

## Package leaflet: Information for the user

### Symtuza 800 mg/150 mg/200 mg/10 mg - film-coated tablets darunavir/cobicistat/emtricitabine/tenofovir alafenamide

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Symtuza is and what it is used for
2. What you need to know before you take Symtuza
3. How to take Symtuza
4. Possible side effects
5. How to store Symtuza
6. Contents of the pack and other information

#### **1. What Symtuza is and what it is used for**

Symtuza is an antiretroviral medicine used to treat infection with human immunodeficiency virus 1 (HIV-1). It is used in adults and adolescents aged 12 years and older who weigh at least 40 kg.

Symtuza contains four active substances:

- darunavir, an anti-HIV medicine known as a protease inhibitor
- cobicistat, a booster (enhancer) of darunavir
- emtricitabine, an anti-HIV medicine known as a nucleoside reverse transcriptase inhibitor
- tenofovir alafenamide, an anti-HIV medicine known as a nucleotide reverse transcriptase inhibitor

Symtuza reduces HIV-1 in your body and this will improve your immune system (your body's natural defences) and reduce the risk of developing illnesses linked to HIV infection but Symtuza is not a cure for HIV infection.

#### **2. What you need to know before you take Symtuza**

##### **Do not take Symtuza**

- if you are **allergic** (hypersensitive) to darunavir, cobicistat, emtricitabine, tenofovir alafenamide, or any of the other ingredients of Symtuza (listed in section 6).
- if you have **severe liver problems**. Ask your doctor if you are unsure about the severity of your liver disease. Some additional tests might be necessary.

Tell your doctor about **all** medicines you take including medicines taken orally, inhaled, injected or applied to the skin.

##### **Do not combine Symtuza with any of the following medicines**

If you are taking any of these, ask your doctor about switching to another medicine.

Medicine	Purpose of the medicine
<i>Alfuzosin</i>	to treat enlarged prostate

<i>Amiodarone, dronedarone, ivabradine, quinidine, or ranolazine</i>	to treat certain heart disorders (e.g. abnormal heart rhythm)
<i>Carbamazepine, phenobarbital and phenytoin</i>	to prevent seizures
<i>Colchicine (if you have kidney/liver problems)</i>	to treat gout
<i>The combination product lopinavir/ritonavir</i>	anti-HIV medicine
<i>Rifampicin</i>	to treat some infections such as tuberculosis
<i>Pimozide, lurasidone, quetiapine or sertindole</i>	to treat psychiatric conditions
<i>Ergot alkaloids like ergotamine, dihydroergotamine, ergometrine and methylergonovine</i>	to treat migraine headaches
<i>St. John's Wort (Hypericum perforatum)</i>	a herbal product used for depression
<i>Elbasvir/grazoprevir</i>	to treat hepatitis C infection
<i>Lovastatin, simvastatin and lomitapide</i>	to lower cholesterol levels
<i>Triazolam or midazolam (taken by mouth)</i>	to help you sleep and/or relieve anxiety
<i>Sildenafil</i>	to treat a heart and lung disorder called pulmonary arterial hypertension. There are other uses for sildenafil. Please see section 'Other medicines and Symtuza'.
<i>Avanafil</i>	to treat erectile dysfunction
<i>Ticagrelor</i>	to help stop the clumping of platelets in the treatment of patients with a history of a heart attack
<i>Naloxegol</i>	to treat opioid induced constipation
<i>Dapoxetine</i>	to treat premature ejaculation
<i>Domperidone</i>	to treat nausea and vomiting

### Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Symtuza.

People taking Symtuza may still develop infections or other illnesses associated with HIV infection. You must keep in regular contact with your doctor.

People taking Symtuza may develop a skin rash. Infrequently a rash may become severe or potentially life-threatening. Please contact your doctor whenever you develop a rash.

There is a possibility that you may experience kidney problems when taking Symtuza over a long period of time.

Talk to your doctor before taking Symtuza. Tell your doctor immediately, if any of these apply to you.

- if you have had **problems with your liver**, including hepatitis B or C infection. Your doctor may evaluate how severe your liver disease is before deciding if you can take Symtuza.
- if you have **hepatitis B** infection, your liver problems may become worse after you stop taking Symtuza. It is important not to stop taking Symtuza without talking to your doctor first.
- if you have had **kidney disease** or if tests have shown **problems with your kidneys**, before or during treatment. Before starting treatment and during treatment with Symtuza, your doctor may order blood tests to monitor how your kidneys work. Your doctor will consider if Symtuza is the right medicine for you.
- if you have **diabetes**. Symtuza might increase sugar levels in the blood.
- if you notice any **symptoms of infection** (e.g. swollen lymph nodes and fever). In some patients with advanced HIV infection and who had unusual infections due to a weakened immune system (opportunistic infection), signs and symptoms of inflammation from previous infections may occur soon after you start HIV treatment. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms.
- if you notice symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, tell your doctor

immediately. In addition to the opportunistic infections, **autoimmune disorders** (when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection, due to an improvement in the body's immune response. Autoimmune disorders may occur many months after the start of treatment.

- if you have **haemophilia**. Symtuza might increase the risk of bleeding.
- if you are **allergic to sulphonamides** (e.g. used to treat certain infections).
- if you notice any **muscle or bone problems**. Some patients taking anti-HIV medicines may develop a bone disease called osteonecrosis (bone damage caused by loss of blood supply to the bone). This may be more likely with long-term HIV treatment, more severe damage to the immune system, being overweight, or the use of alcohol or medicines called corticosteroids. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms tell your doctor.

### **Elderly**

Symtuza has only been used in limited numbers of patients 65 years or older. If you belong to this age group, please discuss with your doctor if you can use Symtuza.

### **Children and adolescents**

**Symtuza is not for use in children younger than 12 years, or weighing less than 40 kg**, as it has not been studied in children under 12 years.

### **Other medicines and Symtuza**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

There are some medicines that **you must not combine** with Symtuza. These are mentioned above under the heading '**Do not combine Symtuza with any of the following medicines**'.

Symtuza must not be used with another antiviral medicine that contains a booster or another antiviral that requires boosting. In some cases the dose of other medicines might need to be changed. Therefore, always tell your doctor if you take other anti-HIV medicines and follow your doctor's instruction carefully on which medicines can be combined.

You should also not take Symtuza with medicines that contain tenofovir disoproxil (e.g. as fumarate, phosphate, or succinate), lamivudine or adefovir dipivoxil, or medicines that require boosting with ritonavir or cobicistat.

The effects of Symtuza might be reduced if you take any of the following products. Tell your doctor if you take:

- *Bosentan* (to treat high blood pressure in the pulmonary circulation)
- *Dexamethasone* (injection) (corticosteroid)
- *Rifapentine, rifabutin* (to treat bacterial infections)
- *Oxcarbazepine* (to prevent seizures).

The effects of other medicines might be influenced if you take Symtuza and your doctor might want to do some additional blood tests. Tell your doctor if you take:

- *Amlodipine, diltiazem, disopyramide, felodipine, flecainide, mexiletine, nifedipine, propafenone, lidocaine, verapamil* (for heart disease) as the therapeutic effect or side effects of these medicines may be increased.
- *Bosentan* (to treat high blood pressure in the pulmonary circulation)
- *Apixaban, dabigatran etexilate, edoxaban, rivaroxaban, warfarin, clopidogrel* (to reduce clotting of the blood) as their therapeutic effect or side effects may be altered.
- *Clonazepam* (to prevent seizures).
- *Oestrogen-based hormonal contraceptives and hormone replacement therapy*. Symtuza might reduce its effectiveness. When used for birth control, non-hormonal contraception methods are recommended.

- *Ethinylestradiol/drospirenone*. Symtuza might increase the risk for elevated potassium levels by drospirenone.
- *Corticosteroids including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone*. These medicines are used to treat allergies, asthma, inflammatory bowel diseases, inflammatory conditions of the skin, eyes, joints and muscles and other inflammatory conditions. These medicines are generally taken orally, inhaled, injected or applied to the skin. If alternatives cannot be used, its use should only take place after medical evaluation and under close monitoring by your doctor for corticosteroid side effects.
- *Buprenorphine/naloxone, methadone* (medicines to treat opioid dependence)
- *Salmeterol* (medicine to treat asthma)
- *Artemether/lumefantrine* (a combination medicine to treat malaria)
- *Dasatinib, irinotecan, nilotinib, vinblastine, vincristine* (medicines to treat cancer)
- *Sildenafil, tadalafil, vardenafil* (for erectile dysfunction or to treat a heart and lung disorder called pulmonary arterial hypertension)
- *Glecaprevir/pibrentasvir* (to treat hepatitis C virus infection).
- *Fentanyl, oxycodone, tramadol* (to treat pain).
- *Fesoterodine, solifenacin* (to treat urologic disorders).

Your doctor might want to do some additional blood tests and the dose of other medicines might need to be changed since either their own or Symtuza's therapeutic effect or side effects may be influenced when combined.

Tell your doctor if you take:

- *Dabigatran etexilate, edoxaban, warfarin* (to reduce clotting of the blood)
- *Alfentanil* (injectable, strong and short-acting, painkiller that is used for surgical procedures)
- *Carvedilol, metoprolol, timolol* (for heart disease)
- *Digoxin* (to treat certain heart disorders)
- *Clarithromycin* (antibiotic)
- *Clotrimazole, fluconazole, isavuconazole, itraconazole, posaconazole* (for treating fungal infections). *Voriconazole* should only be taken after medical evaluation.
- *Atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin* (to lower cholesterol levels). The risk of muscle damage might be increased. Your doctor will evaluate which cholesterol lowering regimen is best for your specific situation.
- *Rifabutin* (against bacterial infections)
- *Tadalafil, sildenafil, vardenafil* (for erectile dysfunction or high blood pressure in the pulmonary circulation)
- *Amitriptyline, desipramine, imipramine, nortriptyline, paroxetine, sertraline, trazodone* (to treat depression and anxiety)
- *Perphenazine, risperidone, thioridazine* (psychiatric medicines)
- *Ciclosporin, everolimus, tacrolimus, sirolimus* (for dampening down your immune system) as the therapeutic effect or side effects of these medicines might be increased.
- *Colchicine* (antigout). If you have kidney or liver problems see section '**Do not combine Symtuza with any of the following medicines**'.
- *Buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem, midazolam* when used as an injection (medicines to treat trouble with sleeping or anxiety)
- *Metformin* (to treat type 2 diabetes)

This is **not** a complete list of medicines. Tell your healthcare provider about **all** medicines that you are taking.

### **Pregnancy and breast-feeding**

Tell your doctor immediately if you are pregnant or planning to become pregnant. Pregnant women should not take Symtuza.

Because of the potential for side effects in breast-fed infants, women should not breast-feed if they are receiving Symtuza.

Breast-feeding is not recommended in women living with HIV because HIV infection can be passed on to the baby in breast milk. If you are breast-feeding, or thinking about breast-feeding, you should discuss it with your doctor as soon as possible.

### **Driving and using machines**

Symtuza can cause dizziness. Do not operate machines or drive if you feel dizzy after taking Symtuza.

### **Symtuza contains sodium**

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

## **3. How to take Symtuza**

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

**The recommended dose for adults and adolescents 12 years of age and older, who weigh at least 40 kg is one tablet each day with food.**

You must take Symtuza every day and always **with food**. You must eat a meal or a snack within 30 minutes before taking your Symtuza. The type of food is not important.

- The tablet should not be crushed, but swallowed whole. The tablet can be taken with a drink such as water, milk or any nutritional drink. Take Symtuza at around the same time each day.

### **Removing the child resistant cap**



The plastic bottle comes with a child resistant cap and must be opened as follows:

- Push the plastic screw cap down while turning it counter clockwise.
- Remove the unscrewed cap.

### **If you take more Symtuza than you should**

Contact your doctor or nearest emergency department immediately for advice. Keep the tablet bottle with you so that you can show what you have taken.

### **If you forget to take Symtuza**

It is important not to miss a dose of Symtuza.

If you do miss a dose:

- **If you notice within 12 hours** of the time you usually take Symtuza, you must take the tablet immediately, with food. Then take the next dose at your usual time.
- **If you notice 12 hours or more** after the time you usually take Symtuza, then do not take the missed dose and take the next doses with food at your usual time. Do not take a double dose to make up for a forgotten dose.

If you vomit within 1 hour of taking the medicine, another dose of Symtuza should be taken with food as soon as possible. If you vomit more than 1 hour after taking the medicine, then you do not need to take another dose of Symtuza until the next regularly scheduled time.

Contact your doctor if you are uncertain about what to do if you miss a dose or vomit.

### **Do not stop taking Symtuza without talking to your doctor first**

Anti-HIV medicines may make you feel better. Even when you feel better, do not stop taking Symtuza. Talk to your doctor first.

**When your supply of Symtuza starts to run low**, get more from your doctor or pharmacist. This is very important because the amount of virus may start to increase if the medicine is stopped for even a short time. The disease may then become harder to treat.

**If you have both HIV infection and hepatitis B**, it is very important not to stop taking Symtuza without talking to your doctor first. You may require blood tests for several months after stopping treatment with Symtuza. In some patients with advanced liver disease or cirrhosis, stopping treatment may lead to worsening of hepatitis, which may be life-threatening.

**Tell your doctor immediately** about new or unusual symptoms after you stop treatment, particularly symptoms you associate with hepatitis B infection.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

#### **4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

##### **Tell your doctor if you develop any of the following side effects.**

Liver problems that may occasionally be severe have been reported. Your doctor should do blood tests before you start Symtuza. If you have chronic hepatitis B or C infection, your doctor should check your blood tests more often because you have an increased chance of developing liver problems. Talk to your doctor about the signs and symptoms of liver problems. These may include yellowing of your skin or whites of your eyes, dark (tea coloured) urine, pale-coloured stools (bowel movements), nausea, vomiting, loss of appetite, or pain, aching, or pain and discomfort on your right side below your ribs.

Skin rash may affect more than 1 in 10 patients receiving Symtuza. Although most rashes are mild and disappear after a while as treatment is continued, a rash can occasionally be severe or potentially life-threatening. It is important to talk to your doctor if you develop a rash. Your doctor will advise you how to deal with your symptoms or whether Symtuza must be stopped.

Other severe side effects, seen up to 1 patient in 10, were diabetes, increased blood fat levels and symptoms of infection. Inflammation of the pancreas (pancreatitis) has been reported in up to 1 patient in 100.

Very common side effects (may affect more than 1 in 10 people)

- headache
- diarrhoea
- rash

Common side effects (may affect up to 1 in 10 people)

- low red blood cell count (anaemia)
- allergic reactions such as nettle rash (urticaria), itching, decreased appetite (anorexia)
- abnormal dreams
- vomiting, pain or swelling of the belly, indigestion, flatulence (wind)
- abnormal blood test results such as some tests for your kidney. Your doctor will explain these to you.
- dizziness
- joint pain
- muscle pain, muscle cramps or weakness
- weakness
- tiredness (fatigue)
- feeling sick (nausea)

Uncommon side effects (may affect up to 1 in 100 people)

- severe swelling of the skin and other tissues (most often the lips or the eyes)
- symptoms of infection or of autoimmune disorders (immune reconstitution inflammatory syndrome)
- enlargement of breasts
- osteonecrosis (bone damage caused by loss of blood supply to the bone)
- abnormal blood test results such as some tests for your pancreas. Your doctor will explain these to you.

Rare side effects (may affect up to 1 in 1 000 people)

- a reaction called DRESS [severe rash, which may be accompanied by fever, fatigue, swelling of the face or lymph glands, increase of eosinophils (type of white blood cells), effects on liver, kidney or lung].
- darunavir crystals in the kidney causing kidney disease
- severe rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome)

Side effects with unknown frequency: a rash may become severe or potentially life-threatening:

- rash with blisters and peeling skin over much of the body
- red rash covered with small pus-filled bumps that can spread over the body, sometimes with a fever

Some side effects are typical for anti-HIV medicines similar to Symtuza. These are:

- raised blood sugar and worsening of diabetes
- muscle pain, tenderness or weakness. On rare occasions, these muscle disorders have been serious.
- immune reconstitution inflammatory syndrome. In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection (unusual infections due to a weakened immune system), signs and symptoms of inflammation from previous infections may occur soon after HIV treatment is started, including Symtuza. In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment.

**If you notice any of these symptoms tell your doctor.**

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

**Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: <https://yellowcard.mhra.gov.uk/> or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

**5. How to store Symtuza**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the bottle after "EXP". The expiry date refers to the last day of that month.

Do not use this medicine after 6 weeks of first opening the bottle.

Store in the original package in order to protect from moisture. **Keep the bottle tightly closed.** Tablets may be stored outside of the original container for up to 7 days and should be discarded after that time if not taken. Tablets stored outside of the original container should not be placed back into the container.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away any medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What Symtuza contains**

The active substances are darunavir, cobicistat, emtricitabine, and tenofovir alafenamide. Each film-coated tablet (tablet) contains 800 mg darunavir (as ethanolate), 150 mg cobicistat, 200 mg emtricitabine, and 10 mg tenofovir alafenamide (as fumarate).

### **The other ingredients are**

#### *Tablet core:*

The tablet core contains croscarmellose sodium, magnesium stearate, microcrystalline cellulose and colloidal silicon dioxide (please refer to section 2 “Symtuza contains sodium”).

#### *Film coating:*

The film-coating contains polyethylene glycol (macrogol), polyvinyl alcohol (partially hydrolysed), talc, titanium dioxide (E171) and yellow ferric oxide (E172).

### **What Symtuza looks like and contents of the pack**

Yellow to yellowish-brown capsule shaped film-coated tablet, mentioning “8121” on one side and “JG” on the other side.

Symtuza comes in bottles of 30 tablets (with a silica gel desiccant that must be kept in the bottle to help protect your tablets). The silica gel desiccant is contained in a separate sachet or canister and should not be swallowed.

The Symtuza tablets are available in packs containing one bottle or three bottles per carton.

Not all pack sizes may be marketed.

### **Marketing Authorisation Holder**

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### **Manufacturer**

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**For information in large print, tape, CD or Braille, telephone 0800 7318450**

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