

## PACKAGE LEAFLET: INFORMATION FOR THE USER

### Darunavir 600 mg film-coated tablets

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 or pharmacist
- 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 or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

#### What is in this leaflet

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

### 1. WHAT DARUNAVIR IS AND WHAT IT IS USED FOR

Darunavir contains the active substance darunavir. Darunavir is an antiretroviral medicine used in the treatment of human immunodeficiency virus (HIV) infection. It belongs to a group of medicines called protease inhibitors. Darunavir works by reducing the amount of HIV in your body. This will improve your immune system and reduces the risk of developing illnesses linked to HIV infection.

#### What it is used for?

Darunavir is used to treat adults and children of 3 years of age and above, and at least 15 kg body weight who are infected by HIV and who have already used other antiretroviral medicines. Darunavir must be taken in combination with a low

dose of ritonavir and other anti-HIV medicines. Your doctor will discuss with you which combination of medicines is best for you.

### 2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE DARUNAVIR

#### Do not take darunavir:

- If you are **allergic** to darunavir or any of the other ingredients of this medicine (listed in section 6) or to ritonavir.
- 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 darunavir with any of the following medicines

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

- Avanafil (to treat erectile dysfunction).
- Astemizole or terfenadine (to treat allergy symptoms).
- Triazolam and oral (taken by mouth) midazolam (to help you sleep and/or relieve anxiety).
- Cisapride (to treat some stomach conditions).
- Colchicine (if you have kidney and/or liver problems; to treat gout or familial Mediterranean fever).
- Lurasidone, pimozide, quetiapine or sertindole (to treat psychiatric conditions).
- Ergot alkaloids like ergotamine, dihydroergotamine, ergometrine and methylergonovine (to treat migraine headaches).
- Amiodarone, bepridil, dronedarone, ivabradine, quinidine, ranolazine (to treat certain heart disorders e.g. abnormal heart beat).
- Lovastatin, simvastatin and lomitapide (to lower cholesterol levels).
- Rifampicin (to treat some infections such as tuberculosis).
- The combination product lopinavir/ritonavir (this anti-HIV medicine belongs to the same class as darunavir).

- Elbasvir/grazoprevir (to treat hepatitis C infection).
- Alfuzosin (to treat enlarged prostate).
- Sildenafil (to treat high blood pressure in the pulmonary circulation).
- Ticagrelor (to help stop the clumping of platelets in the treatment of patients with a history of a heart attack).
- Naloxegol (to treat opioid induced constipation).
- Dapoxetine (to treat premature ejaculation).
- Domperidone (to treat nausea and vomiting).

Do not combine darunavir with products that contain St. John's wort (*Hypericum perforatum*).

#### Warnings and precautions

Talk to your doctor or pharmacist before taking darunavir.

Darunavir is not a cure for HIV infection.

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

People taking darunavir may develop a **widespread rash** with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome) or a **more severe form of rash** causing skin peeling in more than 30% of the body surface (toxic epidermal necrolysis). Infrequently a rash may become severe or potentially life-threatening. Please contact your doctor whenever you develop a rash.

In patients taking **darunavir and raltegravir** (for HIV infection), rashes (generally mild or moderate) may occur more frequently than in patients taking either medicine separately.

#### Tell your doctor about your situation BEFORE and DURING your treatment

Make sure that you check the following points and tell your doctor if any of these apply to you.

- Tell your doctor if you have had **problems with your liver** before, including hepatitis B or C infection. Your doctor may evaluate how severe your liver disease is before deciding if you can take darunavir.
- Tell your doctor if you have **diabetes**. Darunavir might increase sugar levels in the blood.

- Tell your doctor immediately if you notice any **symptoms of infection** (for example enlarged lymph nodes and fever). In some patients with advanced HIV infection and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. 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.

- 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 symptoms of infection or other 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, please inform your doctor immediately to seek necessary treatment.

- Tell your doctor if you have **haemophilia**. Darunavir might increase the risk of bleeding.

- Tell your doctor if you are **allergic to sulphonamides** (e.g. used to treat certain infections).

- Tell your doctor if you notice any **musculoskeletal problems**. Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. 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 please inform your doctor.

#### Elderly

Darunavir 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 darunavir.

#### Children and adolescents

Darunavir is not for use in children younger than 3 years of age or weighing less than 15 kg.

#### Other medicines and darunavir

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 darunavir. These are mentioned above under the heading "Do not combine darunavir with any of the following medicines".

In most cases, darunavir can be combined with anti-HIV medicines belonging to another class [e.g. NRTIs (nucleoside reverse transcriptase inhibitors), NNRTIs (non-nucleoside reverse transcriptase inhibitors), CCR5 antagonists and FIs (fusion inhibitors)]. Darunavir with ritonavir has not been tested with all PIs (protease inhibitors) and must not be used with other HIV PIs. In some cases dosage 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.

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

- Phenobarbital, phenytoin (to prevent seizures).
- Dexamethasone (corticosteroid).
- Efavirenz (HIV infection).
- Rifapentine, rifabutin (medicines to treat some infections such as tuberculosis).
- Saquinavir (HIV infection).

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

- Amlodipine, diltiazem, disopyramide, carvedilol, felodipine, flecainide, lidocaine, metoprolol, mexiletine, nifedipine, nicardipine, propafenone, timolol, verapamil (for heart disease) as the

therapeutic effect or side effects of these medicines may be increased.

- Apixaban, dabigatran etexilate, edoxaban, rivaroxaban, warfarin, clopidogrel (to reduce clotting of the blood) as their therapeutic effect or side effects may be altered.
- Oestrogen-based hormonal contraceptives and hormonal replacement therapy. Darunavir might reduce its effectiveness. When used for birth control, alternative methods of non-hormonal contraception are recommended.
- Ethinylestradiol/drospirenone. Darunavir might increase the risk for elevated potassium levels by drospirenone.
- Atorvastatin, 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.
- Clarithromycin (antibiotic).
- Ciclosporin, everolimus, tacrolimus, sirolimus (for dampening down your immune system) as the therapeutic effect or side effects of these medicines might be increased.
- 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 (medicines to treat opioid dependence).
- Salmeterol (medicine to treat asthma).
- Artemether/lumefantrine (a combination medicine to treat malaria).
- Dasatinib, everolimus, irinotecan, nilotinib, vinblastine, vincristine (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 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 **dosage of other medicines might need to be changed** since either their own or therapeutic effect of darunavir 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).
- Digoxin (to treat certain heart disorders).
- Clarithromycin (antibiotic).
- Itraconazole, isavuconazole, fluconazole, posaconazole, clotrimazole (to treat fungal infections). Voriconazole should only be taken after medical evaluation.
- Rifabutin (against bacterial infections).
- Cyclosporin, everolimus, tacrolimus, sirolimus (for dampening down your immune system) as the therapeutic effect or side effects of these medicines might be increased.
- 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.
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- Sildenafil, tadalafil, vardenafil (for erectile dysfunction or to treat a heart and lung disorder called pulmonary arterial hypertension).
- Glecaprevir/pibrentasvir (to treat hepatitis C infection).

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

#### Darunavir with food and drink

See section 3 "How to take darunavir".

#### Pregnancy and breast-feeding

Tell your doctor immediately if you are pregnant or planning to become pregnant. Pregnant women should not take darunavir with ritonavir unless specifically directed by the doctor. Pregnant women should not take darunavir with cobicistat.

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

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

Do not operate machines or drive if you feel dizzy after taking darunavir.

#### Darunavir contains sodium

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

#### Darunavir 600 mg film-coated tablets contain Sunset yellow FCF (E110)

It may cause allergic reactions.

### 3. HOW TO TAKE DARUNAVIR

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

Even if you feel better, do not stop taking darunavir and ritonavir without talking to your doctor. After therapy has been initiated, the dose or dosage form must not be changed or therapy must not be stopped without instruction of the doctor.

Darunavir is not suitable for all dosages described below. For these dosages, other medicines containing darunavir should be used.

#### Dose for adults who have not taken antiretroviral medicines before (your doctor will determine this).

You will require a different dose of darunavir which cannot be administered with this strength. Other strengths of darunavir are available.

### Dose for adults who have taken antiretroviral medicines before (your doctor will determine this)

The dose is either:

- 600 mg darunavir (1 tablet of darunavir containing 600 mg darunavir) together with 100 mg ritonavir twice daily.

OR

- 800 mg darunavir (2 tablets of darunavir containing 400 mg darunavir or 1 tablet of darunavir containing 800 mg darunavir) together with 100 mg ritonavir once daily.

Darunavir strength 400 and 800 mg tablets are only to be used to construct the once daily 800 mg regimen

Please discuss with your doctor which dose is right for you.

### Instructions for adults

- Always take darunavir together with ritonavir. Darunavir cannot work properly without ritonavir.
- Take darunavir with food. Darunavir cannot work properly without food. The type of food is not important.
- Swallow the tablets with a drink such as water or milk.
- Darunavir 75 mg and 150 mg tablets and 100 mg/ml oral suspension containing darunavir have been developed for use in children, but in some cases, can also be used in adults.

### Dose for children 3 years of age and above, weighing at least 15 kg who have not taken antiretroviral medicines before (your child's doctor will determine this)

The doctor will work out the right once daily dose based on the weight of the child (see table below). This dose must not exceed the recommended adult dose, which is 800 mg darunavir together with 100 mg ritonavir once a day. The doctor will inform you on how much darunavir tablets and how much ritonavir (capsules, tablets or solution) the child must take.

Weight	One darunavir dose is	One ritonavir <sup>a</sup> dose is
between 15 and 30 kg	600 mg	100 mg
between 30 and 40 kg	675 mg	100 mg
more than 40 kg	800 mg	100 mg

<sup>a</sup> ritonavir oral solution: 80 mg/ml

### Dose for children 3 years of age and above, weighing at least 15 kg who have taken antiretroviral medicines before (your child's doctor will determine this)

The doctor will work out the right dose based on the weight of the child (see table below). The doctor will determine if once daily dosing or twice daily dosing is appropriate for the child. This dose must not exceed the recommended adult dose, which is 600 mg darunavir together with 100 mg ritonavir two times per day or 800 mg darunavir together with 100 mg ritonavir once a day.

The doctor will inform you on how many darunavir tablets and how much ritonavir (capsules, tablets or solution) the child must take. Tablets of other strengths are available and your doctor may have prescribed a certain combination of tablets to construct the appropriate dosing regimen. Darunavir oral suspension may be also available. Your doctor will determine whether darunavir tablets or oral suspension is right for the child.

Twice daily dosing

Weight	One dose is
between 15 and 30 kg	375 mg darunavir + 50 mg ritonavir twice a day
between 30 and 40 kg	450 mg darunavir + 60 mg ritonavir twice a day
more than 40 kg*	600 mg darunavir + 100 mg ritonavir twice a day

\* For children aged 12 or more and weighing at least 40 kg, your child's doctor will determine if

darunavir 800 mg once daily dosing may be used. This cannot be administered with these 600 mg tablets. Other strengths of darunavir are available.

Once daily dosing

Weight	One darunavir dose is	One ritonavir <sup>a</sup> dose is
between 15 and 30 kg	600 mg	100 mg
between 30 and 40 kg	675 mg	100 mg
more than 40 kg*	800 mg	100 mg

<sup>a</sup> ritonavir oral solution: 80 mg/ml

### Instructions for children

- The child must take darunavir always together with ritonavir. Darunavir cannot work properly without ritonavir.
- The child must take the appropriate doses of darunavir and ritonavir two times per day or once a day. If prescribed darunavir twice daily the child must take one dose in the morning, and one dose in the evening. Your child's doctor will determine the appropriate dosing regimen for your child.
- The child must take darunavir with food. Darunavir cannot work properly without food. The type of food is not important.
- The child must swallow the tablets with a drink such as water or milk.
- Darunavir 75 mg and 150 mg tablets and 100 mg/ml oral suspension containing darunavir have been developed for use in children weighing less than 40 kg, but can also be used in some cases.

### 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 darunavir than you should

Contact your doctor, pharmacist or nurse immediately.

### If you forget to take darunavir

If you notice **within 6 hours**, you must take your missed dose immediately. Always take with ritonavir and food. If you notice **after 6 hours**, then skip the intake and take the next doses as usual. Do not take a double dose to make up for a forgotten dose.

### If you vomit after taking darunavir and ritonavir

If you vomit **within 4 hours** of taking the medicine, another dose of darunavir and ritonavir should be taken with food as soon as possible. If you vomit **more than 4 hours** after taking the medicine, then you do not need to take another dose of darunavir and ritonavir 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 darunavir without talking to your doctor first

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

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

## 4. POSSIBLE SIDE EFFECTS

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.

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

- 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] (reported with frequency rare).

- Severe skin reactions (Stevens Johnson Syndrome and Toxic Epidermal Necrolysis), causing flu like symptoms, (cough, runny nose, fever, decreased appetite and malaise) and skin rashes which may develop into blisters and peeling skin (reported with frequency rare/ not known); a widespread rash with blisters and peeling skin, particularly around the mouth, nose and genitals (Stevens-Johnson syndrome) or a more severe form of rash causing skin peeling in more than 30% of the body surface.
- Liver problems that may occasionally be severe have been reported. Your doctor should do blood tests before you start darunavir. 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 (more often when used in combination with raltegravir), itching. The rash is usually mild to moderate. A skin rash might also be a symptom of a rare severe situation. It is therefore important to talk to your doctor if you develop a rash. Your doctor will advise you how to deal with your symptoms or whether darunavir must be stopped.
- Other severe side effects were diabetes (common) and inflammation of the pancreas (uncommon). Symptoms of inflammation of the pancreas include severe stomach pain, which may reach through to your back.

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

- Diarrhoea.

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

- Vomiting, nausea, abdominal pain or distension, dyspepsia, flatulence.
- Headache, tiredness, dizziness, drowsiness, numbness, tingling or pain in hands or feet, loss of strength, difficulty falling asleep.

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

- Chest pain, changes in electrocardiogram, rapid heart beat.
- Decreased or abnormal skin sensibility, pins and needles, attention disturbance, loss of memory, problems with your balance.
- Difficulty breathing, cough, nosebleed, throat irritation.
- Inflammation of the stomach or mouth, heartburn, retching, dry mouth, discomfort of the abdomen, constipation, belching.
- Kidney failure, kidney stones, difficult discharge of urine, frequent or excessive passage of urine, sometimes at night.
- Urticaria, severe swelling of the skin and other tissues (most often the lips or the eyes), eczema, excessive sweating, night sweats, hair loss, acne, scaly skin, colouration of nails.
- Muscle pain, muscle cramps or weakness, pain in extremity, osteoporosis.
- Slowing down of the thyroid gland function. This can be seen in a blood test.
- High blood pressure, flushing.
- Red or dry eyes.
- Fever, swelling of lower limbs due to fluids, malaise, irritability, pain.
- Symptoms of infection, herpes simplex.
- Erectile dysfunction, enlargement of breasts.
- Sleeping problems, sleepiness, depression, anxiety, abnormal dreams, decrease in sexual drive.

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

- Heart attack, slow heart beat, palpitations.
- Visual disturbance.
- Chills, feeling abnormal.
- A feeling of confusion or disorientation, altered mood, restlessness.
- Fainting, epileptic fits, changes or loss of taste.
- Mouth sores, vomiting blood, inflammation of the lips, dry lips, coated tongue.
- Running nose.
- Skin lesions, dry skin.
- Stiffness of muscles or joints, joint pain with or without inflammation.

- Changes in some values of your blood cells or chemistry. These can be seen in the results of blood and/or urine tests. Your doctor will explain these to you. Examples are: increase in some white blood cells.
- Darunavir crystals in the kidney causing kidney disease.

Some side effects are typical for anti-HIV medicines in the same family as darunavir. These are:

- Muscle pain, tenderness or weakness. On rare occasions, these muscle disorders have been serious.

### Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) 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 DARUNAVIR

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.

This medicine does not require any special storage conditions.

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

## 6. CONTENTS OF THE PACK AND OTHER INFORMATION

### What darunavir contains:

- The active substance is darunavir. Each tablet contains 600 mg of darunavir.
- The other ingredients are: dry granulation agent (mixture of microcrystalline cellulose and anhydrous calcium hydrogen phosphate),

croscarmellose sodium, microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate, Opadry II Orange 85F23888 [mixture of poly(vinyl alcohol) – partially hydrolysed, titanium dioxide (E171), macrogol 3350, talc, Sunset yellow FCF aluminium lake (E 110) and yellow iron oxide (E172)].

### What darunavir looks like and contents of the pack:

Plain, oval, biconvex, orange film-coated tablets of approx. 19 mm length and 1 mm width. 60 film-coated tablets in HDPE bottle with child-resistant screw cap.

Bundle pack of 3 HDPE bottles with 60 film-coated tablets in each bottle.

Darunavir is also available as 400 mg and 800 mg film-coated tablets.

Not all pack sizes may be marketed.

### The Marketing Authorisation Holder is

Zentiva Pharma UK Limited, 12 New Fetter Lane, London, EC4A 1JP, United Kingdom

### The Manufacturer is

S.C. Laropharm S.R.L., Șos. Alexandriei nr. 145 A, Oraș Bragadiru, Jud. Ilfov, 077025, Romania

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