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.

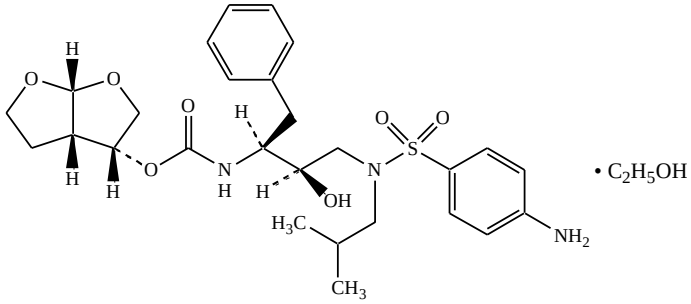
11. DESCRIPTION

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

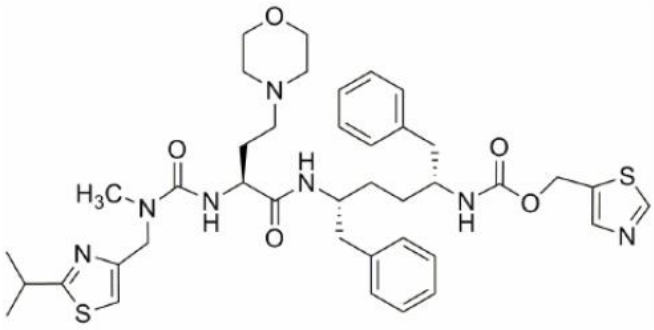
- Darunavir is an inhibitor of the HIV-1 protease.
- Cobicistat is a mechanism-based inhibitor of cytochrome P450 (CYP) enzymes of the CYP3A family.
- Emtricitabine, a synthetic nucleoside analog of cytidine, is an HIV nucleoside analog reverse transcriptase inhibitor (HIV NRTI).
- Tenofovir alafenamide, 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.

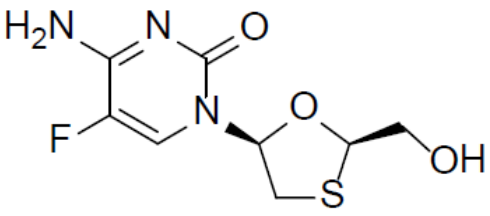
Darunavir: Darunavir, in the form of darunavir ethanolate, has the following chemical name: [(1*S*,2*R*)-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-yl ester monoethanolate. Its molecular formula is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

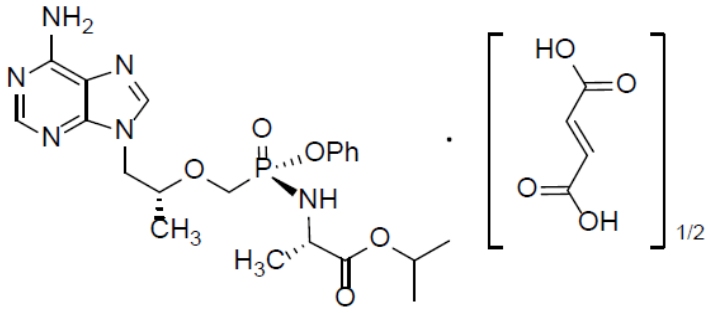


Emtricitabine: The chemical name of emtricitabine is 4-amino-5-fluoro-1-(2*R*-hydroxymethyl-[1,3]-oxathiolan-5*S*-yl)-(1H)-pyrimidin-2-one. Emtricitabine is the (-)enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5 position. Emtricitabine 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.

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} LSmean 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} LSmean 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 coadministration 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 coadministered 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.

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 were observed between subjects with severe renal impairment (creatinine clearance below 30 mL/min, estimated by Cockcroft-Gault method) and healthy subjects *[see Use in Special 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 Special 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.

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.

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.

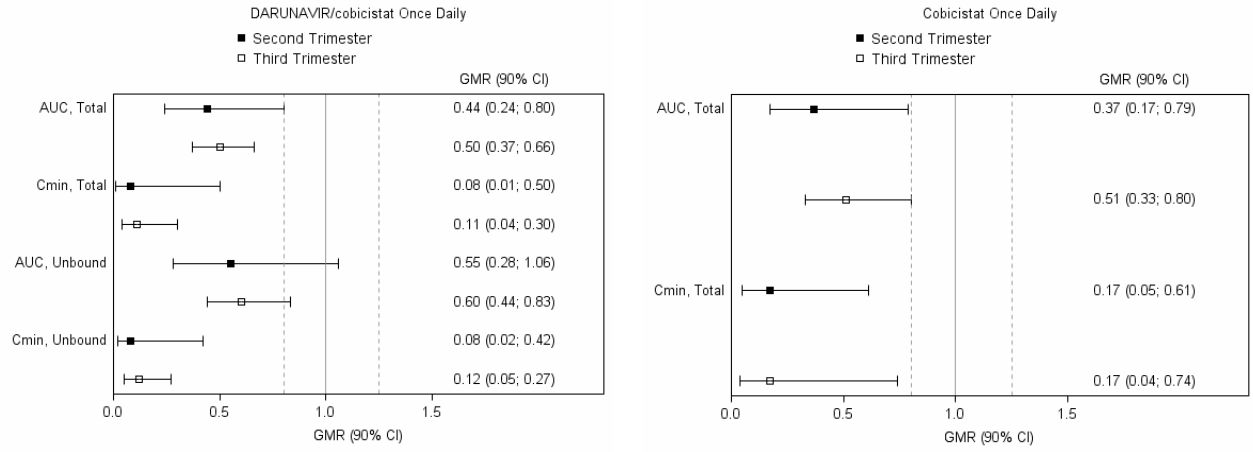
Pregnancy and Postpartum

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 7 and Figure 1).

Table 7: 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*.

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 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 reverse transcriptase, 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.

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 0.0013–0.64 µM. Emtricitabine displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007–0.075 µM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.007–1.5 µM).

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 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 substitutions. In the control arm, there were 3 subjects who rebounded with post-baseline genotypes and no resistance 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 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.

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 HIV-1 Subjects 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 (fixed-dose combination of darunavir and cobicistat) and fixed-dose combination of emtricitabine and tenofovir disoproxil fumarate (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 17% 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 8.

Table 8: 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 HIV-1 Virologically-Suppressed Subjects 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) HIV-1 infected subjects. 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 boosted protease inhibitor (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. Seven subjects had archived tenofovir resistance-associated substitutions and 53 subjects had archived emtricitabine resistance-associated substitutions, mainly at reverse transcriptase 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 9. Prior virologic failure did not impact treatment outcomes.

Table 9: 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]	0.8%	0.5%
Treatment difference[b]	0.3 (95% CI: -0.7; 1.2)	
HIV-1 RNA <50 copies/mL	94.9%	93.7%
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	0.4%	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] Other includes reasons such as withdrew consent, loss to follow-up, and non-compliance

[d] Day 295 – Day 378

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.

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).
- Keep container tightly closed with desiccant inside to protect from moisture.
- Dispense only in the original container. Keep container tightly closed with desiccant inside to protect from moisture.

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)]*.

Product of Canada

Manufactured by:
Patheon Inc,
2100 Syntex Ct
Mississauga ON L5N 7K9, Canada

Manufactured for:
Janssen Therapeutics, Division of Janssen Products, LP, Titusville NJ 08560

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 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 under 18 years of age.

Who should not take SYMTUZA?

Do not take SYMTUZA with any of the following medicines:

- alfuzosin
- carbamazepine
- cisapride
- colchicine, if you have liver or kidney problems
- dronedarone
- elbasvir and grazoprevir
- ergot-containing medicines, such as:
  - dihydroergotamine
  - ergotamine tartrate
  - methylergonovine
- lovastatin or a product that contains lovastatin
- lurasidone
- midazolam, when taken by mouth
- 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.

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, 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.

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 by: Patheon Inc, Mississauga ON L5N 7K9, Canada

Manufactured for: Janssen Therapeutics, Division of Janssen Products, LP, Titusville NJ 08560

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

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 07/2018