

**PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE
PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986**

The medicine is dispensed with a doctor's prescription only

Name and form of the preparation:

REZOLSTA[®]

Film-coated tablets

darunavir 800 mg (as ethanolate), cobicistat 150 mg.

Inactive and allergenic ingredients in the preparation: See "Further Information" in section 6 and "Important information about some of the ingredients of the medicine" in section 2.

Read this leaflet carefully in its entirety before using this medicine. The leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.

This medicine has been prescribed to treat your ailment. Do not pass it on to others. It may harm them even if it seems to you that their ailment is similar.

1. WHAT IS THE MEDICINE INTENDED FOR?

Rezolsta is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV 1) infection in treatment-naïve and treatment-experienced adults with no darunavir resistance-associated substitutions (V11i, V32i, L33F, i47V, i50V, i54L, i54M, T74P, L76V, i84V, L89V).

Therapeutic group: Darunavir belongs to a group of HIV medicines of the protease inhibitor group.

Cobicistat is a cytochrome P450 inhibitor.

The medicine contains the active ingredients: darunavir, which acts by reducing the level of HIV in the blood to a very low level, and cobicistat, which increases the amount of the active ingredient darunavir in the blood.

Treatment with Rezolsta will improve your immune system (your body's natural defence) and will reduce the risk of developing illnesses linked to HIV infection; however, Rezolsta does not cure HIV infection.

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

- You are sensitive (allergic) to the active ingredients or to any of the other ingredients contained in the medicine (listed in section 6 "Further Information").
- You are suffering from **severe liver problems**. Ask the doctor if you are uncertain about the severity of your liver disease. Additional tests may be required.
- The medicine must not be used during pregnancy and when breastfeeding.

Tell your doctor about **all** the medicines you take orally, by inhalation, by injection

or by applying to the skin.

- **Do not take Rezolsta together with the following medicines;** if you are taking any of these medicines, ask the doctor about switching to another medicine:
 - Alfuzosin (to treat an enlarged prostate).
 - Amiodarone, bepridil, dronedarone, ivabradine, quinidine or ranolazine (to treat certain heart disorders, e.g., abnormal heart rate).
 - Carbamazepine, phenobarbital and phenytoin (to prevent seizures).
 - Astemizole or terfenadine (to treat allergy symptoms).
 - Colchicine (if you have kidney/liver problems) (to treat gout or familial Mediterranean fever).
 - A combination preparation containing lopinavir/ritonavir (to treat HIV).
 - Rifampicin (to treat infections, such as tuberculosis).
 - Lurasidone, pimozide, quetiapine or sertindole (to treat psychiatric conditions).
 - Medicines of the ergot alkaloid group, such as ergotamine, dihydroergotamine, ergometrine and methylergonovine (to treat migraine headaches).
 - Cisapride (to treat stomach conditions).
 - St. John's wort (*Hypericum perforatum*) (an herbal preparation used for treatment of depression).
 - Elbasvir or grazoprevir (to treat hepatitis C infection).
 - Lovastatin, simvastatin and lomitapide (to lower cholesterol levels).
 - Triazolam or midazolam (taken orally) (to induce sleep and/or relieve anxiety).
 - Sildenafil (to treat a heart and lung problem called pulmonary arterial hypertension. There are other uses for sildenafil. See section "Drug interactions").
 - Avanafil (to treat erection problems).
 - Ticagrelor (helps 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).

Special warnings regarding use of the medicine

Talk to the doctor or nurse before taking the medicine.

People taking Rezolsta may still develop infections or other illnesses associated with HIV. You must therefore continue with routine check-ups by the doctor.

People taking Rezolsta may develop a skin rash. Infrequently, the rash may be severe or life-threatening. Contact the doctor as soon as you develop a rash.

In patients taking Rezolsta and raltegravir (to treat HIV infection), a rash (generally mild or moderate) may occur more frequently than in patients taking each medicine separately.

Rezolsta has been given to a small number of patients 65 years of age and above. If you belong to this age group, consult your doctor on whether you can use Rezolsta.

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

Before treatment with Rezolsta, tell the doctor if:

- You suffered **from liver problems** in the past, including hepatitis B or C infection. The doctor may evaluate the severity of the liver disease to determine if you may receive treatment with Rezolsta.
- You suffered **from kidney problems** in the past. The doctor will carefully consider whether you can receive the medicine.
- You have **diabetes**, since Rezolsta may increase blood sugar levels.
- Inform the doctor immediately if you notice any **symptoms of infection** (e.g., enlarged lymph nodes and fever). In some advanced-stage HIV carriers with a history of unusual infections due to a weakened immune system (opportunistic infections), signs and symptoms of inflammation from previous infections can manifest themselves immediately after HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response and its ability to fight infections that were pre-existing in the body with no obvious symptoms.
- In addition to opportunistic infections, **autoimmune problems** (a condition in which the immune system attacks healthy body tissues) may also occur after starting to take medicines to treat HIV. Autoimmune problems can even occur many months after starting the treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness that starts in the hands and feet and rises toward the trunk of the body, palpitations, tremor or hyperactivity, inform the doctor immediately so you can receive the necessary treatment.
- Tell your doctor if you have **hemophilia** (impaired blood coagulation); Rezolsta may increase the risk of bleeding.
- Tell your doctor if you are **allergic to sulfonamides** (used to treat certain infections).
- Tell your doctor if you notice any **musculoskeletal problems**. Some patients taking a combination of antiretroviral medicines may develop a bone disease called osteonecrosis (death of bone tissue 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, overweight, alcohol consumption or use of medicines called corticosteroids. The signs of osteonecrosis are joint stiffness, pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms, inform the doctor.

Children and adolescents

The medicine is not intended for use in children and adolescents under the age of 18.

Drug interactions

If you are taking, or have recently taken, other medicines, including non-

prescription medicines and nutritional supplements, tell the doctor or pharmacist.

- There are some medicines that **must not be combined together with Rezolsta**. These medicines are listed in section 2 “Before Using the Medicine” – “Do not take Rezolsta together with the following medicines”.
- Do not use Rezolsta together with another antiviral medicine that contains a booster or another antiviral medicine that requires boosting. In some cases, the dose of the other medicine must be adjusted. Therefore, always inform the doctor about any other anti-HIV medicines and follow the doctor’s instructions carefully regarding which medicines can be combined.
- **The following medicines might reduce the effectiveness of Rezolsta. Tell the doctor if you are taking:**
 - Bosentan (to treat heart disease).
 - Dexamethasone (by injection) (a corticosteroid).
 - Efavirenz, etravirine, nevirapine (to treat HIV infection).
 - Rifapentine, rifabutin (to treat bacterial infections).
- **The effects of the following medicines may be altered if taken together with Rezolsta. Your doctor may wish to perform additional blood tests. Tell the doctor if you are taking:**
 - Amlodipine, carvedilol, diltiazem, disopyramide, felodipine, flecainide, lidocaine, metoprolol, mexiletine, nifedipine, nifedipine, propafenone, timolol, verapamil (to treat heart diseases), since 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.
 - Clonazepam (to prevent seizures).
 - Estrogen-based preparations used as contraceptives and as hormone replacement therapy. Rezolsta may reduce their effectiveness. When used for contraception, it is recommended to use alternative methods of non-hormonal contraception.
 - Ethinylestradiol/drospirenone. Rezolsta may increase the risk of elevated potassium levels due to drospirenone.
 - Atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin (to lower cholesterol levels). The risk of muscle damage might be increased. The doctor will evaluate which cholesterol-lowering treatment is appropriate for your specific condition.
 - Ciclosporin, everolimus, tacrolimus, sirolimus (to suppress the immune system), as the therapeutic effect or side effects of these medicines may 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 no other treatment is possible, they should only be used after medical evaluation and under close monitoring by a doctor for corticosteroid side effects.

- Buprenorphine/naloxone, methadone (medicines to treat opioid dependence).
 - Salmeterol (to treat asthma).
 - Artemether/lumefantrine (a combination medicine to treat malaria).
 - Dasatinib, irinotecan, nilotinib, vinblastine, vincristine (medicines to treat cancer).
 - Perphenazine, risperidone, thioridazine (psychiatric medicines).
 - Clorazepate, diazepam, estazolam, flurazepam (to treat sleeping problems or anxiety).
 - Sildenafil, tadalafil, vardenafil (to treat erection problems or to treat a heart and lung disorder called pulmonary arterial hypertension).
 - Glecaprevir/pibrentasvir (to treat hepatitis C infection).
 - Fesoterodine, solifenacin (to treat urological problems).
- **The doctor may wish to perform additional blood tests and the dosage of the following medicines may have to be changed since either their own or Rezolsta’s therapeutic effect or side effects may be influenced when combined. Tell the doctor if you are taking:**
- Dabigatran etexilate, edoxaban, warfarin (to reduce clotting of the blood).
 - Alfentanil (by injection, a strong and short-acting painkiller used in surgical procedures).
 - Digoxin (to treat certain heart problems).
 - Clarithromycin (an antibiotic).
 - Clotrimazole, fluconazole, itraconazole, isavuconazole, posaconazole (to treat fungal infections). Voriconazole should only be taken after medical evaluation.
 - Rifabutin (against bacterial infections).
 - Tadalafil, sildenafil, vardenafil (to treat erection problems or high blood pressure in the pulmonary circulation).
 - Amitriptyline, desipramine, imipramine, nortriptyline, paroxetine, sertraline, trazodone (to treat depression and anxiety).
 - Maraviroc (to treat HIV infection).
 - Colchicine (to treat gout or familial Mediterranean fever). If you have impaired kidney or liver function, see section 2 “Before Using the Medicine” – “Do not take Rezolsta together with the following medicines”.
 - Bosentan (to treat high blood pressure in the pulmonary circulation).
 - Buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem, midazolam by injection (to treat sleeping problems and/or anxiety).
 - Metformin (to treat type 2 diabetes).
 - Fentanyl, oxycodone, tramadol (to treat pain).

This **is not** the complete list. Tell your doctor or pharmacist about any medicine that you are taking.

Use of the medicine and food

Take the medicine every day and always with food. Rezolsta cannot work properly without food. Eat a meal or a snack within 30 minutes prior to taking Rezolsta. The type of food is not important.

Pregnancy and breastfeeding

Tell the doctor immediately if you are pregnant or are planning to become pregnant. Pregnant women must not use Rezolsta.

Because of the potential for side effects in breastfed infants, women should not breastfeed if they are receiving Rezolsta.

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

Driving and using machines

Do not drive a vehicle or operate dangerous machines if you feel dizzy after taking Rezolsta.

Important information about some of the ingredients of the medicine

Rezolsta contains sodium

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

3. HOW SHOULD THE MEDICINE BE USED?

Always use the preparation according to the doctor’s instructions.

Check with the doctor or pharmacist if you are uncertain about the dosage and treatment regimen of the preparation.

The dosage and treatment regimen will be determined by the doctor only.

Do not exceed the recommended dose.

- Swallow the medicine whole with a drink, such as water or milk. If you have trouble swallowing Rezolsta, inform the doctor. The tablet may be split using a tablet cutter. After splitting the tablet, the entire dose (both halves) should be taken right away with a drink such as water or milk.
- Take your other HIV medicines that you are taking in combination with Rezolsta according to the instructions given to you by the doctor.

Instructions for opening the bottle:

The bottle has a safety cap that prevents accidental opening by children.

Open the bottle by pressing down on the cap (1) while turning counterclockwise (2).

Remove the cap.



- **If you have accidentally taken a higher dosage of Rezolsta than that prescribed by the doctor**, refer to the doctor or pharmacist immediately.
- **If you forgot to take this medicine** at the designated time and you remembered **within 12 hours** of the time you were supposed to take it, take a dose as soon

as you remember and always together with food. If **more than 12 hours** have elapsed from the time you were supposed to take the medicine, skip the forgotten dose. Take the next dose as planned. Never take two doses together!

- **If you vomit after taking Rezolsta**

If you vomit **within 4 hours** of taking the medicine, take another dose of Rezolsta immediately together with food. If you vomit **more than 4 hours** after taking the medicine, do not take another dose of Rezolsta until the next regularly scheduled time.

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

Adhere to the treatment regimen as recommended by the doctor.

Do not stop treatment with this medicine without consulting the doctor.

After starting treatment, it must not be stopped without an instruction from the doctor.

Medicines to treat HIV can improve the way you feel. Even if there is an improvement in your health, do not stop treatment with the medicine without consulting the doctor.

Do not take medicines in the dark! Check the label and the dose each time you take medicine. Wear glasses if you need them.

If you have further questions regarding use of the medicine, consult the doctor or pharmacist.

4. SIDE EFFECTS

During HIV therapy, there may be an increase in body weight and in levels of blood lipids and glucose. This is partly linked to restored health and lifestyle. In the case of blood lipids, it is possible that the cause may be the HIV medicines themselves. The attending doctor will test for these changes.

As with any medicine, use of Rezolsta may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not suffer from any of them.

Inform the doctor if you develop any of the following side effects:

- Liver problems that may occasionally be severe have been reported. The doctor must perform blood tests before starting treatment with Rezolsta. If you suffer from chronic hepatitis B or C infection, your doctor must perform 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 the skin or the whites of the eyes, dark (tea-colored) urine, pale-colored stools (bowel movements), nausea, vomiting, loss of appetite or pain, or pain and discomfort on the right side below the ribs.
- A common side effect of Rezolsta is a skin rash (more common 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 and severe situation. It is therefore

important to talk to the doctor if you develop a rash.

The doctor will advise you how to deal with the symptoms or whether treatment with Rezolsta should be stopped.

- Another severe side effect, which occurs in up to one user in 10, is diabetes. Inflammation of the pancreas (pancreatitis) has been reported in up to one user in 100.

Very common side effects – effects that may occur in more than one user in 10:

- headaches
- diarrhea, nausea

Common side effects – effects that may occur in up to one user in 10:

- allergic reaction, itching
- decreased appetite
- unusual dreams
- vomiting, pain or swelling of the abdomen, indigestion, flatulence
- muscle pains
- tiredness
- abnormal results of certain blood tests, such as tests for liver or kidney function. The doctor will explain this to you
- weakness

Uncommon side effects – effects that may occur in up to one user in 100:

- symptoms of infection or of an autoimmune problem (immune reconstitution inflammatory syndrome)
- osteonecrosis (death of bone tissue caused by loss of blood supply to the bone)
- enlargement of the breasts
- abnormal results for certain blood tests, such as tests for pancreas function, high sugar level, abnormal levels of lipids (fats). The doctor will explain this to you
- allergic reaction such as nettle rash (urticaria), severe swelling of the skin and other tissues (most often the lips or the eyes)
- severe rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals

Rare side effects – effects that may occur up to one user in 1,000:

- a reaction called DRESS: a severe skin rash, which may be accompanied by fever, fatigue, swelling of the face or lymph nodes, increase in eosinophils (a type of white blood cell), effects on the liver, kidneys or lungs
- darunavir crystals in the kidneys causing kidney disease

Side effects with unknown frequency:

A rash may be severe or life-threatening:

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

The following effects are typical of HIV medicines from the same family as Rezolsta:

muscle pain, tenderness or weakness. On rare occasions, these muscle disorders were serious.

If a side effect occurs, if one of the side effects worsens, or if you suffer from a side effect not mentioned in this leaflet, consult with the doctor.

Reporting side effects

Side effects can be reported to the Ministry of Health by clicking on the link “Report Side Effects of Drug Treatment” found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link:

<https://sideeffects.health.gov.il>

5. HOW SHOULD THE MEDICINE BE STORED?

Avoid poisoning! This medicine and any other medicine must be kept in a safe place out of the reach and sight of children and/or infants to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.

Do not use the medicine after the expiry date (exp.date) that appears on the package. The expiry date refers to the last day of that month.

- Do not store above 30° C.
- Can be used for 6 weeks after first opening.

6. FURTHER INFORMATION

In addition to the active ingredients, the medicine also contains:

Silicified Microcrystalline Cellulose; Colloidal Silicon Dioxide; Crospovidone (Type B); Hypromellose 2910 15 mPa.s; Magnesium Stearate

Coating:

Polyvinyl Alcohol-Partially Hydrolyzed; Titanium Dioxide; Macrogol/PEG 3350; Talc; Iron Oxide Red; Iron Oxide Black

What the medicine looks like and the contents of the package:

A film-coated, oval-shaped, pink tablet, with TG written on one side and 800 on the other side. Each package contains a plastic bottle with 30 tablets.

Manufacturer: Janssen Cilag S.P.A., Via C. Janssen, Borgo S.Michele, 04100, Latina, Italy.

Registration Holder: J-C Health Care Ltd., Kibbutz Shefayim 6099000, Israel.

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 154-69-34386-00

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