistat, 86% and 8.2% of the dose were recovered in feces and urine, respectively. The median terminal elimination half-life of cobicistat is approximately 3 to 4 hours following administration of SYMTUZA™.

Emtricitabine: FTC and TAF are primarily excreted by the kidney, by both glomerular filtration and active tubular secretion. Following administration of SYMTUZA™, the elimination half-life of FTC is approximately 17 hours.

Tenofovir alafenamide: TAF is mainly eliminated following metabolism to tenofovir. The terminal elimination half-life of TAF is approximately 0.3 hours following administration of SYMTUZA™. Tenofovir is eliminated from the body in the feces and urine by both glomerular filtration and active tubular secretion. Tenofovir alafenamide and tenofovir have a median plasma half-life of 0.51 and 32.37 hours, respectively. Renal excretion of intact tenofovir alafenamide is a minor pathway with less than 1% of the dose eliminated in urine. The pharmacologically active metabolite, tenofovir diphosphate, has an elimination half-life of approximately 150-180 hours within PBMCs.

Special Populations and Conditions

Pediatrics

The pharmacokinetics of SYMTUZA™ in pediatric patients have not been investigated. However, available pharmacokinetic data for the different components of SYMTUZA™ indicate that doses of 800 mg darunavir, 150 mg cobicistat, 200 mg emtricitabine, and 10 mg tenofovir alafenamide result in similar exposures in adolescents aged 12 years and older, weighing at least 40 kg, and adults.

Darunavir: A dosage of 800 mg once daily in pediatric patients weighing ≥40 kg resulted in darunavir exposure that was comparable to that achieved in adults receiving the same dose.

Cobicistat: Exposures of cobicistat 150 mg achieved in pediatric patients aged 12 to <18 years were similar to exposures achieved in treatment-naïve adults.

Emtricitabine and tenofovir alafenamide: Exposures of FTC 200 mg and TAF 10 mg achieved in pediatric patients aged 12 to <18 years were similar to exposures achieved in treatment-naïve adults.

Pregnancy

Darunavir/cobicistat (administered as the fixed dose combination PREZCOBIX®) in combination with a background regimen was evaluated in a clinical trial of 7 pregnant women

taking PREZCOBIX® prior to enrollment and who were willing to remain on PREZCOBIX® throughout the study. The study period included the second and third trimesters, and through 12 weeks postpartum. Six women completed the trial. One out of 6 women who completed the study experienced virologic failure with HIV-1 RNA >1,000 copies/mL from the third trimester visit through the postpartum period. Five women had sustained virologic response (HIV RNA <50 copies/mL) throughout the study period. There are no clinical data on the virologic response when PREZCOBIX® is initiated during pregnancy.

The exposure to total darunavir boosted with cobicistat after intake of PREZCOBIX® as part of an antiretroviral regimen was substantially lower during the second and third trimesters of pregnancy compared with 6-12 weeks postpartum. The decrease in unbound (i.e., active) darunavir pharmacokinetic parameters (C_{max} and AUC_{24h}) during pregnancy compared to postpartum was less pronounced than for total darunavir.

In women receiving PREZCOBIX® during the 2nd trimester of pregnancy, mean intra-individual values for total darunavir C_{max}, AUC_{24h} and C_{min} were 49%, 56% and 92% lower, respectively, as compared with postpartum; during the 3rd trimester of pregnancy, total darunavir C_{max}, AUC_{24h} and C_{min} values were 37%, 50% and 89% lower, respectively, as compared with postpartum.

Geriatrics

Population pharmacokinetic analysis in HIV-infected patients showed that darunavir (co-administered with low dose ritonavir) pharmacokinetics are not considerably different in the age range (18 to 75 years) evaluated in HIV-infected patients (n=12, age ≥ 65) (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Geriatrics**).

No clinically relevant pharmacokinetic differences due to age have been identified for cobicistat, emtricitabine, or tenofovir alafenamide.

Gender

Darunavir: Population pharmacokinetic analysis showed a slightly higher darunavir (co-administered with low dose ritonavir) exposure (16.8%) in HIV-infected females (n=68) compared to males. This difference is not considered clinically relevant.

Cobicistat: No clinically relevant pharmacokinetic differences due to gender have been identified for cobicistat.

Emtricitabine: No clinically relevant pharmacokinetic differences have been observed between men and women for emtricitabine.

Tenofovir Alafenamide: No clinically relevant pharmacokinetic differences have been observed between men and women for tenofovir alafenamide.

Race

Darunavir: Population pharmacokinetic analysis of darunavir (co-administered with low dose ritonavir) in HIV-infected patients indicated that race had no apparent effect on the exposure to darunavir.

Cobicistat: No clinically relevant pharmacokinetic differences due to ethnicity have been identified for cobicistat.

Emtricitabine: No pharmacokinetic differences due to race have been identified following the administration of EMTRIVA.

Tenofovir Alafenamide: Population pharmacokinetics analysis of tenofovir alafenamide in HIV-1 infected patients indicated that race had no clinically relevant effect on the exposure of tenofovir alafenamide.

Hepatic Insufficiency

The pharmacokinetics of SYMTUZA™ have not been investigated in patients with hepatic impairment. However, there are data for the components of SYMTUZA™.

Darunavir: In a multiple dose study with DRV co-administered with ritonavir (600/100 mg) twice daily, it was demonstrated that the steady-state pharmacokinetic parameters of darunavir in patients with mild (Child-Pugh Class A, n=8) and moderate (Child-Pugh Class B, n=8) hepatic impairment were comparable with those in healthy patients. The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been studied (see **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS**, and **DOSAGE AND ADMINISTRATION**).

Cobicistat: Cobicistat is primarily metabolized and eliminated by the liver. A study of the pharmacokinetics of cobicistat was performed in non-HIV-1 infected subjects with moderate hepatic impairment (Child-Pugh Class B). No clinically relevant differences in cobicistat pharmacokinetics were observed between subjects with moderate impairment and healthy subjects. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of cobicistat has not been studied.

Emtricitabine: The pharmacokinetics of FTC have not been studied in subjects with hepatic impairment; however, FTC is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.

Tenofovir alafenamide: Clinically relevant changes in the pharmacokinetics of tenofovir alafenamide or its metabolite tenofovir were not observed in patients with mild or moderate hepatic impairment; no TAF dose adjustment is required in patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of tenofovir alafenamide has not been studied.

Hepatitis B or Hepatitis C Virus Co-infection

There were insufficient pharmacokinetic data in the clinical trials to determine the effect of hepatitis B and/or C virus infection on the pharmacokinetics of SYMTUZA™.

Darunavir: The primary 48-week analysis of the data from Study TMC114-C211 and TMC114-C214 in HIV-1-infected patients taking DRV/rtv indicated that hepatitis B and/or hepatitis C virus co-infection status had no apparent effect on the exposure to darunavir.

Cobicistat: There were insufficient pharmacokinetic data in the clinical trials to determine the effect of hepatitis B and/or C virus infection on the pharmacokinetics of cobicistat.

Emtricitabine and tenofovir alafenamide: Pharmacokinetics of FTC and TAF have not been fully evaluated in patients co-infected with hepatitis B and/or C virus.

Renal Insufficiency

The pharmacokinetics of SYMTUZA™ have not been investigated in patients with renal impairment. However, there are data for the components of SYMTUZA™.

Darunavir: Results from a mass balance study with ^{14}C-darunavir/ritonavir showed that approximately 7.7% of the administered dose of darunavir is excreted in the urine as unchanged drug. As darunavir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis. Although darunavir has not been studied in patients with renal impairment, population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected in HIV-infected patients with moderate renal impairment (CrCL between 30–60 mL/min, n=20) (see **WARNINGS AND PRECAUTIONS**, **Renal** and **DOSAGE AND ADMINISTRATION**, **Recommended Dose and Dosage Adjustment**, **Renal Impairment**).

Cobicistat: A study of the pharmacokinetics of cobicistat was performed in non-HIV-1 infected subjects with severe renal impairment (estimated creatinine clearance below 30 mL/min). No meaningful differences in cobicistat pharmacokinetics were observed between subjects with severe renal impairment and healthy subjects, consistent with low renal clearance of cobicistat.

Emtricitabine: Mean systemic FTC exposure was higher in patients with severe renal impairment (eGFRCG <30 mL/min) than in subjects with normal renal function.

Tenofovir alafenamide: No clinically relevant differences in TAF or tenofovir pharmacokinetics were observed between healthy subjects and subjects with severe renal impairment (eGFRCG <30 mL/min) in studies of TAF. There are no pharmacokinetic data on TAF in patients with eGFRCG <15 mL/min.

The safety, virologic, and immunologic responses of DESCOVY in HIV-1 infected patients with mild to moderate renal impairment (eGFR by Cockcroft-Gault method 30-69 mL/min) were evaluated with emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat as a fixed-dose combination tablet (administered as GENVOYA) in an open-label trial, Study 112. The safety profile of DESCOVY in patients with mild to moderate renal impairment was similar to safety data from patients with normal renal function.

STORAGE AND STABILITY

Store SYMTUZA™ tablets in the original package with desiccant inside the bottle in order to protect the tablets from moisture. Keep the bottle tightly closed. Store between 15 – 30°C. Keep out of the sight and reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

SYMTUZA™ Tablets
SYMTUZA™ (darunavir/cobicistat/ emtricitabine/ tenofovir alafenamide) 800/150/200/10-mg film coated tablets are supplied as a yellow to yellowish-brown capsule-shaped tablet of 22 mm × 10 mm, debossed with "8121" on one side and "JG" on the opposite side.

SYMTUZA™ tablets are supplied in a white, high density polyethylene (HDPE) bottle with a silica gel desiccant pouch and a polypropylene child resistant closure. Each bottle contains 30 tablets.

The core tablet contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The film coating contains polyethylene glycol (macrogol), polyvinyl alcohol (partially hydrolyzed), talc, titanium dioxide, and yellow ferric oxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

SYMTUZA™ is a fixed-dose combination tablet contains 867 mg of darunavir ethanolate (equivalent to 800 mg of darunavir free form), 288.5 mg of cobicistat on silicon dioxide (equivalent to 150 mg of cobicistat free form), 200 mg of emtricitabine, and 11.2 mg of tenofovir alafenamide fumarate (equivalent to 10 mg of tenofovir alafenamide free form).

Common name:

Darunavir ethanolate (DRV)

Chemical name:

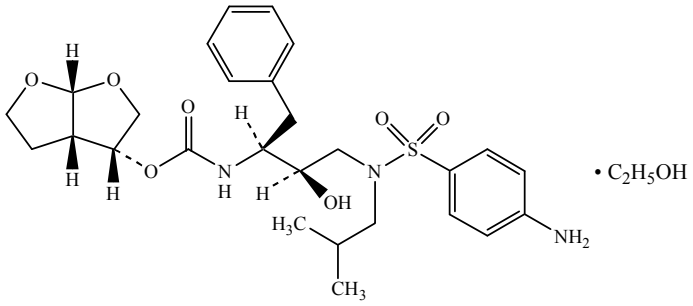
[(1*S*,2*R*)-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-yl ester ethanolate

Molecular formula and molecular mass:

Molecular formula: $C_{27}H_{37}N_3O_7S.C_2H_5OH$

Molecular mass: 593.73 g/mol

Structural formula:



Physicochemical properties:

Physical Description: Darunavir ethanolate is a white to off-white powder.

Solubility: The solubility of darunavir (or darunavir ethanolate) is approximately 0.015 mg/mL in water at 20°C.

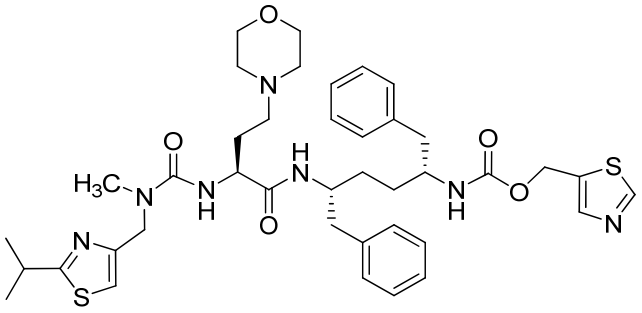
Common name:
Cobicistat (COBI)

Chemical name:
1,3-Thiazol-5-ylmethyl[(*2R,5R*)-5-{[(*2S*)-2-[(methyl{[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl}carbamoyl)amino]-4-(morpholin-4-yl)butanoyl]amino}-1,6-diphenylhexan-2-yl)carbamate

Molecular formula and molecular mass:
Molecular formula: $C_{40}H_{53}N_7O_5S_2$

Molecular mass: 776.0 g/mol

Structural formula:



Physicochemical properties:

Physical Description: Cobicistat is a white to yellow solid. Cobicistat is adsorbed onto silicon dioxide.

Solubility: The solubility of cobicistat is approximately 0.1 mg/mL in water at 20°C.

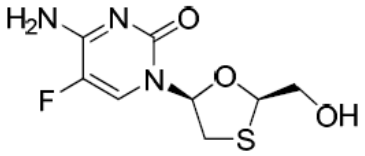
Common Name:
Emtricitabine (FTC)

Chemical Name:
5-fluoro-1-(2R,5S)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine

Molecular formula and molecular mass:
Molecular Formula: $C_8H_{10}FN_3O_3S$

Molecular Mass: 247.24 g/mol

Structural Formula:



Physicochemical properties:

Physical Description: Emtricitabine is a white to off-white powder**.**

Solubility: Solubility of emtricitabine is approximately 112 mg/mL in water at 25 °C.

Common Name:

Tenofovir alafenamide hemifumarate (TAF)
Tenofovir alafenamide fumarate (USAN)

Chemical Name:

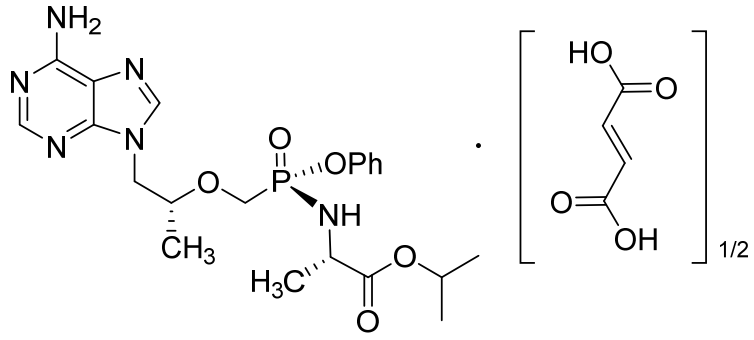
Propan-2-yl N-[(S)-({[(2R)-1-(6-amino-9H-purin-9 yl) propan-2-yl]-oxy}methyl)(phenoxy) phosphoryl]- L alaninate, (2E)-but-2-enedioate (2:1)

Molecular formula and molecular mass:

Molecular formula: $C_{21}H_{29}O_5N_6P \bullet 1/2(C_4H_4O_4)$

Molecular mass: 534.5 g/mol

Structural Formula:



Physicochemical properties:

Physical Description: Tenofovir alafenamide fumarate is a white to off-white or tan powder**.**

Solubility: The solubility of TAF in water pH 8.0 (50 mM phosphate buffer) at 20 °C is 4.86 mg/mL.

CLINICAL TRIALS

General

The antiretroviral effect of SYMTUZA™ is due to the darunavir, emtricitabine, and tenofovir alafenamide. The activity of cobicistat as a pharmacokinetic enhancer to darunavir has been demonstrated in pharmacokinetic studies. Darunavir, emtricitabine, and tenofovir alafenamide administered as a component of SYMTUZA™ is bioequivalent to the administration as single agents or in other combination products (see **CLINICAL TRIALS, Pivotal Comparative Bioavailability Study**).

Efficacy in adult patients

The evidence of efficacy of SYMTUZA™ once daily in HIV-1 infected patients is based on the established efficacy of the constituents (refer to the prescribing information for the fixed-dose combinations of darunavir/cobicistat and of emtricitabine/tenofovir alafenamide for more details) supported by the analysis of 24 week and 48 week data from the randomized, double-blinded, comparative Phase 2 study GS US 299 0102.

In study GS US 299 0102, treatment-naïve patients were randomized to receive either SYMTUZA™ (N=103) or cobicistat-boosted darunavir (as single agents) plus emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) fixed-dose combination (N=50) once daily. HIV-1 infected patients who were eligible for this trial had plasma HIV-1 RNA levels ≥5000 copies/mL and CD4+ cell count >50 cells/μL at screening. Virologic response was defined as confirmed plasma HIV-1 RNA viral load <50 copies/mL.

The 153 patients in total had a median age of 33 years (range 18-68), 92.8% were male, 60.1% White, 34.6% Black, 2% Asian, and 1.3% Native Hawaiian or other Pacific Islander. The mean baseline plasma HIV-1 RNA and the median baseline CD4+ cell count were 4.68 log10 copies/mL and 384 × 10^6 cells/L (range 7 x 10^6 cells/L to 1463 × 10^6 cells/L), respectively.

The table below shows the efficacy data of the 24 week and 48 week analyses from the GS US 299-0102 trial.

Table 8: Virologic Outcomes of Trial GS-US-299-0102 at Week 24 and Week 48[a]

	Week 24		Week 48	
	SYMTUZA™ (N=103)	D+C+F/TDF (N=50)	SYMTUZA™ (N=103)	D+C+F/TDF (N=50)
Virologic Response (Snapshot Analysis) % (N)				
HIV-1 RNA <50 copies/mL[b]	75% (77)	74% (37)	77% (79)	84% (42)
Treatment difference (95% CI)[c]	3.3% (-11.4% to 18.1%)		-6.2% (-19.9% to 7.4%)	
HIV-1 RNA <50 copies/mL - PP[d]	85% (77)	79% (37)	93% (79)	91% (42)
Treatment difference (95% CI)[c]	8.3% (-5.3% to 22%)		2.4% (-8.8% to 13.7%)	
Virologic Failure	20% (21)	24% (12)	16% (16)	12% (6)
HIV-1 RNA ≥50 copies/mL	14% (14)	22% (11)	7% (7)	8% (4)
Discontinued study drug due to other reasons and last available HIV-1 RNA ≥50 copies/mL[e]	7% (7)	2% (1)	9% (9)	4% (2)
No virologic data	5% (5)	2% (1)	8% (8)	4% (2)
Discontinued study drug due to AE or death[f]	1% (1)	0	1% (1)	2% (1)
Discontinued study drug due to other reasons and last available HIV-1 RNA <50 copies/mL[e]	4% (4)	2% (1)	7% (7)	2% (1)
CD4+ cell count mean change from™ baseline	186	139	231	212

SYMTUZA™ = fixed-dose combination of darunavir, cobicistat, emtricitabine, and tenofovir alafenamide
D+C+F/TDF = cobicistat-boosted darunavir plus emtricitabine/tenofovir disoproxil fumarate fixed-dose combination

[a] Week 24 and 48 window was between Day 140 and 195 (inclusive), and Day 294 and 377 (inclusive), respectively.

[b] The primary analysis set for the efficacy analysis was the Full Analysis Set, which included all subjects who (1) were randomized into the study and (2) received ≥1 dose of study medication.

[c] Treatment difference (SYMTUZA™ minus D+C+F/TDF) and 95% CI based on baseline HIV-1 RNA and race stratum-adjusted Mantel-Haenszel proportions.

[d] The Per-Protocol (PP) analysis set was defined as all subjects who (1) were randomized into the study, (2) received ≥1 dose of study drug, and (3) did not commit any major protocol violation (such as having an adherence rate for study drug up to Week 48 visit below the 2.5th percentile, or discontinued for reasons other than lack of efficacy with no Week 48 data).

[e] Included patients who discontinued for reasons other than an AE, death, or lack or loss of efficacy (eg, withdrew consent, loss to follow-up).

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

Efficacy in pediatric patients

The efficacy of SYMTUZA™ in pediatric patients has not been investigated. However, the use of SYMTUZA™ in adolescent patients from the age of 12 years to <18 years, and weighing at least 40 kg is supported by two clinical studies in HIV-1 infected pediatric patients: TMC114 C230 and GS-US-292-0106. (For more details, refer to the prescribing information of PREZISTA® and DESCOVY®.)

The open-label, Phase 2 trial TMC114-C230 was conducted for evaluating the pharmacokinetics, safety, tolerability, and efficacy of darunavir with low dose ritonavir in 12 treatment-naïve HIV 1 infected pediatric patients aged 12 to less than 18 years and weighing at least 40 kg. These patients received darunavir/ritonavir 800/100 mg once daily in combination with other antiretroviral agents. Virologic response was defined as a decrease in plasma HIV-1 RNA viral

load of at least 1.0 $\log_{10}$ versus baseline. Patients had a median age of 14.4 years (range: 12.6-17.3), and 66.7% were female, 58.3% were White, and 41.7% were Black. At baseline, median plasma HIV-1 RNA was 4.92 $\log_{10}$ copies/mL, median CD4+ cell count was 282×10^6 cells/L (range: 204-515 $\times 10^6$ cells/L), and median CD4+ % was 18.3% (range: 12.1-40.8%). Overall, 41.7% had baseline plasma HIV-1 RNA ≥100000 copies/mL. The table below shows the virologic outcomes of study TMC114-C230 at Week 48.

Table 9: Virologic Outcomes of Trial TMC114-C230 at Week 48 (TLOVR algorithm)

	Darunavir/ritonavir (N=12)
≥1.0 $\log_{10}$ decrease from baseline in plasma viral load	100%
HIV-1 RNA <50 copies/mL[a]	83.3% (10)
CD4+ cell count mean change from baseline[b]	221

[a] Imputations according to the TLOVR algorithm.

[b] Non-completer is failure imputation: patients who discontinued prematurely are imputed with a change equal to 0.

In study GS-US-292-0106, the efficacy, safety, and pharmacokinetics of emtricitabine and tenofovir alafenamide were evaluated in an open-label study, in which HIV-1-infected treatment-naïve adolescents received emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet (GENVOYA). Twenty-three patients treated with GENVOYA for 24 weeks had a mean age of 14 years (range: 12 to 17), were 52% male, 17% Asian, and 83% Black. At baseline, mean plasma HIV-1 RNA was 4.8 log10 copies/mL, median CD4+ cell count was 456 cells/mm3 (range: 104 to 748), and median CD4+% was 23% (range: 7% to 41%). Overall, 35% had baseline plasma HIV-1 RNA >100,000 copies/mL.

At Week 24, out of 23 patients assessed for efficacy, 91% achieved HIV-1 RNA <50 copies/mL, similar to response rates in trials of treatment-naïve HIV-1 infected adults. The mean increase from baseline in CD4+ cell count at Week 24 was 212 cells per mm^3. Two patients had virologic failure at Week 24; neither patient had evidence of resistance to emtricitabine and tenofovir alafenamide.

Fifty patients were assessed for safety at Week 24 (these patients received emtricitabine and tenofovir alafenamide (10 mg) given with elvitegravir+cobicistat as a fixed-dose combination tablet (GENVOYA) for 24 weeks). BMD by DXA was assessed in 47 patients for spine and 45 patients for total body less head. Mean (SD) BMD increased from baseline to Week 24, +1.6% (3.9%) at the lumbar spine and +0.6% (2.5%) for total body less head. Only those patients who had a height-age-adjusted BMD Z-score both at baseline and at Week 24 were assessed. At Week 24, 4 patients experienced treatment-emergent worsening in the spine (39 out of 47 patients assessed) and/or TBLH (37 out of 45 patients assessed) height-age-adjusted BMD Z-score clinical status from baseline, where a relationship to GENVOYA could not be excluded. However, in 2 of these patients, improvements in BMD were subsequently observed at Week 48.

Pivotal Comparative Bioavailability Study

In a Phase 1, single-dose, open-label, randomized, crossover trial the bioequivalence of darunavir 800 mg, emtricitabine 200 mg, and tenofovir alafenamide 10 mg, in the presence of cobicistat 150 mg, administered as either SYMTUZA™ (800/150/200/10 mg darunavir/cobicistat/emtricitabine/tenofovir alafenamide fixed-dose combination tablet) or as separate agents PREZISTA® (800 mg darunavir), DESCOVY™ (200/10mg emtricitabine/tenofovir alafenamide fixed dose combination) and TYBOST® (150 mg cobicistat) tablets in healthy subjects was assessed in 94 healthy male and female subjects under fed conditions, consisting of stardardized breakfast. Treatment sessions were separated by a washout period of at least 7 days.

The results indicate that SYMTUZA™ is bioequivalent to combined administration of the separate agents PREZISTA®, DESCOVY™ and TYBOST®.

The summary results are presented in Table 10.

Table 10: Summary of Pharmacokinetic Results for Individual Components After a Single Dose Administration of SYMTUZA™ (800/150/200/10 mg darunavir/cobicistat/emtricitabine/tenofovir alafenamide) and as Separate Agents PREZISTA® (800 mg darunavir), DESCOVY™ (200/10mg emtricitabine/tenofovir alafenamide) and TYBOST® (150 mg cobicistat), Under Fed Conditions

From measured data
Geometric Least Square Mean
Arithmetic Mean (CV%)

Darunavir (800 mg)

Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means (90% Confidence Interval)
AUC_{last} (ng.h/mL)	82994 87200 (31.4%)	79703 84406 (34.9%)	104.84 (100.87-108.97)
AUC_{∞} (ng.h/mL)	82883 87280 (32.2%)	80569 85210 (34.7%)	103.74 (90.30 – 102.07)
C_{max} (ng/mL)	6886 7042 (21.0%)	6483 6620 (21.6%)	106.73 (103.50-110.06)
T_{max}[3] (h)	4.00 (1.5-8.00)	4.00 (2.00-12.00)	
$T_{½}$[4] (h)	5.9 (35.2%)	6.2 (42.9%)	

Cobicistat (150 mg)

Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means (90% Confidence Interval)
AUC_{last} (ng.h/mL)	6238 6681 (37.2)	6352 6763 (36.0)	98.77 (95.14-102.52)
AUC_{∞} (ng.h/mL)	6336 6785 (37.1)	6452 6868 (35.8)	98.76 (95.15-102.52)
C_{max} (ng/mL)	859 894 (28.5)	856 881 (23.5)	100.69 (96.80-104.73)
T_{max}[3] (h)	4.00 (1.50-6.00)	4.00 (1.50-5.05)	
$T_{½}$[4] (h)	3.7 (18.7)	3.7 (20.1)	

Emtricitabine (200 mg)			
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means (90% Confidence Interval)
AUC_{last} (ng.h/mL)	11552 11722 (16.7%)	11597 11746 (15.9%)	100.04 (98.46-101.66)
AUC_{∞} (ng.h/mL)	11706 11882 (16.9%)	11769 11927 (16.2%)	100.13 (98.36-101.93)
C_{max} (ng/mL)	1984 2041 (23.5%)	2003 2053 (22.8%)	99.32 (95.61-103.17)
T_{max}[3] (h)	2.00 (0.60-5.00)	2.00 (0.50-5.00)	
$T_{½}$[4] (h)	16.5 (19.7)	17.0 (19.8%)	
Tenofovir alafenamide (10 mg)			
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means (90% Confidence Interval)
AUC_{last} (ng.h/mL)	116 123 (34.2%)	122 132 (43.9%)	96.59 (91.72-101.73)
AUC_{∞} (ng.h/mL)	121 127 (31.1%)	130 141 (42.5%)	95.42 (90.62-100.48)
C_{max} (ng/mL)	98.1 110 (49.0%)	102 120 (61.7%)	96.87 (88.95-105.50)
T_{max}[3] (h)	1.50 (0.25-3.50)	1.01 (0.25-4.00)	
$T_{½}$[4] (h)	0.3 (37.3%)	0.3 (37.9%)	

[1] SYMTUZA™ (800/150/200/10 mg darunavir/cobicistat/emtricitabine/tenofovir alafenamide fixed-dose combination tablet).
[2] PREZISTA® (800 mg darunavir), DESCOVY™ (200/10mg emtricitabine/tenofovir alafenamide fixed dose combination) and TYBOST® (150 mg cobicistat)
[3] Expressed arithmetic median (range) only.
[4] Expressed as the arithmetic mean (CV%) only.

DETAILED PHARMACOLOGY

Antiviral Activity *In Vitro*

Darunavir: DRV exhibits activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T-cell lines, human peripheral blood mononuclear cells and human monocytes/macrophages with median EC_{50} (50% effective concentration) values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/mL). Darunavir demonstrates antiviral activity *in vitro* against a broad panel of HIV-1 group M (A, B, C, D, E, F, G) and group O primary isolates with EC_{50} values ranging from < 0.1 to 4.3 nM.

These EC_{50} values are well below the 50% cellular toxicity concentration range of 87 µM to > 100 µM. The EC_{50} value of darunavir increases by a median factor of 5.4 in the presence of human serum.

Darunavir showed synergistic antiviral activity when studied in combination with the PIs ritonavir, nelfinavir, or amprenavir, and additive antiviral activity when studied in combination with the PIs indinavir, saquinavir, lopinavir, atazanavir, or tipranavir, the nucleoside (nucleotide) reverse transcriptase inhibitors (N(t)RTIs) zidovudine, lamivudine, zalcitabine, didanosine, stavudine, abacavir, emtricitabine, or tenofovir, the non-nucleoside reverse transcriptase inhibitors (NNRTIs) nevirapine, delavirdine, etravirine, or efavirenz, and the fusion inhibitor enfuvirtide. No antagonism was observed between darunavir and any of these antiretrovirals *in vitro*.

Cobicistat: COBI has no detectable antiviral activity against HIV-1, HBV, or HCV and does not antagonize the antiviral effect of darunavir.

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

In two-drug combination studies of FTC with NRTIs (abacavir, didanosine, lamivudine, stavudine, tenofovir, and zidovudine), NNRTIs (delavirdine, efavirenz, nevirapine, and rilpivirine), PIs (amprenavir, nelfinavir, ritonavir, and saquinavir), and the integrase strand transfer inhibitor elvitegravir additive to synergistic effects were observed. No antagonism was observed for these combinations.

Tenofovir alafenamide: The antiviral activity of TAF against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/ macrophage cells, and CD4+ T lymphocytes. The EC_{50} values for TAF were in the range of 2.0 to 14.7 nM. TAF displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including sub-types A, B, C, D, E, F, and G (EC_{50} values ranged from 0.10 to 12.0 nM) and strain specific activity against HIV-2 (EC_{50} values ranged from 0.91 to 2.63 nM). Overall, tenofovir alafenamide showed potent antiviral activity against the HIV-1 groups/subtypes evaluated.

In a study of TAF with a broad panel of representatives from the major classes of approved anti-HIV agents (NRTIs, NNRTIs, INSTIs, and PIs), additive to synergistic effects were observed. No antagonism was observed for these combinations.

MICROBIOLOGY

Resistance *In Vitro*

Darunavir: In vitro selection of darunavir-resistant virus from wild-type HIV-1 was lengthy (more than 2 years). The selected viruses were unable to grow in the presence of darunavir concentrations above 220 nM. Viruses selected in these conditions and showing decreased

susceptibility to darunavir (range: 23- to 50-fold) harboured 2 to 4 amino acid mutations in the protease gene. The decreased susceptibility to darunavir of the emerging viruses in the selection experiment could not be explained by the emergence of these protease mutations.

In vitro selection of darunavir-resistant HIV-1 (range: 53- to 641-fold change in EC_{50} values) from 9 HIV-1 strains harbouring multiple PI resistance-associated mutations (RAMs) resulted in the overall emergence of 22 mutations in the protease, of which L10F, V32I, L33F, S37N, M46I, I47V, I50V, L63P, A71V, and I84V were present in more than 50% of the 9 darunavir-resistant isolates. A minimum of 8 of these darunavir *in vitro* selected mutations, from which at least 2 were already present in the protease prior to selection, were required in the HIV-1 protease to render a virus resistant (fold change (FC) > 10) to darunavir.

In 1113 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and/or tipranavir, and in 886 baseline isolates from treatment-experienced patients only the subgroups with > 10 PI resistance-associated mutations showed a median FC for darunavir > 10.

In vivo, DRV RAMs (V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V and L89V) in HIV-1 protease were derived from clinical trial data of antiretroviral therapy experienced patients, which were all protease inhibitor experienced patients.

Cobicistat: No in vitro resistance can be demonstrated due to its lack of antiviral activity.

Emtricitabine: HIV-1 isolates with reduced susceptibility to FTC have been selected in cell culture. Reduced susceptibility to FTC was associated with M184V/I mutations in HIV-1 reverse transcriptase (RT).

Tenofovir alafenamide: HIV-1 isolates with reduced susceptibility to TAF have been selected in cell culture. HIV-1 isolates selected by TAF expressed a K65R mutation in HIV-1 RT; in addition, a K70E mutation in HIV-1 RT has been transiently observed. HIV-1 isolates with the K65R mutation have low-level reduced susceptibility to abacavir, FTC, tenofovir, and lamivudine. *In vitro* drug resistance selection studies with TAF have shown no development of resistence increases above 2.5 fold after 6 months in culture.

Cross-Resistance *In Vitro*

Darunavir: Cross-resistance has been observed among PIs. DRV has a < 10-fold decreased susceptibility against 90% of 3309 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and/or tipranavir showing that viruses resistant to most PIs remain susceptible to darunavir.

Cross-resistance between darunavir and the nucleoside/nucleotide reverse transcriptase inhibitors, the non-nucleoside reverse transcriptase inhibitors the fusion inhibitors, CCR5 co-receptors agonists, or the integrase inhibitor is unlikely because the viral targets for those inhibitors are different.

Emtricitabine: Cross-resistance has been observed among NRTIs. FTC-resistant isolates harboring an-M184V/I mutation in HIV-1 RT were cross-resistant to lamivudine. HIV-1 isolates containing the K65R RT mutation, selected *in vivo* by abacavir, didanosine, and tenofovir, demonstrated reduced susceptibility to inhibition by emtricitabine.

Tenofovir alafenamide: The K65R and K70E mutations result in reduced susceptibility to abacavir, didanosine, lamivudine, FTC, and tenofovir, but retain sensitivity to zidovudine. Multinucleoside resistant HIV-1 with a T69S double insertion mutation or with a Q151M mutation complex including K65R showed reduced susceptibility to TAF. HIV-1 containing the K103N or Y181C mutations associated with resistance to NNRTIs were susceptible to TAF. HIV-1 containing mutations associated with resistance to PIs such as M46I, I54V, V82F/T, and L90M were susceptible to TAF.

In Vivo Selection of Viral Resistance During SYMTUZA™ Therapy

The resistance profile of SYMTUZA™ is driven by darunavir, emtricitabine, and tenofovir alafenamide. Cobicistat does not select any HIV resistance mutations due to its lack of antiviral activity.

In the comparative Phase 2 study GS-US-299-0102 in HIV-1 infected treatment-naïve patients, no subject developed any darunavir or primary protease resistance-associated mutations from baseline through Week 48. One subject, receiving SYMTUZA™, had an NRTI-resistance mutation emerging at the unblinding visit after Week 48 with the emergence of a mutant/wild-type mixture at position K65 (K65K/R) and a mutant/wild-type mixture at position M184 (M184M/I). These mutations are associated with resistance to tenofovir disoproxil fumarate/tenofovir alafenamide and emtricitabine, respectively. However, phenotypic susceptibilities to both emtricitabine and tenofovir disoproxil fumarate were in the sensitive range despite the presence of those mutations. The subject had a viral load increase above 50 copies/mL at Week 40 followed by re-suppression of HIV-1 RNA <50 copies/mL, suggesting improper treatment compliance.

These data are in line with the low level of resistance development observed in historical studies investigating: (1) darunavir once daily, boosted with either ritonavir or cobicistat, in combination with other antiretroviral products (primarily emtricitabine/tenofovir disoproxil fumarate) in treatment-naïve patients and treatment-experienced patients with no darunavir RAMs, and (2) emtricitabine and tenofovir alafenamide in treatment-naïve and virologically suppressed patients.

In Vivo Cross-Resistance

In treatment-naïve virologic failures on boosted darunavir no cross-resistance with other HIV PIs has been observed.

Emtricitabine-resistant viruses with the M184V/I substitution were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir, and zidovudine.

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

For more details on the clinical resistance profile of darunavir, boosted with ritonavir or cobicistat, and emtricitabine/tenofovir alafenamide please refer to the PREZCOBIX® and DESCOVY™ Product Monographs.

TOXICOLOGY

Darunavir: Animal toxicology studies have been conducted with darunavir alone, in mice, rats and dogs and in combination with ritonavir in rats and dogs. In chronic toxicology studies in rats and dogs, there were only limited effects of treatment with darunavir. In the rat the key target organs identified were the hematopoietic system, the blood coagulation system, liver and thyroid, observed at 100 mg/kg/day and above and at exposures below clinical levels. A variable but limited decrease in red blood cell-related parameters was observed, together with increases in activated PTT. The observed liver and thyroid changes were considered to reflect an adaptive response to enzyme induction in the rat rather than an adverse effect. In combination toxicity studies with ritonavir, no additional target organs of toxicity were reported in rats. In the dog, no major toxicity findings or key target organs were identified at doses up to 120 mg/kg/day and exposures equivalent to clinical exposure at the recommended dose.

Cobicistat: Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity. *Ex vivo* rabbit studies and *in vivo* dog studies suggest that cobicistat has a low potential for QT prolongation, and may slightly prolong the PR interval and decrease left ventricular function at mean concentrations at least 10-fold higher than the human exposure at the recommended 150 mg daily dose.

Emtricitabine: Non-clinical data on emtricitabine reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity.

Tenofovir alafenamide: The general toxicology profile of tenofovir alafenamide has been studied in mice, rats, dogs and monkeys. The target organs were the kidney and bone. The effects on the kidneys included cortical tubular basophilia and tubular karyomegaly in both rats and dogs and additionally cortical tubular degeneration/regeneration in dogs. These effects did not appear to meaningfully affect renal function except for possibly related reduction in serum calcitriol (1,25-dihydroxyvitamin D3) that may be implicated in the bone effects (see below). The tenofovir alafenamide-related effects on the bone included decreases in bone mineral density and mineral content observed in both rats and dogs. In the 9-month dog study, animals dosed at 18/12 mg/kg/day (approximately 47 times the clinical exposure based on AUC) failed to mature skeletally. The NOAEL in the rat and dog was 25 mg/kg/day (approximately 13 times clinical tenofovir exposure based on AUC) and 2 mg/kg/day (approximately 4 times the clinical tenofovir exposure based on AUC), respectively. These effects were partially reversible upon treatment discontinuation.

Electrocardiographic effects occurred in the 9-month dog study and included prolongation of PR intervals at ≥6 mg/kg (approximately 15 times the clinical exposure based on AUC) and reduction in heart rate with an associated QT prolongation at 18/12 mg/kg (approximately 47 times the clinical

exposure based on AUC); the heart rate changes were reversible following a three-month recovery period. The NOAEL was 2 mg/kg (approximately 4 times the clinical tenofovir exposure based on AUC). These effects might have been due to a reduction in triiodothryonine (T3) levels.

Carcinogenesis and Mutagenesis

Darunavir: Darunavir was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 150, 450 and 1000 mg/kg were administered to mice and doses of 50, 150 and 500 mg/kg were administered to rats. A dose related increase in the incidences of hepatocellular adenomas and carcinomas were observed in males and females of both species. Thyroid follicular cell adenomas were noted in male rats. Administration of darunavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. The observed hepatocellular findings in rodents are considered to be of limited relevance to humans. Repeated administration of darunavir to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination, which predispose rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures (based on AUC) to darunavir were between 0.5- and 0.6-fold (mice) and 0.9-fold (rats), relative to those observed in humans at the recommended therapeutic doses (600/100 mg twice daily or 800/100 mg once daily). Darunavir was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays including bacterial reverse mutation (Ames), chromosomal aberration in human lymphocytes and *in vivo* micronucleus test in mice.

In a long-term carcinogenicity study of cobicistat in mice, no drug-related increases in tumour incidence were observed at doses up to 50 and 100 mg/kg/day (males and females, respectively).

Cobicistat: Cobicistat exposures at these doses were approximately 7 (males) and 16 (females) times, respectively, the human systemic exposure at the therapeutic daily dose. In a long-term carcinogenicity study of cobicistat in rats, an increased incidence of follicular cell adenomas and/or carcinomas in the thyroid gland was observed at doses of 25 and 50 mg/kg/day in males, and at 30 mg/kg/day in females. The follicular cell findings are considered to be rat-specific, secondary to hepatic microsomal enzyme induction and thyroid hormone imbalance, and are not relevant for humans. At the highest doses tested in the rat carcinogenicity study, systemic exposures were approximately 2 times the human systemic exposure at the therapeutic daily dose.

Cobicistat was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays.

Emtricitabine: In long-term carcinogenicity studies of emtricitabine, no drug-related increases in tumor incidence were found in mice at doses up to 750 mg/kg/day (23 times the human systemic exposure at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (28 times the human systemic exposure at the therapeutic dose). Emtricitabine was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or mouse micronucleus assays.

Tenofovir alafenamide: Because there is a lower tenofovir exposure in rats and mice after TAF compared to tenofovir disoproxil fumarate (TDF), carcinogenicity studies were conducted only with TDF. Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate in mice and

rats were carried out at exposures up to approximately 10 times (mice) and 4 times (rats) those observed in humans at the 300 mg therapeutic dose of tenofovir disoproxil fumarate for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures 10 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 4 times that observed in humans at the therapeutic dose. Tenofovir alafenamide was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays.

Reproductive and Developmental Toxicity

Darunavir: Investigation of fertility and early embryonic development with darunavir was performed in rats, teratogenicity studies were conducted in mice, rats and rabbits, and the pre- and post-natal development study was conducted in rats.

In the fertility and early embryonic development study conducted with darunavir, a significant decrease in body weight gain with subsequent related reduction in the number of ovulations resulting in a reduction in the number of live fetuses was observed in female rats treated with 1000 mg/kg. Otherwise, there were no effects on mating or fertility with darunavir treatment up to 1000 mg/kg/day and exposure levels below (AUC 0.5-fold) that in humans at the clinically recommended dose. Up to the same dose levels, there was no teratogenicity with darunavir in rats and rabbits when treated alone nor in mice when treated in combination with ritonavir. The exposure levels were lower than those observed with the recommended clinical dose in humans. In a pre- and post-natal development assessment in rats, darunavir with and without ritonavir caused a transient reduction in body weight gain of the offspring during lactation. This was attributed to drug exposure via the milk. No post-weaning functions were affected with darunavir alone or in combination with ritonavir.

In juvenile rats directly dosed with darunavir (from 20 mg/kg to 1000 mg/kg) up to days 23 to 26 of age, mortality was observed and, in some of the animals, convulsions. Within this age range exposures in plasma, liver and brain were dose and age dependent and were considerably greater than those observed in adult rats. These findings were attributed to the ontogeny of the CYP450 liver enzymes involved in the metabolism of darunavir and the immaturity of the blood-brain barrier. No treatment-related mortalities were noted in juvenile rats dosed at 1000 mg/kg darunavir (single dose) on day 26 of age or at 500 mg/kg (repeated dose) from day 23 to 50 of age, and the exposures and toxicity profile were comparable to those observed in adult rats. In humans, the activity of drug-metabolizing enzymes approaches adult values by 3 years of age.

Cobicistat: Reproductive studies with cobicistat were conducted in rats and rabbits. Animal studies do not indicate direct or indirect harmful effects of cobicistat with respect to pregnancy, fetal development, parturition or postnatal development. There were no effects on mating and 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 cobicistat during pregnancy, there were no toxicologically significant effects on developmental endpoints. The exposures at the embryo-fetal NOAELs in rats and rabbits were respectively 1.4 and 3.3 times higher than the exposure in humans at the recommended daily dose of 150 mg.

Cobicistat did not affect fertility in male or female rats at daily exposures (AUC) approximately 3.3-fold higher than human exposures at the recommended 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 1.2-fold higher than human exposures at the recommended 150 mg daily dose.

Emtricitabine: The incidence of fetal variations and malformations was not increased in embryo-fetal toxicity studies performed with emtricitabine in mice at exposures (AUC) approximately 60 times higher and in rabbits at approximately 120 times higher than human exposures at the recommended daily dose.

Emtricitabine did not affect fertility in male rats at approximately 140-fold or in male and female mice at approximately 60 fold higher exposures (AUC) than in humans given the recommended 200 mg daily dose. Fertility was normal in the offspring of mice exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 60-fold higher than human exposures at the recommended 200 mg daily dose.

Tenofovir alafenamide: There were no effects on fertility, mating performance or early embryonic development when tenofovir alafenamide was administered to male rats at a dose equivalent to 155 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 14 days prior to mating through day seven of gestation.

REFERENCES

1. Clotet B, Bellos N, Molina J, Cooper D et al. Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2 a pooled subgroup analysis of data from two randomised trials. Lancet 2007;369:1169-78.

2. Mills A, Nelson M, Jayaweera D et al. Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96-week analysis. AIDS 2009;23:1679-1688.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION
PrSYMTUZA™
(darunavir/cobicistat/emtricitabine/tenofovir alafenamide) Tablets

Read this carefully before you start taking SYMTUZA™ and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about SYMTUZA™.

Serious Warnings and Precautions

"Flare-ups" of Hepatitis B Virus infection can occur if you also have hepatitis B and stop taking SYMTUZA™. In these cases, your infection may return and become worse than it was before. Do not stop taking SYMTUZA™ without your doctor's advice. If you stop taking SYMTUZA™, tell your doctor right away. Tell your doctor about any new, unusual or worsening symptoms that you notice after stopping treatment. After you stop taking SYMTUZA™, your doctor will still need to check your health and take blood tests to check your liver. SYMTUZA™ is not approved for the treatment of hepatitis B virus infection.

What is SYMTUZA™ used for?

- SYMTUZA™ is a single tablet regimen containing antiretroviral medicine used to treat human immunodeficiency virus (HIV) infection. HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).
- SYMTUZA™ is for adults and children 12 years of age and older and who weigh at least 40 kg (88 lbs).

How does SYMTUZA™ work?

SYMTUZA™ works by reducing the amount of HIV in your blood (called "viral load"). HIV infection affects the immune system. The immune system helps fight infection. Reducing the amount of HIV may improve your immune system (your body's natural defences).

SYMTUZA™ does not cure HIV infection or AIDS. At present, there is no cure for HIV infection. People taking SYMTUZA™ may still develop infections or other conditions associated with HIV infection. Because of this, it is very important for you to remain under the care of a doctor.

What are the ingredients in SYMTUZA™?

Each SYMTUZA™ tablet contains

Medicinal ingredients:

Darunavir (800 mg) as ethanolate, Cobicistat (150 mg), Emtricitabine (200 mg) and Tenofovir alafenamide (10 mg) as hemifumarate.

Non-medicinal ingredients:

Tablet core: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose.

Film-coating: polyethylene glycol (macrogol), polyvinyl alcohol (partially hydrolyzed), talc, titanium dioxide, yellow ferric oxide.

SYMTUZA™ comes in the following dosage forms:

SYMTUZA™ is available as film-coated tablets. Tablets are yellow to yellowish-brown, capsule-shaped, debossed on one side with "8121" and the number "JG" on the other side.

Do not use SYMTUZA™ if:

- you are taking any medication that is listed in this leaflet under "**Drugs that should not be taken with SYMTUZA™**".
- you are allergic to SYMTUZA™ or any of its ingredients (see "**What are the ingredients in SYMTUZA™?**").
- Have severe liver problems.

To help avoid side effects and ensure proper use, talk to your doctor before you take SYMTUZA™. Talk about any health conditions or problems you may have, including if you:

- Have lactic acidosis (high levels of acid in the blood). See "**Serious side effects and what to do about them**" table for symptoms. Contact your doctor right away if you get these side effects.
- Have hepatitis B and/or C or severe liver problems (hepatotoxicity) including enlarged or fatty liver. See "**Serious side effects and what to do about them**" table for symptoms. Cases leading to death have been reported.
- If you have hepatitis B virus (HBV) infection at the same time and take SYMTUZA™**.** Do not stop taking SYMTUZA™. Your HBV infection may get worse (flare-up) and symptoms worsen if you stop taking SYMTUZA™ (see "**Serious Warnings and Precautions**" box and **"Serious side effects and what to do about them**" table). Worsening of hepatitis may be life-threatening for patients with advanced liver disease or cirrhosis.
- Have a history of pancreatitis (swelling of the pancreas). See the **"Serious side effects and what to do about them**" table for symptoms.
- Have kidney problems. Kidney problems, including kidney failure, have occurred. Your kidney problems could get worse if you take SYMTUZA™ with some medicines such as non-steroidal anti-inflammatory drugs.
- Have a history of bone fracture, bone loss or osteoporosis.
- Have diabetes. In general, anti-HIV medicines, such as SYMTUZA™, might increase sugar levels in the blood. Some patients have diabetes before starting treatment with SYMTUZA™, which gets worse. Some patients get diabetes during treatment with SYMTUZA™. Some patients will need changes in their diabetes medicine. Some patients may need new diabetes medicine. See "**Serious side effects and what to do about them**" table.
- Have hemophilia. SYMTUZA™, might increase the risk of bleeding.
- Are allergic sulfa medicines.
- Notice any symptoms of infection. Tell your doctor right away if you have high fever, joint or muscle pain, redness, rash, swelling, or fatigue.

Other warnings you should know about:

If you are pregnant or plan to become pregnant:

It is not known if SYMTUZA™ can harm your unborn child. Talk to your doctor. You should not take SYMTUZA™ during pregnancy.

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 SYMTUZA™, 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. Do not breast-feed if you take SYMTUZA. One of the ingredients of SYMTUZA™, emtricitabine, can be passed to your baby in your breast milk and may cause harm to your baby. It is not known if the other components can be passed to your baby in breast milk. If you are a woman who has or will have a baby, talk with your doctor about the best way to feed your baby.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Drugs that must not be taken with SYMTUZA™ (contraindicated):

Type of Drug	**Examples of Generic Names (Brand Names)**
Alpha1-Adrenoreceptor Antagonists (to treat enlarged prostate	alfuzosin
Antiarrhythmics (to treat abnormal heart rhythms)	amiodarone (Cordarone), bepridil[1],dronedarone (Multaq), lidocaine (when given by injection), quinidine
Anticoagulants (to prevent the clotting of red blood cells)	apixaban (Eliquis), rivaroxaban (Xarelto)
Anti-convulsants (to prevent seizures)	carbamazepine (Tegretol), phenobarbital phenytoin (Dilantin)
Anti-gout (to treat gout and familial Mediterranean fever)	colchicine
Antihistamines (to treat allergy symptoms)	astemizole[1], terfenadine[1]
Antimycobacterial (to treat tuberculosis)	rifampin (Rifadin, Rifater, Rifamate, Rofact)
Ergot Derivatives (to treat migraine and headaches)	dihydroergotamine (Migranal), ergonovine, ergotamine (Cafergot), methylergonovine
Gastrointestinal Motility Agents (to treat some digestive conditions)	cisapride[1]
Hepatitis C Virus Direct-Acting Antivirals (to treat hepatitis C infection)	elbasvir/grazoprevir
Herbal products (to improve mood)	St. John's Wort *(Hypericum perforatum)*
Drugs used to lower cholesterol	lovastatin (Mevacor), simvastatin (Zocor), lomitapide (Juxtapid)
Inhaled Beta-Agonists (to treat asthma and/or chronic obstructive pulmonary disease)	salmeterol (Advair)
Neuroleptics (to treat psychiatric conditions)	lurasidone, pimozide (Orap)
PDE-5 Inhibitor (to treat pulmonary arterial hypertension)	sildenafil (Revatio)
Platelet Aggregation Inhibitor (to prevent	ticagrelor (Brilinta)

blood clots)	
Sedatives/Hypnotics (to treat trouble with sleeping and/or anxiety)	oral midazolam, triazolam (Halcion)

[1]Not marketed in Canada.

Drugs that should not be taken with SYMTUZA™:

- Any other medicines to treat HIV-1 infection.
- Any other medicines that contain protease inhibitors (PREZISTA®, PREZCOBIX®, Reyataz, Crixivan, Invirase, Kaletra).
- Any other medicines that contain tenofovir (GENVOYA, ATRIPLA, COMPLERA, ODEFSY, STRIBILD, TRUVADA, VEMLIDY, VIREAD).
- Any other medicines that contain emtricitabine or lamivudine (ATRIPLA, COMPLERA, EMTRIVA, GENVOYA, ODEFSY, STRIBILD, TRUVADA; 3TC, Combivir, Heptovir, Kivexa, Triumeq, Trizivir.
- Any other medicines containing ritonavir or cobicistat (Norvir, Kaletra, Holkira Pak, PREZCOBIX®, TYBOST, STRIBILD).
- adefovir (HEPSERA).
- medications that may affect your kidneys and have not been discussed with your doctor.

Drugs that interact with SYMTUZA™ and where the dose of SYMTUZA™ or the dose of the other drug should be changed or more instruction from your doctor is needed:

- Tell your doctor if you are taking hormonal contraceptives. SYMTUZA™ might reduce the effectiveness of this type of birth control and/or increase their side effects. Additional or other methods of non-hormonal birth control, such as a condom, are recommended.
- Tell your doctor if you are taking any of the following medicines.

Type of Drug	**Examples of Generic Names (Brand Names)**
Antiarrhythmics (for the heart)	digoxin, disopyramide, flecainide, mexiletine, propafenone
Anticancer Agents (to treat cancer)	dasatinib (Sprycel), nilotinib (Tasigna), vinblastine, vincristine, everolimus (Afinitor)
Anticoagulants (to prevent the clotting of red blood cells)	dabigatran etexilate (Pradaxa), edoxaban (Lixiana), warfarin (Coumadin)
Anticonvulsants (to treat epilepsy and prevent seizures)	clonazepam (Clonapam), ethosuximide (Zarontin), oxcarbazepine (Trileptal)
Antidepressants (to treat depression, anxiety, or panic disorder)	amitriptyline, desipramine, imipramine, nortriptyline, paroxetine (Paxil), sertraline (Zoloft), trazodone (Oleptro)
Anti-infectives (to treat bacterial infections)	clarithromycin (Biaxin), erythromycin (Eryc)
Antifungals (to treat fungal infections)	fluconazole (Diflucan), ketoconazole (Nizoral®), itraconazole (Sporanox®), posaconazole (Posanol), voriconazole (Vfend)
Anti-gout (to treat gout and familial Mediterranean fever)	colchicine
Antimalarials (to treat malarial infections)	artemether/lumefantrine (Riamet and Coartem), Artemether/lumefantrine are not approved for use in Canada.
Antimycobacterials (to treat bacterial infections)	rifabutin (Mycobutin), rifapentine[1]
Beta-Blockers (to treat heart disease)	carvedilol, metoprolol (Betaloc, Lopresor), timolol
Calcium Channel Blockers (to treat heart disease)	amlodipine (Caduet. Twynsta), diltiazem (Cardizem, Tiazac) felodipine, nifedipine (Adalat), nicardipine, verapamil (Isoptin, Verelan)

Corticosteroids (to treat inflammation or asthma)	bethamethasone, budesonide (Pulmicort, Rhinocort, Symbicort), dexamethasone, fluticasone propionate (Advair Diskus, Cutivate, Flonase, Flovent Diskus), mometasone, prednisone (Winpred), triamcinolone
Endothelin Receptor Antagonists (to treat pulmonary arterial hypertension)	bosentan (Tracleer®)
Hormonal Contraceptives	ethinyl estradiol, norethindrone, norgestimate, drospirenone
Eugeroics	modafinil
Hepatitis C Virus direct-acting antivirals (to treat Hepatitis C Virus [HCV])	glecaprevir/pibrentasvir (Maviret)
HMG-CoA Reductase Inhibitors (to lower cholesterol levels)	atorvastatin (Lipitor), pravastatin (Pravachol), rosuvastatin (Crestor)
Immunosuppressants (to prevent organ transplant rejection)	cyclosporine (Sandimmune, Neoral), tacrolimus (Prograf), sirolimus (Rapamune), everolimus (Afinitor)
Narcotic Analgesics (to treat opioid dependence)	buprenorphine/naloxone (Suboxone), fentanyl (Abstral, Duragesic®), methadone, meperidine, oxycodone tramadol (Durela, Ralivia, Tramacet®, Tridural, Ultram®, Zytram XL)
Neuroleptics (to treat psychotic disorders)	perphenazine, risperidone (Risperdal®, Risperdal Consta®), thioridazine, quetiapine (Seroquel)
PDE-5 Inhibitors (to treat erectile dysfunction)	sildenafil (Viagra), vardenafil (Levitra), tadalafil (Cialis)
Sedatives/Hypnotics (to treat trouble with sleeping and/or anxiety)	buspirone, clorazepate, diazepam (Diazemuls, Valium), estazolam, midazolam (taken by injection), flurazepam (Dalmane, Som-Pam), zoldipem

[1]Not marketed in Canada.

This is not a complete list of medicines that you should tell your doctor that you are taking. You can ask your doctor or pharmacist for a list of medicines that can interact with SYMTUZA™**.** Do not start any new medicines while you are taking SYMTUZA™ without first talking with your doctor or pharmacist.

How to take SYMTUZA™:

Always use SYMTUZA™ exactly as your doctor has told you. You must check with your doctor or pharmacist if you are not sure.

You should always take SYMTUZA™ with food. The type of food is not important. SYMTUZA™ cannot work properly without food. Take SYMTUZA™ within 30 minutes of eating.

Swallow SYMTUZA™ tablets whole without breaking or crushing. Swallow the tablet with a drink such as water, milk, or a nutritional drink. If you have trouble swallowing SYMTUZA™, tell your doctor or pharmacist. Your doctor will determine whether SYMTUZA™ or its individual components are right for you.

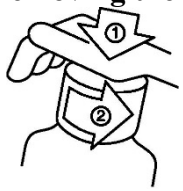
Take SYMTUZA™ at about the same time each day, every day. Talk to your doctor if you need help with making a schedule that works for you.

Do not stop using SYMTUZA™ without talking to your doctor first.

Even when you feel better.
If you have both HIV infection and hepatitis B, it is very important not to stop taking SYMTUZA™ without talking to your doctor first (see "**Serious Warnings and Precautions**").
Do not run out of SYMTUZA™. Refill your prescription or talk to your doctor before your SYMTUZA™ is all gone. This is very important because the amount of virus may start to increase if the medicine is stopped for even a short time.

Usual dose:
The dose of SYMTUZA™ is 1 tablet once a day for adults and adolescents 12 years of age and older, who weigh at least 40 kg.

Removing the child resistant cap



The plastic bottle comes with a child resistant cap and should be opened as follows:
- Push the plastic screw cap down while turning it counter clockwise.
- Remove the unscrewed cap.

Overdose:

If you think you have taken too much SYMTUZA™**,** contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
It is important that you do not miss any doses. If you forget to take SYMTUZA™.
- If you notice **within 12 hours** of the time you usually take SYMTUZA™, take the tablet immediately, with food. Then take the next dose at your usual time.
- If you notice **after 12 hours, do NOT take the missed dose**. Wait to take the next dose with food at your usual time.
- **Do NOT take a double dose (two doses together).**
- Call your doctor or pharmacist if you are not sure what to do.

Do not take more or less than your prescribed dose of SYMTUZA™ at any one time.

What are possible side effects from using SYMTUZA™?
Like all prescription drugs, SYMTUZA™ can cause side effects. The following are not all the possible side effects you may feel when taking SYMTUZA™. Do not rely on this leaflet alone for information about side effects. If you experience any side effects, even those not listed here, contact your doctor or pharmacist.

The most common side effects with SYMTUZA™ include:
- Diarrhea, rash, tiredness (fatigue), swelling of the belly (abdominal distension), feeling sick (nausea), muscle aches (myalgia).

Some side effects are typical for anti-HIV medicines in the same family as SYMTUZA™. These are:

- High blood sugar (hyperglycemia) and diabetes.
- Increases in triglycerides and cholesterol (forms of fat that are found in your blood).
- Changes in your immune system (Immune Reconstitution Inflammatory Syndrome) can happen when you start taking HIV medicines. 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 straight away.
- Bone problems including bone pain, softening or thinning (which may lead to fractures).
- Kidney problems.

Tell your doctor promptly about these or any other unusual symptoms. If the condition persists or worsens, seek medical attention.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON Severe and sometimes life-threatening rash (blisters, peeling skin) which may be accompanied by - fever - fatigue - swelling of the face or lymph glands - muscle aches and pain - liver problems			✓
Liver problems with symptoms such as - yellowing of the skin or whites of the eyes - dark (tea coloured) urine - pale coloured stools (bowel movements) - nausea - vomiting - loss of appetite - pain, aching, or - sensitivity on right side below ribs		✓	
Diabetes with symptoms such as - excessive thirst - excessive urination - excessive eating - unexplained weight loss - poor wound healing - infections		✓	
Inflammation of the pancreas with symptoms such as - abdominal pain - nausea and - vomiting		✓	
RARE Lactic acidosis with symptoms such as - feeling very weak or tired, unusual muscle pain - stomach pain with nausea and vomiting - feeling unusually cold especially in arms and legs - feeling dizzy or lightheaded - fast or irregular heartbeat - fast and deep breathing		✓	
VERY RARE Hepatotoxicity (severe liver problems) with hepatomegaly (liver enlargement) and steatosis (fat in the liver) with symptoms such as - jaundice (skin or the white part of eyes turn yellow) - urine turns dark - bowel movements (stools) turn light in color - loss of appetite for several days or longer - feeling sick to your stomach (nausea) - lower stomach pain		✓	
VERY RARE Flare-ups of hepatitis B virus infection following drug discontinuation with symptoms such as		✓	

- jaundice (skin or the white part of eyes turn yellow) - urine turns dark - bowel movements (stools) turn light in color - loss of appetite for several days or longer - feeling sick to your stomach (nausea) - lower stomach pain			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store SYMTUZA™ in the original package with desiccant inside the bottle in order to protect the tablets from moisture. Keep the bottle tightly closed. Store between 15 - 30°C. **Keep out of reach and sight of children.**

If you want more information about SYMTUZA™:

- Talk to your healthcare professional.
- For questions or concerns, contact the manufacturer, Janssen Inc. (www.janssen.com/canada)
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website http://hc-sc.gc.ca/index-eng.php; the manufacturer's website www.janssen.com/canada, or by contacting the manufacturer at: 1-800-567-3331 or 1-800-387-8781.

This leaflet was prepared by Janssen Inc., Toronto, Ontario, M3C 1L9.

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