Brand Name	Symtuza
Active Ingredient(s)	darunavir, cobicistat, emtricitabine, tenofovir alafenamide
Strength	800-150-200-10 mg
Dosage Form	tablet
Inactive Ingredients	colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The coating contains polyethylene glycol (macrogol), polyvinyl alcohol (partially hydrolyzed), talc, titanium dioxide, and yellow ferric oxide.
NDC	59676-800-30
DIN	02473720
Canadian Distributor	Janssen Inc. 19 Green Belt Drive, Toronto, Ontario, Canada M3C 1L9
NDA Number	NDA210455
US Distributor (NDA Holder)	Janssen Products LP 800 Ridgeview Dr Horsham, PA, 19044
Manufacturer (Final Packager)	Patheon Inc 2100 Syntex Ct, Mississauga ON L5N 7K9, Canada Janssen Cilag SpA Latina, Italy
API Manufacturer	Not available
Relationship to Sponsor	The Sponsor may have or have had agreements with the U.S. manufacturer for rebates. The Sponsor has no relationship with the foreign manufacturer.

Current FDA-approved Package Insert

SYMTUZA®

(darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets, for oral use

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SYMTUZA safely and effectively. See full prescribing information for SYMTUZA.

SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets, for oral use
Initial U.S. Approval: 2018

WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

See full prescribing information for complete boxed warning.

Severe acute exacerbations of hepatitis B (HBV) have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of SYMTUZA. Hepatic function should be monitored closely in these patients. If appropriate, anti-hepatitis B therapy may be warranted. (5.1)

----------RECENT MAJOR CHANGES----------

Contraindications (4) 04/2022

----------INDICATIONS AND USAGE----------

SYMTUZA is a four-drug combination of darunavir (DRV), a human immunodeficiency virus (HIV-1) protease inhibitor, cobicistat (COBI), a CYP3A inhibitor, and emtricitabine (FTC) and tenofovir alafenamide (TAF), both HIV-1 nucleoside analog reverse transcriptase inhibitors, and is indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 40 kg:

- who have no prior antiretroviral treatment history or
- who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months and have no known substitutions associated with resistance to darunavir or tenofovir. (1)

----------DOSAGE AND ADMINISTRATION----------

Testing: Prior to or when initiating SYMTUZA, test patients for HBV infection.

Prior to or when initiating SYMTUZA, and during treatment with SYMTUZA, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. (2.1)

Recommended dosage: One tablet taken once daily with food in adults and pediatric patients, weighing at least 40 kg. (2.2)

Renal Impairment: SYMTUZA is not recommended in patients with estimated creatinine clearance below 30 mL/min. (2.3)

Hepatic Impairment: SYMTUZA is not recommended in patients with severe hepatic impairment. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 800 mg of darunavir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (equivalent to 11.2 mg of tenofovir alafenamide fumarate). (3)

----------CONTRAINDICATIONS----------

SYMTUZA is contraindicated to be co-administered with certain drugs for which altered plasma concentrations are associated with serious and/or life-threatening events or which may lead to loss of therapeutic effect of SYMTUZA and development of resistance. (4)

----------WARNINGS AND PRECAUTIONS----------

- Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) including some fatalities can occur with SYMTUZA. Monitor liver function before and during therapy, especially in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases. (5.2)
- Severe skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis may occur with SYMTUZA. Discontinue treatment if severe skin reaction develops. (5.3)
- Patients receiving SYMTUZA may develop new onset or exacerbations of immune reconstitution syndrome. (5.5)
- Monitor in patients with a known sulfonamide allergy. (5.7)
- Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.8)
- Patients receiving SYMTUZA may develop new onset or exacerbation of diabetes mellitus/hyperglycemia and redistribution/accumulation of body fat. (5.9, 5.10)
- Patients with hemophilia may develop increase bleeding events. (5.11)

----------ADVERSE REACTIONS----------

The most common adverse reactions (all grades, incidence greater than or equal to 2%) were diarrhea, rash, nausea, fatigue, headache, abdominal discomfort, and flatulence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Products, LP at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

Co-administration of SYMTUZA with other drugs can alter the concentration of other drugs and other drugs may alter the concentrations of SYMTUZA components. Consult the full prescribing information prior to and during treatment for potential drug interactions. (4, 5.4, 7, 12.3)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: SYMTUZA is not recommended during pregnancy due to substantially lower exposures of darunavir and cobicistat during pregnancy. (2.5, 8.1, 12.3)
- Lactation: Breastfeeding is not recommended. (8.2)
- Pediatrics: Not recommended for pediatric patients weighing less than 40 kg (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

Severe acute exacerbations of hepatitis B (HBV) have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of SYMTUZA. Closely monitor hepatic function 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, anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.1)]*.

1. INDICATIONS AND USAGE

SYMTUZA is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients weighing at least 40 kg:

- who have no prior antiretroviral treatment history or
- who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months and have no known substitutions associated with resistance to darunavir or tenofovir.

2. DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation of SYMTUZA

Prior to or when initiating SYMTUZA, test patients for hepatitis B (HBV) virus infection *[see Warnings and Precautions (5.1)]*.

Prior to or when initiating SYMTUZA, and during treatment with SYMTUZA, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus *[see Warnings and Precautions (5.6)]*.

2.2 Recommended Dosage

SYMTUZA is a four-drug fixed-dose combination product containing 800 mg of darunavir (DRV), 150 mg of cobicistat (COBI), 200 mg of emtricitabine (FTC), and 10 mg of tenofovir alafenamide (TAF). The recommended dosage of SYMTUZA is one tablet taken orally once daily with food in adults and pediatric patients weighing at least 40 kg. For patients who are unable to swallow the whole tablet, SYMTUZA may be split into two pieces using a tablet-cutter, and the entire dose should be consumed immediately after splitting *[see Clinical Pharmacology (12.3)]*.

2.3 Not Recommended in Patients with Severe Renal Impairment

SYMTUZA is not recommended in patients with creatinine clearance below 30 mL per minute *[see Use in Specific Populations (8.6)]*.

2.4 Not Recommended in Patients with Severe Hepatic Impairment

SYMTUZA is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C) *[see Use in Specific Populations (8.7)]*.

2.5 Not Recommended During Pregnancy

SYMTUZA is not recommended during pregnancy because of substantially lower exposures of darunavir and cobicistat during the second and third trimesters *[see Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)]*.

SYMTUZA should not be initiated in pregnant individuals. An alternative regimen is recommended for those who become pregnant during therapy with SYMTUZA.

3. DOSAGE FORMS AND STRENGTHS

Each SYMTUZA tablet contains darunavir ethanolate equivalent to 800 mg of darunavir, 150 mg of cobicistat, 200 mg of emtricitabine (FTC), and tenofovir alafenamide fumarate equivalent to 10 mg of tenofovir alafenamide (TAF). The yellow to yellowish-brown, capsule-shaped, film-coated tablet is debossed with "8121" on one side and "JG" on the other side.

4. CONTRAINDICATIONS

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). Darunavir and cobicistat are both substrates of the cytochrome P450 3A (CYP3A) isoform. Co-administration of SYMTUZA with CYP3A inducers is expected to lower plasma concentrations of darunavir and cobicistat which may lead to loss of efficacy of darunavir and development of resistance. Examples of drugs that are contraindicated for co-administration with SYMTUZA due to the potential for serious and/or life-threatening events or loss of therapeutic effect *[see Drug Interactions (7.5)]* are listed below.

- Alpha 1-adrenoreceptor antagonist: alfuzosin
- Anticonvulsants: carbamazepine, phenobarbital, phenytoin
- Anti-gout: colchicine, in patients with renal and/or hepatic impairment
- Antimycobacterial: rifampin
- Antipsychotics: lurasidone, pimozide
- Cardiac Disorders: dronedarone, ivabradine, ranolazine
- Ergot derivatives, e.g., dihydroergotamine, ergotamine, methylergonovine
- Herbal product: St. John's wort (*Hypericum perforatum*)
- Hepatitis C direct acting antiviral: elbasvir/grazoprevir
- Lipid modifying agents: lomitapide, lovastatin, simvastatin
- Opioid Antagonist: naloxegol
- PDE-5 inhibitor: sildenafil when used for treatment of pulmonary arterial hypertension
- Sedatives/hypnotics: orally administered midazolam, triazolam

5. WARNINGS AND PRECAUTIONS

5.1 Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV

Patients with HIV-1 should be tested for the presence of chronic hepatitis B virus before initiating antiretroviral therapy *[see Dosage and Administration (2.1)]*. Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine and/or tenofovir disoproxil fumarate, and may occur with discontinuation of SYMTUZA. Patients coinfected with HIV-1 and HBV who discontinue SYMTUZA should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis, since post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

5.2 Hepatotoxicity

Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported in clinical trials with darunavir, a component of SYMTUZA. Patients with pre-existing liver dysfunction, including chronic active hepatitis B or C, have an increased risk for liver function abnormalities including severe hepatic adverse reactions.

Post-marketing cases of liver injury, including some fatalities, have been reported with darunavir. These have generally occurred in patients with advanced HIV-1 disease taking multiple concomitant medications, having co-morbidities including hepatitis B or C co-infection, and/or developing immune reconstitution syndrome. A causal relationship with darunavir therapy has not been established.

Appropriate laboratory testing should be conducted prior to initiating therapy with SYMTUZA and patients should be monitored during treatment as clinically appropriate. Increased AST/ALT monitoring should be considered in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases, 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, hepatomegaly) should prompt consideration of interruption or discontinuation of SYMTUZA.

5.3 Severe Skin Reactions

In patients receiving darunavir, a component of SYMTUZA, severe skin reactions may occur. These include conditions accompanied by fever and/or elevations of transaminases. Stevens-Johnson syndrome was reported with darunavir co-administered with cobicistat in clinical trials at a rate of 0.1%. During darunavir post-marketing experience, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis have been reported. 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.

Rash events of any cause and any grade occurred in 15% of subjects with no prior antiretroviral treatment history treated with SYMTUZA in the AMBER trial *[see Adverse Reactions (6.1)]*. Rash events were mild-to-moderate, often occurring within the first four weeks of treatment and resolving with continued dosing. The discontinuation rate due to rash in subjects using SYMTUZA was 2%.

5.4 Risk of Serious Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

The concomitant use of SYMTUZA and other drugs may result in known or potentially significant drug interactions which may lead to *[see Contraindications (4) and Drug Interactions (7.5)]:*

- Clinically significant adverse reactions from greater exposures of concomitant drugs.
- Clinically significant adverse reactions from greater exposures of SYMTUZA.
- Loss of therapeutic effect of the concomitant drugs from lower exposures of active metabolite(s).
- Loss of therapeutic effect of SYMTUZA and possible development of resistance from lower exposures of SYMTUZA.

See Table 4 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during SYMTUZA therapy; review concomitant medications during SYMTUZA therapy; and monitor for the adverse reactions associated with concomitant medications *[see Contraindications (4) and Drug Interactions (7)]*.

When used with concomitant medications, SYMTUZA, which contains darunavir boosted with cobicistat, may result in different drug interactions than those observed or expected with darunavir co-administered with ritonavir. Complex or unknown mechanisms of drug interactions preclude extrapolation of drug interactions with darunavir co-administered with ritonavir to certain SYMTUZA interactions *[see Drug Interactions (7) and Clinical Pharmacology (12.3)]*.

5.5 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, Guillain-Barré syndrome, and autoimmune hepatitis) 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 antiretroviral treatment.

5.6 New Onset or Worsening Renal Impairment

Postmarketing cases of renal impairment, including acute renal failure, proximal renal tubulopathy (PRT), and Fanconi syndrome have been reported with TAF-containing products; while most of these cases were characterized by potential confounders that may have contributed to the reported renal events, it is also possible these factors may have predisposed patients to tenofovir-related adverse events *[see Adverse Reactions (6.1, 6.2)]*. SYMTUZA is not recommended in patients with estimated creatinine clearance below 30 mL per minute.

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.

Prior to or when initiating SYMTUZA and during treatment with SYMTUZA, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. Discontinue SYMTUZA in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

Cobicistat, a component of SYMTUZA, produces elevations of serum creatinine due to inhibition of tubular secretion of creatinine without affecting glomerular filtration. This effect should be considered when interpreting changes in estimated creatinine clearance in patients initiating SYMTUZA, particularly in patients with medical conditions or receiving drugs needing monitoring with estimated creatinine clearance. The elevation is typically seen within 2 weeks of starting therapy and is reversible after discontinuation. Patients who experience a confirmed increase in serum creatinine of greater than 0.4 mg/dL should be closely monitored for renal safety.

5.7 Sulfa Allergy

Darunavir contains a sulfonamide moiety. Monitor patients with a known sulfonamide allergy after initiating SYMTUZA. In clinical studies with darunavir co-administered with ritonavir, the incidence and severity of rash were similar in subjects with or without a history of sulfonamide allergy.

5.8 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, a component of SYMTUZA, and 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).

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5.9 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 HIV 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 HIV PI therapy and these events have not been established.

5.10 Fat Redistribution

Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

5.11 Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis in patients with hemophilia type A and B treated with HIV protease inhibitors (PIs). In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with HIV PIs was continued or reintroduced if treatment had been discontinued. A causal relationship between PI therapy and these episodes has not been established.

6. ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Severe acute exacerbations of hepatitis B *[see Warnings and Precautions (5.1)]*
- Hepatotoxicity *[see Warnings and Precautions (5.2)]*
- Severe skin reactions *[see Warnings and Precautions (5.3)]*
- Immune reconstitution syndrome *[see Warnings and Precautions (5.5)]*
- New onset or worsening renal impairment *[see Warnings and Precautions (5.6)]*
- Lactic acidosis/severe hepatomegaly with steatosis *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials in Adults

Adverse Reactions in Adults with No Prior Antiretroviral Treatment History

The safety profile of SYMTUZA in HIV-1 infected adults with no prior antiretroviral treatment history is based on Week 48 data from the AMBER trial, a randomized, double-blind, active-controlled trial where a total of 362 subjects received SYMTUZA once daily and 363 subjects received a combination of PREZCOBIX® (fixed-dose combination of darunavir and cobicistat) and fixed-dose combination of emtricitabine and tenofovir disoproxil fumarate (FTC/TDF).

The proportion of subjects who discontinued treatment with SYMTUZA or PREZCOBIX+FTC/TDF due to adverse events, regardless of severity, were 2% and 4% respectively.

An overview of the most frequent (occurring in at least 2% of subjects) adverse reactions irrespective of severity reported in AMBER are presented in Table 1. An overview of the most frequent laboratory abnormalities of at least Grade 2 severity reported in AMBER are presented in Table 2. Changes from baseline in lipid parameters for patients receiving SYMTUZA and those receiving PREZCOBIX + FTC/TDF are presented in Table 3.

Most adverse reactions during treatment with SYMTUZA were grade 1 or 2 in severity. One grade 3 adverse reaction was reported and no grade 4 adverse reactions were reported during treatment with SYMTUZA.

Table 1: Adverse Reactions Reported in ≥2% of HIV-1 Infected Adults With No Prior Antiretroviral Treatment History in AMBER (Week 48 Analysis)

	SYMTUZA (N=362)		PREZCOBIX+FTC/TDF (N=363)	
	All Grades	At least Grade 2	All Grades	At least Grade 2
Diarrhea	9%	2%	11%	2%
Rash[a]	8%	4%	7%	5%
Nausea	6%	1%	10%	3%
Fatigue	4%	1%	4%	1%
Headache	3%	1%	2%	1%
Abdominal discomfort	2%	-	4%	<1%
Flatulence	2%	<1%	1%	-

[a] Includes pooled reported terms: dermatitis, dermatitis allergic, erythema, photosensitivity reaction, rash, rash generalized, rash macular, rash maculo-papular, rash morbilliform, rash pruritic, toxic skin eruption, urticaria

Adverse Reactions in Virologically-Suppressed Adults

The safety profile of SYMTUZA in virologically-suppressed HIV-1 infected adults is based on Week 48 data from 1,141 subjects in the EMERALD trial, a randomized, open-label, active-controlled trial where 763 subjects with a stable antiretroviral regimen consisting of a boosted protease inhibitor (bPI) [either darunavir once daily or atazanavir (both boosted with ritonavir or cobicistat), or lopinavir with ritonavir] combined with FTC/TDF switched to SYMTUZA, and 378 subjects who continued their treatment regimen of a bPI with FTC/TDF. Overall, the safety profile of SYMTUZA in subjects in this study was similar to that in subjects with no prior antiretroviral treatment history. The proportion of subjects who discontinued treatment with SYMTUZA due to adverse events, regardless of severity, was 1%.

Less Frequent Adverse Reactions

The following adverse reactions occurred in less than 2% of adults with no antiretroviral treatment history or virologically suppressed subjects receiving SYMTUZA, or are from studies described in the prescribing information of the individual component PREZISTA (darunavir).

Gastrointestinal Disorders: dyspepsia, pancreatitis (acute), vomiting

Skin and Subcutaneous Tissue Disorders: angioedema, pruritus, Stevens-Johnson syndrome

Metabolism and Nutrition Disorders: anorexia, diabetes mellitus, lipodystrophy

Reproductive System and Breast Disorders: gynecomastia

Musculoskeletal and Connective Tissue Disorders: myalgia, osteonecrosis

Psychiatric Disorders: abnormal dreams

Immune System Disorders: (drug) hypersensitivity, immune reconstitution inflammatory syndrome

Hepatobiliary Disorders: acute hepatitis

Laboratory Abnormalities

Table 2: Laboratory Abnormalities (Grade 2-4) Reported in ≥2% of Adults With No Prior Antiretroviral Treatment History in AMBER (Week 48 Analysis)

Laboratory Parameter Grade	Limit	SYMTUZA N=362	PREZCOBIX+FTC/TDF N=363
Creatinine			
Grade 2	>1.3 to 1.8 x ULN	4%	14%
Grade 4	≥3.5x ULN	<1%	0
Triglycerides			
Grade 2	301-500 mg/dL	7%	4%
Grade 3	501-1,000 mg/dL	1%	1%
Grade 4	>1,000 mg/dL	<1%	<1%
Total Cholesterol			
Grade 2	240-<300 mg/dL	17%	4%
Grade 3	≥ 300 mg/dL	2%	1%
Low-Density Lipoprotein Cholesterol			
Grade 2	160-189 mg/dL	9%	4%
Grade 3	≥190 mg/dL	5%	1%
Elevated Glucose Levels			
Grade 2	126-250 mg/dL	6%	6%
Grade 3	251-500 mg/dL	<1%	0

ALT and/or AST elevations (Grade 2-4 combined) occurred in 2% of adult subjects receiving SYMTUZA with no antiretroviral treatment history in AMBER (Week 48 Analysis). Results were consistent in subjects receiving PREZCOBIX+FTC/TDF.

Table 3: Lipid Values, Mean Change from Baseline, Reported in Adults With No Prior Antiretroviral Treatment History in AMBER (Week 48 Analysis)

	SYMTUZA N=362		PREZCOBIX+FTC/TDF N=363	
Mean[a]	**Baseline mg/dL**	**Week 48 Change**	**Baseline mg/dL**	**Week 48 Change**
N[b]	N=304[c]		N=290	
Total cholesterol	168	+30	164	+11
HDL cholesterol	45	+6	44	+2
LDL cholesterol	100	+19	98	+5
Triglycerides	117	+34	112	+21
Total cholesterol to HDL ratio	4.1	0.2	4.0	0.1

[a] The change from baseline is the mean of within-subject changes from baseline for subjects with both baseline and Week 48 values, or the last value carried forward prior to initiating lipid-lowering agent post-baseline.

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[b] N corresponds to the number of subjects with paired values and not on a lipid-lowering agent at screening/baseline. Subjects on lipid-lowering agents at screening/baseline were excluded from the analysis (6 out of 362 subjects on SYMTUZA, 8 out of 363 subjects on PREZCOBIX+FTC/TDF). Subjects initiating a lipid-lowering agent post-baseline had their last fasted on-treatment value (prior to starting the agent) carried forward (6 on SYMTUZA, 2 on PREZCOBIX+FTC/TDF).

[c] One subject did not have a Week 48 result for LDL cholesterol (n=303).

The percentage of subjects starting any lipid lowering drug during treatment in the SYMTUZA and PREZCOBIX + FTC/TDF arm were 1.7% (n=6) and 0.6% (n=2), respectively.

Renal Laboratory Tests

In the AMBER trial, which enrolled 725 adults with no prior antiretroviral treatment history, subjects had a median baseline eGFR (estimated glomerular filtration rate) of 119 mL/min (SYMTUZA) and 118 mL/min (PREZCOBIX + FTC/TDF). From baseline to Week 48, mean (SD) serum creatinine increased by 0.05 (0.10) mg/dL in the SYMTUZA group and by 0.09 (0.11) mg/dL in the PREZCOBIX + FTC/TDF group. Median serum creatinine was 0.90 mg/dL (SYMTUZA) and 0.89 mg/dL (PREZCOBIX + FTC/TDF) at baseline and 0.95 mg/dL (SYMTUZA) and 0.97 mg/dL (PREZCOBIX +FTC/TDF) at Week 48. Increases in serum creatinine occurred by Week 2 of treatment and remained stable. Median urine protein-to-creatinine ratio (UPCR) was 47 mg/g (SYMTUZA) and 51 mg/g (PREZCOBIX + FTC/TDF) at baseline and 30 mg/g (SYMTUZA) and 34 mg/g (PREZCOBIX + FTC/TDF) at Week 48.

In the EMERALD trial which had 1,141 virologically-suppressed adults treated with an HIV protease inhibitor and TDF containing regimen with a median baseline eGFR of 104 mL/min (SYMTUZA) and 103 mL/min (bPI+FTC/TDF) who were randomized to continue their treatment regimen or switch to SYMTUZA, at Week 48, mean serum creatinine was similar to baseline for both those continuing baseline treatment and those switching to SYMTUZA. Mean (SD) serum creatinine was 0.98 (0.18) mg/dL (SYMTUZA) and 0.98 (0.19) mg/dL (bPI+FTC/TDF) at baseline and 0.99 (0.18) mg/dL (SYMTUZA) and 0.99 (0.21) mg/dL (bPI+FTC/TDF) at Week 48. Median serum creatinine was 0.97 mg/dL (SYMTUZA) and 0.98 mg/dL (bPI+FTC/TDF) at baseline and 1.0 mg/dL (SYMTUZA) and 0.97 mg/dL (bPI+FTC/TDF) at Week 48. Median UPCR was 62 mg/g (SYMTUZA) and 63 mg/g (bPI+FTC/TDF) at baseline and 37 mg/g (SYMTUZA) and 53 mg/g (bPI+FTC/TDF) at Week 48.

Bone Mineral Density

AMBER

The effects of SYMTUZA compared to PREZCOBIX + FTC/TDF on bone mineral density (BMD) change from baseline to Week 48 were assessed by dual-energy X-ray absorptiometry (DXA). The mean percentage change in BMD from baseline to Week 48 was –0.7% with SYMTUZA compared to –2.4% with PREZCOBIX + FTC/TDF at the lumbar spine and 0.2% compared to –2.7% at the total hip. BMD declines of 5% or greater at the lumbar spine were experienced by 16% of SYMTUZA subjects and 22% of PREZCOBIX + FTC/TDF subjects. BMD declines of 7% or greater at the femoral neck were experienced by 2% of SYMTUZA subjects and 15% of PREZCOBIX + FTC/TDF subjects. The long-term clinical significance of these BMD changes is not known.

EMERALD

In EMERALD, bPI and TDF-treated subjects were randomized to continue their TDF-based regimen or switch to SYMTUZA; changes in BMD from baseline to Week 48 were assessed by DXA. The mean percentage change in BMD from baseline to Week 48 was 1.5% with SYMTUZA compared to –0.6% with bPI + FTC/TDF at the lumbar spine and 1.4% compared to -0.3% at the total hip. BMD declines of 5% or greater at the lumbar spine were experienced by 2% of SYMTUZA subjects and 9% of bPI + FTC/TDF subjects. BMD declines of 7% or greater at the femoral neck were experienced by no SYMTUZA subjects and 2% of bPI + FTC/TDF subjects. The long-term clinical significance of these BMD changes is not known.

Clinical Trials in Pediatric Patients

Adverse Reactions in Pediatric Patients Weighing At Least 40 kg

No clinical trials with SYMTUZA were performed in pediatric patients. However, the safety of the components of SYMTUZA was evaluated in pediatric subjects of 12 to less than 18 years of age through clinical trials GS-US-216-0128 (virologically-suppressed, N=7 with weight ≥40 kg) for darunavir co-administered with cobicistat and other antiretroviral agents, and GS-US-292-0106 (treatment-naïve, N=50 with weight ≥35 kg) for a fixed-dose combination regimen containing cobicistat, emtricitabine, and tenofovir alafenamide together with elvitegravir. Safety analyses of the trials in these pediatric subjects did not identify new safety concerns compared to the known safety profile of SYMTUZA in adult subjects *[see Clinical Studies (14.3)]*.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of darunavir. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Metabolism and Nutrition Disorders:

Redistribution of body fat

Musculoskeletal and Connective Tissue Disorders:

Rhabdomyolysis (associated with co-administration with HMG-CoA reductase inhibitors)

Skin and Subcutaneous Tissue Disorders:

Toxic epidermal necrolysis, acute generalized exanthematous pustulosis, drug rash with eosinophilia and systemic symptoms *[see Warnings and Precautions (5.3)]*

Renal and Urinary Disorders:

Acute renal failure, acute tubular necrosis, proximal renal tubulopathy, Fanconi syndrome *[see Warnings and Precautions (5.6)]*, crystal nephropathy, and crystalluria

7. DRUG INTERACTIONS

7.1 Not Recommended With Other Antiretroviral Medications

SYMTUZA is a complete regimen for HIV-1 infection and co-administration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended. For this reason, information regarding potential drug-drug interactions with other antiretroviral medications is not provided.

7.2 Potential for SYMTUZA to Affect Other Drugs

Darunavir co-administered with cobicistat is an inhibitor of CYP3A and CYP2D6. Cobicistat inhibits the following transporters: P-glycoprotein (P-gp), BCRP, MATE1, OATP1B1 and OATP1B3. Therefore, co-administration of SYMTUZA with drugs that are primarily metabolized by CYP3A and/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 can be associated with adverse events. Co-administration of SYMTUZA with drugs that have active metabolite(s) formed by CYP3A may result in reduced plasma concentrations of these active metabolite(s), potentially leading to loss of their therapeutic effect (see Table 4).

7.3 Potential for Other Drugs to Affect SYMTUZA

Darunavir is metabolized by CYP3A. Cobicistat is metabolized by CYP3A and, to a minor extent, by CYP2D6. Co-administration of drugs that induce CYP3A activity are expected to increase the clearance of darunavir and cobicistat, resulting in lowered plasma concentrations which may lead to loss of therapeutic effect and development of resistance. Co-administration of SYMTUZA with other drugs that inhibit CYP3A may result in increased plasma concentrations of darunavir and cobicistat (see Table 4).

Tenofovir alafenamide (TAF) is a substrate of P-gp, BCRP, OATP1B1, and OATP1B3. Drugs that strongly affect P-gp activity may lead to changes in TAF absorption. Drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentrations of TAF, which may lead to loss of therapeutic effect of SYMTUZA and development of resistance. Co-administration of SYMTUZA with other drugs that inhibit P-gp may increase the absorption and plasma concentrations of TAF (see Table 4).

7.4 Drugs Affecting Renal Function

Because emtricitabine and tenofovir are primarily excreted by the kidneys through glomerular filtration and active tubular secretion, co-administration of SYMTUZA with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of emtricitabine, tenofovir, and other renally eliminated drugs and this may increase the risk of adverse reactions. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs *[see Warnings and Precautions (5.6)]*.

7.5 Significant Drug Interactions

Table 4 provides examples of established or potentially clinically significant drug interactions with SYMTUZA and recommended steps to prevent or manage these interactions. These recommendations are based on drug interaction trials conducted with the components of SYMTUZA, as individual agents or in combination, or are predicted interactions. No drug interaction trials have been performed with SYMTUZA or with all the components administered together. Drug interaction trials have been conducted with darunavir co- administered with ritonavir or cobicistat or with emtricitabine and tenofovir prodrugs. The table includes potentially significant interactions but is not all inclusive, and therefore the label of each drug that is co-administered with SYMTUZA should be consulted for information related to the route of metabolism, interaction pathways, potential risks, and specific actions to be taken with regard to co- administration.

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Table 4: Significant Drug Interactions

Concomitant Drug Class: Drug Name Examples	Effect on Concentration	Clinical Comment
Alpha 1-adrenoreceptor antagonist: alfuzosin	↑ alfuzosin	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as hypotension.
Antibacterials: clarithromycin, erythromycin, telithromycin	↑ darunavir ↑ cobicistat ↑ antibacterial	Consider alternative antibiotics with concomitant use of SYMTUZA.
Anticancer agents: dasatinib, nilotinib	↑ anticancer agent	A decrease in the dosage or an adjustment of the dosing interval of dasatinib or nilotinib may be necessary when co-administered with SYMTUZA. Consult the dasatinib and nilotinib prescribing information for dosing instructions.
vinblastine, vincristine		For vincristine and vinblastine, consider temporarily withholding the cobicistat-containing antiretroviral regimen in patients who develop significant hematologic or gastrointestinal side effects when SYMTUZA is administered concurrently with vincristine or vinblastine. If the antiretroviral regimen must be withheld for a prolonged period, consider initiating a revised regimen that does not include a CYP3A or P-gp inhibitor.
Anticoagulants: Direct Oral Anticoagulants (DOACs) apixaban	↑ apixaban	Due to potentially increased bleeding risk, dosing recommendations for co-administration of apixaban with SYMTUZA depend on the apixaban dose. Refer to apixaban dosing instructions for co-administration with P-gp and strong CYP3A inhibitors in apixaban prescribing information.
rivaroxaban	↑ rivaroxaban	Co-administration of rivaroxaban with SYMTUZA is not recommended because it may lead to an increased bleeding risk.
dabigatran etexilate edoxaban	↑ dabigatran ↑ edoxaban	Refer to the dabigatran etexilate or edoxaban prescribing information for recommendations regarding co-administration. The specific recommendations are based on indication, renal function, and effect of the co-administered P-gp inhibitors on the concentration of dabigatran or edoxaban. Clinical monitoring is recommended when a DOAC not affected by CYP3A4 but transported by P-gp, including dabigatran etexilate and edoxaban, is co-administered with SYMTUZA.
Other Anticoagulants warfarin	warfarin: effect unknown	Monitor international normalized ratio (INR) upon co-administration of SYMTUZA with warfarin.
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ cobicistat ↓ darunavir ↓ tenofovir alafenamide	Co-administration is contraindicated due to potential for loss of therapeutic effect and development of resistance.
Anticonvulsants with CYP3A induction effects that are NOT contraindicated: e.g., eslicarbazepine, oxcarbazepine	↓ cobicistat ↓ tenofovir alafenamide darunavir: effect unknown	Consider alternative anticonvulsant or antiretroviral therapy to avoid potential changes in exposures. If co-administration is necessary, monitor for lack or loss of virologic response.
Anticonvulsants that are metabolized by CYP3A: e.g., clonazepam	↑ clonazepam	Clinical monitoring of anticonvulsants is recommended.

Table 4: Significant Drug Interactions (continued)

Concomitant Drug Class: Drug Name Examples	Effect on Concentration	Clinical Comment
Antidepressants: Selective Serotonin Reuptake Inhibitors (SSRIs): e.g., paroxetine, sertraline	SSRIs: effects unknown	When co-administering with SSRIs, TCAs, or trazodone, careful dose titration of the antidepressant to the desired effect, including using the lowest feasible initial or maintenance dose, and monitoring for antidepressant response are recommended.
Tricyclic Antidepressants (TCAs): e.g., amitriptyline, desipramine, imipramine, nortriptyline	↑ TCAs	
Other antidepressants: trazodone	↑ trazodone	
Antifungals: itraconazole, isavuconazole, ketoconazole, posaconazole	↑ darunavir ↑ cobicistat	Monitor for increased darunavir or cobicistat and/or antifungal adverse reactions.
	↑ itraconazole ↑ isavuconazole ↑ ketoconazole ↔ posaconazole (not studied)	Specific dosing recommendations are not available for co-administration with these antifungals. Monitor for increased itraconazole or ketoconazole adverse reactions.
voriconazole	voriconazole: effects unknown	Co-administration with voriconazole is not recommended unless benefit/risk assessment justifies the use of voriconazole.
Anti-gout: colchicine	↑ colchicine	Co-administration is contraindicated in patients with renal and/or hepatic impairment due to potential for serious and/or life-threatening reactions. For patients without renal or hepatic impairment: • Treatment of gout flares – co-administration of colchicine: 0.6 mg (1 tablet) ×1 dose, followed by 0.3 mg (half tablet) 1 hour later. Treatment course to be repeated no earlier than 3 days. • Prophylaxis of gout flares – co-administration of colchicine: If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day. If the original regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day. • Treatment of familial Mediterranean fever – co-administration of colchicine: Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
Antimalarial: artemether/ lumefantrine	artemether: effect unknown lumefantrine: effect unknown	Monitor for a potential decrease of antimalarial efficacy or potential QT prolongation.

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Table 4: Significant Drug Interactions (continued)

Concomitant Drug Class: Drug Name Examples	Effect on Concentration	Clinical Comment
Antimycobacterials: rifampin	↓ cobicistat ↓ darunavir ↓ tenofovir alafenamide	Co-administration is contraindicated due to potential for loss of therapeutic effect and development of resistance.
rifabutin	↑ rifabutin ↓ TAF cobicistat: effects unknown darunavir: effects unknown	Co-administration of SYMTUZA with rifabutin is not recommended. If the combination is needed, the recommended dose of rifabutin is 150 mg every other day. Monitor for rifabutin-associated adverse reactions including neutropenia and uveitis.
rifapentine	↓ darunavir ↓ TAF	Co-administration with rifapentine is not recommended.
Antipsychotics: lurasidone	↑ lurasidone	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions.
pimozide	↑ pimozide	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
e.g., perphenazine, risperidone, thioridazine	↑ antipsychotic	A decrease in the dose of antipsychotics that are metabolized by CYP3A or CYP2D6 may be needed when co-administered with SYMTUZA.
quetiapine	↑ quetiapine	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.
β-Blockers: e.g., carvedilol, metoprolol, timolol	↑ beta-blockers	Clinical monitoring is recommended for co-administration with beta-blockers that are metabolized by CYP2D6.
Calcium channel blockers: e.g., amlodipine, diltiazem, felodipine, nifedipine, verapamil	↑ calcium channel blockers	Clinical monitoring is recommended for co-administration with calcium channel blockers metabolized by CYP3A.

Table 4: Significant Drug Interactions (continued)

Concomitant Drug Class: Drug Name Examples	Effect on Concentration	Clinical Comment
Cardiac Disorders: ranolazine, ivabradine	↑ ranolazine	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions.
dronedarone	↑ dronedarone	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias
Other antiarrhythmics e.g., amiodarone, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine	↑ antiarrhythmics	Clinical monitoring is recommended upon co-administration with antiarrhythmics.
digoxin	↑ digoxin	When co-administering with digoxin, titrate the digoxin dose and monitor digoxin concentrations.
Corticosteroids: dexamethasone (systemic)	↓ darunavir ↓ cobicistat	Co-administration with systemic dexamethasone or other systemic corticosteroids that induce CYP3A may result in loss of therapeutic effect and development of resistance to SYMTUZA. Consider alternative corticosteroids.
Corticosteroids primarily metabolized by CYP3A: e.g., betamethasone budesonide ciclesonide fluticasone methylprednisolone mometasone triamcinolone	↑ corticosteroids	Co-administration with corticosteroids (all routes of administration) of which exposures are significantly increased by strong CYP3A inhibitors can increase the risk for Cushing's syndrome and adrenal suppression. Alternative corticosteroids including beclomethasone, prednisone, and prednisolone (for which PK and/or PD are less affected by strong CYP3A inhibitors relative to other steroids) should be considered, particularly for long term use.
Endothelin receptor antagonists: bosentan	↓ darunavir ↓ cobicistat ↑ bosentan	Initiation of bosentan in patients taking SYMTUZA: In patients who have been receiving SYMTUZA for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability. Initiation of SYMTUZA in patients on bosentan: Discontinue use of bosentan at least 36 hours prior to initiation of SYMTUZA. After at least 10 days following the initiation of SYMTUZA, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability. Switching from darunavir co-administered with ritonavir to SYMTUZA in patients on bosentan: Maintain bosentan dose.

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Table 4: Significant Drug Interactions (continued)

Concomitant Drug Class: Drug Name Examples	Effect on Concentration	Clinical Comment
Ergot derivatives: e.g., dihydroergotamine, ergotamine, methylergonovine	↑ ergot derivatives	Co-administration is 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.
Hepatitis C virus (HCV): Direct-Acting Antivirals: elbasvir/grazoprevir	↑ elbasvir/grazoprevir	Co-administration is contraindicated due to potential for the increased risk of alanine transaminase (ALT) elevations.
glecaprevir/pibrentasvir	↑ glecaprevir ↑ pibrentasvir	Co-administration of SYTMUZA with glecaprevir/pibrentasvir is not recommended.
Herbal product: St. John's wort (*Hypericum perforatum*)	↓ cobicistat ↓ darunavir ↓ tenofovir alafenamide	Co-administration is contraindicated due to potential for loss of therapeutic effect and development of resistance.
Hormonal contraceptives:		Additional or alternative (non-hormonal) forms of contraception should be considered when estrogen based contraceptives are co-administered with SYMTUZA.
drosperinone/ethinylestradiol	↑ drosperinone ↓ ethinylestradiol	For co-administration with drospirenone, clinical monitoring is recommended due to the potential for hyperkalemia.
other progestin/estrogen contraceptives	progestin: effects unknown estrogen: effects unknown	No data are available to make recommendations on co-administration with oral or other hormonal contraceptives.
Immunosuppressants: cyclosporine, sirolimus, tacrolimus	↑ immunosuppressants	These immunosuppressant agents are metabolized by CYP3A. Therapeutic drug monitoring is recommended with concomitant use.
Immunosuppressant/neoplastic: everolimus		Co-administration of everolimus and SYMTUZA is not recommended.
irinotecan		Discontinue SYMTUZA at least 1 week prior to starting irinotecan therapy. Do not administer SYMTUZA with irinotecan unless there are no therapeutic alternatives.
Inhaled beta agonist: salmeterol	↑ salmeterol	Co-administration with salmeterol is not recommended and may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.

Table 4: Significant Drug Interactions (continued)

Concomitant Drug Class: Drug Name Examples	Effect on Concentration	Clinical Comment
Lipid modifying agents: HMG-CoA reductase inhibitors: lovastatin, simvastatin	↑ lovastatin ↑ simvastatin	Co-administration is contraindicated due to potential for serious reactions such as myopathy including rhabdomyolysis.
e.g., atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin	↑ atorvastatin ↑ fluvastatin ↑ pravastatin ↑ rosuvastatin pitavastatin: effect unknown	For atorvastatin, fluvastatin, pitavastatin, pravastatin, and rosuvastatin, start with the lowest recommended dose and titrate while monitoring for safety. Dosage recommendations with atorvastatin or rosuvastatin are as follows: • atorvastatin dosage should not exceed 20 mg/day • rosuvastatin dosage should not exceed 20 mg/day
Other lipid modifying agents: lomitapide	↑ lomitapide	Co-administration is contraindicated due to potential for markedly increased transaminases associated with increased plasma concentrations of lomitapide.
Narcotic analgesics metabolized by CYP3A: e.g., fentanyl, oxycodone	↑ fentanyl ↑ oxycodone	Careful monitoring of therapeutic effects and adverse reactions associated with CYP3A-metabolized narcotic analgesics (including potentially fatal respiratory depression) is recommended with co-administration.
tramadol	↑ tramadol	A dose decrease may be needed for tramadol with concomitant use.
Narcotic analgesic for treatment of opioid dependence: buprenorphine, buprenorphine/naloxone, methadone	buprenorphine or buprenorphine/naloxone: effects unknown methadone: effects unknown	Initiation of buprenorphine, buprenorphine/naloxone or methadone in patients taking SYMTUZA: Carefully titrate the dose of buprenorphine, buprenorphine/naloxone or methadone to the desired effect; use the lowest feasible initial or maintenance dose. Initiation of SYMTUZA in patients taking buprenorphine, buprenorphine/naloxone, or methadone: A dose adjustment for buprenorphine, buprenorphine/naloxone, or methadone may be needed. Monitor clinical signs and symptoms.
Opioid Antagonist naloxegol	↑ naloxegol	Co-administration of SYMTUZA and naloxegol is contraindicated due to potential for precipitating opioid withdrawal symptoms.

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Table 4: Significant Drug Interactions (continued)

Concomitant Drug Class: Drug Name Examples	Effect on Concentration	Clinical Comment
Phosphodiesterase PDE-5 inhibitors: e.g., avanafil, sildenafil, tadalafil, vardenafil	↑ PDE-5 inhibitors	Co-administration with avanafil is not recommended because a safe and effective avanafil dosage regimen has not been established. Co-administration with PDE-5 inhibitors may result in an increase in PDE-5 inhibitor-associated adverse reactions including hypotension, syncope, visual disturbances, and priapism. Use of PDE-5 inhibitors for pulmonary arterial hypertension (PAH): Co-administration with sildenafil used for PAH is contraindicated due to potential for sildenafil associated adverse reactions (which include visual disturbances, hypotension, prolonged erection, and syncope). The following dose adjustments are recommended for use of tadalafil with SYMTUZA: • *Initiation of tadalafil in patients taking SYMTUZA:* In patients receiving SYMTUZA for at least one week, start tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. • *Initiation of SYMTUZA in patients taking tadalafil:* Avoid use of tadalafil during the initiation of SYMTUZA. Stop tadalafil at least 24 hours prior to starting SYMTUZA. After at least one week following the initiation of SYMTUZA, resume tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. • *Patients switching from darunavir co-administered with ritonavir to SYMTUZA:* Maintain tadalafil dose. Use of PDE-5 inhibitors for erectile dysfunction: Sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg dose in 72 hours, or tadalafil at a single dose not exceeding 10 mg dose in 72 hours can be used with increased monitoring for PDE-5 inhibitor-associated adverse reactions.
Platelet aggregation inhibitor: ticagrelor	↑ticagrelor	Co-administration of SYMTUZA and ticagrelor is not recommended.
clopidogrel	↓ clopidogrel active metabolite	Co-administration of SYMTUZA and clopidogrel is not recommended due to potential reduction of the antiplatelet activity of clopidogrel.
prasugrel	↔ prasugrel active metabolite	No dose adjustment is needed when prasugrel is co-administered with SYMTUZA.

Table 4: Significant Drug Interactions (continued)

Concomitant Drug Class: Drug Name Examples	Effect on Concentration	Clinical Comment
Sedatives/hypnotics: orally administered midazolam, triazolam	↑ midazolam ↑ triazolam	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
metabolized by CYP3A: e.g., buspirone, diazepam, estazolam, zolpidem	↑ sedatives/ hypnotics	With concomitant use, titration is recommended with sedatives/ hypnotics metabolized by CYP3A and a lower dose of the sedatives/ hypnotics should be considered with monitoring for increased and prolonged effects or adverse reactions.
parenterally administered midazolam		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.
Urinary antispasmodics fesoterodine	↑ fesoterodine	When fesoterodine is co-administered with SYMTUZA, do not exceed a fesoterodine dose of 4 mg once daily.
solifenacin	↑ solifenacin	When solifenacin is co-administered with SYMTUZA, do not exceed a solifenacin dose of 5 mg once daily.

This table is not all inclusive
↑ = increase, ↓ = decrease, ↔ = no effect

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to SYMTUZA during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

SYMTUZA is not recommended during pregnancy because of substantially lower exposures of darunavir and cobicistat during the second and third trimesters *[see Dosage and Administration (2.5)]*. A study evaluating the pharmacokinetics of antiretrovirals during pregnancy demonstrated substantially lower exposures of darunavir and cobicistat in the second and third trimesters compared to the post-partum period *(see Data)* and *[see Clinical Pharmacology (12.3)]*.

Prospective pregnancy data from the APR are not sufficient to adequately assess the risk of birth defects or miscarriage. However, available data from the APR show no statistically significant difference in the overall risk of major birth defects for darunavir, cobicistat, emtricitabine, or tenofovir alafenamide (TAF) compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) *(see Data)*. The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15-20%. The background risk of major birth defects and miscarriage for the indicated population is unknown.

In animal reproduction studies, no adverse developmental effects were observed when the components of SYMTUZA were administered separately at darunavir exposures less than 1- (mice and rabbits) and 2.6-times (rats) higher, at cobicistat exposures 1.7- and 4.1-times higher (rats and rabbits respectively), at emtricitabine exposures 88- and 7.3- times higher (mice and rabbits, respectively), and tenofovir alafenamide exposures equal to or 85- times higher (rats and rabbits, respectively) than human exposures at the recommended daily dose of these components in SYMTUZA *(see Data)*. No adverse developmental effects were seen when cobicistat was administered to rats through lactation at cobicistat exposures up to 1.1 times the human exposure at the recommended therapeutic dose.

Clinical Considerations

Not Recommended During Pregnancy

SYMTUZA is not recommended for use during pregnancy because of substantially lower exposures of darunavir and cobicistat during pregnancy *(see Data)* and *[see Clinical Pharmacology (12.3)]*.

SYMTUZA should not be initiated in pregnant individuals. An alternative regimen is recommended for individuals who become pregnant during therapy with SYMTUZA.

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Data

Human Data

Darunavir and cobicistat in combination with a background regimen was evaluated in a clinical trial of 7 pregnant individuals taking darunavir and cobicistat prior to enrollment and who were willing to remain on darunavir and cobicistat throughout the study. The study period included the second and third trimesters, and through 12 weeks postpartum. Six pregnant individuals completed the trial.

Exposure to darunavir and cobicistat as part of an antiretroviral regimen was substantially lower during the second and third trimesters of pregnancy compared with postpartum *[see Clinical Pharmacology (12.3)]*.

One out of 6 pregnant individuals 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 pregnant individuals had sustained virologic response (HIV RNA <50 copies/mL) throughout the study period. There are no clinical data on the virologic response when darunavir and cobicistat are initiated during pregnancy.

Prospective reports from the APR of overall major birth defects in pregnancies exposed to the components of SYMTUZA are compared with a U.S. background major birth defect rate. Methodological limitations of the APR include the use of MACDP as the external comparator group. Limitations of using an external comparator include differences in methodology and populations, as well as confounding due to the underlying disease.

Darunavir: Based on prospective reports to the APR of over 960 exposures to darunavir-containing regimens during pregnancy resulting in live births (including over 640 exposed in the first trimester and over 320 exposed in the second/third trimester), the prevalence of birth defects in live births was 3.7% (95% CI: 2.4% to 5.5%) with first trimester exposure to darunavir containing-regimens and 2.5% (95% CI: 1.1% to 4.9%) with second/third trimester exposure to darunavir-containing regimens.

Cobicistat: Based on prospective reports to the APR of over 560 exposures to cobicistat-containing regimens during pregnancy resulting in live births (including over 470 exposed in the first trimester and over 80 exposed in the second/third trimester), the prevalence of birth defects in live births was 3.6% (95% CI: 2.1% to 5.7%) and 1.1% (95% CI: 0.0% to 6.2%) with first and second/third trimester, respectively, to cobicistat-containing regimens.

Emtricitabine: Based on prospective reports to the APR of over 5400 exposures to emtricitabine-containing regimens during pregnancy resulting in live births (including over 3900 exposed in the first trimester and over 1500 exposed in the second/third trimester), the prevalence of birth defects in live births was 2.6% (95% CI: 2.2% to 3.2%) with first trimester exposure to emtricitabine-containing regimens and 2.7% (95% CI: 1.9% to 3.7%) with the second/third trimester exposure to emtricitabine-containing regimens.

Tenofovir alafenamide (TAF): Based on prospective reports to the APR of over 660 exposures to TAF-containing regimens during pregnancy resulting in live births (including over 520 exposed in the first trimester and over 130 exposed in the second/third trimester), the prevalence of birth defects in live births was 4.2% (95% CI: 2.6% to 6.3%) and 3.0% (95% CI: 0.8% to 7.5%) with first and second/third trimester exposure, respectively, to TAF-containing regimens.

Animal Data

Darunavir: Reproduction studies conducted with darunavir showed no embryotoxicity or teratogenicity in mice (doses up to 1000 mg/kg from gestation day (GD) 6-15 with darunavir alone) and rats (doses up to 1000 mg/kg from GD 7-19 in the presence or absence of ritonavir) as well as in rabbits (doses up to 1000 mg/kg/day from GD 8-20 with darunavir alone). In these studies, darunavir exposures (based on AUC) were higher in rats (2.6-fold), whereas in mice and rabbits, exposures were lower (less than 1-fold) compared to those obtained in humans at the recommended daily dose of darunavir in SYMTUZA.

Cobicistat: Cobicistat was administered orally to pregnant rats at doses up to 125 mg/kg/day on GD 6-17. Increases in post-implantation loss and decreased fetal weights were observed at a maternal toxic dose of 125 mg/kg/day. No malformations were noted at doses up to 125 mg/kg/day. Systemic exposures (AUC) at 50 mg/kg/day in pregnant females were 1.7 times higher than human exposures at the recommended daily dose of cobicistat in SYMTUZA.

In pregnant rabbits, cobicistat was administered orally at doses up to 100 mg/kg/day during GD 7-20. No maternal or embryo/fetal effects were noted at the highest dose of 100 mg/kg/day. Systemic exposures (AUC) at 100 mg/kg/day were 4.1 times higher than human exposures at the recommended daily dose of cobicistat in SYMTUZA.

In a pre/postnatal developmental study in rats, cobicistat was administered orally at doses up to 75 mg/kg from GD 6 to postnatal day 20, 21, or 22. At doses of 75 mg/kg/day, neither maternal nor developmental toxicity was noted. Systemic exposures (AUC) at this dose were 1.1 times the human exposures at the recommended daily dose of cobicistat in SYMTUZA.

Emtricitabine: Emtricitabine was administered orally to pregnant mice and rabbits (up to 1000 mg/kg/day) through organogenesis (on GD 6 through 15, and 7 through 19, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with emtricitabine in mice at exposures approximately 88 times higher and in rabbits approximately 7.3 times higher than human exposures at the recommended daily dose of emtricitabine in SYMTUZA.

In a pre/postnatal development study, mice were administered doses up to 1000 mg/kg/day; no significant adverse effects directly related to drug were observed in the offspring exposed daily from before birth (*in utero*) through sexual maturity at daily exposures of approximately 88 times higher than human exposures at the recommended daily dose of emtricitabine in SYMTUZA.

Tenofovir Alafenamide (TAF): TAF was administered orally to pregnant rats (up to 250 mg/kg/day) and rabbits (up to 100 mg/kg/day) through organogenesis (on GD 6 through 17, and 7 through 20, respectively). No adverse embryo-fetal effects were observed in rats and rabbits at TAF exposures approximately similar to (rats) and 85 times higher (rabbits) than the exposure in humans at the recommended daily dose. TAF is rapidly converted to tenofovir; the observed tenofovir exposure in rats and rabbits were 51 (rats) and 80 (rabbits) times higher than human tenofovir exposures at the recommended daily dose of TAF in SYMTUZA.

Since TAF is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice was observed after TAF administration compared to TDF (another prodrug of tenofovir) administration, a pre/postnatal development study in rats was conducted only with TDF. Doses up to 600 mg/kg/day were administered through lactation; no adverse effects were observed in the offspring on GD 7 [and lactation day 20] at tenofovir exposures of approximately 14 [21] times higher than the exposure in humans at the recommended daily dose of TDF.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-infected mothers in the United States must not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

Based on published data, emtricitabine has been shown to be present in human breast milk. There are no data on the presence of darunavir, cobicistat, or TAF in human milk, the effects on the breastfed infant, or the effects on milk production. Darunavir and cobicistat are present in the milk of lactating rats. Tenofovir has been shown to be present in the milk of lactating rats and rhesus monkeys after administration of TDF *(see Data).* Because of the potential for (1) HIV transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) serious adverse reactions in breastfed infants, instruct mothers not to breastfeed if they are receiving SYMTUZA.

Data

Animal Data

Darunavir: Studies in rats (with darunavir alone or with ritonavir) have demonstrated that darunavir is excreted in milk. In the rat pre- and post-natal development study, a reduction in pup body weight gain was observed due to exposure of pups to drug substances via milk. The maximal maternal plasma exposures achieved with darunavir (up to 1000 mg/kg with ritonavir) were approximately 66% of those obtained in humans at the recommended clinical dose of darunavir with ritonavir.

Cobicistat: During the pre/postnatal developmental toxicology study, at doses up to 75 mg/kg/day, mean cobicistat milk to plasma ratio of up to 1.9 was measured 2 hours after administration to rats on lactation day 10.

Tenofovir Alafenamide: Studies in rats and monkeys have demonstrated that tenofovir is excreted in milk. Tenofovir was excreted into the milk of lactating rats following oral administration of TDF (up to 600 mg/kg/day) at up to approximately 24% of the median plasma concentration in the highest dosed animals at lactation day 11. Tenofovir was excreted into the milk of lactating rhesus monkeys, following a single subcutaneous (30 mg/kg) dose of tenofovir at concentrations up to approximately 4% of plasma concentration resulting in exposure (AUC) of approximately 20% of plasma exposure.

8.4 Pediatric Use

The safety and effectiveness of SYMTUZA for the treatment of HIV-1 infection in pediatric patients weighing at least 40 kg was established through studies with components of SYMTUZA. Use of SYMTUZA in this group is supported by evidence from adequate and well-controlled studies of SYMTUZA in adults with additional pharmacokinetic, safety, and virologic data from studies of components of SYMTUZA (Trials GS-US-216-0128 and GS-US-292-0106) in pediatric subjects with HIV-1 infection aged 12 to less than 18 years *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.3)].*

The safety and effectiveness of SYMTUZA have not been established in pediatric patients weighing less than 40 kg.

Darunavir, a component of SYMTUZA is not recommended in pediatric patients below 3 years of age because of toxicity and mortality observed in juvenile rats dosed with darunavir.

Juvenile Animal Toxicity Data

Darunavir: In a juvenile toxicity study where rats were directly dosed with darunavir (up to 1000 mg/kg), deaths occurred from post-natal day 5 at plasma exposure levels ranging from 0.1 to 1.0 of the human exposure levels. In a 4-week rat toxicology study, when dosing was initiated on post-natal day 23 (the human equivalent of 2 to 3 years of age), no deaths were observed with a plasma exposure (in combination with ritonavir) 2 times the human plasma exposure levels.

8.5 Geriatric Use

Clinical trials of SYMTUZA included 35 subjects aged above 65 years of which 26 received SYMTUZA. No differences in safety or efficacy have been observed between elderly subjects and those aged 65 years or less. In general, caution should be exercised in the administration and monitoring of SYMTUZA in elderly patients, reflecting the greater frequency of decreased hepatic function and of concomitant disease or other drug therapy *[see Clinical Pharmacology (12.3)].*

SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets

8.6 Renal Impairment

SYMTUZA is not recommended in patients with severe renal impairment (creatinine clearance below 30 mL per minute). No dosage adjustment of SYMTUZA is required in patients with creatinine clearance greater than or equal to 30 mL per minute *[see Clinical Pharmacology (12.3)].*

Cobicistat has been shown to decrease creatinine clearance without affecting actual renal glomerular function. Dosing recommendations are not available for drugs that require dosage adjustment for renal impairment when used in combination with SYMTUZA *[see Warnings and Precautions (5.6)].*

8.7 Hepatic Impairment

No dosage adjustment of SYMTUZA is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. 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. Therefore, SYMTUZA is not recommended for use in patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)].*

10. OVERDOSAGE

Human experience of acute overdose with SYMTUZA is limited. 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 bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis. Hemodialysis treatment removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. It is not known whether emtricitabine or tenofovir can be removed by peritoneal dialysis.

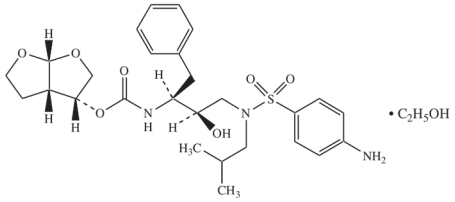
11. DESCRIPTION

SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) is a fixed-dose combination tablet.

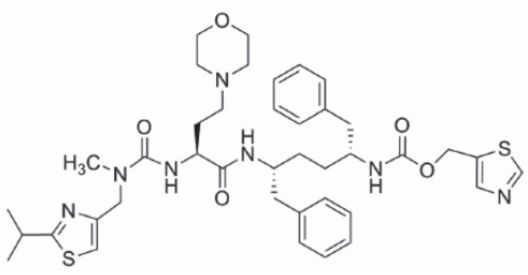
- Darunavir is an inhibitor of the HIV-1 protease.
- Cobicistat is a mechanism-based inhibitor of cytochrome P450 (CYP) enzymes of the CYP3A family.
- Emtricitabine, a synthetic nucleoside analog of cytidine, is an HIV nucleoside analog reverse transcriptase inhibitor (HIV NRTI).
- Tenofovir alafenamide, an HIV NRTI, is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate.

SYMTUZA tablets are for oral administration. Each tablet contains darunavir ethanolate equivalent to 800 mg of darunavir, 150 mg of cobicistat, 200 mg of emtricitabine, and 11.2 mg of tenofovir alafenamide fumarate equivalent to 10 mg of tenofovir alafenamide. The tablets include the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing polyethylene glycol (macrogol), polyvinyl alcohol (partially hydrolyzed), talc, titanium dioxide, and yellow ferric oxide.

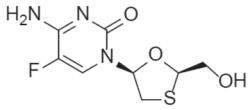
Darunavir: Darunavir, in the form of darunavir ethanolate, has the following chemical name: [(1*S*,2*R*)-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-yl ester monoethanolate. Its molecular formula is $C_{27}H_{37}N_3O_7S \bullet C_2H_5OH$ and its molecular weight is 593.73. Darunavir ethanolate has the following structural formula:



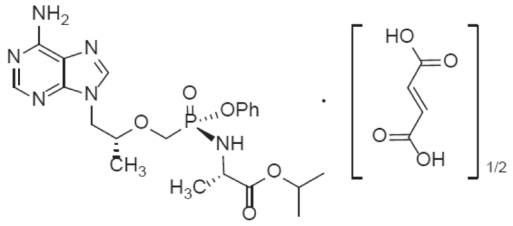
Cobicistat: Cobicistat is adsorbed onto silicon dioxide. The chemical name for cobicistat is 1,3-thiazol-5-ylmethyl[(2*R*,5*R*)-5-{[(2*S*)-2-[(methyl{[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl}carbamoyl)amino]-4-(morpholin-4yl)butanoyl]amino}-1,6-diphenylhexan-2-yl]carbamate. It has a molecular formula of $C_{40}H_{53}N_7O_5S_2$ and a molecular weight of 776.02. It has the following structural formula:



Emtricitabine: The chemical name of emtricitabine is 4-amino-5-fluoro-1-(2*R*-hydroxymethyl-[1,3]-oxathiolan-5*S*-yl)-(1H)-pyrimidin-2-one. Emtricitabine is the (-)enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5 position. Emtricitabine has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24. It has the following structural formula:



Tenofovir alafenamide: The chemical name of tenofovir alafenamide fumarate drug substance is L-alanine, *N*-[(*S*)-[[(1*R*)-2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy] methyl]phenoxyphosphinyl]-,1-methylethyl ester, (2*E*)-2-butenedioate (2:1). Tenofovir alafenamide fumarate has a molecular formula of $C_{21}H_{29}O_5N_6P \bullet ½(C_4H_4O_4)$ and a formula weight of 534.50. It has the following structural formula:



12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

SYMTUZA is a fixed-dose combination of antiretroviral drugs darunavir (plus the CYP3A inhibitor cobicistat), emtricitabine, and tenofovir alafenamide *[see Microbiology (12.4)].*

12.2 Pharmacodynamics

Cardiac Electrophysiology

Thorough QT trials have been conducted for darunavir, cobicistat, and tenofovir alafenamide. The effect of emtricitabine or the combination regimen SYMTUZA on the QT interval has not been evaluated.

Darunavir: In a thorough QT/QTc study in 40 healthy subjects, darunavir doses (co-administered with 100 mg ritonavir) of approximately 2 times the recommended darunavir dose did not affect the QT/QTc interval.

Cobicistat: In a thorough QT/QTc study in 48 healthy subjects, a single dose of cobicistat 250 mg and 400 mg (1.67 and 2.67 times the dose in SYMTUZA) did not affect the QT/QTc interval. Prolongation of the PR interval was noted in subjects receiving cobicistat. The maximum mean (95% upper confidence bound) difference in PR from placebo after baseline-correction was 9.5 (12.1) msec for the 250 mg cobicistat dose and 20.2 (22.8) for the 400 mg cobicistat dose. Because the 150 mg cobicistat dose used in the SYMTUZA fixed-dose combination tablet is lower than the lowest dose studied in the thorough QT study, it is unlikely that treatment with SYMTUZA will result in clinically relevant PR prolongation.

Tenofovir alafenamide: In a thorough QT/QTc study in 48 healthy subjects, tenofovir alafenamide at the recommended dose or at a dose approximately 5 times the recommended 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 trial in subjects with normal renal function ($eGFR_{CG}$ ≥80 mL/min, N=12) and mild-to-moderate renal impairment ($eGFR_{CG}$ 50-79 mL/min, N=18). A statistically significant decrease from baseline in the estimated glomerular filtration rate calculated by Cockcroft-Gault method ($eGFR_{CG}$) 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). No statistically significant changes in $eGFR_{CG}$ were observed compared to baseline for subjects with normal renal function or mild-to-moderate renal impairment 7 days after cobicistat was discontinued. The actual glomerular filtration rate, as determined by the clearance of probe drug iohexol, was not altered from baseline during treatment with cobicistat among subjects with normal renal function and mild-to-moderate renal impairment, indicating that cobicistat inhibits tubular secretion of creatinine, reflected as a reduction in $eGFR_{CG}$, without affecting the actual glomerular filtration rate.

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12.3 Pharmacokinetics

Absorption, Distribution, Metabolism, and Excretion

The bioavailability of the components of SYMTUZA was not affected when administered orally as a split tablet compared to administration as a tablet swallowed whole.

Pharmacokinetic (PK) properties and PK parameters of the components of SYMTUZA are provided in Table 5 and Table 6, respectively.

Table 5: Pharmacokinetic Properties of the Components of SYMTUZA

	Darunavir	Cobicistat	Emtricitabine	TAF
Absorption				
T_{max} (h)	3.0	3.0	1.5	0.5
Effect of high-fat meal[a] (compared to fasting)				
AUC_{last} LS mean ratio, 90% CI	1.52 (1.32-1.76)	1.41 (1.02-1.96)	1.00 (0.96-1.04)	1.12 (1.01-1.23)
C_{max} LS mean ratio, 90% CI	1.82 (1.55-2.14)	1.30 (0.94-1.80)	0.79 (0.71-0.89)	0.55 (0.42-0.71)
Distribution				
% bound to human plasma proteins	95[b]	97-98	<4	~80
Source of protein binding data	*In vitro*	*In vitro*	*In vitro*	*Ex vivo*
Blood-to-plasma ratio	0.64	0.5	0.6	1.0
Metabolism				
Metabolism	CYP3A	CYP3A (major) CYP2D6 (minor)	Not significantly metabolized	Cathepsin A[c] (PBMCs) CES1 (hepatocytes) CYP3A (minimal)
Elimination				
$t_{1/2}$ (h)	9.4	3.2	7.5	0.5[d]
Major route of elimination	Metabolism	Metabolism	Glomerular filtration and active tubular secretion	Metabolism (>80% of oral dose)
% of dose excreted in feces[e]	79.5[f]	86.2	13.7	31.7
% of dose excreted in urine[e]	13.9[f]	8.2	70	<1

PBMCs = peripheral blood mononuclear cells; CES-1 = carboxylesterase-1

[a] Approximately 928 kcal; 504 kcal from fat (56 g), 260 kcal from carbohydrates, and 164 kcal from protein.

[b] Primarily alpha-1-acid glycoprotein

[c] *In vivo*, TAF is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. *In vitro* studies have shown that TAF is metabolized to tenofovir by cathepsin A in PBMCs and macrophages; and by CES1 in hepatocytes. Upon co-administration with the moderate CYP3A inducer probe efavirenz, TAF exposure was unaffected.

[d] Note that the pharmacologically active metabolite tenofovir diphosphate has a half-life of 150-180 hours within PBMCs. Tenofovir in plasma has a median elimination half-life of approximately 44 hours.

[e] Dosing in mass balance studies: darunavir (single dose administration of [^{14}C] darunavir co-administered with multiple dose ritonavir 100 mg); cobicistat (single dose administration of [^{14}C] cobicistat after multiple dosing of cobicistat for six days); emtricitabine (single dose administration of [^{14}C] emtricitabine after multiple dosing of emtricitabine for ten days); TAF (single dose administration of [^{14}C] TAF).

[f] Unchanged darunavir accounted for approximately 41.2% and 7.7% of the administered dose in feces and urine, respectively.

Table 6: Steady State Pharmacokinetic Parameters of Darunavir, Cobicistat, Emtricitabine, Tenofovir Alafenamide (TAF) and its Metabolite Tenofovir Following Oral Administration of SYMTUZA with Food in HIV-Infected Adults

Parameter Mean (SD)	Darunavir		Cobicistat[a]	Emtricitabine[a]	TAF	Tenofovir[a]
C_{max}, ng/mL	8826 (33.3)[a]		1129 (35.3)	2056 (25.3)	163 (51.9)[a]	18.8 (37.6)
AUC_{24h}, ng.h/mL	87909 (20232)[b]	85972 (22413)[c]	8745 (43.9)	11918.0 (35.9)	132 (41)[b]	339 (37.1)
C_{0h}, ng/mL	1899 (759)[b]	1813 (859)[c]	31 (135)	93.1 (58.3)	NA	11.7 (39.3)

[a] From Phase 2 PK substudy (N=21)

[b] From population PK analysis in SYMTUZA Phase 3 study TMC114FD2HTX3001 in ARV naïve subjects (N=355)

[c] From population PK analysis in SYMTUZA Phase 3 study TMC114IFD3013 in ARV experienced subjects (N=750)

Specific Populations

Geriatric Patients

Darunavir: Pharmacokinetic analysis in HIV-infected subjects taking darunavir co-administered with cobicistat, emtricitabine, and tenofovir alafenamide showed no considerable differences in darunavir pharmacokinetics for ages below or equal to 65 years compared to ages greater than 65 years (N=25).

Cobicistat and Emtricitabine: The pharmacokinetics of cobicistat and emtricitabine have not been fully evaluated in the elderly (65 years of age and older).

Tenofovir alafenamide Population pharmacokinetics analysis of HIV-infected subjects in Phase 2 and Phase 3 trials of TAF combined with emtricitabine, elvitegravir, and cobicistat showed that age did not have a clinically relevant effect on exposures of TAF up to 75 years of age.

Pediatric Patients Weighing at Least 40 kg

Available pharmacokinetic data for the different components of SYMTUZA indicate that there were no clinically relevant differences in exposure between adults and pediatric subjects weighing at least 40 kg.

Darunavir and cobicistat: In pediatric subjects aged 12 to less than 18 years, weighing at least 40 kg who received darunavir 800 mg co-administered with cobicistat 150 mg (N=7), geometric mean darunavir C_{max} values were similar between adults and pediatric subjects. Geometric mean darunavir AUC_{24h} and C_{24h} values were 15% and 32% lower, with geometric mean ratios of 0.85 (90% CI: 0.64, 1.13) and 0.68 (90% CI: 0.30, 1.55) in pediatric subjects relative to adults, respectively. These differences were not considered clinically significant. Geometric mean cobicistat AUC_{24h}, C_{max}, and C_{24h} values were comparable in pediatric subjects and adults (Table 7).

Table 7: Multiple-Dose PK Parameters of Darunavir and Cobicistat Following Administration of Darunavir with Cobicistat in HIV 1 Infected Adults and Pediatric Subjects Weighing at least 40 kg[a]

Parameter Geometric mean (CV%)	Darunavir	Cobicistat
Pediatric Subjects[a]	N=7	N=7
AUC_{24h} (mcg.hr/mL)	77.22 (29.5)	8.33 (34.9)
C_{max} (mcg/mL)	7.32 (21.7)	1.10 (20.0)
C_{24h} (mcg/mL)	0.68 (91.6)	0.02 (123.9)[b]
Adults[c]	N=21	N=21
AUC_{24h} (mcg.hr/mL)	90.56 (45.3)	7.69 (43.9)
C_{max} (mcg/mL)	8.34 (33.3)	1.04 (35.3)
C_{24h} (mcg/mL)	1.00 (108.0)	0.02 (135.1)[d]

CV = Coefficient of Variation; mcg = microgram

[a] From intensive PK analysis of trial GS-US-216-0128, where HIV-infected subjects were administered darunavir 800 mg and cobicistat 150 mg once daily with 2 NRTIs

[b] N=5; Data from two subjects who had undetectable cobicistat C_{24h} concentrations were excluded from summary statistics

[c] From intensive PK analysis of trial GS-US-299-0102 where HIV-infected subjects were administered SYMTUZA once daily

[d] N=18

Emtricitabine and tenofovir alafenamide: In 24 pediatric subjects aged 12 to less than 18 years, who received emtricitabine + TAF with elvitegravir + cobicistat, geometric mean emtricitabine C_{max}, and C_{24h} values were comparable to adults, with geometric mean ratios of 1.10 (90% CI: 0.98, 1.23) and 1.07 (90% CI: 0.88, 1.29), respectively (Table 8). Geometric mean emtricitabine AUC_{24h} was 21% higher, with a geometric mean ratio of 1.21 (90% CI: 1.09, 1.34) in pediatric subjects relative to adults. Geometric mean tenofovir alafenamide C_{max} and AUC_{last} values were 29% and 23% lower in pediatric subjects versus adults with geometric mean ratios of 0.71 (90% CI: 0.50, 1.00) and 0.77 (90% CI: 0.59, 1.02), respectively (Table 8). The observed differences were not considered clinically significant.

Table 8: Multiple-Dose PK Parameters of Emtricitabine and Tenofovir Alafenamide Following Oral Administration with Food in HIV 1 Infected Adults and Pediatric Subjects

Parameter Geometric mean (CV%)	Emtricitabine	Tenofovir alafenamide
Pediatric Subjects[a]	N=24	N=24
AUC_{24h} (mcg.hr/mL)[b]	14.0 (23.9)	0.16 (55.8)
C_{max} (mcg/mL)	2.2 (22.5)	0.14 (64.4)
C_{24h} (mcg/mL)	0.10 (38.9)[c]	NA
Adults[d]	N=19	N=19
AUC_{24h} (mcg.hr/mL)[b]	11.6 (16.6)	0.21 (47.3)
C_{max} (mcg/mL)	2.0 (20.2)	0.19 (64.6)
C_{24h} (mcg/mL)	0.09 (46.7)	NA

CV = Coefficient of Variation; mcg = microgram; NA = not applicable

[a] From intensive PK analysis in trial GS-US-292-0106 in treatment-naïve pediatric subjects with HIV-1 infection

[b] AUC_{last} for tenofovir alafenamide

[c] N=23

[d] From intensive PK analysis in trial GS-US-292-0102 in HIV-infected adults treated with emtricitabine+tenofovir alafenamide and elvitegravir+cobicistat

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Gender and Race

There were no clinically relevant differences in the pharmacokinetics of darunavir, cobicistat, emtricitabine, or tenofovir alafenamide based on gender or race.

Patients with Renal Impairment

Darunavir: The pharmacokinetics of darunavir were not altered in HIV-1 infected subjects with moderate renal impairment taking darunavir co-administered with ritonavir (creatinine clearance between 30-60 mL/min, estimated by Cockcroft-Gault method, N=20). There are no pharmacokinetic data available in HIV-1 infected patients with severe renal impairment or end-stage renal disease taking darunavir co-administered with cobicistat *[see Use in Specific Populations (8.6)].*

Cobicistat: There were no clinically relevant differences in cobicistat pharmacokinetics observed between subjects with severe renal impairment (creatinine clearance below 30 mL/min, estimated by Cockcroft-Gault method) and healthy subjects *[see Use in Specific Populations (8.6)].*

Emtricitabine: Mean systemic emtricitabine exposure was higher in patients with severe renal impairment (creatinine clearance less than 30 mL/min, estimated by Cockcroft-Gault method) than in subjects with normal renal function *[see Use in Specific Populations (8.6)].*

Tenofovir alafenamide: In studies of TAF, no clinically relevant differences in the pharmacokinetics of TAF or its metabolite tenofovir were observed between subjects with severe renal impairment (creatinine clearance of 15-30 mL/min, estimated by Cockcroft-Gault method) and healthy subjects *[see Use in Specific Populations (8.6)].*

Patients with Hepatic Impairment

Darunavir: There were no clinically relevant differences in the pharmacokinetics of darunavir (600 mg with ritonavir 100 mg twice daily) in subjects with mild hepatic impairment (Child-Pugh Class A, n=8), and moderate hepatic impairment (Child-Pugh Class B, n=8), compared to subjects with normal hepatic function (n=16). The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been evaluated *[see Use in Specific Populations (8.7)].*

Cobicistat: There were no clinically relevant differences in the cobicistat pharmacokinetics between subjects with moderate hepatic impairment (Child-Pugh Class B) and healthy subjects. The effect of severe hepatic impairment on the pharmacokinetics of cobicistat has not been evaluated *[see Use in Specific Populations (8.7)].*

Emtricitabine: The pharmacokinetics of emtricitabine have not been studied in subjects with hepatic impairment; however, emtricitabine is not significantly metabolized by liver enzymes, so the impact of hepatic impairment should be limited *[see Use in Specific Populations (8.7)].*

Tenofovir Alafenamide: Clinically relevant changes in the pharmacokinetics of tenofovir alafenamide or its metabolite tenofovir were not observed in patients with mild, moderate (Child-Pugh Class A and B), or severe hepatic impairment (Child-Pugh Class C); *[see Use in Specific Populations (8.7)].*

Patients with Hepatitis B and/or Hepatitis C Virus Coinfection

Darunavir: In HIV-infected subjects taking darunavir co-administered with ritonavir, the 48-week analysis of the data from clinical trials indicated that hepatitis B and/or hepatitis C virus coinfection status had no apparent effect on the exposure of 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: The pharmacokinetics of emtricitabine and tenofovir alafenamide have not been fully evaluated in subjects coinfected with hepatitis B and/or C virus.

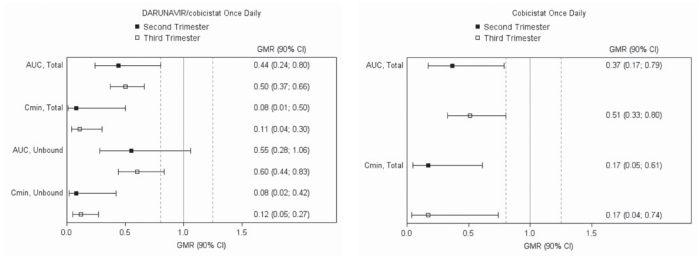
Pregnancy and Postpartum

The exposure to total and unbound darunavir boosted with cobicistat after intake of darunavir/cobicistat as part of an antiretroviral regimen was substantially lower during the second and third trimesters of pregnancy compared with 6-12 weeks postpartum (see Table 9 and Figure 1).

Table 9: Pharmacokinetic Results of Total Darunavir after Administration of Darunavir/Cobicistat Once Daily as Part of an Antiretroviral Regimen, During the 2nd Trimester of Pregnancy, the 3rd Trimester of Pregnancy, and Postpartum

Pharmacokinetics of total darunavir (mean ± SD)	2nd Trimester of pregnancy N=7	3rd Trimester of pregnancy N=6	Postpartum (6-12 weeks) N=6
C_{max}, ng/mL	4340 ± 1616	4910 ± 970	7918 ± 2199
AUC_{24h}, ng.h/mL	47293 ± 19058	47991 ± 9879	99613 ± 34862
C_{min}, ng/mL	168 ± 149	184 ± 99	1538 ± 1344

Figure 1: Pharmacokinetic Results (Within-Subject Comparison) of Total and Unbound Darunavir and Total Cobicistat After Administration of Darunavir/Cobicistat at 800/150 mg Once Daily as Part of an Antiretroviral Regimen, During the 2nd and 3rd Trimester of Pregnancy Compared to Postpartum



Legend: 90% CI: 90% confidence interval; GMR: geometric mean ratio (i.e., second or third trimester/postpartum). Solid vertical line: ratio of 1.0; dotted vertical lines: reference lines of 0.8 and 1.25.

Drug Interactions

Darunavir is metabolized by CYP3A. Cobicistat is metabolized by CYP3A and, to a minor extent, by CYP2D6. Darunavir co-administered with cobicistat is an inhibitor of CYP3A and CYP2D6. Cobicistat inhibits the following transporters: P-gp, BCRP, MATE1, OATP1B1, and OATP1B3. Based on *in vitro* data, cobicistat is not expected to induce CYP1A2 or CYP2B6 and based on *in vivo* data, cobicistat is not expected to induce MDR1 or, in general, CYP3A to a clinically significant extent. The induction effect of cobicistat on CYP2C9, CYP2C19, or UGT1A1 is unknown, but is expected to be low based on CYP3A *in vitro* induction data.

Emtricitabine is not an inhibitor of human CYP450 enzymes. *In vitro* and clinical drug interaction studies have shown that the potential for CYP-mediated interactions involving emtricitabine with other medicinal products is low. Tenofovir alafenamide is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or UGT1A. It is not an inhibitor or inducer of CYP3A *in vivo*.

A drug-drug interaction study between darunavir/cobicistat and dabigatran etexilate was conducted in healthy participants. The effects of darunavir on co-administration with dabigatran etexilate are summarized in Table 10.

Table 10: Drug Interactions: Pharmacokinetic Parameters for Co-Administered Drugs in the Presence of darunavir/cobicistat

Co-administered drug	Dose/Schedule: Co-administered drug	Dose/Schedule: Darunavir/cobicistat	N	PK	LS Mean ratio (90% CI) of co-administered drug pharmacokinetic parameters with/without darunavir no effect =1.00: C_{max}	AUC	C_{min}
Dabigatran etexilate	150 mg	800/150 mg single dose	14	↑	2.64 (2.29-3.05)	2.64 (2.32-3.00)	-
		800/150 mg q.d.[a]	14	↑	1.99 (1.72-2.30)	1.88 (1.65-2.13)	-

N = number of subjects with data

q.d. = once daily

[a] 800/150 mg q.d. for 14 days before co-administered with dabigatran etexilate.

12.4 Microbiology

Mechanism of Action

Darunavir: Darunavir is an inhibitor of the HIV-1 protease. It selectively inhibits the cleavage of HIV-1 encoded Gag-Pol polyproteins in infected cells, thereby preventing the formation of mature virus particles.

Cobicistat: Cobicistat is a selective, mechanism-based inhibitor of CYPP450 of the CYP3A subfamily. Inhibition of CYP3A-mediated metabolism by cobicistat enhances the systemic exposure of CYP3A substrates.

Emtricitabine: Emtricitabine, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5′-triphosphate. Emtricitabine 5′-triphosphate inhibits the activity of the HIV-1 reverse transcriptase (RT) by competing with the natural substrate deoxycytidine 5′-triphosphate and by being incorporated into nascent viral DNA, which results in chain termination. Emtricitabine 5′-triphosphate is a weak inhibitor of mammalian DNA polymerases α, β, ε, and mitochondrial DNA polymerase γ.

Tenofovir alafenamide: TAF is a phosphonamidate prodrug of tenofovir (2′-deoxyadenosine monophosphate analog). Plasma exposure to TAF allows for permeation into cells and then TAF is intracellularly converted to tenofovir through hydrolysis by cathepsin A. Tenofovir is subsequently phosphorylated by cellular kinases to the active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV-1 replication through incorporation into viral DNA by the HIV RT, which results in DNA chain-termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of toxicity to mitochondria in cell culture.

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Antiviral Activity

Darunavir: Darunavir exhibits activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T-cell lines, human PBMCs, and human monocytes/macrophages with median EC_{50} values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/mL). Darunavir demonstrates antiviral activity in cell culture 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 less than 0.1 to 4.3 nM. The EC_{50} value of darunavir increases by a median factor of 5.4 in the presence of human serum.

Cobicistat: Cobicistat has no detectable antiviral activity in cell culture against HIV-1.

Emtricitabine: The antiviral activity of emtricitabine against laboratory and clinical isolates of HIV-1 was assessed in T lymphoblastoid cell lines, the MAGI-CCR5 cell line, and primary PBMCs. The EC_{50} values for emtricitabine were in the range of 1.3–640 nM. Emtricitabine displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 7–75 nM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 7–1,500 nM).

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 ranged from 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).

The combination of darunavir, emtricitabine, and tenofovir alafenamide was not antagonistic in cell culture combination antiviral activity assays. In addition, darunavir, emtricitabine, and tenofovir alafenamide were not antagonistic with a panel of representative agents from the major classes of approved HIV antivirals (PIs, NRTIs, NNRTIs, and INSTIs). The antiviral activity of approved HIV antivirals was not antagonized by cobicistat.

Resistance

Cell Culture

Darunavir: In cell culture, HIV-1 isolates with a decreased susceptibility to darunavir have been selected and obtained from subjects treated with darunavir co-administered with ritonavir. Darunavir-resistant virus derived in cell culture from wild-type HIV-1 had 21- to 88-fold decreased susceptibility to darunavir and developed 2 to 4 of the following amino acid substitutions S37D, R41E/T, K55Q, H69Q, K70E, T74S, V77I, or I85V in the protease. Selection in cell culture of darunavir-resistant HIV-1 from nine HIV-1 strains harboring multiple PI resistance-associated substitutions resulted in the overall emergence of 22 mutations in the protease gene, coding for amino acid substitutions L10F, V11I, I13V, I15V, G16E, L23I, V32I, L33F, S37N, M46I, I47V, I50V, F53L, L63P, A71V, G73S, L76V, V82I, I84V, T91A/S, and Q92R, of which L10F, V32I, L33F, S37N, M46I, I47V, I50V, L63P, A71V, and I84V were the most prevalent. These darunavir-resistant viruses had at least eight protease substitutions and exhibited 50- to 641-fold decreases in darunavir susceptibility with final EC_{50} values ranging from 125 nM to 3461 nM.

Emtricitabine: HIV-1 isolates with reduced susceptibility to emtricitabine were selected in cell culture and in subjects treated with emtricitabine. Reduced susceptibility to emtricitabine was associated with M184V or I substitutions in HIV-1 RT.

Tenofovir alafenamide: HIV-1 isolates with reduced susceptibility to TAF were selected in cell culture. HIV-1 isolates selected by TAF expressed a K65R substitution in HIV-1 RT, sometimes in the presence of S68N or L429I substitutions. In addition, a K70E substitution in HIV-1 RT was observed.

Clinical Trials

Darunavir resistance-associated substitutions (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. Baseline International AIDS Society-USA (IAS-USA)-defined PI resistance substitutions confer reduced virologic response to darunavir.

In the AMBER clinical trial of subjects with no prior antiretroviral treatment history, there were 7 subjects with protocol-defined virologic failure and with HIV-1 RNA ≥400 copies/mL at failure or later timepoints who had post-baseline resistance data in the SYMTUZA arm. None of the subjects had detectable emergent darunavir resistance-associated substitutions or other primary protease inhibitor resistance-associated substitutions and only one subject had emergent M184M/I/V, which confers resistance to emtricitabine and lamivudine. In the comparative PREZCOBIX + emtricitabine/tenofovir disoproxil fumarate arm, there were 2 protocol-defined virologic failures with post-baseline resistance data and neither had detectable resistance emergence.

In the EMERALD clinical trial of virologically-suppressed subjects who switched to SYMTUZA, 1 subject who rebounded and 2 subjects who discontinued early from the study had post-baseline resistance genotypes. None of the subjects had darunavir, primary protease inhibitor, emtricitabine, or tenofovir resistance-associated substitutions. In the control arm, there were 3 subjects who rebounded with post-baseline genotypes and no resistance-associated substitutions were observed.

Cross-Resistance

Darunavir: Cross-resistance among PIs has been observed. Darunavir has a less than 10-fold decreased susceptibility in cell culture against 90% of 3309 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and/or tipranavir showing that viruses resistant to these PIs remain susceptible to darunavir. A less than 10-fold decreased susceptibility was observed for the other PIs in 26% to 96% of these PI resistant clinical isolates [nelfinavir (26%), ritonavir (34%), lopinavir (46%), indinavir (57%), atazanavir (59%), saquinavir (64%), amprenavir (70%), and tipranavir (96%)].

Cross-resistance between darunavir and nucleoside/nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, gp41 fusion inhibitors, CCR5 co-receptor antagonists, or integrase strand transfer inhibitors is unlikely because the viral targets are different.

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

Tenofovir Alafenamide: Tenofovir resistance-associated substitutions K65R and K70E result in reduced susceptibility to abacavir, didanosine, emtricitabine, lamivudine, and tenofovir. HIV-1 with multiple thymidine analog substitutions (M41L, D67N, K70R, L210W, T215F/Y, K219Q/E/N/R) or multinucleoside resistant HIV-1 with a T69S double insertion mutation or with a Q151M substitution complex including K65R, showed reduced susceptibility to TAF in cell culture.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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 incidence of hepatocellular adenomas and carcinomas was observed in males and females of both species and an increase in thyroid follicular cell adenomas was observed in male 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 to darunavir (based on AUC) were between 0.5- and 0.6-fold (mice) and was 0.9-fold (rats) of exposures observed in humans at the recommended therapeutic dose of darunavir in SYMTUZA. 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.

Cobicistat: In a long-term carcinogenicity study in mice, no drug-related increases in tumor incidence were observed at doses up to 50 and 100 mg/kg/day in males and females, respectively. Cobicistat exposures at these doses were approximately 8.6 (male) and 20 (females) times, respectively, the human systemic exposure at the therapeutic daily dose of cobicistat in SYMTUZA. 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 of cobicistat in SYMTUZA. 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 per kg per day (26 times the human systemic exposure at the recommended dose of emtricitabine in SYMTUZA) or in rats at doses up to 600 mg per kg per day (31 times the human systemic exposure at the recommended dose). Emtricitabine was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma, or mouse micronucleus assays. Emtricitabine did not affect fertility in male rats at approximately 107 times or in male and female mice at approximately 88 times higher exposures (AUC) than in humans given the recommended 200 mg daily dose in SYMTUZA. Fertility was normal in the offspring of mice exposed daily from before birth (*in utero*) through sexual maturity at daily exposures (AUC) of approximately 88 times higher than human exposures at the recommended 200 mg daily dose.

Tenofovir alafenamide: Since TAF is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice was observed after TAF administration compared to TDF administration, carcinogenicity studies were conducted only with TDF. Long-term oral carcinogenicity studies of TDF 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 TDF for HIV-1 infection. The tenofovir exposure in these studies was approximately 167 times (mice) and 55 times (rat) those observed in humans after administration of the daily recommended dose of TAF. At the high dose in female mice, liver adenomas were increased at tenofovir exposures approximately 10 times (300 mg TDF) and 167 times (10 mg TAF) the exposure observed in humans. In rats, the study was negative for carcinogenic findings.

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TAF was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma, or rat micronucleus assays. There were no effects on fertility, mating performance, or early embryonic development when TAF 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 7 of gestation.

13.2 Animal Toxicology and/or Pharmacology

Minimal to slight infiltration of mononuclear cells in the posterior uvea was observed in dogs with similar severity after 3 and 9 month administration of tenofovir alafenamide; reversibility was seen after a 3-month recovery period. No eye toxicity was observed in the dog at systemic exposures of 3.5 (TAF) and 0.62 (tenofovir) times the exposure seen in humans with the recommended daily dose of TAF in SYMTUZA.

14. CLINICAL STUDIES

14.1 Clinical Trial Results in Subjects with HIV-1 Infection with no Prior Antiretroviral Treatment History

The efficacy of SYMTUZA in HIV-1 subjects with no prior antiretroviral treatment history was evaluated in the Phase 3 trial TMC114FD2HTX3001 [NCT02431247, (AMBER)] in which subjects were randomized in a 1:1 ratio to receive either SYMTUZA (N=362) or a combination of PREZCOBIX and FTC/TDF (N=363) once daily. The median age was 34.0 years (range 18-71), 88.3% were male, 83% White, 11% Black, and 2% Asian. The mean baseline plasma HIV-1 RNA was 4.5 $\log_{10}$ copies/mL (range 1.3-6.7), and 18% had a baseline viral load ≥100,000 copies/mL. The median baseline CD4+ cell count was 453 cells/mm^3 (range 38 to 1456 cells/mm^3).

Virologic outcomes at 48 weeks of treatment are presented in Table 11.

Table 11: Virologic Outcomes in AMBER at Week 48 in HIV-1 Subjects with No Prior Antiretroviral Treatment History

	SYMTUZA N=362	PREZCOBIX + FTC/TDF N=363
Virologic Response		
HIV-1 RNA <50 copies/mL	91%	88%
Treatment difference[a]	2.7 (95% CI: -1.6; 7.1)	
Virologic Failure[b]	4%	3%
No virologic data at Week 48 window[c]	4%	8%
Reasons		
Discontinued trial due to adverse event or death	2%	4%
Discontinued trial for other reasons[d]	1%	3%
Missing data during window but on trial	1%	1%

[a] Based on stratum adjusted MH test where stratification factors are HIV-1 RNA level (≤100,000 or > 100,000 copies/mL) and CD4+ cell count (< 200 or ≥200 cells/μL).
[b] Included subjects who had ≥50 copies/mL in the Week 48 window; subjects who discontinued early due to lack or loss of efficacy; subjects who discontinued for reasons other than an adverse event (AE), death, or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.
[c] Day 295 – Day 378
[d] Other includes reasons such as withdrew consent, loss to follow-up, and non-compliance.

The mean increase from baseline in CD4+ cell count at Week 48 was 189 and 174 cells/mm^3 in the SYMTUZA and PREZCOBIX + FTC/TDF groups, respectively.

14.2 Clinical Trial Results in Virologically-Suppressed Subjects with HIV-1 Infection Who Switched to SYMTUZA

Phase 3 trial TMC114IFD3013 [NCT02269917, (EMERALD)] evaluated the efficacy of SYMTUZA in virologically-suppressed (HIV-1 RNA less than 50 copies/mL) subjects with HIV-1 infection. Subjects were virologically suppressed for at least 2 months and no more than once had a viral load elevation above 50 HIV-1 RNA copies/mL during the year prior to enrollment. Subjects were on a stable antiretroviral regimen (for at least 6 months), consisting of a bPI [either darunavir once daily or atazanavir (both boosted with ritonavir or cobicistat), or lopinavir with ritonavir] combined with emtricitabine and TDF. Subjects had no history of failure on darunavir treatment and no known or suspected darunavir resistance-associated substitutions. Emtricitabine or tenofovir resistance-associated substitutions were not specifically excluded by the protocol. They either switched to SYMTUZA (N=763) or continued their treatment regimen (N=378) (randomized 2:1). Subjects had a median age of 46 years (range 19-78), 82% were male, 75% White, 21% Black, and 2% Asian. The median baseline CD4+ cell count was 628 cells/mm^3 (range 111-1921 cells/mm^3). Overall, 15% (N=169) of subjects had prior virologic failure. Five subjects had archived tenofovir resistance-associated substitutions and 53 subjects had archived emtricitabine resistance-associated substitutions, mainly at RT position M184. All of these subjects with emtricitabine resistance-associated substitutions had HIV-1 RNA<50 copies/mL at Week 48 (N=50) or at the last on-treatment viral load (N=3). Virologic outcomes are presented in Table 12. Prior virologic failure did not impact treatment outcomes.

Table 12: Virologic Outcomes in EMERALD at Week 48 in HIV-1 Virologically-Suppressed Subjects Who Switched to SYMTUZA

	SYMTUZA N=763	bPI+FTC/TDF N=378
Virologic Failure[a]	1%	1%
Treatment difference[b]	0.3 (95% CI: -0.7; 1.2)	
HIV-1 RNA <50 copies/mL	95%	94%
No virologic data at Week 48 window[c]	4%	6%
Reasons		
Discontinued trial due to adverse event or death	1%	1%
Discontinued trial for other reasons[d]	3%	4%
Missing data during window[c] but on trial	<1%	1%

[a] Included subjects who had ≥50 copies/mL in the Week 48 window; subjects who discontinued early due to lack or loss of efficacy; subjects who discontinued for reasons other than an adverse event (AE), death, or lack or loss of efficacy and at the time of discontinuation had a viral value ≥ 50 copies/mL.
[b] Based on MH test adjusting for bPI at screening (ATV with rtv or COBI, DRV with rtv or COBI, LPV with rtv).
[c] Day 295 – Day 378
[d] Other includes reasons such as withdrew consent, loss to follow-up, and non-compliance

The mean increase from baseline in CD4+ cell count at Week 48 was 20 cells/mm^3 in subjects who switched to SYMTUZA and 8 cells/mm^3 in subjects who stayed on their baseline PI + FTC/TDF.

14.3 Clinical Trial Results in Pediatric Subjects with HIV-1 Infection

The pharmacokinetic profile, safety, and antiviral activity of the components of SYMTUZA were evaluated in open-label clinical trials in pediatric subjects with HIV-1 infection aged 12 to less than 18 years: GS-US-216-0128 (N=7) and GS-US-292-0106 (N=50).

In the Phase 2/3 trial GS-US-216-0128, darunavir 800 mg and cobicistat 150 mg once daily with 2 NRTIs were evaluated in 7 virologically suppressed pediatric subjects aged 12 to less than 18 years and weighing at least 40 kg. Subjects had a median (range) age of 14 (12-16) years and a median (range) weight of 57 (45-78) kg. At baseline, plasma HIV-1 RNA was <50 copies/mL in all subjects, and the median (range) CD4+ cell count was 1,117 (658-2,416) cells/mm^3. At Week 48, the proportion of subjects who maintained HIV-1 RNA <50 copies/mL was 86%, and the median change in CD4+ cell count from baseline was -342 cells/mm^3 (range -1,389 to 210 cells/mm^3). All 6 subjects with available data had CD4+ cell counts above 800 cells/mm^3 at Week 48.

In the Phase 2/3 trial GS-US-292-0106, cobicistat 150 mg, emtricitabine 200 mg, and tenofovir alafenamide 10 mg, as part of a fixed-dose combination regimen together with elvitegravir 150 mg, were evaluated in 50 treatment-naïve pediatric subjects with HIV-1 aged 12 to less than 18 years and weighing at least 35 kg. Subjects had a median (range) age of 15 (12-17) years. At baseline, median (range) plasma HIV-1 RNA was 4.7 (3.3-6.5) $\log_{10}$ copies/mL, median (range) CD4+ cell count was 456 (95-1,110) cells/mm^3, and 22% had baseline plasma HIV-1 RNA >100,000 copies/mL). At Week 48, the proportion of subjects who had HIV-1 RNA <50 copies/mL was 92%, and the median increase in CD4+ cell count from baseline was 220 cells/mm^3.

The use of SYMTUZA in pediatric patients weighing less than 40 kg has not been established *[see Use in Specific Populations (8.4)]*.

16. HOW SUPPLIED/STORAGE AND HANDLING

SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets are supplied as yellow to yellowish-brown, capsule-shaped, film-coated tablets debossed with "8121" on one side and "JG" on the other side.

SYMTUZA is packaged in bottles of 30 tablets (NDC 59676-800-30), with a silica gel desiccant and child-resistant closure.

Storage

- Store at 20°C-25°C (between 68°F-77°F); with excursions permitted to 15°C-30°C (59°F-86°F).
- Dispense only in the original container. Keep container tightly closed with desiccant inside to protect from moisture.
- Keep SYMTUZA out of reach of children.

17. PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Instructions for Use

Advise patients to take SYMTUZA with food every day on a regular dosing schedule, as missed doses can result in development of resistance. Inform patients not to alter the dose of SYMTUZA or discontinue therapy with SYMTUZA without consulting their physician. For patients who are unable to swallow tablets whole, SYMTUZA may be split using a tablet-cutter, and the entire dose should be consumed immediately after splitting *[see Dosage and Administration (2.2)]*.

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Post-treatment Acute Exacerbation of Hepatitis B in Patients with HBV Co-Infection

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued products containing emtricitabine and/or TDF, and may likewise occur with discontinuation of SYMTUZA *[see Warnings and Precautions (5.1)]*. Advise the patient to not discontinue SYMTUZA without first informing their healthcare provider.

Hepatotoxicity

Inform patients that drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) and liver injury, including some fatalities, could potentially occur with SYMTUZA. Advise patients to contact their healthcare provider immediately if signs and symptoms of liver problems develop *[see Warnings and Precautions (5.2)]*.

Severe Skin Reactions

Inform patients that skin reactions ranging from mild to severe, including Stevens-Johnson syndrome, drug rash with eosinophilia and systemic symptoms, and toxic epidermal necrolysis, could potentially occur with SYMTUZA. Advise patients to contact their healthcare provider immediately if signs or symptoms of severe skin reactions develop, including but not limited to severe rash or rash accompanied with fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, and/or conjunctivitis *[see Warnings and Precautions (5.3)]*.

Pregnancy

Advise patients that SYMTUZA is not recommended during pregnancy and to alert their healthcare provider if they get pregnant while taking SYMTUZA. Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant individuals exposed to SYMTUZA *[see Use in Specific Populations (8.1)]*.

Lactation

Instruct individuals with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in breast milk *[see Use in Specific Populations (8.2)]*.

Drug Interactions

SYMTUZA may interact with many drugs; therefore, inform patients of the potential serious drug interactions with SYMTUZA, and that some drugs are contraindicated with SYMTUZA and other drugs may require dosage adjustment. Advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John's wort *[see Contraindications (4), Warnings and Precautions (5.4), and Drug Interactions (7)]*.

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any symptoms of infection, as in some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started *[see Warnings and Precautions (5.5)]*.

Renal Impairment

Advise patients to avoid taking SYMTUZA with concurrent or recent use of nephrotoxic agents. Renal impairment, including cases of acute renal failure, has been reported in association with the use of tenofovir prodrugs *[see Warnings and Precautions (5.6)]*.

Lactic Acidosis and Severe Hepatomegaly

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with use of drugs similar to SYMTUZA. Advise patients that they should stop SYMTUZA if they develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity *[see Warnings and Precautions (5.8)]*.

Fat Redistribution

Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including SYMTUZA, and that the cause and long-term health effects of these conditions are not known at this time *[see Warnings and Precautions (5.10)]*.

Manufactured for:
Janssen Products, LP, Horsham PA 19044, USA

PATIENT INFORMATION
SYMTUZA® (sim toó zah)
(darunavir, cobicistat, emtricitabine, and tenofovir alafenamide)
tablets

What is the most important information I should know about SYMTUZA?

SYMTUZA can cause serious side effects, including:

- **Worsening of Hepatitis B virus infection (HBV).** Your healthcare provider will test you for HBV before starting treatment with SYMTUZA. If you have HBV infection and take SYMTUZA, your HBV may get worse (flare-up) if you stop taking SYMTUZA. A "flare-up" is when your HBV infection suddenly returns in a worse way than before.
  - Do not stop taking SYMTUZA without first talking to your healthcare provider.
  - Do not run out of SYMTUZA. Refill your prescription or talk to your healthcare provider before your SYMTUZA is all gone.
  - If you stop taking SYMTUZA, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your HBV infection, or give you a medicine to treat your HBV infection. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking SYMTUZA.
- **Change in liver enzymes.** People with a history of hepatitis B or C virus infection or who have certain liver enzyme changes may have an increased risk of developing new or worsening liver problems during treatment with SYMTUZA. Liver problems can also happen during treatment with SYMTUZA in people without a history of liver disease. Your healthcare provider may need to do tests to check your liver enzymes before and during treatment with SYMTUZA.
- **Severe liver problems.** In rare cases, severe liver problems can happen that can lead to death. **Tell your healthcare provider right away if you get these symptoms:** skin or the white part of your eyes turns yellow, dark "tea-colored" urine, light-colored stools, loss of appetite for several days or longer, nausea, vomiting, or stomach-area pain.

SYMTUZA may cause severe or life-threatening skin reactions or rash. Sometimes these skin reactions and skin rashes can become severe and require treatment in a hospital. Call your healthcare provider right away if you develop a rash. **Stop taking SYMTUZA** and call your healthcare provider right away if you develop any skin changes with symptoms below:

- fever
- tiredness
- muscle or joint pain
- blisters or skin lesions
- mouth sores or ulcers
- red or inflamed eyes, like "pink eye" (conjunctivitis)

See "What are the possible side effects of SYMTUZA?" for more information about side effects.

What is SYMTUZA?

SYMTUZA is a prescription medicine that is used without other antiretroviral medicines to treat Human Immunodeficiency Virus-1 (HIV-1) infection in adults and in children who weigh at least 88 pounds (40 kg) who:

- have not received anti-HIV-1 medicines in the past, **or**
- when their healthcare provider determines that they meet certain requirements.

HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

SYMTUZA contains the prescription medicines darunavir, cobicistat, emtricitabine, and tenofovir alafenamide.

It is not known if SYMTUZA is safe and effective in children weighing less than 88 pounds (40 kg).

Who should not take SYMTUZA?

Do not take SYMTUZA with any of the following medicines:

- alfuzosin
- carbamazepine
- colchicine, if you have liver or kidney problems
- dronedarone
- elbasvir and grazoprevir
- ergot-containing medicines, such as:
  - dihydroergotamine
  - ergotamine tartrate
  - methylergonovine

Who should not take SYMTUZA? (continued)

Do not take SYMTUZA with any of the following medicines:

- ivabradine
- lomitapide
- lovastatin or a product that contains lovastatin
- lurasidone
- midazolam, when taken by mouth
- naloxegol
- phenobarbital
- phenytoin
- pimozide
- ranolazine
- rifampin
- sildenafil, when used for the treatment of pulmonary arterial hypertension (PAH)
- simvastatin or a product that contains simvastatin
- St. John's wort (*Hypericum perforatum*), or a product that contains St. John's wort
- triazolam

Serious problems can happen if you take any of these medicines with SYMTUZA. This is not a complete list of medicines. Therefore, tell your healthcare provider about all medicines you take.

Before taking SYMTUZA, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems, including hepatitis B or hepatitis C
- have kidney problems
- are allergic to sulfa (sulfonamide)
- have diabetes
- have hemophilia
- are pregnant or plan to become pregnant.
  - It is not known if SYMTUZA will harm your unborn baby.
  - SYMTUZA should not be used during pregnancy because you may not have enough SYMTUZA in your body during pregnancy.
  - Tell your healthcare provider if you become pregnant while taking SYMTUZA. Your healthcare provider will prescribe different medicines if you become pregnant while taking SYMTUZA.

    Pregnancy Registry: There is a pregnancy registry for those who take antiretroviral medicines during pregnancy. The purpose of the registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.
- are breastfeeding or plan to breastfeed. Do not breastfeed if you take SYMTUZA.
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV to your baby.
  - One of the medicines in SYMTUZA called emtricitabine can pass into your breast milk. It is not known if the other medicines in SYMTUZA can pass into your breast milk.
  - Talk to your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, topical creams, vitamins, and herbal supplements. Some medicines interact with SYMTUZA. Keep a list of your medicines to show your healthcare provider and pharmacist.

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with SYMTUZA.
- **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take SYMTUZA with other medicines.

How should I take SYMTUZA?

- Take SYMTUZA exactly as your healthcare provider tells you.
- Do not change your dose or stop taking SYMTUZA without talking to your healthcare provider.
- Take SYMTUZA 1 time a day with food.
- If you have difficulty swallowing, the tablet may be split using a tablet-cutter. After splitting the tablet, the entire dose (both halves) should then be taken right away.
- Do not miss a dose of SYMTUZA.
- When your SYMTUZA supply starts to run low, get more from your healthcare provider or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to SYMTUZA and become harder to treat.
- If you take too much SYMTUZA, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of SYMTUZA?

SYMTUZA may cause serious side effects, including:

- See **"What is the most important information I should know about SYMTUZA?"**
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having new symptoms after starting your HIV-1 medicine.
- **New or worse kidney problems, including kidney failure.** Your healthcare provider should do blood and urine tests to check your kidneys before you start and while you are taking SYMTUZA. Your healthcare provider may tell you to stop taking SYMTUZA if you develop new or worse kidney problems.
- **Too much lactic acid in your blood (lactic acidosis).** Too much lactic acid is a serious but rare medical emergency that can lead to death. **Tell your healthcare provider right away if you get these symptoms:** weakness or being more tired than usual, unusual muscle pain, being short of breath or fast breathing, stomach pain with nausea and vomiting, cold or blue hands and feet, feel dizzy or lightheaded, or a fast or abnormal heartbeat.
- **Diabetes and high blood sugar (hyperglycemia).** Some people who take protease inhibitors including SYMTUZA can get high blood sugar, develop diabetes, or your diabetes can get worse. Tell your healthcare provider if you notice an increase in thirst or if you start urinating more often while taking SYMTUZA.
- **Changes in body fat** can happen in people who take HIV-1 medicines. The changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the middle of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term health effects of these conditions are not known.
- **Increased bleeding for hemophiliacs.** Some people with hemophilia have increased bleeding with protease inhibitors.

The most common side effects of SYMTUZA, include:

- diarrhea
- rash
- nausea
- fatigue
- headache
- stomach problems
- gas

These are not all of the possible side effects of SYMTUZA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SYMTUZA?

- Store SYMTUZA tablets at room temperature between 68°F to 77°F (20°C to 25°C).
- The SYMTUZA bottle contains a desiccant and has a child-resistant cap.
- Keep the SYMTUZA container tightly closed with the desiccant inside of it to protect SYMTUZA from moisture.

Keep SYMTUZA out of reach of children.

General information about the safe and effective use of SYMTUZA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use SYMTUZA for a condition for which it was not prescribed. Do not give SYMTUZA to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about SYMTUZA that is written for health professionals.

What are the ingredients in SYMTUZA?

Active ingredient: darunavir, cobicistat, emtricitabine, and tenofovir alafenamide

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing polyethylene glycol (macrogol), polyvinyl alcohol (partially hydrolyzed), talc, titanium dioxide, and yellow ferric oxide.

Manufactured for: Janssen Products, LP, Horsham PA 19044, USA

For more information call 1-800-526-7736.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 03/2023

cp-62057v20

Proposed Package Insert

SYMTUZA®

(darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets, for oral use

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SYMTUZA safely and effectively. See full prescribing information for SYMTUZA.

SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets, for oral use
Initial U.S. Approval: 2018

WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

See full prescribing information for complete boxed warning.

Severe acute exacerbations of hepatitis B (HBV) have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of SYMTUZA. Hepatic function should be monitored closely in these patients. If appropriate, anti-hepatitis B therapy may be warranted. (5.1)

----------RECENT MAJOR CHANGES----------

Contraindications (4) 04/2022

----------INDICATIONS AND USAGE----------

SYMTUZA is a four-drug combination of darunavir (DRV), a human immunodeficiency virus (HIV-1) protease inhibitor, cobicistat (COBI), a CYP3A inhibitor, and emtricitabine (FTC) and tenofovir alafenamide (TAF), both HIV-1 nucleoside analog reverse transcriptase inhibitors, and is indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 40 kg:

- who have no prior antiretroviral treatment history or
- who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months and have no known substitutions associated with resistance to darunavir or tenofovir. (1)

----------DOSAGE AND ADMINISTRATION----------

Testing: Prior to or when initiating SYMTUZA, test patients for HBV infection.

Prior to or when initiating SYMTUZA, and during treatment with SYMTUZA, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. (2.1)

Recommended dosage: One tablet taken once daily with food in adults and pediatric patients, weighing at least 40 kg. (2.2)

Renal Impairment: SYMTUZA is not recommended in patients with estimated creatinine clearance below 30 mL/min. (2.3)

Hepatic Impairment: SYMTUZA is not recommended in patients with severe hepatic impairment. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 800 mg of darunavir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (equivalent to 11.2 mg of tenofovir alafenamide fumarate). (3)

----------CONTRAINDICATIONS----------

SYMTUZA is contraindicated to be co-administered with certain drugs for which altered plasma concentrations are associated with serious and/or life-threatening events or which may lead to loss of therapeutic effect of SYMTUZA and development of resistance. (4)

----------WARNINGS AND PRECAUTIONS----------

- Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) including some fatalities can occur with SYMTUZA. Monitor liver function before and during therapy, especially in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases. (5.2)
- Severe skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis may occur with SYMTUZA. Discontinue treatment if severe skin reaction develops. (5.3)
- Patients receiving SYMTUZA may develop new onset or exacerbations of immune reconstitution syndrome. (5.5)
- Monitor in patients with a known sulfonamide allergy. (5.7)
- Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.8)
- Patients receiving SYMTUZA may develop new onset or exacerbation of diabetes mellitus/hyperglycemia and redistribution/accumulation of body fat. (5.9, 5.10)
- Patients with hemophilia may develop increase bleeding events. (5.11)

----------ADVERSE REACTIONS----------

The most common adverse reactions (all grades, incidence greater than or equal to 2%) were diarrhea, rash, nausea, fatigue, headache, abdominal discomfort, and flatulence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact LifeScience Logistics at 1-855-738-6171 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

Co-administration of SYMTUZA with other drugs can alter the concentration of other drugs and other drugs may alter the concentrations of SYMTUZA components. Consult the full prescribing information prior to and during treatment for potential drug interactions. (4, 5.4, 7, 12.3)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: SYMTUZA is not recommended during pregnancy due to substantially lower exposures of darunavir and cobicistat during pregnancy. (2.5, 8.1, 12.3)
- Lactation: Breastfeeding is not recommended. (8.2)
- Pediatrics: Not recommended for pediatric patients weighing less than 40 kg (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

Severe acute exacerbations of hepatitis B (HBV) have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of SYMTUZA. Closely monitor hepatic function 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, anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.1)]*.

1. INDICATIONS AND USAGE

SYMTUZA is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients weighing at least 40 kg:

- who have no prior antiretroviral treatment history or
- who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months and have no known substitutions associated with resistance to darunavir or tenofovir.

2. DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation of SYMTUZA

Prior to or when initiating SYMTUZA, test patients for hepatitis B (HBV) virus infection *[see Warnings and Precautions (5.1)]*.

Prior to or when initiating SYMTUZA, and during treatment with SYMTUZA, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus *[see Warnings and Precautions (5.6)]*.

2.2 Recommended Dosage

SYMTUZA is a four-drug fixed-dose combination product containing 800 mg of darunavir (DRV), 150 mg of cobicistat (COBI), 200 mg of emtricitabine (FTC), and 10 mg of tenofovir alafenamide (TAF). The recommended dosage of SYMTUZA is one tablet taken orally once daily with food in adults and pediatric patients weighing at least 40 kg. For patients who are unable to swallow the whole tablet, SYMTUZA may be split into two pieces using a tablet-cutter, and the entire dose should be consumed immediately after splitting *[see Clinical Pharmacology (12.3)]*.

2.3 Not Recommended in Patients with Severe Renal Impairment

SYMTUZA is not recommended in patients with creatinine clearance below 30 mL per minute *[see Use in Specific Populations (8.6)]*.

2.4 Not Recommended in Patients with Severe Hepatic Impairment

SYMTUZA is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C) *[see Use in Specific Populations (8.7)]*.

2.5 Not Recommended During Pregnancy

SYMTUZA is not recommended during pregnancy because of substantially lower exposures of darunavir and cobicistat during the second and third trimesters *[see Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)]*.

SYMTUZA should not be initiated in pregnant individuals. An alternative regimen is recommended for those who become pregnant during therapy with SYMTUZA.

3. DOSAGE FORMS AND STRENGTHS

Each SYMTUZA tablet contains darunavir ethanolate equivalent to 800 mg of darunavir, 150 mg of cobicistat, 200 mg of emtricitabine (FTC), and tenofovir alafenamide fumarate equivalent to 10 mg of tenofovir alafenamide (TAF). The yellow to yellowish-brown, capsule-shaped, film-coated tablet is debossed with "8121" on one side and "JG" on the other side.

4. CONTRAINDICATIONS

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). Darunavir and cobicistat are both substrates of the cytochrome P450 3A (CYP3A) isoform. Co-administration of SYMTUZA with CYP3A inducers is expected to lower plasma concentrations of darunavir and cobicistat which may lead to loss of efficacy of darunavir and development of resistance. Examples of drugs that are contraindicated for co-administration with SYMTUZA due to the potential for serious and/or life-threatening events or loss of therapeutic effect *[see Drug Interactions (7.5)]* are listed below.

- Alpha 1-adrenoreceptor antagonist: alfuzosin
- Anticonvulsants: carbamazepine, phenobarbital, phenytoin
- Anti-gout: colchicine, in patients with renal and/or hepatic impairment
- Antimycobacterial: rifampin
- Antipsychotics: lurasidone, pimozide
- Cardiac Disorders: dronedarone, ivabradine, ranolazine
- Ergot derivatives, e.g., dihydroergotamine, ergotamine, methylergonovine
- Herbal product: St. John's wort (*Hypericum perforatum*)
- Hepatitis C direct acting antiviral: elbasvir/grazoprevir
- Lipid modifying agents: lomitapide, lovastatin, simvastatin
- Opioid Antagonist: naloxegol
- PDE-5 inhibitor: sildenafil when used for treatment of pulmonary arterial hypertension
- Sedatives/hypnotics: orally administered midazolam, triazolam

5. WARNINGS AND PRECAUTIONS

5.1 Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV

Patients with HIV-1 should be tested for the presence of chronic hepatitis B virus before initiating antiretroviral therapy *[see Dosage and Administration (2.1)]*. Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine and/or tenofovir disoproxil fumarate, and may occur with discontinuation of SYMTUZA. Patients coinfected with HIV-1 and HBV who discontinue SYMTUZA should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis, since post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

5.2 Hepatotoxicity

Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported in clinical trials with darunavir, a component of SYMTUZA. Patients with pre-existing liver dysfunction, including chronic active hepatitis B or C, have an increased risk for liver function abnormalities including severe hepatic adverse reactions.

Post-marketing cases of liver injury, including some fatalities, have been reported with darunavir. These have generally occurred in patients with advanced HIV-1 disease taking multiple concomitant medications, having co-morbidities including hepatitis B or C co-infection, and/or developing immune reconstitution syndrome. A causal relationship with darunavir therapy has not been established.

Appropriate laboratory testing should be conducted prior to initiating therapy with SYMTUZA and patients should be monitored during treatment as clinically appropriate. Increased AST/ALT monitoring should be considered in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases, 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, hepatomegaly) should prompt consideration of interruption or discontinuation of SYMTUZA.

5.3 Severe Skin Reactions

In patients receiving darunavir, a component of SYMTUZA, severe skin reactions may occur. These include conditions accompanied by fever and/or elevations of transaminases. Stevens-Johnson syndrome was reported with darunavir co-administered with cobicistat in clinical trials at a rate of 0.1%. During darunavir post-marketing experience, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis have been reported. 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.

Rash events of any cause and any grade occurred in 15% of subjects with no prior antiretroviral treatment history treated with SYMTUZA in the AMBER trial *[see Adverse Reactions (6.1)]*. Rash events were mild-to-moderate, often occurring within the first four weeks of treatment and resolving with continued dosing. The discontinuation rate due to rash in subjects using SYMTUZA was 2%.

5.4 Risk of Serious Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

The concomitant use of SYMTUZA and other drugs may result in known or potentially significant drug interactions which may lead to *[see Contraindications (4) and Drug Interactions (7.5)]:*

- Clinically significant adverse reactions from greater exposures of concomitant drugs.
- Clinically significant adverse reactions from greater exposures of SYMTUZA.
- Loss of therapeutic effect of the concomitant drugs from lower exposures of active metabolite(s).
- Loss of therapeutic effect of SYMTUZA and possible development of resistance from lower exposures of SYMTUZA.

See Table 4 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during SYMTUZA therapy; review concomitant medications during SYMTUZA therapy; and monitor for the adverse reactions associated with concomitant medications *[see Contraindications (4) and Drug Interactions (7)]*.

When used with concomitant medications, SYMTUZA, which contains darunavir boosted with cobicistat, may result in different drug interactions than those observed or expected with darunavir co-administered with ritonavir. Complex or unknown mechanisms of drug interactions preclude extrapolation of drug interactions with darunavir co-administered with ritonavir to certain SYMTUZA interactions *[see Drug Interactions (7) and Clinical Pharmacology (12.3)]*.

5.5 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, Guillain-Barré syndrome, and autoimmune hepatitis) 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 antiretroviral treatment.

5.6 New Onset or Worsening Renal Impairment

Postmarketing cases of renal impairment, including acute renal failure, proximal renal tubulopathy (PRT), and Fanconi syndrome have been reported with TAF-containing products; while most of these cases were characterized by potential confounders that may have contributed to the reported renal events, it is also possible these factors may have predisposed patients to tenofovir-related adverse events *[see Adverse Reactions (6.1, 6.2)]*. SYMTUZA is not recommended in patients with estimated creatinine clearance below 30 mL per minute.

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.

Prior to or when initiating SYMTUZA and during treatment with SYMTUZA, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. Discontinue SYMTUZA in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

Cobicistat, a component of SYMTUZA, produces elevations of serum creatinine due to inhibition of tubular secretion of creatinine without affecting glomerular filtration. This effect should be considered when interpreting changes in estimated creatinine clearance in patients initiating SYMTUZA, particularly in patients with medical conditions or receiving drugs needing monitoring with estimated creatinine clearance. The elevation is typically seen within 2 weeks of starting therapy and is reversible after discontinuation. Patients who experience a confirmed increase in serum creatinine of greater than 0.4 mg/dL should be closely monitored for renal safety.

5.7 Sulfa Allergy

Darunavir contains a sulfonamide moiety. Monitor patients with a known sulfonamide allergy after initiating SYMTUZA. In clinical studies with darunavir co-administered with ritonavir, the incidence and severity of rash were similar in subjects with or without a history of sulfonamide allergy.

5.8 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, a component of SYMTUZA, and 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).

SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets

5.9 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 HIV 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 HIV PI therapy and these events have not been established.

5.10 Fat Redistribution

Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

5.11 Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis in patients with hemophilia type A and B treated with HIV protease inhibitors (PIs). In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with HIV PIs was continued or reintroduced if treatment had been discontinued. A causal relationship between PI therapy and these episodes has not been established.

6. ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Severe acute exacerbations of hepatitis B *[see Warnings and Precautions (5.1)]*
- Hepatotoxicity *[see Warnings and Precautions (5.2)]*
- Severe skin reactions *[see Warnings and Precautions (5.3)]*
- Immune reconstitution syndrome *[see Warnings and Precautions (5.5)]*
- New onset or worsening renal impairment *[see Warnings and Precautions (5.6)]*
- Lactic acidosis/severe hepatomegaly with steatosis *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials in Adults

Adverse Reactions in Adults with No Prior Antiretroviral Treatment History

The safety profile of SYMTUZA in HIV-1 infected adults with no prior antiretroviral treatment history is based on Week 48 data from the AMBER trial, a randomized, double-blind, active-controlled trial where a total of 362 subjects received SYMTUZA once daily and 363 subjects received a combination of PREZCOBIX® (fixed-dose combination of darunavir and cobicistat) and fixed-dose combination of emtricitabine and tenofovir disoproxil fumarate (FTC/TDF).

The proportion of subjects who discontinued treatment with SYMTUZA or PREZCOBIX+FTC/TDF due to adverse events, regardless of severity, were 2% and 4% respectively.

An overview of the most frequent (occurring in at least 2% of subjects) adverse reactions irrespective of severity reported in AMBER are presented in Table 1. An overview of the most frequent laboratory abnormalities of at least Grade 2 severity reported in AMBER are presented in Table 2. Changes from baseline in lipid parameters for patients receiving SYMTUZA and those receiving PREZCOBIX + FTC/TDF are presented in Table 3.

Most adverse reactions during treatment with SYMTUZA were grade 1 or 2 in severity. One grade 3 adverse reaction was reported and no grade 4 adverse reactions were reported during treatment with SYMTUZA.

Table 1: Adverse Reactions Reported in ≥2% of HIV-1 Infected Adults With No Prior Antiretroviral Treatment History in AMBER (Week 48 Analysis)

	SYMTUZA (N=362)		PREZCOBIX+FTC/TDF (N=363)	
	All Grades	At least Grade 2	All Grades	At least Grade 2
Diarrhea	9%	2%	11%	2%
Rash[a]	8%	4%	7%	5%
Nausea	6%	1%	10%	3%
Fatigue	4%	1%	4%	1%
Headache	3%	1%	2%	1%
Abdominal discomfort	2%	-	4%	<1%
Flatulence	2%	<1%	1%	-

[a] Includes pooled reported terms: dermatitis, dermatitis allergic, erythema, photosensitivity reaction, rash, rash generalized, rash macular, rash maculo-papular, rash morbilliform, rash pruritic, toxic skin eruption, urticaria

Adverse Reactions in Virologically-Suppressed Adults

The safety profile of SYMTUZA in virologically-suppressed HIV-1 infected adults is based on Week 48 data from 1,141 subjects in the EMERALD trial, a randomized, open-label, active-controlled trial where 763 subjects with a stable antiretroviral regimen consisting of a boosted protease inhibitor (bPI) [either darunavir once daily or atazanavir (both boosted with ritonavir or cobicistat), or lopinavir with ritonavir] combined with FTC/TDF switched to SYMTUZA, and 378 subjects who continued their treatment regimen of a bPI with FTC/TDF. Overall, the safety profile of SYMTUZA in subjects in this study was similar to that in subjects with no prior antiretroviral treatment history. The proportion of subjects who discontinued treatment with SYMTUZA due to adverse events, regardless of severity, was 1%.

Less Frequent Adverse Reactions

The following adverse reactions occurred in less than 2% of adults with no antiretroviral treatment history or virologically suppressed subjects receiving SYMTUZA, or are from studies described in the prescribing information of the individual component PREZISTA (darunavir).

Gastrointestinal Disorders: dyspepsia, pancreatitis (acute), vomiting

Skin and Subcutaneous Tissue Disorders: angioedema, pruritus, Stevens-Johnson syndrome

Metabolism and Nutrition Disorders: anorexia, diabetes mellitus, lipodystrophy

Reproductive System and Breast Disorders: gynecomastia

Musculoskeletal and Connective Tissue Disorders: myalgia, osteonecrosis

Psychiatric Disorders: abnormal dreams

Immune System Disorders: (drug) hypersensitivity, immune reconstitution inflammatory syndrome

Hepatobiliary Disorders: acute hepatitis

Laboratory Abnormalities

Table 2: Laboratory Abnormalities (Grade 2-4) Reported in ≥2% of Adults With No Prior Antiretroviral Treatment History in AMBER (Week 48 Analysis)

Laboratory Parameter Grade	Limit	SYMTUZA N=362	PREZCOBIX+FTC/TDF N=363
Creatinine			
Grade 2	>1.3 to 1.8 x ULN	4%	14%
Grade 4	≥3.5x ULN	<1%	0
Triglycerides			
Grade 2	301-500 mg/dL	7%	4%
Grade 3	501-1,000 mg/dL	1%	1%
Grade 4	>1,000 mg/dL	<1%	<1%
Total Cholesterol			
Grade 2	240-<300 mg/dL	17%	4%
Grade 3	≥ 300 mg/dL	2%	1%
Low-Density Lipoprotein Cholesterol			
Grade 2	160-189 mg/dL	9%	4%
Grade 3	≥190 mg/dL	5%	1%
Elevated Glucose Levels			
Grade 2	126-250 mg/dL	6%	6%
Grade 3	251-500 mg/dL	<1%	0

ALT and/or AST elevations (Grade 2-4 combined) occurred in 2% of adult subjects receiving SYMTUZA with no antiretroviral treatment history in AMBER (Week 48 Analysis). Results were consistent in subjects receiving PREZCOBIX+FTC/TDF.

Table 3: Lipid Values, Mean Change from Baseline, Reported in Adults With No Prior Antiretroviral Treatment History in AMBER (Week 48 Analysis)

	SYMTUZA N=362		PREZCOBIX+FTC/TDF N=363	
Mean[a]	**Baseline mg/dL**	**Week 48 Change**	**Baseline mg/dL**	**Week 48 Change**
N[b]	N=304[c]		N=290	
Total cholesterol	168	+30	164	+11
HDL cholesterol	45	+6	44	+2
LDL cholesterol	100	+19	98	+5
Triglycerides	117	+34	112	+21
Total cholesterol to HDL ratio	4.1	0.2	4.0	0.1

[a] The change from baseline is the mean of within-subject changes from baseline for subjects with both baseline and Week 48 values, or the last value carried forward prior to initiating lipid-lowering agent post-baseline.

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[b] N corresponds to the number of subjects with paired values and not on a lipid-lowering agent at screening/baseline. Subjects on lipid-lowering agents at screening/baseline were excluded from the analysis (6 out of 362 subjects on SYMTUZA, 8 out of 363 subjects on PREZCOBIX+FTC/TDF). Subjects initiating a lipid-lowering agent post-baseline had their last fasted on-treatment value (prior to starting the agent) carried forward (6 on SYMTUZA, 2 on PREZCOBIX+FTC/TDF).

[c] One subject did not have a Week 48 result for LDL cholesterol (n=303).

The percentage of subjects starting any lipid lowering drug during treatment in the SYMTUZA and PREZCOBIX + FTC/TDF arm were 1.7% (n=6) and 0.6% (n=2), respectively.

Renal Laboratory Tests

In the AMBER trial, which enrolled 725 adults with no prior antiretroviral treatment history, subjects had a median baseline eGFR (estimated glomerular filtration rate) of 119 mL/min (SYMTUZA) and 118 mL/min (PREZCOBIX + FTC/TDF). From baseline to Week 48, mean (SD) serum creatinine increased by 0.05 (0.10) mg/dL in the SYMTUZA group and by 0.09 (0.11) mg/dL in the PREZCOBIX + FTC/TDF group. Median serum creatinine was 0.90 mg/dL (SYMTUZA) and 0.89 mg/dL (PREZCOBIX + FTC/TDF) at baseline and 0.95 mg/dL (SYMTUZA) and 0.97 mg/dL (PREZCOBIX +FTC/TDF) at Week 48. Increases in serum creatinine occurred by Week 2 of treatment and remained stable. Median urine protein-to-creatinine ratio (UPCR) was 47 mg/g (SYMTUZA) and 51 mg/g (PREZCOBIX + FTC/TDF) at baseline and 30 mg/g (SYMTUZA) and 34 mg/g (PREZCOBIX + FTC/TDF) at Week 48.

In the EMERALD trial which had 1,141 virologically-suppressed adults treated with an HIV protease inhibitor and TDF containing regimen with a median baseline eGFR of 104 mL/min (SYMTUZA) and 103 mL/min (bPI+FTC/TDF) who were randomized to continue their treatment regimen or switch to SYMTUZA, at Week 48, mean serum creatinine was similar to baseline for both those continuing baseline treatment and those switching to SYMTUZA. Mean (SD) serum creatinine was 0.98 (0.18) mg/dL (SYMTUZA) and 0.98 (0.19) mg/dL (bPI+FTC/TDF) at baseline and 0.99 (0.18) mg/dL (SYMTUZA) and 0.99 (0.21) mg/dL (bPI+FTC/TDF) at Week 48. Median serum creatinine was 0.97 mg/dL (SYMTUZA) and 0.98 mg/dL (bPI+FTC/TDF) at baseline and 1.0 mg/dL (SYMTUZA) and 0.97 mg/dL (bPI+FTC/TDF) at Week 48. Median UPCR was 62 mg/g (SYMTUZA) and 63 mg/g (bPI+FTC/TDF) at baseline and 37 mg/g (SYMTUZA) and 53 mg/g (bPI+FTC/TDF) at Week 48.

Bone Mineral Density

AMBER

The effects of SYMTUZA compared to PREZCOBIX + FTC/TDF on bone mineral density (BMD) change from baseline to Week 48 were assessed by dual-energy X-ray absorptiometry (DXA). The mean percentage change in BMD from baseline to Week 48 was –0.7% with SYMTUZA compared to –2.4% with PREZCOBIX + FTC/TDF at the lumbar spine and 0.2% compared to –2.7% at the total hip. BMD declines of 5% or greater at the lumbar spine were experienced by 16% of SYMTUZA subjects and 22% of PREZCOBIX + FTC/TDF subjects. BMD declines of 7% or greater at the femoral neck were experienced by 2% of SYMTUZA subjects and 15% of PREZCOBIX + FTC/TDF subjects. The long-term clinical significance of these BMD changes is not known.

EMERALD

In EMERALD, bPI and TDF-treated subjects were randomized to continue their TDF-based regimen or switch to SYMTUZA; changes in BMD from baseline to Week 48 were assessed by DXA. The mean percentage change in BMD from baseline to Week 48 was 1.5% with SYMTUZA compared to –0.6% with bPI + FTC/TDF at the lumbar spine and 1.4% compared to -0.3% at the total hip. BMD declines of 5% or greater at the lumbar spine were experienced by 2% of SYMTUZA subjects and 9% of bPI + FTC/TDF subjects. BMD declines of 7% or greater at the femoral neck were experienced by no SYMTUZA subjects and 2% of bPI + FTC/TDF subjects. The long-term clinical significance of these BMD changes is not known.

Clinical Trials in Pediatric Patients

Adverse Reactions in Pediatric Patients Weighing At Least 40 kg

No clinical trials with SYMTUZA were performed in pediatric patients. However, the safety of the components of SYMTUZA was evaluated in pediatric subjects of 12 to less than 18 years of age through clinical trials GS-US-216-0128 (virologically-suppressed, N=7 with weight ≥40 kg) for darunavir co-administered with cobicistat and other antiretroviral agents, and GS-US-292-0106 (treatment-naïve, N=50 with weight ≥35 kg) for a fixed-dose combination regimen containing cobicistat, emtricitabine, and tenofovir alafenamide together with elvitegravir. Safety analyses of the trials in these pediatric subjects did not identify new safety concerns compared to the known safety profile of SYMTUZA in adult subjects *[see Clinical Studies (14.3)]*.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of darunavir. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Metabolism and Nutrition Disorders:

Redistribution of body fat

Musculoskeletal and Connective Tissue Disorders:

Rhabdomyolysis (associated with co-administration with HMG-CoA reductase inhibitors)

Skin and Subcutaneous Tissue Disorders:

Toxic epidermal necrolysis, acute generalized exanthematous pustulosis, drug rash with eosinophilia and systemic symptoms *[see Warnings and Precautions (5.3)]*

Renal and Urinary Disorders:

Acute renal failure, acute tubular necrosis, proximal renal tubulopathy, Fanconi syndrome *[see Warnings and Precautions (5.6)]*, crystal nephropathy, and crystalluria

7. DRUG INTERACTIONS

7.1 Not Recommended With Other Antiretroviral Medications

SYMTUZA is a complete regimen for HIV-1 infection and co-administration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended. For this reason, information regarding potential drug-drug interactions with other antiretroviral medications is not provided.

7.2 Potential for SYMTUZA to Affect Other Drugs

Darunavir co-administered with cobicistat is an inhibitor of CYP3A and CYP2D6. Cobicistat inhibits the following transporters: P-glycoprotein (P-gp), BCRP, MATE1, OATP1B1 and OATP1B3. Therefore, co-administration of SYMTUZA with drugs that are primarily metabolized by CYP3A and/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 can be associated with adverse events. Co-administration of SYMTUZA with drugs that have active metabolite(s) formed by CYP3A may result in reduced plasma concentrations of these active metabolite(s), potentially leading to loss of their therapeutic effect (see Table 4).

7.3 Potential for Other Drugs to Affect SYMTUZA

Darunavir is metabolized by CYP3A. Cobicistat is metabolized by CYP3A and, to a minor extent, by CYP2D6. Co-administration of drugs that induce CYP3A activity are expected to increase the clearance of darunavir and cobicistat, resulting in lowered plasma concentrations which may lead to loss of therapeutic effect and development of resistance. Co-administration of SYMTUZA with other drugs that inhibit CYP3A may result in increased plasma concentrations of darunavir and cobicistat (see Table 4).

Tenofovir alafenamide (TAF) is a substrate of P-gp, BCRP, OATP1B1, and OATP1B3. Drugs that strongly affect P-gp activity may lead to changes in TAF absorption. Drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentrations of TAF, which may lead to loss of therapeutic effect of SYMTUZA and development of resistance. Co-administration of SYMTUZA with other drugs that inhibit P-gp may increase the absorption and plasma concentrations of TAF (see Table 4).

7.4 Drugs Affecting Renal Function

Because emtricitabine and tenofovir are primarily excreted by the kidneys through glomerular filtration and active tubular secretion, co-administration of SYMTUZA with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of emtricitabine, tenofovir, and other renally eliminated drugs and this may increase the risk of adverse reactions. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs *[see Warnings and Precautions (5.6)]*.

7.5 Significant Drug Interactions

Table 4 provides examples of established or potentially clinically significant drug interactions with SYMTUZA and recommended steps to prevent or manage these interactions. These recommendations are based on drug interaction trials conducted with the components of SYMTUZA, as individual agents or in combination, or are predicted interactions. No drug interaction trials have been performed with SYMTUZA or with all the components administered together. Drug interaction trials have been conducted with darunavir co- administered with ritonavir or cobicistat or with emtricitabine and tenofovir prodrugs. The table includes potentially significant interactions but is not all inclusive, and therefore the label of each drug that is co-administered with SYMTUZA should be consulted for information related to the route of metabolism, interaction pathways, potential risks, and specific actions to be taken with regard to co- administration.

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Table 4: Significant Drug Interactions

Concomitant Drug Class: Drug Name Examples	Effect on Concentration	Clinical Comment
Alpha 1-adrenoreceptor antagonist: alfuzosin	↑ alfuzosin	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as hypotension.
Antibacterials: clarithromycin, erythromycin, telithromycin	↑ darunavir ↑ cobicistat ↑ antibacterial	Consider alternative antibiotics with concomitant use of SYMTUZA.
Anticancer agents: dasatinib, nilotinib	↑ anticancer agent	A decrease in the dosage or an adjustment of the dosing interval of dasatinib or nilotinib may be necessary when co-administered with SYMTUZA. Consult the dasatinib and nilotinib prescribing information for dosing instructions.
vinblastine, vincristine		For vincristine and vinblastine, consider temporarily withholding the cobicistat-containing antiretroviral regimen in patients who develop significant hematologic or gastrointestinal side effects when SYMTUZA is administered concurrently with vincristine or vinblastine. If the antiretroviral regimen must be withheld for a prolonged period, consider initiating a revised regimen that does not include a CYP3A or P-gp inhibitor.
Anticoagulants: Direct Oral Anticoagulants (DOACs) apixaban	↑ apixaban	Due to potentially increased bleeding risk, dosing recommendations for co-administration of apixaban with SYMTUZA depend on the apixaban dose. Refer to apixaban dosing instructions for co-administration with P-gp and strong CYP3A inhibitors in apixaban prescribing information.
rivaroxaban	↑ rivaroxaban	Co-administration of rivaroxaban with SYMTUZA is not recommended because it may lead to an increased bleeding risk.
dabigatran etexilate edoxaban	↑ dabigatran ↑ edoxaban	Refer to the dabigatran etexilate or edoxaban prescribing information for recommendations regarding co-administration. The specific recommendations are based on indication, renal function, and effect of the co-administered P-gp inhibitors on the concentration of dabigatran or edoxaban. Clinical monitoring is recommended when a DOAC not affected by CYP3A4 but transported by P-gp, including dabigatran etexilate and edoxaban, is co-administered with SYMTUZA.
Other Anticoagulants warfarin	warfarin: effect unknown	Monitor international normalized ratio (INR) upon co-administration of SYMTUZA with warfarin.
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ cobicistat ↓ darunavir ↓ tenofovir alafenamide	Co-administration is contraindicated due to potential for loss of therapeutic effect and development of resistance.
Anticonvulsants with CYP3A induction effects that are NOT contraindicated: e.g., eslicarbazepine, oxcarbazepine	↓ cobicistat ↓ tenofovir alafenamide darunavir: effect unknown	Consider alternative anticonvulsant or antiretroviral therapy to avoid potential changes in exposures. If co-administration is necessary, monitor for lack or loss of virologic response.
Anticonvulsants that are metabolized by CYP3A: e.g., clonazepam	↑ clonazepam	Clinical monitoring of anticonvulsants is recommended.

Table 4: Significant Drug Interactions (continued)

Concomitant Drug Class: Drug Name Examples	Effect on Concentration	Clinical Comment
Antidepressants: Selective Serotonin Reuptake Inhibitors (SSRIs): e.g., paroxetine, sertraline	SSRIs: effects unknown	When co-administering with SSRIs, TCAs, or trazodone, careful dose titration of the antidepressant to the desired effect, including using the lowest feasible initial or maintenance dose, and monitoring for antidepressant response are recommended.
Tricyclic Antidepressants (TCAs): e.g., amitriptyline, desipramine, imipramine, nortriptyline	↑ TCAs	
Other antidepressants: trazodone	↑ trazodone	
Antifungals: itraconazole, isavuconazole, ketoconazole, posaconazole	↑ darunavir ↑ cobicistat	Monitor for increased darunavir or cobicistat and/or antifungal adverse reactions.
	↑ itraconazole ↑ isavuconazole ↑ ketoconazole ↔ posaconazole (not studied)	Specific dosing recommendations are not available for co-administration with these antifungals. Monitor for increased itraconazole or ketoconazole adverse reactions.
voriconazole	voriconazole: effects unknown	Co-administration with voriconazole is not recommended unless benefit/risk assessment justifies the use of voriconazole.
Anti-gout: colchicine	↑ colchicine	Co-administration is contraindicated in patients with renal and/or hepatic impairment due to potential for serious and/or life-threatening reactions. For patients without renal or hepatic impairment: • Treatment of gout flares – co-administration of colchicine: 0.6 mg (1 tablet) ×1 dose, followed by 0.3 mg (half tablet) 1 hour later. Treatment course to be repeated no earlier than 3 days. • Prophylaxis of gout flares – co-administration of colchicine: If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day. If the original regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day. • Treatment of familial Mediterranean fever – co-administration of colchicine: Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
Antimalarial: artemether/ lumefantrine	artemether: effect unknown lumefantrine: effect unknown	Monitor for a potential decrease of antimalarial efficacy or potential QT prolongation.

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Table 4: Significant Drug Interactions (continued)

Concomitant Drug Class: Drug Name Examples	Effect on Concentration	Clinical Comment
Antimycobacterials: rifampin	↓ cobicistat ↓ darunavir ↓ tenofovir alafenamide	Co-administration is contraindicated due to potential for loss of therapeutic effect and development of resistance.
rifabutin	↑ rifabutin ↓ TAF cobicistat: effects unknown darunavir: effects unknown	Co-administration of SYMTUZA with rifabutin is not recommended. If the combination is needed, the recommended dose of rifabutin is 150 mg every other day. Monitor for rifabutin-associated adverse reactions including neutropenia and uveitis.
rifapentine	↓ darunavir ↓ TAF	Co-administration with rifapentine is not recommended.
Antipsychotics: lurasidone	↑ lurasidone	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions.
pimozide	↑ pimozide	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
e.g., perphenazine, risperidone, thioridazine	↑ antipsychotic	A decrease in the dose of antipsychotics that are metabolized by CYP3A or CYP2D6 may be needed when co-administered with SYMTUZA.
quetiapine	↑ quetiapine	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.
β-Blockers: e.g., carvedilol, metoprolol, timolol	↑ beta-blockers	Clinical monitoring is recommended for co-administration with beta-blockers that are metabolized by CYP2D6.
Calcium channel blockers: e.g., amlodipine, diltiazem, felodipine, nifedipine, verapamil	↑ calcium channel blockers	Clinical monitoring is recommended for co-administration with calcium channel blockers metabolized by CYP3A.

Table 4: Significant Drug Interactions (continued)

Concomitant Drug Class: Drug Name Examples	Effect on Concentration	Clinical Comment
Cardiac Disorders: ranolazine, ivabradine	↑ ranolazine	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions.
dronedarone	↑ dronedarone	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias
Other antiarrhythmics e.g., amiodarone, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine	↑ antiarrhythmics	Clinical monitoring is recommended upon co-administration with antiarrhythmics.
digoxin	↑ digoxin	When co-administering with digoxin, titrate the digoxin dose and monitor digoxin concentrations.
Corticosteroids: dexamethasone (systemic)	↓ darunavir ↓ cobicistat	Co-administration with systemic dexamethasone or other systemic corticosteroids that induce CYP3A may result in loss of therapeutic effect and development of resistance to SYMTUZA. Consider alternative corticosteroids.
Corticosteroids primarily metabolized by CYP3A: e.g., betamethasone budesonide ciclesonide fluticasone methylprednisolone mometasone triamcinolone	↑ corticosteroids	Co-administration with corticosteroids (all routes of administration) of which exposures are significantly increased by strong CYP3A inhibitors can increase the risk for Cushing's syndrome and adrenal suppression. Alternative corticosteroids including beclomethasone, prednisone, and prednisolone (for which PK and/or PD are less affected by strong CYP3A inhibitors relative to other steroids) should be considered, particularly for long term use.
Endothelin receptor antagonists: bosentan	↓ darunavir ↓ cobicistat ↑ bosentan	Initiation of bosentan in patients taking SYMTUZA: In patients who have been receiving SYMTUZA for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability. Initiation of SYMTUZA in patients on bosentan: Discontinue use of bosentan at least 36 hours prior to initiation of SYMTUZA. After at least 10 days following the initiation of SYMTUZA, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability. Switching from darunavir co-administered with ritonavir to SYMTUZA in patients on bosentan: Maintain bosentan dose.

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Table 4: Significant Drug Interactions (continued)

Concomitant Drug Class: Drug Name Examples	Effect on Concentration	Clinical Comment
Ergot derivatives: e.g., dihydroergotamine, ergotamine, methylergonovine	↑ ergot derivatives	Co-administration is 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.
Hepatitis C virus (HCV): Direct-Acting Antivirals: elbasvir/grazoprevir	↑ elbasvir/grazoprevir	Co-administration is contraindicated due to potential for the increased risk of alanine transaminase (ALT) elevations.
glecaprevir/pibrentasvir	↑ glecaprevir ↑ pibrentasvir	Co-administration of SYTMUZA with glecaprevir/pibrentasvir is not recommended.
Herbal product: St. John's wort (*Hypericum perforatum*)	↓ cobicistat ↓ darunavir ↓ tenofovir alafenamide	Co-administration is contraindicated due to potential for loss of therapeutic effect and development of resistance.
Hormonal contraceptives:		Additional or alternative (non-hormonal) forms of contraception should be considered when estrogen based contraceptives are co-administered with SYMTUZA.
drosperinone/ethinylestradiol	↑ drosperinone ↓ ethinylestradiol	For co-administration with drospirenone, clinical monitoring is recommended due to the potential for hyperkalemia.
other progestin/estrogen contraceptives	progestin: effects unknown estrogen: effects unknown	No data are available to make recommendations on co-administration with oral or other hormonal contraceptives.
Immunosuppressants: cyclosporine, sirolimus, tacrolimus	↑ immunosuppressants	These immunosuppressant agents are metabolized by CYP3A. Therapeutic drug monitoring is recommended with concomitant use.
Immunosuppressant/neoplastic: everolimus		Co-administration of everolimus and SYMTUZA is not recommended.
irinotecan		Discontinue SYMTUZA at least 1 week prior to starting irinotecan therapy. Do not administer SYMTUZA with irinotecan unless there are no therapeutic alternatives.
Inhaled beta agonist: salmeterol	↑ salmeterol	Co-administration with salmeterol is not recommended and may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.

Table 4: Significant Drug Interactions (continued)

Concomitant Drug Class: Drug Name Examples	Effect on Concentration	Clinical Comment
Lipid modifying agents: HMG-CoA reductase inhibitors: lovastatin, simvastatin	↑ lovastatin ↑ simvastatin	Co-administration is contraindicated due to potential for serious reactions such as myopathy including rhabdomyolysis.
e.g., atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin	↑ atorvastatin ↑ fluvastatin ↑ pravastatin ↑ rosuvastatin pitavastatin: effect unknown	For atorvastatin, fluvastatin, pitavastatin, pravastatin, and rosuvastatin, start with the lowest recommended dose and titrate while monitoring for safety. Dosage recommendations with atorvastatin or rosuvastatin are as follows: • atorvastatin dosage should not exceed 20 mg/day • rosuvastatin dosage should not exceed 20 mg/day
Other lipid modifying agents: lomitapide	↑ lomitapide	Co-administration is contraindicated due to potential for markedly increased transaminases associated with increased plasma concentrations of lomitapide.
Narcotic analgesics metabolized by CYP3A: e.g., fentanyl, oxycodone	↑ fentanyl ↑ oxycodone	Careful monitoring of therapeutic effects and adverse reactions associated with CYP3A-metabolized narcotic analgesics (including potentially fatal respiratory depression) is recommended with co-administration.
tramadol	↑ tramadol	A dose decrease may be needed for tramadol with concomitant use.
Narcotic analgesic for treatment of opioid dependence: buprenorphine, buprenorphine/naloxone, methadone	buprenorphine or buprenorphine/naloxone: effects unknown methadone: effects unknown	Initiation of buprenorphine, buprenorphine/naloxone or methadone in patients taking SYMTUZA: Carefully titrate the dose of buprenorphine, buprenorphine/naloxone or methadone to the desired effect; use the lowest feasible initial or maintenance dose. Initiation of SYMTUZA in patients taking buprenorphine, buprenorphine/naloxone, or methadone: A dose adjustment for buprenorphine, buprenorphine/naloxone, or methadone may be needed. Monitor clinical signs and symptoms.
Opioid Antagonist naloxegol	↑ naloxegol	Co-administration of SYMTUZA and naloxegol is contraindicated due to potential for precipitating opioid withdrawal symptoms.

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Table 4: Significant Drug Interactions (continued)

Concomitant Drug Class: Drug Name Examples	Effect on Concentration	Clinical Comment
Phosphodiesterase PDE-5 inhibitors: e.g., avanafil, sildenafil, tadalafil, vardenafil	↑ PDE-5 inhibitors	Co-administration with avanafil is not recommended because a safe and effective avanafil dosage regimen has not been established. Co-administration with PDE-5 inhibitors may result in an increase in PDE-5 inhibitor-associated adverse reactions including hypotension, syncope, visual disturbances, and priapism. Use of PDE-5 inhibitors for pulmonary arterial hypertension (PAH): Co-administration with sildenafil used for PAH is contraindicated due to potential for sildenafil associated adverse reactions (which include visual disturbances, hypotension, prolonged erection, and syncope). The following dose adjustments are recommended for use of tadalafil with SYMTUZA: • *Initiation of tadalafil in patients taking SYMTUZA:* In patients receiving SYMTUZA for at least one week, start tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. • *Initiation of SYMTUZA in patients taking tadalafil:* Avoid use of tadalafil during the initiation of SYMTUZA. Stop tadalafil at least 24 hours prior to starting SYMTUZA. After at least one week following the initiation of SYMTUZA, resume tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. • *Patients switching from darunavir co-administered with ritonavir to SYMTUZA:* Maintain tadalafil dose. Use of PDE-5 inhibitors for erectile dysfunction: Sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg dose in 72 hours, or tadalafil at a single dose not exceeding 10 mg dose in 72 hours can be used with increased monitoring for PDE-5 inhibitor-associated adverse reactions.
Platelet aggregation inhibitor: ticagrelor	↑ticagrelor	Co-administration of SYMTUZA and ticagrelor is not recommended.
clopidogrel	↓ clopidogrel active metabolite	Co-administration of SYMTUZA and clopidogrel is not recommended due to potential reduction of the antiplatelet activity of clopidogrel.
prasugrel	↔ prasugrel active metabolite	No dose adjustment is needed when prasugrel is co-administered with SYMTUZA.

Table 4: Significant Drug Interactions (continued)

Concomitant Drug Class: Drug Name Examples	Effect on Concentration	Clinical Comment
Sedatives/hypnotics: orally administered midazolam, triazolam	↑ midazolam ↑ triazolam	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
metabolized by CYP3A: e.g., buspirone, diazepam, estazolam, zolpidem	↑ sedatives/ hypnotics	With concomitant use, titration is recommended with sedatives/ hypnotics metabolized by CYP3A and a lower dose of the sedatives/ hypnotics should be considered with monitoring for increased and prolonged effects or adverse reactions.
parenterally administered midazolam		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.
Urinary antispasmodics fesoterodine	↑ fesoterodine	When fesoterodine is co-administered with SYMTUZA, do not exceed a fesoterodine dose of 4 mg once daily.
solifenacin	↑ solifenacin	When solifenacin is co-administered with SYMTUZA, do not exceed a solifenacin dose of 5 mg once daily.

This table is not all inclusive
↑ = increase, ↓ = decrease, ↔ = no effect

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to SYMTUZA during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

SYMTUZA is not recommended during pregnancy because of substantially lower exposures of darunavir and cobicistat during the second and third trimesters *[see Dosage and Administration (2.5)]*. A study evaluating the pharmacokinetics of antiretrovirals during pregnancy demonstrated substantially lower exposures of darunavir and cobicistat in the second and third trimesters compared to the post-partum period *(see Data)* and *[see Clinical Pharmacology (12.3)]*.

Prospective pregnancy data from the APR are not sufficient to adequately assess the risk of birth defects or miscarriage. However, available data from the APR show no statistically significant difference in the overall risk of major birth defects for darunavir, cobicistat, emtricitabine, or tenofovir alafenamide (TAF) compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) *(see Data)*. The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15-20%. The background risk of major birth defects and miscarriage for the indicated population is unknown.

In animal reproduction studies, no adverse developmental effects were observed when the components of SYMTUZA were administered separately at darunavir exposures less than 1- (mice and rabbits) and 2.6-times (rats) higher, at cobicistat exposures 1.7- and 4.1-times higher (rats and rabbits respectively), at emtricitabine exposures 88- and 7.3- times higher (mice and rabbits, respectively), and tenofovir alafenamide exposures equal to or 85- times higher (rats and rabbits, respectively) than human exposures at the recommended daily dose of these components in SYMTUZA *(see Data)*. No adverse developmental effects were seen when cobicistat was administered to rats through lactation at cobicistat exposures up to 1.1 times the human exposure at the recommended therapeutic dose.

Clinical Considerations

Not Recommended During Pregnancy

SYMTUZA is not recommended for use during pregnancy because of substantially lower exposures of darunavir and cobicistat during pregnancy *(see Data)* and *[see Clinical Pharmacology (12.3)]*.

SYMTUZA should not be initiated in pregnant individuals. An alternative regimen is recommended for individuals who become pregnant during therapy with SYMTUZA.

SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets

Data

Human Data

Darunavir and cobicistat in combination with a background regimen was evaluated in a clinical trial of 7 pregnant individuals taking darunavir and cobicistat prior to enrollment and who were willing to remain on darunavir and cobicistat throughout the study. The study period included the second and third trimesters, and through 12 weeks postpartum. Six pregnant individuals completed the trial.

Exposure to darunavir and cobicistat as part of an antiretroviral regimen was substantially lower during the second and third trimesters of pregnancy compared with postpartum *[see Clinical Pharmacology (12.3)]*.

One out of 6 pregnant individuals 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 pregnant individuals had sustained virologic response (HIV RNA <50 copies/mL) throughout the study period. There are no clinical data on the virologic response when darunavir and cobicistat are initiated during pregnancy.

Prospective reports from the APR of overall major birth defects in pregnancies exposed to the components of SYMTUZA are compared with a U.S. background major birth defect rate. Methodological limitations of the APR include the use of MACDP as the external comparator group. Limitations of using an external comparator include differences in methodology and populations, as well as confounding due to the underlying disease.

Darunavir: Based on prospective reports to the APR of over 960 exposures to darunavir-containing regimens during pregnancy resulting in live births (including over 640 exposed in the first trimester and over 320 exposed in the second/third trimester), the prevalence of birth defects in live births was 3.7% (95% CI: 2.4% to 5.5%) with first trimester exposure to darunavir containing-regimens and 2.5% (95% CI: 1.1% to 4.9%) with second/third trimester exposure to darunavir-containing regimens.

Cobicistat: Based on prospective reports to the APR of over 560 exposures to cobicistat-containing regimens during pregnancy resulting in live births (including over 470 exposed in the first trimester and over 80 exposed in the second/third trimester), the prevalence of birth defects in live births was 3.6% (95% CI: 2.1% to 5.7%) and 1.1% (95% CI: 0.0% to 6.2%) with first and second/third trimester, respectively, to cobicistat-containing regimens.

Emtricitabine: Based on prospective reports to the APR of over 5400 exposures to emtricitabine-containing regimens during pregnancy resulting in live births (including over 3900 exposed in the first trimester and over 1500 exposed in the second/third trimester), the prevalence of birth defects in live births was 2.6% (95% CI: 2.2% to 3.2%) with first trimester exposure to emtricitabine-containing regimens and 2.7% (95% CI: 1.9% to 3.7%) with the second/third trimester exposure to emtricitabine-containing regimens.

Tenofovir alafenamide (TAF): Based on prospective reports to the APR of over 660 exposures to TAF-containing regimens during pregnancy resulting in live births (including over 520 exposed in the first trimester and over 130 exposed in the second/third trimester), the prevalence of birth defects in live births was 4.2% (95% CI: 2.6% to 6.3%) and 3.0% (95% CI: 0.8% to 7.5%) with first and second/third trimester exposure, respectively, to TAF-containing regimens.

Animal Data

Darunavir: Reproduction studies conducted with darunavir showed no embryotoxicity or teratogenicity in mice (doses up to 1000 mg/kg from gestation day (GD) 6-15 with darunavir alone) and rats (doses up to 1000 mg/kg from GD 7-19 in the presence or absence of ritonavir) as well as in rabbits (doses up to 1000 mg/kg/day from GD 8-20 with darunavir alone). In these studies, darunavir exposures (based on AUC) were higher in rats (2.6-fold), whereas in mice and rabbits, exposures were lower (less than 1-fold) compared to those obtained in humans at the recommended daily dose of darunavir in SYMTUZA.

Cobicistat: Cobicistat was administered orally to pregnant rats at doses up to 125 mg/kg/day on GD 6-17. Increases in post-implantation loss and decreased fetal weights were observed at a maternal toxic dose of 125 mg/kg/day. No malformations were noted at doses up to 125 mg/kg/day. Systemic exposures (AUC) at 50 mg/kg/day in pregnant females were 1.7 times higher than human exposures at the recommended daily dose of cobicistat in SYMTUZA.

In pregnant rabbits, cobicistat was administered orally at doses up to 100 mg/kg/day during GD 7-20. No maternal or embryo/fetal effects were noted at the highest dose of 100 mg/kg/day. Systemic exposures (AUC) at 100 mg/kg/day were 4.1 times higher than human exposures at the recommended daily dose of cobicistat in SYMTUZA.

In a pre/postnatal developmental study in rats, cobicistat was administered orally at doses up to 75 mg/kg from GD 6 to postnatal day 20, 21, or 22. At doses of 75 mg/kg/day, neither maternal nor developmental toxicity was noted. Systemic exposures (AUC) at this dose were 1.1 times the human exposures at the recommended daily dose of cobicistat in SYMTUZA.

Emtricitabine: Emtricitabine was administered orally to pregnant mice and rabbits (up to 1000 mg/kg/day) through organogenesis (on GD 6 through 15, and 7 through 19, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with emtricitabine in mice at exposures approximately 88 times higher and in rabbits approximately 7.3 times higher than human exposures at the recommended daily dose of emtricitabine in SYMTUZA.

In a pre/postnatal development study, mice were administered doses up to 1000 mg/kg/day; no significant adverse effects directly related to drug were observed in the offspring exposed daily from before birth (*in utero*) through sexual maturity at daily exposures of approximately 88 times higher than human exposures at the recommended daily dose of emtricitabine in SYMTUZA.

Tenofovir Alafenamide (TAF): TAF was administered orally to pregnant rats (up to 250 mg/kg/day) and rabbits (up to 100 mg/kg/day) through organogenesis (on GD 6 through 17, and 7 through 20, respectively). No adverse embryo-fetal effects were observed in rats and rabbits at TAF exposures approximately similar to (rats) and 85 times higher (rabbits) than the exposure in humans at the recommended daily dose. TAF is rapidly converted to tenofovir; the observed tenofovir exposure in rats and rabbits were 51 (rats) and 80 (rabbits) times higher than human tenofovir exposures at the recommended daily dose of TAF in SYMTUZA.

Since TAF is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice was observed after TAF administration compared to TDF (another prodrug of tenofovir) administration, a pre/postnatal development study in rats was conducted only with TDF. Doses up to 600 mg/kg/day were administered through lactation; no adverse effects were observed in the offspring on GD 7 [and lactation day 20] at tenofovir exposures of approximately 14 [21] times higher than the exposure in humans at the recommended daily dose of TDF.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-infected mothers in the United States must not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

Based on published data, emtricitabine has been shown to be present in human breast milk. There are no data on the presence of darunavir, cobicistat, or TAF in human milk, the effects on the breastfed infant, or the effects on milk production. Darunavir and cobicistat are present in the milk of lactating rats. Tenofovir has been shown to be present in the milk of lactating rats and rhesus monkeys after administration of TDF *(see Data).* Because of the potential for (1) HIV transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) serious adverse reactions in breastfed infants, instruct mothers not to breastfeed if they are receiving SYMTUZA.

Data

Animal Data

Darunavir: Studies in rats (with darunavir alone or with ritonavir) have demonstrated that darunavir is excreted in milk. In the rat pre- and post-natal development study, a reduction in pup body weight gain was observed due to exposure of pups to drug substances via milk. The maximal maternal plasma exposures achieved with darunavir (up to 1000 mg/kg with ritonavir) were approximately 66% of those obtained in humans at the recommended clinical dose of darunavir with ritonavir.

Cobicistat: During the pre/postnatal developmental toxicology study, at doses up to 75 mg/kg/day, mean cobicistat milk to plasma ratio of up to 1.9 was measured 2 hours after administration to rats on lactation day 10.

Tenofovir Alafenamide: Studies in rats and monkeys have demonstrated that tenofovir is excreted in milk. Tenofovir was excreted into the milk of lactating rats following oral administration of TDF (up to 600 mg/kg/day) at up to approximately 24% of the median plasma concentration in the highest dosed animals at lactation day 11. Tenofovir was excreted into the milk of lactating rhesus monkeys, following a single subcutaneous (30 mg/kg) dose of tenofovir at concentrations up to approximately 4% of plasma concentration resulting in exposure (AUC) of approximately 20% of plasma exposure.

8.4 Pediatric Use

The safety and effectiveness of SYMTUZA for the treatment of HIV-1 infection in pediatric patients weighing at least 40 kg was established through studies with components of SYMTUZA. Use of SYMTUZA in this group is supported by evidence from adequate and well-controlled studies of SYMTUZA in adults with additional pharmacokinetic, safety, and virologic data from studies of components of SYMTUZA (Trials GS-US-216-0128 and GS-US-292-0106) in pediatric subjects with HIV-1 infection aged 12 to less than 18 years *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.3)].*

The safety and effectiveness of SYMTUZA have not been established in pediatric patients weighing less than 40 kg.

Darunavir, a component of SYMTUZA is not recommended in pediatric patients below 3 years of age because of toxicity and mortality observed in juvenile rats dosed with darunavir.

Juvenile Animal Toxicity Data

Darunavir: In a juvenile toxicity study where rats were directly dosed with darunavir (up to 1000 mg/kg), deaths occurred from post-natal day 5 at plasma exposure levels ranging from 0.1 to 1.0 of the human exposure levels. In a 4-week rat toxicology study, when dosing was initiated on post-natal day 23 (the human equivalent of 2 to 3 years of age), no deaths were observed with a plasma exposure (in combination with ritonavir) 2 times the human plasma exposure levels.

8.5 Geriatric Use

Clinical trials of SYMTUZA included 35 subjects aged above 65 years of which 26 received SYMTUZA. No differences in safety or efficacy have been observed between elderly subjects and those aged 65 years or less. In general, caution should be exercised in the administration and monitoring of SYMTUZA in elderly patients, reflecting the greater frequency of decreased hepatic function and of concomitant disease or other drug therapy *[see Clinical Pharmacology (12.3)].*

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8.6 Renal Impairment

SYMTUZA is not recommended in patients with severe renal impairment (creatinine clearance below 30 mL per minute). No dosage adjustment of SYMTUZA is required in patients with creatinine clearance greater than or equal to 30 mL per minute *[see Clinical Pharmacology (12.3)].*

Cobicistat has been shown to decrease creatinine clearance without affecting actual renal glomerular function. Dosing recommendations are not available for drugs that require dosage adjustment for renal impairment when used in combination with SYMTUZA *[see Warnings and Precautions (5.6)].*

8.7 Hepatic Impairment

No dosage adjustment of SYMTUZA is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. 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. Therefore, SYMTUZA is not recommended for use in patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)].*

10. OVERDOSAGE

Human experience of acute overdose with SYMTUZA is limited. 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 bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis. Hemodialysis treatment removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. It is not known whether emtricitabine or tenofovir can be removed by peritoneal dialysis.

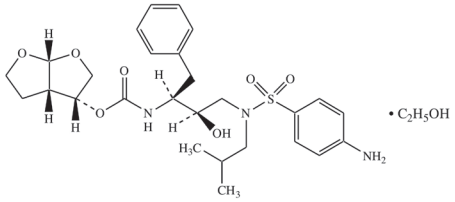
11. DESCRIPTION

SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) is a fixed-dose combination tablet.

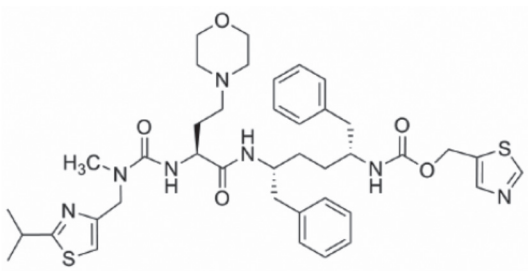
- Darunavir is an inhibitor of the HIV-1 protease.
- Cobicistat is a mechanism-based inhibitor of cytochrome P450 (CYP) enzymes of the CYP3A family.
- Emtricitabine, a synthetic nucleoside analog of cytidine, is an HIV nucleoside analog reverse transcriptase inhibitor (HIV NRTI).
- Tenofovir alafenamide, an HIV NRTI, is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate.

SYMTUZA tablets are for oral administration. Each tablet contains darunavir ethanolate equivalent to 800 mg of darunavir, 150 mg of cobicistat, 200 mg of emtricitabine, and 11.2 mg of tenofovir alafenamide fumarate equivalent to 10 mg of tenofovir alafenamide. The tablets include the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing polyethylene glycol (macrogol), polyvinyl alcohol (partially hydrolyzed), talc, titanium dioxide, and yellow ferric oxide.

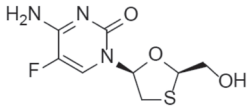
Darunavir: Darunavir, in the form of darunavir ethanolate, has the following chemical name: [(1*S*,2*R*)-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-yl ester monoethanolate. Its molecular formula is $C_{27}H_{37}N_3O_7S \bullet C_2H_5OH$ and its molecular weight is 593.73. Darunavir ethanolate has the following structural formula:



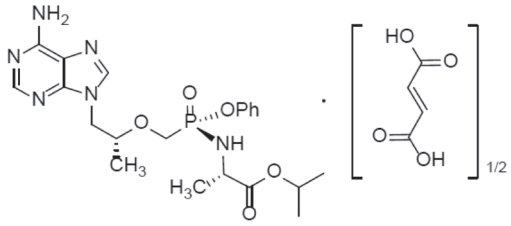
Cobicistat: Cobicistat is adsorbed onto silicon dioxide. The chemical name for cobicistat is 1,3-thiazol-5-ylmethyl[(2*R*,5*R*)-5-{[(2*S*)-2-[(methyl{[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl}carbamoyl)amino]-4-(morpholin-4yl)butanoyl]amino}-1,6-diphenylhexan-2-yl]carbamate. It has a molecular formula of $C_{40}H_{53}N_7O_5S_2$ and a molecular weight of 776.02. It has the following structural formula:



Emtricitabine: The chemical name of emtricitabine is 4-amino-5-fluoro-1-(2*R*-hydroxymethyl-[1,3]-oxathiolan-5*S*-yl)-(1H)-pyrimidin-2-one. Emtricitabine is the (-)enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5 position. Emtricitabine has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24. It has the following structural formula:



Tenofovir alafenamide: The chemical name of tenofovir alafenamide fumarate drug substance is L-alanine, *N*-[(*S*)-[[(1*R*)-2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy] methyl]phenoxyphosphinyl]-,1-methylethyl ester, (2*E*)-2-butenedioate (2:1). Tenofovir alafenamide fumarate has a molecular formula of $C_{21}H_{29}O_5N_6P \bullet ½(C_4H_4O_4)$ and a formula weight of 534.50. It has the following structural formula:



12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

SYMTUZA is a fixed-dose combination of antiretroviral drugs darunavir (plus the CYP3A inhibitor cobicistat), emtricitabine, and tenofovir alafenamide *[see Microbiology (12.4)].*

12.2 Pharmacodynamics

Cardiac Electrophysiology

Thorough QT trials have been conducted for darunavir, cobicistat, and tenofovir alafenamide. The effect of emtricitabine or the combination regimen SYMTUZA on the QT interval has not been evaluated.

Darunavir: In a thorough QT/QTc study in 40 healthy subjects, darunavir doses (co-administered with 100 mg ritonavir) of approximately 2 times the recommended darunavir dose did not affect the QT/QTc interval.

Cobicistat: In a thorough QT/QTc study in 48 healthy subjects, a single dose of cobicistat 250 mg and 400 mg (1.67 and 2.67 times the dose in SYMTUZA) did not affect the QT/QTc interval. Prolongation of the PR interval was noted in subjects receiving cobicistat. The maximum mean (95% upper confidence bound) difference in PR from placebo after baseline-correction was 9.5 (12.1) msec for the 250 mg cobicistat dose and 20.2 (22.8) for the 400 mg cobicistat dose. Because the 150 mg cobicistat dose used in the SYMTUZA fixed-dose combination tablet is lower than the lowest dose studied in the thorough QT study, it is unlikely that treatment with SYMTUZA will result in clinically relevant PR prolongation.

Tenofovir alafenamide: In a thorough QT/QTc study in 48 healthy subjects, tenofovir alafenamide at the recommended dose or at a dose approximately 5 times the recommended 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 trial in subjects with normal renal function ($eGFR_{CG}$ ≥80 mL/min, N=12) and mild-to-moderate renal impairment ($eGFR_{CG}$ 50-79 mL/min, N=18). A statistically significant decrease from baseline in the estimated glomerular filtration rate calculated by Cockcroft-Gault method ($eGFR_{CG}$) 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). No statistically significant changes in $eGFR_{CG}$ were observed compared to baseline for subjects with normal renal function or mild-to-moderate renal impairment 7 days after cobicistat was discontinued. The actual glomerular filtration rate, as determined by the clearance of probe drug iohexol, was not altered from baseline during treatment with cobicistat among subjects with normal renal function and mild-to-moderate renal impairment, indicating that cobicistat inhibits tubular secretion of creatinine, reflected as a reduction in $eGFR_{CG}$, without affecting the actual glomerular filtration rate.

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12.3 Pharmacokinetics

Absorption, Distribution, Metabolism, and Excretion

The bioavailability of the components of SYMTUZA was not affected when administered orally as a split tablet compared to administration as a tablet swallowed whole.

Pharmacokinetic (PK) properties and PK parameters of the components of SYMTUZA are provided in Table 5 and Table 6, respectively.

Table 5: Pharmacokinetic Properties of the Components of SYMTUZA

	Darunavir	Cobicistat	Emtricitabine	TAF
Absorption				
T_{max} (h)	3.0	3.0	1.5	0.5
Effect of high-fat meal[a] (compared to fasting)				
AUC_{last} LS mean ratio, 90% CI	1.52 (1.32-1.76)	1.41 (1.02-1.96)	1.00 (0.96-1.04)	1.12 (1.01-1.23)
C_{max} LS mean ratio, 90% CI	1.82 (1.55-2.14)	1.30 (0.94-1.80)	0.79 (0.71-0.89)	0.55 (0.42-0.71)
Distribution				
% bound to human plasma proteins	95[b]	97-98	<4	~80
Source of protein binding data	*In vitro*	*In vitro*	*In vitro*	*Ex vivo*
Blood-to-plasma ratio	0.64	0.5	0.6	1.0
Metabolism				
Metabolism	CYP3A	CYP3A (major) CYP2D6 (minor)	Not significantly metabolized	Cathepsin A[c] (PBMCs) CES1 (hepatocytes) CYP3A (minimal)
Elimination				
$t_{1/2}$ (h)	9.4	3.2	7.5	0.5[d]
Major route of elimination	Metabolism	Metabolism	Glomerular filtration and active tubular secretion	Metabolism (>80% of oral dose)
% of dose excreted in feces[e]	79.5[f]	86.2	13.7	31.7
% of dose excreted in urine[e]	13.9[f]	8.2	70	<1

PBMCs = peripheral blood mononuclear cells; CES-1 = carboxylesterase-1

[a] Approximately 928 kcal; 504 kcal from fat (56 g), 260 kcal from carbohydrates, and 164 kcal from protein.

[b] Primarily alpha-1-acid glycoprotein

[c] *In vivo*, TAF is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. *In vitro* studies have shown that TAF is metabolized to tenofovir by cathepsin A in PBMCs and macrophages; and by CES1 in hepatocytes. Upon co-administration with the moderate CYP3A inducer probe efavirenz, TAF exposure was unaffected.

[d] Note that the pharmacologically active metabolite tenofovir diphosphate has a half-life of 150-180 hours within PBMCs. Tenofovir in plasma has a median elimination half-life of approximately 44 hours.

[e] Dosing in mass balance studies: darunavir (single dose administration of [^{14}C] darunavir co-administered with multiple dose ritonavir 100 mg); cobicistat (single dose administration of [^{14}C] cobicistat after multiple dosing of cobicistat for six days); emtricitabine (single dose administration of [^{14}C] emtricitabine after multiple dosing of emtricitabine for ten days); TAF (single dose administration of [^{14}C] TAF).

[f] Unchanged darunavir accounted for approximately 41.2% and 7.7% of the administered dose in feces and urine, respectively.

Table 6: Steady State Pharmacokinetic Parameters of Darunavir, Cobicistat, Emtricitabine, Tenofovir Alafenamide (TAF) and its Metabolite Tenofovir Following Oral Administration of SYMTUZA with Food in HIV-Infected Adults

Parameter Mean (SD)	Darunavir		Cobicistat[a]	Emtricitabine[a]	TAF	Tenofovir[a]
C_{max}, ng/mL	8826 (33.3)[a]		1129 (35.3)	2056 (25.3)	163 (51.9)[a]	18.8 (37.6)
AUC_{24h}, ng.h/mL	87909 (20232)[b]	85972 (22413)[c]	8745 (43.9)	11918.0 (35.9)	132 (41)[b]	339 (37.1)
C_{0h}, ng/mL	1899 (759)[b]	1813 (859)[c]	31 (135)	93.1 (58.3)	NA	11.7 (39.3)

[a] From Phase 2 PK substudy (N=21)

[b] From population PK analysis in SYMTUZA Phase 3 study TMC114FD2HTX3001 in ARV naïve subjects (N=355)

[c] From population PK analysis in SYMTUZA Phase 3 study TMC114IFD3013 in ARV experienced subjects (N=750)

Specific Populations

Geriatric Patients

Darunavir: Pharmacokinetic analysis in HIV-infected subjects taking darunavir co-administered with cobicistat, emtricitabine, and tenofovir alafenamide showed no considerable differences in darunavir pharmacokinetics for ages below or equal to 65 years compared to ages greater than 65 years (N=25).

Cobicistat and Emtricitabine: The pharmacokinetics of cobicistat and emtricitabine have not been fully evaluated in the elderly (65 years of age and older).

Tenofovir alafenamide Population pharmacokinetics analysis of HIV-infected subjects in Phase 2 and Phase 3 trials of TAF combined with emtricitabine, elvitegravir, and cobicistat showed that age did not have a clinically relevant effect on exposures of TAF up to 75 years of age.

Pediatric Patients Weighing at Least 40 kg

Available pharmacokinetic data for the different components of SYMTUZA indicate that there were no clinically relevant differences in exposure between adults and pediatric subjects weighing at least 40 kg.

Darunavir and cobicistat: In pediatric subjects aged 12 to less than 18 years, weighing at least 40 kg who received darunavir 800 mg co-administered with cobicistat 150 mg (N=7), geometric mean darunavir C_{max} values were similar between adults and pediatric subjects. Geometric mean darunavir AUC_{24h} and C_{24h} values were 15% and 32% lower, with geometric mean ratios of 0.85 (90% CI: 0.64, 1.13) and 0.68 (90% CI: 0.30, 1.55) in pediatric subjects relative to adults, respectively. These differences were not considered clinically significant. Geometric mean cobicistat AUC_{24h}, C_{max}, and C_{24h} values were comparable in pediatric subjects and adults (Table 7).

Table 7: Multiple-Dose PK Parameters of Darunavir and Cobicistat Following Administration of Darunavir with Cobicistat in HIV 1 Infected Adults and Pediatric Subjects Weighing at least 40 kg[a]

Parameter Geometric mean (CV%)	Darunavir	Cobicistat
Pediatric Subjects[a]	N=7	N=7
AUC_{24h} (mcg.hr/mL)	77.22 (29.5)	8.33 (34.9)
C_{max} (mcg/mL)	7.32 (21.7)	1.10 (20.0)
C_{24h} (mcg/mL)	0.68 (91.6)	0.02 (123.9)[b]
Adults[c]	N=21	N=21
AUC_{24h} (mcg.hr/mL)	90.56 (45.3)	7.69 (43.9)
C_{max} (mcg/mL)	8.34 (33.3)	1.04 (35.3)
C_{24h} (mcg/mL)	1.00 (108.0)	0.02 (135.1)[d]

CV = Coefficient of Variation; mcg = microgram

[a] From intensive PK analysis of trial GS-US-216-0128, where HIV-infected subjects were administered darunavir 800 mg and cobicistat 150 mg once daily with 2 NRTIs

[b] N=5; Data from two subjects who had undetectable cobicistat C_{24h} concentrations were excluded from summary statistics

[c] From intensive PK analysis of trial GS-US-299-0102 where HIV-infected subjects were administered SYMTUZA once daily

[d] N=18

Emtricitabine and tenofovir alafenamide: In 24 pediatric subjects aged 12 to less than 18 years, who received emtricitabine + TAF with elvitegravir + cobicistat, geometric mean emtricitabine C_{max}, and C_{24h} values were comparable to adults, with geometric mean ratios of 1.10 (90% CI: 0.98, 1.23) and 1.07 (90% CI: 0.88, 1.29), respectively (Table 8). Geometric mean emtricitabine AUC_{24h} was 21% higher, with a geometric mean ratio of 1.21 (90% CI: 1.09, 1.34) in pediatric subjects relative to adults. Geometric mean tenofovir alafenamide C_{max} and AUC_{last} values were 29% and 23% lower in pediatric subjects versus adults with geometric mean ratios of 0.71 (90% CI: 0.50, 1.00) and 0.77 (90% CI: 0.59, 1.02), respectively (Table 8). The observed differences were not considered clinically significant.

Table 8: Multiple-Dose PK Parameters of Emtricitabine and Tenofovir Alafenamide Following Oral Administration with Food in HIV 1 Infected Adults and Pediatric Subjects

Parameter Geometric mean (CV%)	Emtricitabine	Tenofovir alafenamide
Pediatric Subjects[a]	N=24	N=24
AUC_{24h} (mcg.hr/mL)[b]	14.0 (23.9)	0.16 (55.8)
C_{max} (mcg/mL)	2.2 (22.5)	0.14 (64.4)
C_{24h} (mcg/mL)	0.10 (38.9)[c]	NA
Adults[d]	N=19	N=19
AUC_{24h} (mcg.hr/mL)[b]	11.6 (16.6)	0.21 (47.3)
C_{max} (mcg/mL)	2.0 (20.2)	0.19 (64.6)
C_{24h} (mcg/mL)	0.09 (46.7)	NA

CV = Coefficient of Variation; mcg = microgram; NA = not applicable

[a] From intensive PK analysis in trial GS-US-292-0106 in treatment-naïve pediatric subjects with HIV-1 infection

[b] AUC_{last} for tenofovir alafenamide

[c] N=23

[d] From intensive PK analysis in trial GS-US-292-0102 in HIV-infected adults treated with emtricitabine+tenofovir alafenamide and elvitegravir+cobicistat

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Gender and Race

There were no clinically relevant differences in the pharmacokinetics of darunavir, cobicistat, emtricitabine, or tenofovir alafenamide based on gender or race.

Patients with Renal Impairment

Darunavir: The pharmacokinetics of darunavir were not altered in HIV-1 infected subjects with moderate renal impairment taking darunavir co-administered with ritonavir (creatinine clearance between 30-60 mL/min, estimated by Cockcroft-Gault method, N=20). There are no pharmacokinetic data available in HIV-1 infected patients with severe renal impairment or end-stage renal disease taking darunavir co-administered with cobicistat *[see Use in Specific Populations (8.6)].*

Cobicistat: There were no clinically relevant differences in cobicistat pharmacokinetics observed between subjects with severe renal impairment (creatinine clearance below 30 mL/min, estimated by Cockcroft-Gault method) and healthy subjects *[see Use in Specific Populations (8.6)].*

Emtricitabine: Mean systemic emtricitabine exposure was higher in patients with severe renal impairment (creatinine clearance less than 30 mL/min, estimated by Cockcroft-Gault method) than in subjects with normal renal function *[see Use in Specific Populations (8.6)].*

Tenofovir alafenamide: In studies of TAF, no clinically relevant differences in the pharmacokinetics of TAF or its metabolite tenofovir were observed between subjects with severe renal impairment (creatinine clearance of 15-30 mL/min, estimated by Cockcroft-Gault method) and healthy subjects *[see Use in Specific Populations (8.6)].*

Patients with Hepatic Impairment

Darunavir: There were no clinically relevant differences in the pharmacokinetics of darunavir (600 mg with ritonavir 100 mg twice daily) in subjects with mild hepatic impairment (Child-Pugh Class A, n=8), and moderate hepatic impairment (Child-Pugh Class B, n=8), compared to subjects with normal hepatic function (n=16). The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been evaluated *[see Use in Specific Populations (8.7)].*

Cobicistat: There were no clinically relevant differences in the cobicistat pharmacokinetics between subjects with moderate hepatic impairment (Child-Pugh Class B) and healthy subjects. The effect of severe hepatic impairment on the pharmacokinetics of cobicistat has not been evaluated *[see Use in Specific Populations (8.7)].*

Emtricitabine: The pharmacokinetics of emtricitabine have not been studied in subjects with hepatic impairment; however, emtricitabine is not significantly metabolized by liver enzymes, so the impact of hepatic impairment should be limited *[see Use in Specific Populations (8.7)].*

Tenofovir Alafenamide: Clinically relevant changes in the pharmacokinetics of tenofovir alafenamide or its metabolite tenofovir were not observed in patients with mild, moderate (Child-Pugh Class A and B), or severe hepatic impairment (Child-Pugh Class C); *[see Use in Specific Populations (8.7)].*

Patients with Hepatitis B and/or Hepatitis C Virus Coinfection

Darunavir: In HIV-infected subjects taking darunavir co-administered with ritonavir, the 48-week analysis of the data from clinical trials indicated that hepatitis B and/or hepatitis C virus coinfection status had no apparent effect on the exposure of 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: The pharmacokinetics of emtricitabine and tenofovir alafenamide have not been fully evaluated in subjects coinfected with hepatitis B and/or C virus.

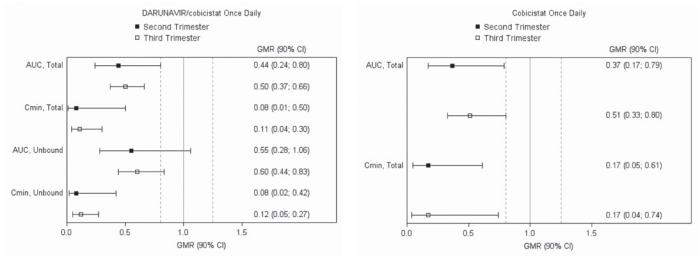
Pregnancy and Postpartum

The exposure to total and unbound darunavir boosted with cobicistat after intake of darunavir/cobicistat as part of an antiretroviral regimen was substantially lower during the second and third trimesters of pregnancy compared with 6-12 weeks postpartum (see Table 9 and Figure 1).

Table 9: Pharmacokinetic Results of Total Darunavir after Administration of Darunavir/Cobicistat Once Daily as Part of an Antiretroviral Regimen, During the 2nd Trimester of Pregnancy, the 3rd Trimester of Pregnancy, and Postpartum

Pharmacokinetics of total darunavir (mean ± SD)	2nd Trimester of pregnancy N=7	3rd Trimester of pregnancy N=6	Postpartum (6-12 weeks) N=6
C_{max}, ng/mL	4340 ± 1616	4910 ± 970	7918 ± 2199
AUC_{24h}, ng.h/mL	47293 ± 19058	47991 ± 9879	99613 ± 34862
C_{min}, ng/mL	168 ± 149	184 ± 99	1538 ± 1344

Figure 1: Pharmacokinetic Results (Within-Subject Comparison) of Total and Unbound Darunavir and Total Cobicistat After Administration of Darunavir/Cobicistat at 800/150 mg Once Daily as Part of an Antiretroviral Regimen, During the 2nd and 3rd Trimester of Pregnancy Compared to Postpartum



Legend: 90% CI: 90% confidence interval; GMR: geometric mean ratio (i.e., second or third trimester/postpartum). Solid vertical line: ratio of 1.0; dotted vertical lines: reference lines of 0.8 and 1.25.

Drug Interactions

Darunavir is metabolized by CYP3A. Cobicistat is metabolized by CYP3A and, to a minor extent, by CYP2D6. Darunavir co-administered with cobicistat is an inhibitor of CYP3A and CYP2D6. Cobicistat inhibits the following transporters: P-gp, BCRP, MATE1, OATP1B1, and OATP1B3. Based on *in vitro* data, cobicistat is not expected to induce CYP1A2 or CYP2B6 and based on *in vivo* data, cobicistat is not expected to induce MDR1 or, in general, CYP3A to a clinically significant extent. The induction effect of cobicistat on CYP2C9, CYP2C19, or UGT1A1 is unknown, but is expected to be low based on CYP3A *in vitro* induction data.

Emtricitabine is not an inhibitor of human CYP450 enzymes. *In vitro* and clinical drug interaction studies have shown that the potential for CYP-mediated interactions involving emtricitabine with other medicinal products is low. Tenofovir alafenamide is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or UGT1A. It is not an inhibitor or inducer of CYP3A *in vivo*.

A drug-drug interaction study between darunavir/cobicistat and dabigatran etexilate was conducted in healthy participants. The effects of darunavir on co-administration with dabigatran etexilate are summarized in Table 10.

Table 10: Drug Interactions: Pharmacokinetic Parameters for Co-Administered Drugs in the Presence of darunavir/cobicistat

Co-administered drug	Dose/Schedule: Co-administered drug	Dose/Schedule: Darunavir/cobicistat	N	PK	LS Mean ratio (90% CI) of co-administered drug pharmacokinetic parameters with/without darunavir no effect =1.00: C_{max}	AUC	C_{min}
Dabigatran etexilate	150 mg	800/150 mg single dose	14	↑	2.64 (2.29-3.05)	2.64 (2.32-3.00)	-
		800/150 mg q.d.[a]	14	↑	1.99 (1.72-2.30)	1.88 (1.65-2.13)	-

N = number of subjects with data

q.d. = once daily

[a] 800/150 mg q.d. for 14 days before co-administered with dabigatran etexilate.

12.4 Microbiology

Mechanism of Action

Darunavir: Darunavir is an inhibitor of the HIV-1 protease. It selectively inhibits the cleavage of HIV-1 encoded Gag-Pol polyproteins in infected cells, thereby preventing the formation of mature virus particles.

Cobicistat: Cobicistat is a selective, mechanism-based inhibitor of CYPP450 of the CYP3A subfamily. Inhibition of CYP3A-mediated metabolism by cobicistat enhances the systemic exposure of CYP3A substrates.

Emtricitabine: Emtricitabine, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5′-triphosphate. Emtricitabine 5′-triphosphate inhibits the activity of the HIV-1 reverse transcriptase (RT) by competing with the natural substrate deoxycytidine 5′-triphosphate and by being incorporated into nascent viral DNA, which results in chain termination. Emtricitabine 5′-triphosphate is a weak inhibitor of mammalian DNA polymerases α, β, ε, and mitochondrial DNA polymerase γ.

Tenofovir alafenamide: TAF is a phosphonamidate prodrug of tenofovir (2′-deoxyadenosine monophosphate analog). Plasma exposure to TAF allows for permeation into cells and then TAF is intracellularly converted to tenofovir through hydrolysis by cathepsin A. Tenofovir is subsequently phosphorylated by cellular kinases to the active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV-1 replication through incorporation into viral DNA by the HIV RT, which results in DNA chain-termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of toxicity to mitochondria in cell culture.

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Antiviral Activity

Darunavir: Darunavir exhibits activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T-cell lines, human PBMCs, and human monocytes/macrophages with median EC_{50} values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/mL). Darunavir demonstrates antiviral activity in cell culture 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 less than 0.1 to 4.3 nM. The EC_{50} value of darunavir increases by a median factor of 5.4 in the presence of human serum.

Cobicistat: Cobicistat has no detectable antiviral activity in cell culture against HIV-1.

Emtricitabine: The antiviral activity of emtricitabine against laboratory and clinical isolates of HIV-1 was assessed in T lymphoblastoid cell lines, the MAGI-CCR5 cell line, and primary PBMCs. The EC_{50} values for emtricitabine were in the range of 1.3–640 nM. Emtricitabine displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 7–75 nM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 7–1,500 nM).

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 ranged from 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).

The combination of darunavir, emtricitabine, and tenofovir alafenamide was not antagonistic in cell culture combination antiviral activity assays. In addition, darunavir, emtricitabine, and tenofovir alafenamide were not antagonistic with a panel of representative agents from the major classes of approved HIV antivirals (PIs, NRTIs, NNRTIs, and INSTIs). The antiviral activity of approved HIV antivirals was not antagonized by cobicistat.

Resistance

Cell Culture

Darunavir: In cell culture, HIV-1 isolates with a decreased susceptibility to darunavir have been selected and obtained from subjects treated with darunavir co-administered with ritonavir. Darunavir-resistant virus derived in cell culture from wild-type HIV-1 had 21- to 88-fold decreased susceptibility to darunavir and developed 2 to 4 of the following amino acid substitutions S37D, R41E/T, K55Q, H69Q, K70E, T74S, V77I, or I85V in the protease. Selection in cell culture of darunavir-resistant HIV-1 from nine HIV-1 strains harboring multiple PI resistance-associated substitutions resulted in the overall emergence of 22 mutations in the protease gene, coding for amino acid substitutions L10F, V11I, I13V, I15V, G16E, L23I, V32I, L33F, S37N, M46I, I47V, I50V, F53L, L63P, A71V, G73S, L76V, V82I, I84V, T91A/S, and Q92R, of which L10F, V32I, L33F, S37N, M46I, I47V, I50V, L63P, A71V, and I84V were the most prevalent. These darunavir-resistant viruses had at least eight protease substitutions and exhibited 50- to 641-fold decreases in darunavir susceptibility with final EC_{50} values ranging from 125 nM to 3461 nM.

Emtricitabine: HIV-1 isolates with reduced susceptibility to emtricitabine were selected in cell culture and in subjects treated with emtricitabine. Reduced susceptibility to emtricitabine was associated with M184V or I substitutions in HIV-1 RT.

Tenofovir alafenamide: HIV-1 isolates with reduced susceptibility to TAF were selected in cell culture. HIV-1 isolates selected by TAF expressed a K65R substitution in HIV-1 RT, sometimes in the presence of S68N or L429I substitutions. In addition, a K70E substitution in HIV-1 RT was observed.

Clinical Trials

Darunavir resistance-associated substitutions (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. Baseline International AIDS Society-USA (IAS-USA)-defined PI resistance substitutions confer reduced virologic response to darunavir.

In the AMBER clinical trial of subjects with no prior antiretroviral treatment history, there were 7 subjects with protocol-defined virologic failure and with HIV-1 RNA ≥400 copies/mL at failure or later timepoints who had post-baseline resistance data in the SYMTUZA arm. None of the subjects had detectable emergent darunavir resistance-associated substitutions or other primary protease inhibitor resistance-associated substitutions and only one subject had emergent M184M/I/V, which confers resistance to emtricitabine and lamivudine. In the comparative PREZCOBIX + emtricitabine/tenofovir disoproxil fumarate arm, there were 2 protocol-defined virologic failures with post-baseline resistance data and neither had detectable resistance emergence.

In the EMERALD clinical trial of virologically-suppressed subjects who switched to SYMTUZA, 1 subject who rebounded and 2 subjects who discontinued early from the study had post-baseline resistance genotypes. None of the subjects had darunavir, primary protease inhibitor, emtricitabine, or tenofovir resistance-associated substitutions. In the control arm, there were 3 subjects who rebounded with post-baseline genotypes and no resistance-associated substitutions were observed.

Cross-Resistance

Darunavir: Cross-resistance among PIs has been observed. Darunavir has a less than 10-fold decreased susceptibility in cell culture against 90% of 3309 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and/or tipranavir showing that viruses resistant to these PIs remain susceptible to darunavir. A less than 10-fold decreased susceptibility was observed for the other PIs in 26% to 96% of these PI resistant clinical isolates [nelfinavir (26%), ritonavir (34%), lopinavir (46%), indinavir (57%), atazanavir (59%), saquinavir (64%), amprenavir (70%), and tipranavir (96%)].

Cross-resistance between darunavir and nucleoside/nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, gp41 fusion inhibitors, CCR5 co-receptor antagonists, or integrase strand transfer inhibitors is unlikely because the viral targets are different.

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

Tenofovir Alafenamide: Tenofovir resistance-associated substitutions K65R and K70E result in reduced susceptibility to abacavir, didanosine, emtricitabine, lamivudine, and tenofovir. HIV-1 with multiple thymidine analog substitutions (M41L, D67N, K70R, L210W, T215F/Y, K219Q/E/N/R) or multinucleoside resistant HIV-1 with a T69S double insertion mutation or with a Q151M substitution complex including K65R, showed reduced susceptibility to TAF in cell culture.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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 incidence of hepatocellular adenomas and carcinomas was observed in males and females of both species and an increase in thyroid follicular cell adenomas was observed in male 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 to darunavir (based on AUC) were between 0.5- and 0.6-fold (mice) and was 0.9-fold (rats) of exposures observed in humans at the recommended therapeutic dose of darunavir in SYMTUZA. 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.

Cobicistat: In a long-term carcinogenicity study in mice, no drug-related increases in tumor incidence were observed at doses up to 50 and 100 mg/kg/day in males and females, respectively. Cobicistat exposures at these doses were approximately 8.6 (male) and 20 (females) times, respectively, the human systemic exposure at the therapeutic daily dose of cobicistat in SYMTUZA. 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 of cobicistat in SYMTUZA. 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 per kg per day (26 times the human systemic exposure at the recommended dose of emtricitabine in SYMTUZA) or in rats at doses up to 600 mg per kg per day (31 times the human systemic exposure at the recommended dose). Emtricitabine was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma, or mouse micronucleus assays. Emtricitabine did not affect fertility in male rats at approximately 107 times or in male and female mice at approximately 88 times higher exposures (AUC) than in humans given the recommended 200 mg daily dose in SYMTUZA. Fertility was normal in the offspring of mice exposed daily from before birth (*in utero*) through sexual maturity at daily exposures (AUC) of approximately 88 times higher than human exposures at the recommended 200 mg daily dose.

Tenofovir alafenamide: Since TAF is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice was observed after TAF administration compared to TDF administration, carcinogenicity studies were conducted only with TDF. Long-term oral carcinogenicity studies of TDF 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 TDF for HIV-1 infection. The tenofovir exposure in these studies was approximately 167 times (mice) and 55 times (rat) those observed in humans after administration of the daily recommended dose of TAF. At the high dose in female mice, liver adenomas were increased at tenofovir exposures approximately 10 times (300 mg TDF) and 167 times (10 mg TAF) the exposure observed in humans. In rats, the study was negative for carcinogenic findings.

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TAF was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma, or rat micronucleus assays. There were no effects on fertility, mating performance, or early embryonic development when TAF 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 7 of gestation.

13.2 Animal Toxicology and/or Pharmacology

Minimal to slight infiltration of mononuclear cells in the posterior uvea was observed in dogs with similar severity after 3 and 9 month administration of tenofovir alafenamide; reversibility was seen after a 3-month recovery period. No eye toxicity was observed in the dog at systemic exposures of 3.5 (TAF) and 0.62 (tenofovir) times the exposure seen in humans with the recommended daily dose of TAF in SYMTUZA.

14. CLINICAL STUDIES

14.1 Clinical Trial Results in Subjects with HIV-1 Infection with no Prior Antiretroviral Treatment History

The efficacy of SYMTUZA in HIV-1 subjects with no prior antiretroviral treatment history was evaluated in the Phase 3 trial TMC114FD2HTX3001 [NCT02431247, (AMBER)] in which subjects were randomized in a 1:1 ratio to receive either SYMTUZA (N=362) or a combination of PREZCOBIX and FTC/TDF (N=363) once daily. The median age was 34.0 years (range 18-71), 88.3% were male, 83% White, 11% Black, and 2% Asian. The mean baseline plasma HIV-1 RNA was 4.5 $\log_{10}$ copies/mL (range 1.3-6.7), and 18% had a baseline viral load ≥100,000 copies/mL. The median baseline CD4+ cell count was 453 cells/mm^3 (range 38 to 1456 cells/mm^3).

Virologic outcomes at 48 weeks of treatment are presented in Table 11.

Table 11: Virologic Outcomes in AMBER at Week 48 in HIV-1 Subjects with No Prior Antiretroviral Treatment History

	SYMTUZA N=362	PREZCOBIX + FTC/TDF N=363
Virologic Response		
HIV-1 RNA <50 copies/mL	91%	88%
Treatment difference[a]	2.7 (95% CI: -1.6; 7.1)	
Virologic Failure[b]	4%	3%
No virologic data at Week 48 window[c]	4%	8%
Reasons		
Discontinued trial due to adverse event or death	2%	4%
Discontinued trial for other reasons[d]	1%	3%
Missing data during window but on trial	1%	1%

[a] Based on stratum adjusted MH test where stratification factors are HIV-1 RNA level (≤100,000 or > 100,000 copies/mL) and CD4+ cell count (< 200 or ≥200 cells/μL).
[b] Included subjects who had ≥50 copies/mL in the Week 48 window; subjects who discontinued early due to lack or loss of efficacy; subjects who discontinued for reasons other than an adverse event (AE), death, or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.
[c] Day 295 – Day 378
[d] Other includes reasons such as withdrew consent, loss to follow-up, and non-compliance.

The mean increase from baseline in CD4+ cell count at Week 48 was 189 and 174 cells/mm^3 in the SYMTUZA and PREZCOBIX + FTC/TDF groups, respectively.

14.2 Clinical Trial Results in Virologically-Suppressed Subjects with HIV-1 Infection Who Switched to SYMTUZA

Phase 3 trial TMC114IFD3013 [NCT02269917, (EMERALD)] evaluated the efficacy of SYMTUZA in virologically-suppressed (HIV-1 RNA less than 50 copies/mL) subjects with HIV-1 infection. Subjects were virologically suppressed for at least 2 months and no more than once had a viral load elevation above 50 HIV-1 RNA copies/mL during the year prior to enrollment. Subjects were on a stable antiretroviral regimen (for at least 6 months), consisting of a bPI [either darunavir once daily or atazanavir (both boosted with ritonavir or cobicistat), or lopinavir with ritonavir] combined with emtricitabine and TDF. Subjects had no history of failure on darunavir treatment and no known or suspected darunavir resistance-associated substitutions. Emtricitabine or tenofovir resistance-associated substitutions were not specifically excluded by the protocol. They either switched to SYMTUZA (N=763) or continued their treatment regimen (N=378) (randomized 2:1). Subjects had a median age of 46 years (range 19-78), 82% were male, 75% White, 21% Black, and 2% Asian. The median baseline CD4+ cell count was 628 cells/mm^3 (range 111-1921 cells/mm^3). Overall, 15% (N=169) of subjects had prior virologic failure. Five subjects had archived tenofovir resistance-associated substitutions and 53 subjects had archived emtricitabine resistance-associated substitutions, mainly at RT position M184. All of these subjects with emtricitabine resistance-associated substitutions had HIV-1 RNA<50 copies/mL at Week 48 (N=50) or at the last on-treatment viral load (N=3). Virologic outcomes are presented in Table 12. Prior virologic failure did not impact treatment outcomes.

Table 12: Virologic Outcomes in EMERALD at Week 48 in HIV-1 Virologically-Suppressed Subjects Who Switched to SYMTUZA

	SYMTUZA N=763	bPI+FTC/TDF N=378
Virologic Failure[a]	1%	1%
Treatment difference[b]	0.3 (95% CI: -0.7; 1.2)	
HIV-1 RNA <50 copies/mL	95%	94%
No virologic data at Week 48 window[c]	4%	6%
Reasons		
Discontinued trial due to adverse event or death	1%	1%
Discontinued trial for other reasons[d]	3%	4%
Missing data during window[c] but on trial	<1%	1%

[a] Included subjects who had ≥50 copies/mL in the Week 48 window; subjects who discontinued early due to lack or loss of efficacy; subjects who discontinued for reasons other than an adverse event (AE), death, or lack or loss of efficacy and at the time of discontinuation had a viral value ≥ 50 copies/mL.
[b] Based on MH test adjusting for bPI at screening (ATV with rtv or COBI, DRV with rtv or COBI, LPV with rtv).
[c] Day 295 – Day 378
[d] Other includes reasons such as withdrew consent, loss to follow-up, and non-compliance

The mean increase from baseline in CD4+ cell count at Week 48 was 20 cells/mm^3 in subjects who switched to SYMTUZA and 8 cells/mm^3 in subjects who stayed on their baseline PI + FTC/TDF.

14.3 Clinical Trial Results in Pediatric Subjects with HIV-1 Infection

The pharmacokinetic profile, safety, and antiviral activity of the components of SYMTUZA were evaluated in open-label clinical trials in pediatric subjects with HIV-1 infection aged 12 to less than 18 years: GS-US-216-0128 (N=7) and GS-US-292-0106 (N=50).

In the Phase 2/3 trial GS-US-216-0128, darunavir 800 mg and cobicistat 150 mg once daily with 2 NRTIs were evaluated in 7 virologically suppressed pediatric subjects aged 12 to less than 18 years and weighing at least 40 kg. Subjects had a median (range) age of 14 (12-16) years and a median (range) weight of 57 (45-78) kg. At baseline, plasma HIV-1 RNA was <50 copies/mL in all subjects, and the median (range) CD4+ cell count was 1,117 (658-2,416) cells/mm^3. At Week 48, the proportion of subjects who maintained HIV-1 RNA <50 copies/mL was 86%, and the median change in CD4+ cell count from baseline was -342 cells/mm^3 (range -1,389 to 210 cells/mm^3). All 6 subjects with available data had CD4+ cell counts above 800 cells/mm^3 at Week 48.

In the Phase 2/3 trial GS-US-292-0106, cobicistat 150 mg, emtricitabine 200 mg, and tenofovir alafenamide 10 mg, as part of a fixed-dose combination regimen together with elvitegravir 150 mg, were evaluated in 50 treatment-naïve pediatric subjects with HIV-1 aged 12 to less than 18 years and weighing at least 35 kg. Subjects had a median (range) age of 15 (12-17) years. At baseline, median (range) plasma HIV-1 RNA was 4.7 (3.3-6.5) $\log_{10}$ copies/mL, median (range) CD4+ cell count was 456 (95-1,110) cells/mm^3, and 22% had baseline plasma HIV-1 RNA >100,000 copies/mL). At Week 48, the proportion of subjects who had HIV-1 RNA <50 copies/mL was 92%, and the median increase in CD4+ cell count from baseline was 220 cells/mm^3.

The use of SYMTUZA in pediatric patients weighing less than 40 kg has not been established *[see Use in Specific Populations (8.4)]*.

16. HOW SUPPLIED/STORAGE AND HANDLING

SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets are supplied as yellow to yellowish-brown, capsule-shaped, film-coated tablets debossed with "8121" on one side and "JG" on the other side.

SYMTUZA is packaged in bottles of 30 tablets (NDC 42067-270-30), with a silica gel desiccant and child-resistant closure.

Storage

- Store at 20°C-25°C (between 68°F-77°F); with excursions permitted to 15°C-30°C (59°F-86°F).
- Dispense only in the original container. Keep container tightly closed with desiccant inside to protect from moisture.
- Keep SYMTUZA out of reach of children.

This drug was imported from Canada without the authorization of Janssen Therapeutics, Division of Janssen Products, LP under the State of Florida Section 804 Importation Program. Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets

17. PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Instructions for Use

Advise patients to take SYMTUZA with food every day on a regular dosing schedule, as missed doses can result in development of resistance. Inform patients not to alter the dose of SYMTUZA or discontinue therapy with SYMTUZA without consulting their physician. For patients who are unable to swallow tablets whole, SYMTUZA may be split using a tablet-cutter, and the entire dose should be consumed immediately after splitting *[see Dosage and Administration (2.2)]*.

Post-treatment Acute Exacerbation of Hepatitis B in Patients with HBV Co-Infection

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued products containing emtricitabine and/or TDF, and may likewise occur with discontinuation of SYMTUZA *[see Warnings and Precautions (5.1)]*. Advise the patient to not discontinue SYMTUZA without first informing their healthcare provider.

Hepatotoxicity

Inform patients that drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) and liver injury, including some fatalities, could potentially occur with SYMTUZA. Advise patients to contact their healthcare provider immediately if signs and symptoms of liver problems develop *[see Warnings and Precautions (5.2)]*.

Severe Skin Reactions

Inform patients that skin reactions ranging from mild to severe, including Stevens-Johnson syndrome, drug rash with eosinophilia and systemic symptoms, and toxic epidermal necrolysis, could potentially occur with SYMTUZA. Advise patients to contact their healthcare provider immediately if signs or symptoms of severe skin reactions develop, including but not limited to severe rash or rash accompanied with fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, and/or conjunctivitis *[see Warnings and Precautions (5.3)]*.

Pregnancy

Advise patients that SYMTUZA is not recommended during pregnancy and to alert their healthcare provider if they get pregnant while taking SYMTUZA. Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant individuals exposed to SYMTUZA *[see Use in Specific Populations (8.1)]*.

Lactation

Instruct individuals with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in breast milk *[see Use in Specific Populations (8.2)]*.

Drug Interactions

SYMTUZA may interact with many drugs; therefore, inform patients of the potential serious drug interactions with SYMTUZA, and that some drugs are contraindicated with SYMTUZA and other drugs may require dosage adjustment. Advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John's wort *[see Contraindications (4), Warnings and Precautions (5.4), and Drug Interactions (7)]*.

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any symptoms of infection, as in some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started *[see Warnings and Precautions (5.5)]*.

Renal Impairment

Advise patients to avoid taking SYMTUZA with concurrent or recent use of nephrotoxic agents. Renal impairment, including cases of acute renal failure, has been reported in association with the use of tenofovir prodrugs *[see Warnings and Precautions (5.6)]*.

Lactic Acidosis and Severe Hepatomegaly

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with use of drugs similar to SYMTUZA. Advise patients that they should stop SYMTUZA if they develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity *[see Warnings and Precautions (5.8)]*.

Fat Redistribution

Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including SYMTUZA, and that the cause and long-term health effects of these conditions are not known at this time *[see Warnings and Precautions (5.10)]*.

Manufactured for:
Janssen Products, LP, Horsham PA 19044, USA

PATIENT INFORMATION
SYMTUZA® (sim toó zah)
(darunavir, cobicistat, emtricitabine, and tenofovir alafenamide)
tablets

What is the most important information I should know about SYMTUZA?

SYMTUZA can cause serious side effects, including:

- **Worsening of Hepatitis B virus infection (HBV).** Your healthcare provider will test you for HBV before starting treatment with SYMTUZA. If you have HBV infection and take SYMTUZA, your HBV may get worse (flare-up) if you stop taking SYMTUZA. A "flare-up" is when your HBV infection suddenly returns in a worse way than before.
  - Do not stop taking SYMTUZA without first talking to your healthcare provider.
  - Do not run out of SYMTUZA. Refill your prescription or talk to your healthcare provider before your SYMTUZA is all gone.
  - If you stop taking SYMTUZA, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your HBV infection, or give you a medicine to treat your HBV infection. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking SYMTUZA.
- **Change in liver enzymes.** People with a history of hepatitis B or C virus infection or who have certain liver enzyme changes may have an increased risk of developing new or worsening liver problems during treatment with SYMTUZA. Liver problems can also happen during treatment with SYMTUZA in people without a history of liver disease. Your healthcare provider may need to do tests to check your liver enzymes before and during treatment with SYMTUZA.
- **Severe liver problems.** In rare cases, severe liver problems can happen that can lead to death. **Tell your healthcare provider right away if you get these symptoms:** skin or the white part of your eyes turns yellow, dark "tea-colored" urine, light-colored stools, loss of appetite for several days or longer, nausea, vomiting, or stomach-area pain.

SYMTUZA may cause severe or life-threatening skin reactions or rash. Sometimes these skin reactions and skin rashes can become severe and require treatment in a hospital. Call your healthcare provider right away if you develop a rash. **Stop taking SYMTUZA** and call your healthcare provider right away if you develop any skin changes with symptoms below:

- fever
- tiredness
- muscle or joint pain
- blisters or skin lesions
- mouth sores or ulcers
- red or inflamed eyes, like "pink eye" (conjunctivitis)

See "What are the possible side effects of SYMTUZA?" for more information about side effects.

What is SYMTUZA?

SYMTUZA is a prescription medicine that is used without other antiretroviral medicines to treat Human Immunodeficiency Virus-1 (HIV-1) infection in adults and in children who weigh at least 88 pounds (40 kg) who:

- have not received anti-HIV-1 medicines in the past, **or**
- when their healthcare provider determines that they meet certain requirements.

HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

SYMTUZA contains the prescription medicines darunavir, cobicistat, emtricitabine, and tenofovir alafenamide.

It is not known if SYMTUZA is safe and effective in children weighing less than 88 pounds (40 kg).

Who should not take SYMTUZA?

Do not take SYMTUZA with any of the following medicines:

- alfuzosin
- carbamazepine
- colchicine, if you have liver or kidney problems
- dronedarone
- elbasvir and grazoprevir
- ergot-containing medicines, such as:
  - dihydroergotamine
  - ergotamine tartrate
  - methylergonovine

Who should not take SYMTUZA? (continued)

Do not take SYMTUZA with any of the following medicines:

- ivabradine
- lomitapide
- lovastatin or a product that contains lovastatin
- lurasidone
- midazolam, when taken by mouth
- naloxegol
- phenobarbital
- phenytoin
- pimozide
- ranolazine
- rifampin
- sildenafil, when used for the treatment of pulmonary arterial hypertension (PAH)
- simvastatin or a product that contains simvastatin
- St. John's wort (*Hypericum perforatum*), or a product that contains St. John's wort
- triazolam

Serious problems can happen if you take any of these medicines with SYMTUZA. This is not a complete list of medicines. Therefore, tell your healthcare provider about all medicines you take.

Before taking SYMTUZA, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems, including hepatitis B or hepatitis C
- have kidney problems
- are allergic to sulfa (sulfonamide)
- have diabetes
- have hemophilia
- are pregnant or plan to become pregnant.
  - It is not known if SYMTUZA will harm your unborn baby.
  - SYMTUZA should not be used during pregnancy because you may not have enough SYMTUZA in your body during pregnancy.
  - Tell your healthcare provider if you become pregnant while taking SYMTUZA. Your healthcare provider will prescribe different medicines if you become pregnant while taking SYMTUZA.

    Pregnancy Registry: There is a pregnancy registry for those who take antiretroviral medicines during pregnancy. The purpose of the registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.
- are breastfeeding or plan to breastfeed. Do not breastfeed if you take SYMTUZA.
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV to your baby.
  - One of the medicines in SYMTUZA called emtricitabine can pass into your breast milk. It is not known if the other medicines in SYMTUZA can pass into your breast milk.
  - Talk to your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, topical creams, vitamins, and herbal supplements. Some medicines interact with SYMTUZA. Keep a list of your medicines to show your healthcare provider and pharmacist.

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with SYMTUZA.
- **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take SYMTUZA with other medicines.

How should I take SYMTUZA?

- Take SYMTUZA exactly as your healthcare provider tells you.
- Do not change your dose or stop taking SYMTUZA without talking to your healthcare provider.
- Take SYMTUZA 1 time a day with food.
- If you have difficulty swallowing, the tablet may be split using a tablet-cutter. After splitting the tablet, the entire dose (both halves) should then be taken right away.
- Do not miss a dose of SYMTUZA.
- When your SYMTUZA supply starts to run low, get more from your healthcare provider or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to SYMTUZA and become harder to treat.
- If you take too much SYMTUZA, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of SYMTUZA?

SYMTUZA may cause serious side effects, including:

- See **"What is the most important information I should know about SYMTUZA?"**
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having new symptoms after starting your HIV-1 medicine.
- **New or worse kidney problems, including kidney failure.** Your healthcare provider should do blood and urine tests to check your kidneys before you start and while you are taking SYMTUZA. Your healthcare provider may tell you to stop taking SYMTUZA if you develop new or worse kidney problems.
- **Too much lactic acid in your blood (lactic acidosis).** Too much lactic acid is a serious but rare medical emergency that can lead to death. **Tell your healthcare provider right away if you get these symptoms:** weakness or being more tired than usual, unusual muscle pain, being short of breath or fast breathing, stomach pain with nausea and vomiting, cold or blue hands and feet, feel dizzy or lightheaded, or a fast or abnormal heartbeat.
- **Diabetes and high blood sugar (hyperglycemia).** Some people who take protease inhibitors including SYMTUZA can get high blood sugar, develop diabetes, or your diabetes can get worse. Tell your healthcare provider if you notice an increase in thirst or if you start urinating more often while taking SYMTUZA.
- **Changes in body fat** can happen in people who take HIV-1 medicines. The changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the middle of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term health effects of these conditions are not known.
- **Increased bleeding for hemophiliacs.** Some people with hemophilia have increased bleeding with protease inhibitors.

The most common side effects of SYMTUZA, include:

- diarrhea
- rash
- nausea
- fatigue
- headache
- stomach problems
- gas

These are not all of the possible side effects of SYMTUZA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SYMTUZA?

- Store SYMTUZA tablets at room temperature between 68°F to 77°F (20°C to 25°C).
- The SYMTUZA bottle contains a desiccant and has a child-resistant cap.
- Keep the SYMTUZA container tightly closed with the desiccant inside of it to protect SYMTUZA from moisture.

Keep SYMTUZA out of reach of children.

General information about the safe and effective use of SYMTUZA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use SYMTUZA for a condition for which it was not prescribed. Do not give SYMTUZA to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about SYMTUZA that is written for health professionals.

What are the ingredients in SYMTUZA?

Active ingredient: darunavir, cobicistat, emtricitabine, and tenofovir alafenamide

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing polyethylene glycol (macrogol), polyvinyl alcohol (partially hydrolyzed), talc, titanium dioxide, and yellow ferric oxide.

Manufactured for: Janssen Products, LP, Horsham PA 19044, USA

For more information call 1-800-526-7736.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 03/2023

cp-62057v20

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Annotated Label Comparisons

PI Comparisons FDA VS. FLCPDIP
Differences
Updated information Adverse Reactions Contact
How Supplied/Storage and Handling added SIP804 language
Patient Information added SIP804 language
Listed new NDC #
Added Importation language & Importer name & address
Listed only drug strength purchased for program

FDA

----------ADVERSE REACTIONS----------

The most common adverse reactions (all grades, incidence greater than or equal to 2%) were diarrhea, rash, nausea, fatigue, headache, abdominal discomfort, and flatulence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Products, LP at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

16. HOW SUPPLIED/STORAGE AND HANDLING

SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets are supplied as yellow to yellowish-brown, capsule-shaped, film-coated tablets debossed with "8121" on one side and "JG" on the other side.

SYMTUZA is packaged in bottles of 30 tablets (NDC 59676-800-30), with a silica gel desiccant and child-resistant closure.

Storage

- Store at 20°C-25°C (between 68°F-77°F); with excursions permitted to 15°C-30°C (59°F-86°F).
- Dispense only in the original container. Keep container tightly closed with desiccant inside to protect from moisture.
- Keep SYMTUZA out of reach of children.

What are the ingredients in SYMTUZA?

Active ingredient: darunavir, cobicistat, emtricitabine, and tenofovir alafenamide

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing polyethylene glycol (macrogol), polyvinyl alcohol (partially hydrolyzed), talc, titanium dioxide, and yellow ferric oxide.

Manufactured for: Janssen Products, LP, Horsham PA 19044, USA

For more information call 1-800-526-7736.

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cp-62057v20

FLSIP

----------ADVERSE REACTIONS----------

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To report SUSPECTED ADVERSE REACTIONS, contact LifeScience Logistics at 1-855-738-6171 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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What are the ingredients in SYMTUZA?

Active ingredient: darunavir, cobicistat, emtricitabine, and tenofovir alafenamide

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing polyethylene glycol (macrogol), polyvinyl alcohol (partially hydrolyzed), talc, titanium dioxide, and yellow ferric oxide.

Manufactured for: Janssen Products, LP, Horsham PA 19044, USA

For more information call 1-800-526-7736.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 03/2023

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Proposed Package Label

Label Comparisons FDA VS. FLCPDIP
Differences
NDC
GTN
Bar Codes FPO with Associated NDCs
SIP804 Importation Language
Label SIZE due to production process & adding SIP804 language
Importer Name & Address
Brand logos FPO low resolution. Native art files requested upon SIP804 approval.

Comparisons
FDA to FLSIP

Recent FDA Approved Label	US Proprietary Name	US Generic Name	US Strength	NDC	NDA or ANDA	Applicant Holder Name	Applicant Holder Address	US Active Ingredients	Date Labeling Prepared for FLSIP	LSL Proprietary Name	LSL Generic Name	FLSIP Strength	LSL NDC	LSL Relabeler Name	Applicant Holder Name	Applicant Holder Address	FLSIP Active Ingredients
3/31/2023	SYMTUZA	Darunavir-cobi-emtri-tenof ala	150-800-200-10 mg	59676-800-30	210455	Janssen Products, LP,	Horsham PA 19044	Darunavir-cobi-emtri-tenof ala	Aug-23	SYMTUZA	Darunavir-cobi-emtri-tenof ala	150-800-200-10 mg	42067-270-30	LifeScience Logistics, LLC	Janssen Products, LP,	Horsham PA 19044	Darunavir-cobi-emtri-tenof ala

CANADIAN to FDA

Comparisons
Canada to FDA

Active Ingredient	Canadian Submission Number	Canadian Proprietary Name	Canadian Generic Name	DIN	Date Labeling Approved	Company Name	Address	Canadian Strength	Dosage Form	# of active Ingred.	Canadian Active Ingredients	US Proprietary Name	US Generic Name	US Strength	NDC	NDA or ANDA	Applicant Holder Name	US Active Ingredients
COBICISTAT,DARUNAVIR (DARUNAVIR ETHANOLATE),EMTRICITABINE,TENOFOVIR ALAFENAMIDE (TENOFOVIR ALAFENAMIDE HEMIFUMARATE)	268406	SYMTUZA	COBICISTAT,DARUNAVIR (DARUNAVIR ETHANOLATE),EMTRICITABINE,TENOFOVIR ALAFENAMIDE (TENOFOVIR ALAFENAMIDE HEMIFUMARATE)	2473720	Revision: March 3, 2023	**JANSSEN INC**	19 Green Belt Drive Toronto Ontario Canada M3C 1L9	150-800-200-10 mg	Oral Tablet, Once daily	4	COBICISTAT,DARUNAVIR (DARUNAVIR ETHANOLATE),EMTRICITABINE,TENOFOVIR ALAFENAMIDE (TENOFOVIR ALAFENAMIDE HEMIFUMARATE)	SYMTUZA	Darunavir-cobi-emtri-tenof ala	150-800-200-10 mg	59676-800-30	NDA210455	Janssen Products, LP, Horsham PA 19044	Darunavir-cobi-emtri-tenof ala

Canadian Monograph

PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

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

Janssen Inc.
19 Green Belt Drive
Toronto, Ontario
M3C 1L9

www.janssen.com/canada

Date of Initial Authorization:
March 07, 2018

Date of Revision:
March 3, 2023

Submission Control Number: 268406

RECENT MAJOR LABEL CHANGES

2 CONTRAINDICATIONS	08/2022

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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 **4 DOSAGE AND ADMINISTRATION** and **14 CLINICAL TRIALS**.

1.1 Pediatrics

Pediatrics (≥12 and <18 years of age with body weight ≥40 kg)
Pediatrics (≥12 years of age with body weight ≥40 kg): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of SYMTUZA in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use. (see **4 DOSAGE AND ADMINISTRATION** and **7 WARNINGS AND PRECAUTIONS**).

1.2 Geriatrics

Geriatrics (≥65 years of age)
Limited information is available on the use of SYMTUZA® in patients aged 65 and over (see **4 DOSAGE AND ADMINISTRATION**, **7 WARNINGS AND PRECAUTIONS**, and **10 CLINICAL PHARMACOLOGY**). Therefore, SYMTUZA® should be used with caution in elderly patients.

2 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 **6 DOSAGE FORMS, STRENGTHS, 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 **9.4 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/Antianginals	amiodarone, dronedarone, ivabradine, lidocaine (systemic)
Anti-coagulants	apixaban, dabigatran, rivaroxaban
Anti-convulsants	carbamezepine, phenobarbital, phenytoin
Anti-gout	colchicine (in patients with renal and/or hepatic impairment)
Antimycobacterial	rifampin
Ergot Derivatives	dihydroergotamine, ergonovine, ergotamine
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
Opioid Antagonist	naloxegol
PDE-5 Inhibitor	sildenafil (for treatment of pulmonary arterial hypertension)
Platelet Aggregation Inhibitor	ticagrelor
Sedatives/Hypnotics	triazolam

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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 **7.1 Special Populations**).

4 DOSAGE AND ADMINISTRATION

4.1 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.

4.2 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 **9.5 Drug-Food Interactions**, and **10.3 Pharmacokinetics**, **Effects of Food on Oral Absorption**).

SYMTUZA® should be swallowed whole without breaking or crushing to ensure administration of the entire dose.

Pediatrics (≥12 years and <18 years of age with body weight ≥40 kg

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 **7 WARNINGS AND PRECAUTIONS**, **10 CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Pediatrics** and **16 NON-CLINICAL TOXICOLOGY**, **Reproductive and Developmental Toxicity**).

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. **1 INDICATIONS**, **7 WARNINGS AND PRECAUTIONS** and **10 CLINICAL PHARMACOLOGY**).

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 **7.1.1 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 **10.3 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 **2 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 **7 WARNINGS AND PRECAUTIONS**, **Renal impairment** and **10.3 Pharmacokinetics**).

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

4.4 Administration

SYMTUZA® should be swallowed whole without breaking or crushing to ensure administration of the entire dose.

4.5 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.

5 OVERDOSAGE

Human experience of acute overdose with SYMTUZA® is limited. If overdose occurs, the patient must be monitored for evidence of toxicity (see **8 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table –Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal 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	• 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.

Description

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.

7 WARNINGS AND PRECAUTIONS

Please see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**.

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 **15 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 **2 CONTRAINDICATIONS**, **7 WARNINGS AND PRECAUTIONS, General** and **9 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 **9 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 **16 NON-CLINICAL TOXICOLOGY, Genotoxicity**).

Refer to **16 NON-CLINICAL TOXICOLOGY, Genotoxicity** 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 **9 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 tenofovir 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 **10 CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Hepatic Insufficiency**).

SYMTUZA® is contraindicated in patients with severe hepatic insufficiency (Child-Pugh Class C) (see **2 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 **7.1 Special Populations**).

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.

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 **7 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 complex* (MAC) infection, cytomegalovirus (CMV) infection, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis (TB)), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, autoimmune hepatitis, 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 **8 ADVERSE REACTIONS, Effects on Serum Creatinine**). 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 **4.2 Recommended Dose and Dosage Adjustment**). 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.

Reproductive Health: Female and Male Potential

Fertility

There was no effect on mating or fertility with darunavir, cobicistat, emtricitabine, or tenofovir alafenamide treatment in animals (see **16 NON-CLINICAL TOXICOLOGY**, **Reproductive and Developmental Toxicity**). No effect on reproduction or fertility is expected with SYMTUZA®.

Sensitivity/Resistance
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.

7.1 Special Populations

7.1.1 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 **10.3 Pharmacokinetics**, **Special Populations and Conditions**, **Pregnancy and Breast-feeding**).

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.

7.1.2 Breast-feeding

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. Breast-feeding 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 **16 NON-CLINICAL 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 **16 NON-CLINICAL TOXICOLOGY**, **Reproductive and Developmental Toxicity**).

7.1.3 Pediatrics

Pediatrics (<12 years or weighing <40 kg)
Based on the data submitted and reviewed by Health Canada, the safety and efficacy of SYMTUZA® in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use. (see **1.1 Pediatrics**)

7.1.4 Geriatrics

Geriatrics (≥65 years of age)
Limited information is available on the use of SYMTUZA® in patients aged 65 and over. (see **10.3 Pharmacokinetics**, **Geriatrics**).

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.

8 ADVERSE REACTIONS

8.1 Adverse 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 **7 WARNINGS AND PRECAUTIONS**, **Lactic Acidosis/Severe Hepatomegaly with Steatosis**)
- Severe Acute Exacerbations of Hepatitis B (see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**, **7 WARNINGS AND PRECAUTIONS** , and **Patients co-infected with HIV and hepatitis B (HBV) or C (HCV) virus**)
- Immune Reconstitution Inflammatory Syndrome (see **7 WARNINGS AND PRECAUTIONS**).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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	**SYMTUZA®**	**DRV+COBI+FTC/TDF**
Adverse Reaction	N=103	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%
Angioedema	0.6%
Lipodystrophy	0.9%
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.

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.

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.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

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.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry, and Other Quantitative Data

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

1. 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%

Laboratory Parameter Grade	Limit	SYMTUZA® N=102 %*	DRV+COBI+FTC/TDF N=50 %*
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.

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).

8.5 Post-Market Adverse 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

Immune System Disorder: drug hypersensitivity, immune reconstitution inflammatory syndrome, autoimmune disorders such as Graves' disease and autoimmune hepatitis

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, crystal nephropathy

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.

9 DRUG INTERACTIONS

9.1 Serious 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). Examples include alfuzosin, amiodarone, apixaban, colchicine (in patients with renal and/or hepatic impairment), dabigatran, dronedarone, elbasvir/grazoprevir, the ergot alkaloids (e.g., ergotamine, dihydroergotamine, ergonovine), lidocaine (systemic), ivabradine, lomitapide, lovastatin, lurasidone, naloxegol, pimozide, rivaroxaban, salmeterol, sildenafil (when used for the treatment of pulmonary arterial hypertension), simvastatin, ticagrelor and triazolam (see **2 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 **2 CONTRAINDICATIONS**).

9.2 Drug Interactions Overview

SYMTUZA® can cause and/or is subject to drug interactions which may be life-threatening or result in lack of efficacy (see **2 CONTRAINDICATIONS**, **7 WARNINGS AND PRECAUTIONS**, **General** and **9.4 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 **2 CONTRAINDICATIONS** and **9.4 Drug-Drug Interactions**, Table 6 and Table 7). Co-administration of SYMTUZA® with drugs that have active metabolite(s) formed by CYP3A may result in reduced plasma concentrations of these active metabolite(s), potentially leading to loss of their therapeutic effect (see **9.4 Drug-Drug Interactions**, 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 **2 CONTRAINDICATIONS** and **9.4 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 **7 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.

9.4 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.

The below list of examples of drug-drug interactions is not comprehensive and therefore the label of each drug that is co-administered with SYMTUZA® should be consulted for information related to the route of metabolism, interaction pathways, potential risks, and specific actions to be taken with regards to co-administration.

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/Antianginals: amiodarone dronedarone ivabradine lidocaine (systemic)	CONTRAINDICATED: Concentrations of amiodarone, dronedarone, ivabradine, and lidocaine (systemic), may be increased (inhibition of CYP3A and/or CYP2D6) when co-administered with SYMTUZA®.
Direct Oral Anticoagulants (DOACs): apixaban dabigatran 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, dabigatran 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®.
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.

Drug Class: Drug Name	Clinical Comment
Ergot Derivatives: dihydroergotamine ergonovine ergotamine	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.
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: lomitapide	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.
Opioid Antagonist: naloxegol	CONTRAINDICATED: Concomitant use of naloxegol and SYMTUZA® may increase the exposure to naloxegol (inhibition of CYP3A).
PDE-5 Inhibitors: 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).
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.

Drug Class: Drug Name	Clinical Comment
Sedatives/Hypnotics: triazolam	CONTRAINDICATED due to the potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

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/ Antianginals 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/antianginals	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/antianginals 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 co-administering SYMTUZA® with these anticancer agents.
everolimus, irinotecan		Concomitant use of everolimus or irinotecan and SYMTUZA® is not recommended.

Direct Oral Anticoagulants (DOACs): dabigatran edoxaban	↑ dabigatran ↑ 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. The results of a drug-drug interaction study, between darunavir/cobicistat 800/150 mg and dabigatran 150 mg in healthy participants showed a 2.6-fold increase in dabigatran plasma AUC after single dosing of darunavir/cobicistat, and a 1.9-fold increase in dabigatran plasma AUC after repeated dosing of darunavir/cobicistat. The study demonstrated a 2.6-fold increase in dabigatran plasma C_{max} after single dosing of darunavir/cobicistat and a 2.0-fold increase in dabigatran plasma C_{max} after repeated dosing of darunavir/cobicistat. Use of dabigatran is contraindicated (see Table 6). Clinical monitoring is required when edoxaban, which is not affected by CYP3A4 but is transported by P-gp, is co-administered with SYMTUZA®. A dose reduction of edoxaban may be needed. The combination of darunavir/cobicistat and edoxaban 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	↑ antidepressant	Concomitant use of SYMTUZA® and these antidepressants may increase concentrations of the antidepressant (inhibition of CYP2D6 and/or

imipramine nortriptyline paroxetine sertraline trazodone		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.
Antiemetics: domperidone	↑ domperidone	Use with caution: monitor for domperidone adverse reactions.
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 co-administering SYMTUZA® with these antifungals. When co-administration is required, the daily dose of ketoconazole or itraconazole should not exceed 200 mg.
isavuconazole posaconazole		Clinical monitoring is recommended when co-administering SYMTUZA® with posaconazole or isavuconazole.
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®.**
Antimycobacterials: rifabutin	↓ 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.
Antiplatelets: clopidogrel	↓ clopidogrel active metabolite	Co-administration of SYMTUZA® with clopidogrel is expected to decrease clopidogrel active metabolite plasma concentration, which may reduce the antiplatelet activity of clopidogrel. Co-administration of SYMTUZA® with clopidogrel 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 verapamil	↑ calcium channel blockers	Plasma concentrations of calcium channel blockers (e.g., amlodipine, diltiazem, felodipine, nifedipine, verapamil) may increase when SYMTUZA® are co-administered. Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroids: Systemic Dexamethasone prednisone <u>Primarily metabolized by CYP3A, including inhaled/nasal topical</u> 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. Concomitant use of corticosteroids (systemic and/or inhaled/nasal/topical) and SYMTUZA® may increase plasma concentrations of these corticosteroids. Alternatives should be considered, particularly for long-term use. For co-administration of cutaneously-administered corticosteroids sensitive to CYP3A inhibition, refer to the prescribing information of the corticosteroid for conditions or uses that augment its systemic absorption.
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.
Hormonal Contraceptives: drospirenone	↑ drospirenone ↑ norgestimate ↓ ethinyl estradiol	The results of an interaction trial between DRV+COBI and ethinylestradiol and drospirenone demonstrated that single dose systemic

ethinyl estradiol norethindrone norgestimate	↓ norethindrone	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.

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.

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 meperidine fentanyl oxycodone tramadol	↓ methadone ↔ buprenorphine ↔naloxone ↑ norbuprenorphine ↓ meperidine ↑ fentanyl ↑ oxycodone ↑ tramadol	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. 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). 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.
Neuroleptics: perphenazine risperidone quetiapine	↑ neuroleptics ↑ quetiapine	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. 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.
Sedatives/Hypnotics: buspirone clorazepate diazepam flurazepam zolpidem 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.
Urinary antispasmodics: fesoterodine solifenacin	↑ Urinary antispasmodics	Use with caution. Monitor for fesoterodine or solifenacin adverse reactions, dose reduction of fesoterodine or solifenacin may be necessary.

9.5 Drug-Food Interactions

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

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 **14.3 Comparative Bioavailability Studies**).

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®.

9.6 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 **9.4 Drug-Drug Interactions**, Table 6).

Interactions with other herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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.

10.2 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.

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.

10.3 Pharmacokinetics

Absorption

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.

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*.

Elimination
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.

- **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 **7.1.4 Geriatrics**).

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

- **Sex:** *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.

- **Pregnancy and Breast-feeding:** 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 >1000 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.

  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.

- **Ethnic Origin:** *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 **2 CONTRAINDICATIONS**, **4 DOSAGE AND ADMINISTRATION** and, **7 WARNINGS AND PRECAUTIONS).**

  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 **4.2 Recommended Dose and Dosage Adjustment** and **7 WARNINGS AND PRECAUTIONS**, **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.

11 STORAGE, STABILITY AND DISPOSAL

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.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

SYMTUZA® is a fixed-dose combination tablet which 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).

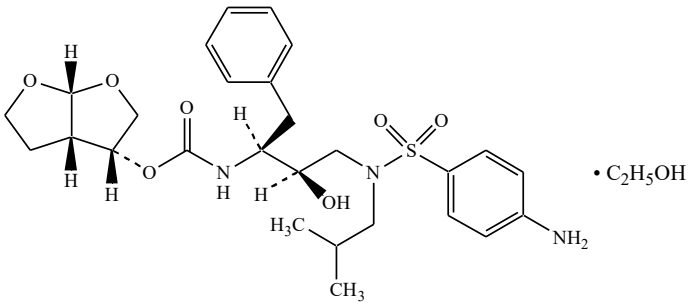
Proper name: Darunavir ethanolate (DRV)

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

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.

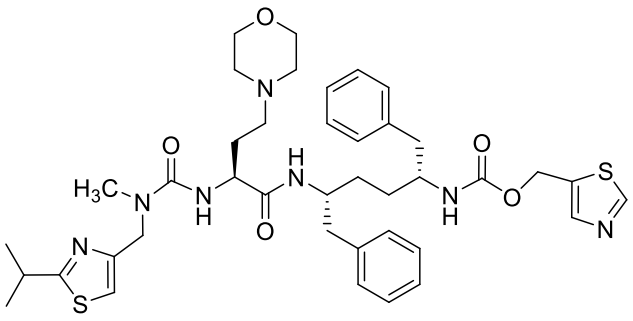
Proper name: Cobicistat (COBI)

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: $C_{40}H_{53}N_7O_5S_2$

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.

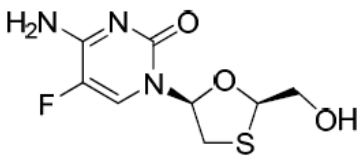
Proper name: Emtricitabine (FTC)

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

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.

Proper name: Tenofovir alafenamide hemifumarate (TAF)

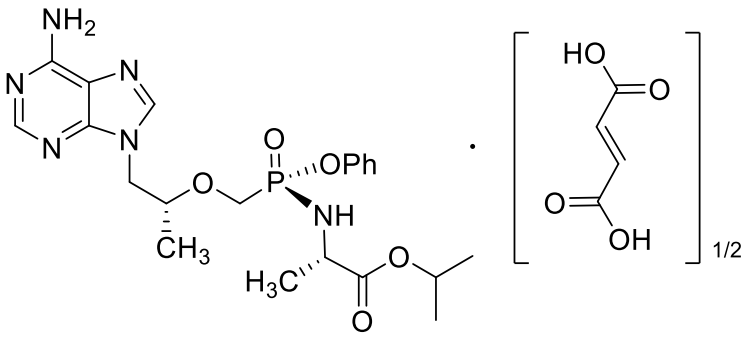
Tenofovir alafenamide fumarate (USAN)

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: $C_{21}H_{29}O_5N_6P•1/2(C_4H_4O_4)$

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.

14 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 **14.3 Comparative Bioavailability Studies**).

14.1 Clinical Trial by Indication

Indication 1

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).

Efficacy, Safety and Pharmacokinetics in adolescents

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 × 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 >100000 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.

14.2 Comparative Bioavailability Studies

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 standardized 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.

15 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 resistance 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.

16 NON-CLINICAL TOXICOLOGY

General 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.

Carcinogenicity

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).

Cobicistat: 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 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.

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).

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.

Genotoxicity

Darunavir: 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.

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

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

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

Reproductive and Developmental Toxicology

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.

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.

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.

Emtricitabine:

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.

Tenofovir alafenamide: There were no effects on fertility, mating performance 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.

Juvenile Toxicity

Darunavir: 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: 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. 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. 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 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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

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 healthcare professional's advice. If you stop taking SYMTUZA®, tell your healthcare professional right away. Tell your healthcare professional about any new, unusual or worsening symptoms that you notice after stopping treatment. After you stop taking SYMTUZA®, your healthcare professional 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 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 healthcare professional.

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® tablets are yellow to yellowish brown, capsule-shaped, debossed on one side with the number “8121” and “JG” on the other side.

SYMTUZA® comes in the following dosage forms:

Film-coated tablet: 800 mg darunavir ethanolate / 150 mg cobicistat/ 200 mg emtricitabine/ 10 mg tenofovir alafenamide hemifumarate (see **“What are the ingredients in SYMTUZA®?**”).

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, including non-medicinal ingredients or components of the container (see “**What are the ingredients in SYMTUZA®?**”).
- Have severe liver problems.

To help avoid side effects and ensure proper use, talk to your healthcare professional 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 healthcare professional 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. Darunavir crystals may form in the kidney. These can cause kidney disease.
- 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 to sulfa medicines.
- Notice any symptoms of infection. Tell your healthcare professional 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 healthcare professional. 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 healthcare professional 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 healthcare professional 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.

The following may interact with SYMTUZA®:

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/Antianginals (to treat abnormal heart rhythms)	amiodarone (CORDARONE), dronedarone (MULTAQ), ivabradine (LANCORA), lidocaine (when given by injection)
Anticoagulants (to prevent the clotting of red blood cells)	apixaban (ELIQUIS), dabigatran (PRADAXA), rivaroxaban (XARELTO)
Anti-convulsants (to prevent seizures)	carbamazepine (TEGRETOL), phenobarbital phenytoin (DILANTIN)
Anti-gout (to treat gout and familial Mediterranean fever)	colchicine
Antimycobacterial (to treat tuberculosis)	rifampin (RIFADIN, RIFATER, RIFAMATE, ROFACT)
Ergot Derivatives (to treat migraine and headaches)	dihydroergotamine (MIGRANAL), ergonovine, ergotamine (CAFERGOT)
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)

Type of Drug	Examples of Generic Names (Brand Names)
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 blood clots)	ticagrelor (BRILINTA)
Sedatives/Hypnotics (to treat trouble with sleeping and/or anxiety)	triazolam (HALCION)
Opioid antagonist (to treat opioid-induced constipation)	naloxegol (MOVANTIK)

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 healthcare professional

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 healthcare professional is needed:

- Tell your healthcare professional 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 healthcare professional if you are taking any of the following medicines. Your healthcare professional might do some additional blood tests.

Type of Drug	Examples of Generic Names (Brand Names)
Antiarrhythmics/Antianginals (for the heart)	digoxin, disopyramide, flecainide, mexiletine, propafenone
Anticancer Agents (to treat cancer)	dasatinib (SPRYCEL), nilotinib (TASIGNA), vinblastine, vincristine, everolimus (AFINITOR), irinotecan
Anticoagulants (to prevent the clotting of red blood cells)	dabigatran (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)

Type of Drug	Examples of Generic Names (Brand Names)
Anti-infectives (to treat bacterial infections)	clarithromycin (BIAXIN), erythromycin (ERYC)
Antifungals (to treat fungal infections)	fluconazole (DIFLUCAN), ketoconazole (NIZORAL®), itraconazole (SPORANOX®), isavuconazole, posaconazole (POSANOL), voriconazole (VFEND)
Anti-gout (to treat gout and familial Mediterranean fever)	colchicine
Antimycobacterials (to treat bacterial infections)	rifabutin (MYCOBUTIN)
Antiplatelets (to prevent the clotting of red blood cells)	clopidogrel (PLAVIX)
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), 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®), 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), midazolam (taken by injection), flurazepam (DALMANE, SOM-PAM), zolpidem
Antiemetics (to manage symtoms of upper gastrointestinal motility disorders)	domperidone
Urinary antispasmodics (to treat overactive bladder)	fesoterodine solifenacin

This is not a complete list of medicines that you should tell your healthcare professional that you are taking. You can ask your healthcare professional 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 healthcare professional.

How to take SYMTUZA®:

Always use SYMTUZA® exactly as your healthcare professional has told you. You must check with your healthcare professional 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 healthcare professional. Your healthcare professional 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 healthcare professional if you need help with making a schedule that works for you.

Do not stop using SYMTUZA® without talking to your healthcare professional first.

Even when you feel better.

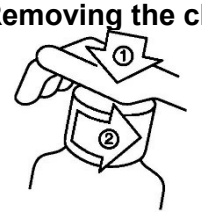
If you have both HIV infection and hepatitis B, it is very important not to stop taking SYMTUZA® without talking to your healthcare professional first (see "**Serious Warnings and Precautions**").

Do not run out of SYMTUZA®. Refill your prescription or talk to your healthcare professional 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, or a person you are caring for, have taken too much SYMTUZA®, contact a 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 healthcare professional 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®?

These are not all the possible side effects you may have when taking SYMTUZA®. If you experience any side effects not listed here, tell your healthcare professional.

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, abdominal pain, yellowing of the skin and eyes, or fatigue or any new symptoms contact your healthcare professional straight away.
- Bone problems including bone pain, softening or thinning (which may lead to fractures).
- Kidney problems.

Tell your healthcare professional 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, tell 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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) 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 to 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: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.janssen.com/canada, or by contacting the manufacturer at: 1-800-567-3331 or 1-800-387-8781.

This information is also available on the Health Canada Drug and Health Product Register at: https://hpr-rps.hres.ca

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

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Marketing Status in United States

Drug Databases (https://www.fda.gov/Drugs/InformationOnDrugs/)

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

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Product Details for NDA 210455

SYMTUZA (COBICISTAT; DARUNAVIR; EMTRICITABINE; TENOFOVIR ALAFENAMIDE FUMARATE)
150MG;800MG;200MG;EQ 10MG BASE
Marketing Status: Prescription

Active Ingredient: COBICISTAT; DARUNAVIR; EMTRICITABINE; TENOFOVIR ALAFENAMIDE FUMARATE
Proprietary Name: SYMTUZA
Dosage Form; Route of Administration: TABLET; ORAL
Strength: 150MG;800MG;200MG;EQ 10MG BASE
Reference Listed Drug: Yes
Reference Standard: Yes
TE Code:
Application Number: N210455
Product Number: 001
Approval Date: Jul 17, 2018
Applicant Holder Full Name: JANSSEN PRODUCTS LP
Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=001&Appl_No=210455&Appl_type=N)