Symtuza

FACT SHEET

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Summary

Symtuza contains four medicines—darunavir, cobicistat, tenofovir alafenamide (TAF) and FTC. Darunavir belongs to the class of drugs called protease inhibitors. Cobicistat is a booster; it raises and maintains levels of darunavir in the blood. TAF and FTC belong to the class of drugs called nucleoside reverse transcriptase inhibitors ("nukes"). Symtuza is taken at a dose of one pill once daily with food. Overall, Symtuza was well-tolerated in clinical trials. General side effects were uncommon and included diarrhea and nausea; these were usually of mild to moderate intensity, and temporary.

What is Symtuza?

Symtuza contains four medicines—darunavir, cobicistat, TAF and FTC. Darunavir belongs to the class of drugs called protease inhibitors. Cobistat belongs to the class of drugs called boosters; it raises and maintains levels of darunavir so that Symtuza need only be taken once daily. TAF and FTC belong to the class of drugs called nucleoside reverse transcriptase inhibitors ("nukes"). Darunavir was approved in Canada in 2006 and the other drugs were approved several years ago. What is new is that Symtuza combines all of these drugs in one pill.

How does Symtuza work?

The drugs in Symtuza work by interfering with enzymes needed by HIV called protease and reverse transcriptase. Using Symtuza greatly reduces HIV's ability to infect cells and make copies of itself.

How do people with HIV use Symtuza?

Symtuza is meant as a complete regimen for the treatment of HIV infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg). Symtuza should be taken with food; the type of food does not matter.

For more information about HIV treatment, see CATIE's *Your Guide to HIV Treatment*.

For many people with HIV, the use of ART (HIV treatment or antiretroviral therapy) has increased their CD4+ cell counts and decreased the amount of HIV in their blood (viral load). These beneficial effects help to greatly reduce

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the risk of developing a life-threatening infection or an AIDS-related cancer. Neither Symtuza nor any other treatment regimen is a cure for HIV. It is therefore important that you see your doctor for checkups and lab tests on a regular basis.

Evidence shows that HIV-positive people who are on ART, engaged in care, and have an ongoing undetectable viral load are substantially less likely to transmit HIV to others, be it through sex, when sharing equipment to use drugs or during pregnancy and birth. In fact, the evidence for sexual transmission shows that people on ART who maintain an undetectable viral load do not pass HIV to their sexual partners. For further information see the CATIE fact sheet *HIV treatment and an undetectable viral load to prevent HIV transmission*. However, it is still a good idea to use condoms because they can reduce your risk for getting and passing on other sexually transmitted infections.

Warnings

Special populations

Pregnant women

A clinical trial has found that levels of darunavir, even when used with the booster cobicistat, are substantially lower in the blood of pregnant HIV-positive women compared with levels in these women after they gave birth. Therefore, the manufacturer of Symtuza, Janssen, recommends "Symtuza should not be initiated in pregnant women. An alternative regimen is recommended for women who become pregnant during therapy with Symtuza." If you are taking Symtuza and are pregnant or want to have a baby, speak to your doctor right away.

Certain children

Symtuza has not been studied in children who were less than 12 years of age or who weighed less than 40 kg.

Older people

Symtuza has not been studied in large numbers of people aged 65 and older.

Hemophiliacs

HIV-positive people who are hemophiliacs and who use protease inhibitors (including those in Symtuza) may experience more frequent bleeding under the skin and/or in the joints. It is not certain why this may occur. However, Janssen recommends "the frequency of bleeding episodes should be closely monitored in patients on Symtuza."

Cholesterol and blood sugar

Levels of cholesterol and sugar in your blood may increase when you take Symtuza or other regimens. Janssen suggests regular monitoring of cholesterol and sugar (glucose) levels in the blood.

Lactic acidosis

Lactic acidosis is rare among HIV-positive people in Canada today as the nukes used are generally safer than in the early days of the HIV pandemic. Also, people tend to start HIV treatment when their CD4+ counts are higher and so they are in generally better health than a decade or two ago when lactic acidosis was more common.

In rare cases, levels of lactic acid may accumulate in the blood of some people who use nukes (such as FTC and TAF, which are in Symtuza). Excess lactic acid levels (lactic acidosis) can cause the liver to become enlarged. Excess lactic acid can be detected with a blood test. Early symptoms of excess lactic acid in the blood can include the following:

- tiredness or lack of energy
- nausea
- stomach pain
- unintentional weight loss

If these are persistent, contact your doctor.

If left untreated, lactic acid levels can become very high and cause life-threatening complications, including the following:

- rapid heartbeat when you are at rest
- rapid breathing when you are at rest

- yellowing of the skin (jaundice) and whites of the eyes
- muscle weakness

If you have these symptoms, contact your doctor or go to the Emergency Department of a hospital.

Here are some typical risk factors for lactic acidosis among HIV-positive people:

- being female
- pregnancy
- obesity
- pre-existing liver injury
- low CD4+ cell count (less than 200 cells/mm^3)

Liver health

Symtuza has not been tested in people with underlying liver injury.

In rare cases, the liver may become injured in some people who take darunavir (in Symtuza). According to the manufacturer of Symtuza, liver injury among darunavir users has "generally occurred" in patients with one or more of the following:

- advanced HIV infection
- infection with hepatitis B virus or hepatitis C virus
- immune reconstitution inflammatory syndrome

In cases 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 swollen liver), you should contact your doctor right away.

Symtuza contains tenofovir and FTC. Both of these drugs have anti-hepatitis B virus (HBV) activity. People with an HBV infection who take Symtuza and then later stop may experience worsening HBV infection. People who are co-infected with HIV and hepatitis-causing viruses and who take ART are sometimes at increased risk for liver injury. It is important to have regular blood tests so that your doctor can assess the health of your liver.

Pancreatic health

In rare cases, inflammation of the pancreas gland (in the abdomen) has occurred in people who were using darunavir. It is not clear if darunavir caused this problem.

General risk factors for inflammation of the pancreas gland include the following:

- smoking tobacco
- excess intake of alcohol
- elevated levels of a fatty substance in the blood called triglycerides
- having disorders such as inflammatory bowel disease, lupus (SLE) and other diseases whereby the immune system attacks the body

Symptoms of an acute inflamed pancreas gland can include pain that:

- begins slowly or suddenly in your upper abdomen
- sometimes spreads to your back
- can be mild or severe
- may last for several days

Other symptoms may include the following:

- fever
- nausea and vomiting
- fast heartbeat
- swollen or tender abdomen

According to the U.S. National Institute of Diabetes and Digestive and Kidney Diseases, "People with acute pancreatitis usually look and feel seriously ill and need to see a doctor right away."

Kidney health

Symtuza contains the newer formulation of tenofovir called TAF (tenofovir alafenamide). Although kidney injury from exposure to TAF is unlikely, Janssen states that it cannot be ruled out. Also, Janssen cautions that people who take Symtuza and who have kidney injury and who also take medicines that can injure the kidneys (such

as non-steroidal anti-inflammatory drugs) "are at increased risk" for developing kidney-related side effects.

The following drugs and substances have the potential to weaken the health of the kidneys (this list is not exhaustive):

- antibiotics – gentamicin, amikacin, vancomycin, rifampin
- anti-cancer drugs – Cisplatin (cis-platinum), carboplatin, Avastin (bevacizumab), gemcitabine
- anti-fungal drugs – amphotericin B, pentamidine
- anti-viral drugs – foscarnet (Foscavir), cidofovir (Vistide), acyclovir, valacyclovir
- non-steroidal anti-inflammatory drugs (NSAIDs) – Aspirin (acetylsalicylic acid), celecoxib (Celebrex), diclofenac (Voltaren), ibuprofen (Advil, Motrin); indomethacin, naproxen, ketorolac (Acular)
- street drugs – cocaine, heroin

Your doctor, nurse or pharmacist may recommend the temporary use of one of these medicines because they are medically necessary. However, repeated or long-term use of some of these medicines, such as NSAIDS, may increase your risk for kidney injury.

Skin and hypersensitivity reactions

In one analysis, Janssen has reported that out of 3,063 people who used darunavir (in Symtuza), 0.4% developed "severe skin reactions… accompanied by fever and/or elevations of liver enzymes." Furthermore, Janssen noted that life-threatening skin reactions (called "Stevens-Johnson Syndrome") were rare, occurring in less than 0.1% of people who used darunavir.

Signs or symptoms of severe skin reactions can include severe rash or rash accompanied by one or more of the following symptoms:

- fever
- generally feeling unwell and in discomfort
- muscle or joint pain/ache
- blisters
- lesions in the mouth and on the lips
- the tissue lining the eyelids and whites of eyes becomes inflamed
- liver inflammation

If these problems occur, contact your doctor right away.

Side effects

General

In clinical trials, Symtuza was generally well-tolerated and effective. However, as with any treatment, there were side effects but these were mostly uncommon and included the following:

- diarrhea
- nausea
- rash
- lack of energy

Note that the HIV-positive people who are typically enrolled in pivotal clinical trials of HIV treatments, including Symtuza, are generally young and healthy. Once a drug is approved and more widely available, it gets used by populations who are not usually in pivotal clinical trials. These people may be older and may have other health issues—such as cardiovascular disease, liver injury, kidney injury, type 2 diabetes, anxiety, depression, and substance use—that require medications or that cause symptoms. As a result, their experience of side effects may be different from those reported in pivotal clinical trials.

The skin

Rash is a common side effect of darunavir-containing medicines such as Symtuza. According to Janssen, such rashes are "mostly mild to moderate, often occurring within the first four weeks of treatment and resolves with continued dosing."

Drug interactions

Some drugs (including prescribed and over-the-counter), herbs and supplements can interfere with the absorption and/or effectiveness of Symtuza. Such interference is called a drug interaction. Some drugs can reduce the levels of the medicines in Symtuza in your blood. This can make Symtuza less effective and lead to treatment failure, reducing your future treatment options. Other drugs can raise the levels of medicines in Symtuza in your blood, resulting in enhanced side effects or new side effects. Therefore it is important to disclose to your doctor and pharmacist all the supplements, drugs, and herbs you are taking.

This factsheet is not comprehensive and only lists some of the potential and actual drug interactions with Symtuza. Speak to your pharmacist to find out more about drug interactions with Symtuza.

Not to be used

Janssen recommends that people taking Symtuza should not use the following drugs:

- for prostate problems – alfuzosin (Xatral)
- for treatment of abnormal heart rhythm – amiodarone, dronedarone, lidocaine (injected into the body), quinidine
- for reducing the risk of blood clots – apixaban, rivaroxaban; ticagrelor
- anti-seizure drugs – carbamazepine, phenobarbital, phenytoin
- for the treatment of gout – colchicine
- anti-histamines – astemizole, terfenadine
- antibiotics – rifampin
- for treatment of migraine and severe headaches – dihydroergotamine, ergonovine, ergotamine, methylergonovine
- for treating hepatitis C virus infection – Zepatier (elbasvir + grazoprevir)
- for treating high cholesterol – lovastatin, simvastatin
- for treating asthma and other lung issues – salmeterol (Advair, Advair Diskus, Serevent Diskhaler Disk, Serevent Diskus)
- for treating psychosis – lurasidone (Latuda), pimozide
- for treating pulmonary arterial hypertension – sildenafil (Revatio)
- for treating sleeping problems – midazolam, triazolam

Symtuza does not interfere (or vice versa) with acid-reducing agents, including those containing aluminum, calcium or magnesium.

Resistance and cross-resistance

Over time, as new copies of HIV are made in the body, the virus changes its structure. These changes, called mutations, can cause HIV to resist the effects of anti-HIV drugs, which means those drugs will no longer work for you.

To reduce the risk of developing drug resistance, all anti-HIV drugs should be taken every day exactly as prescribed and directed. If doses are delayed, missed or not taken as prescribed, the level of drugs in Symtuza in the blood may fall too low. If this happens, the HIV in your body can become resistant to the medication. If you find you are having problems taking your medications as directed, speak to your doctor, nurse or pharmacist about this. They can find ways to help you.

When HIV becomes resistant to one drug in a class, it sometimes becomes resistant to other drugs in that class. This is called cross-resistance. Feel free to talk with your doctor about your current and future treatment options. To help you decide what these future options might be, at some point your doctor can have a small sample of your blood analyzed to test for resistance.

Dosage

Symtuza is supplied as yellow to yellowish-brown capsule-shaped tablets. Each tablet contains 800 mg of darunavir, 150 mg of cobicistat, 200 mg of FTC and 10 mg of TAF. The recommended adult dose of Symtuza is one pill taken once daily with

food; the type of food does not matter. Janssen advises people to take Symtuza "within 30 minutes of eating. Symtuza must be taken with food so that it is absorbed."

If you forget to take a dose, here is advice from Janssen:

- 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 of the time you usually take Symtuza, do not take the missed dose. Wait to take the next dose with food at your usual time.
- Do not take a double dose (two doses together)
- Call your doctor or pharmacist if you are not sure what to do.

Availability

Symtuza is licensed in Canada. Your doctor or pharmacist can tell you more about the availability and coverage of Symtuza in your region. CATIE's online module *Federal, Provincial and Territorial Drug Access Programs* also contains information about Canadian drug coverage.

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