**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----------**

| | |
|---|---|
| Indication and Usage (1) | 03/2020 |
| Dosage and Administration, Recommended Dosage (2.2) | 03/2020 |
| Contraindications (4) | 05/2019 |
| Warnings and Precautions, Immune Reconstitution Syndrome (5.5) | 05/2019 |

**----------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: 03/2020**

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**FULL PRESCRIBING INFORMATION: CONTENTS***

*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

SYMTUZA is contraindicated with the following co-administered drugs due to the potential for serious and/or life-threatening events or loss of therapeutic effect *[see Drug Interactions (7.5)]*.

- 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
- GI motility agent: cisapride
- 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

DOCKET ALARM

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