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

The medicine is dispensed with a doctor's prescription only

**Name of the preparation and its form:**

# **Prezista® 400 mg**, film-coated tablets
# **Prezista® 600 mg**, film-coated tablets

**The active ingredient and its amount:**

Each tablet contains:

Darunavir 400 mg (corresponding to 433.64 mg of darunavir ethanolate)

Darunavir 600 mg (corresponding to 650.46 mg of darunavir ethanolate)

Inactive and allergenic ingredients: See sub-section “Important information about some of the ingredients of the medicine” and section 6 “Further Information”.

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

This medicine has been prescribed for the treatment of 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?

Prezista in combination with ritonavir and other anti-HIV medicines is intended for the treatment of the HIV virus infection, in patients above the age of 18.

**Therapeutic group:** Anti-HIV of the protease inhibitors group

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

## 2. BEFORE USING THE MEDICINE

**☒ Do not use the medicine if:**

- You are sensitive (**allergic**) to the active ingredient or to any of the other ingredients contained in the medicine (see section 6) or to ritonavir.
- Do not use in children and adolescents under 18 years of age.
- You **suffer from severe liver problems.** Ask your doctor if you are unsure about the severity of your liver disease. Additional tests may be necessary.

- **Do not take Prezista with any of the following medicines:** If you are taking any of these, ask your doctor about switching to another medicine.
  Avanafil (for treatment of erectile problems),
  Astemizole or terfenadine (for treatment of allergy symptoms),
  Triazolam and midazolam (taken orally) (to induce sleep and/or for sedation),
  Cisapride (for stomach problems),
  Colchicine (if you have kidney and/or liver problems) (for treatment of gout or Familial Mediterranean Fever),
  Lurasidone, pimozide, quetiapine or sertindole (for treatment of psychiatric conditions),
  Ergot alkaloids such as ergotamine, dihydroergotamine, ergometrine and methylergonovine (for treatment of migraine headaches),

Amiodarone, bepridil, dronedarone, ivabradine, quinidine, ranolazine (for treatment of certain heart disorders such as, for example, abnormal heart rate),

Lovastatin, simvastatin and lomitapide (to lower blood cholesterol levels),

Rifampicin (for treatment of some infections such as tuberculosis),

The combination preparation lopinavir/ritonavir (this anti-HIV medicine belongs to the same class as Prezista),

Elbasvir/grazoprevir (for treatment of hepatitis C),

Alfuzosin (for treatment of an enlarged prostate),

Sildenafil (for treatment of pulmonary hypertension),

Dabigatran, ticagrelor (to help stop the clumping of platelets in the treatment of patients with a history of a heart attack),

Naloxegol (for treatment of opioid induced constipation),

Dapoxetine (for treatment of premature ejaculation),
Domperidone (for treatment of nausea and vomiting).

- Do not combine Prezista with preparations that contain St. John's Wort (*Hypericum perforatum*).

**Special warnings regarding use of the medicine:**

Consult with your doctor, pharmacist or nurse before taking Prezista.

- Treatment with Prezista does not cure HIV infection. You can still pass on HIV to others when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Consult your doctor about the precautions you need to take to prevent infecting others.
- During treatment with the medicine, there is still the possibility of developing infections or other illnesses associated with HIV infection, and therefore continue with regular visits to your doctor.

- People taking Prezista may develop a skin rash. Infrequently a rash may become severe or potentially life-threatening. Refer to your doctor whenever you develop a rash.
- In patients taking Prezista and raltegravir (for HIV infection), rashes (generally mild or moderate) may occur more frequently than in patients taking either medicine separately.

**Tell the 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.

- Inform your doctor if you have suffered in the past **from liver problems**, including hepatitis B or C infection. Your doctor may evaluate the severity of your liver disease before deciding whether you can receive treatment with Prezista.

- Tell your doctor if you have **diabetes**, since Prezista may increase the level of blood sugar.
- 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 infections, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is possible that these symptoms are due to an improvement in the body's immune response and its ability 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 HIV infection. Autoimmune problems 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, inform your doctor immediately to seek necessary treatment.

- Tell your doctor if you have **hemophilia** (a defect in blood clotting ability) since Prezista may increase the risk of bleeding.
- Tell your doctor if **you are sensitive (allergic) to sulphonamides** (such as those used to treat certain infections).
- Tell your doctor if you notice any **musculoskeletal problems.** Some patients taking combination antiretroviral medication 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, pain (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms, you must inform your doctor.

## Elderly

Prezista has only been used in limited numbers of patients aged 65 years or older. If you belong to this age group, consult with your doctor whether you can use Prezista.

## Children and adolescents

Do not use in children and adolescents under 18 years of age.

## Drug interactions

**If you are taking, or have recently taken, other medicines including non-prescription medicines and nutritional supplements, inform the doctor or pharmacist.** Especially if you are taking:

There are some medicines that **must not be taken together** with Prezista. These are listed in the section “Do not use the medicine if”.

- In most cases, Prezista may be taken together 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]). Prezista in combination with ritonavir has not been tested with all protease inhibitors, and therefore it must not be used with other anti-HIV medication belonging to the protease inhibitor class. In some cases, dosages of other medicines may need to be changed. Therefore, always tell your doctor if you are taking any other anti-HIV medicine and follow your doctor's instructions carefully regarding which medicines can be combined.

The effects of Prezista may be reduced if you are taking the following medicines. Tell the doctor if you are taking:

- Phenobarbital, phenytoin (for the prevention of seizures)
- Dexamethasone (a corticosteroid)
- Efavirenz (for treatment of HIV infection)

- Boceprevir (for treatment of hepatitis C)
- Rifapentine, rifabutin (for treatment of some infections such as tuberculosis)
- Saquinavir (for treatment of HIV infection).

The effects of the following medicines may change if you take Prezista. Tell your doctor if you are taking:

- Amlodipine, diltiazem, disopyramide, carvedilol, felodipine, flecainide, lidocaine, metoprolol, mexiletine, nifedipine, nicardipine, propafenone, timolol, verapamil (for treatment of heart problems); as the therapeutic effect or side effects of these medicines may be increased.
- Apixaban, edoxaban, rivaroxaban, warfarin (for treatment of blood clotting problems); their side effects or therapeutic effect may be altered. It is possible that the doctor may need to perform blood tests.
- Estrogen-based hormonal preparations used for birth control and hormonal replacement therapy. Prezista may reduce their effectiveness. When the

preparations are used for birth control, alternative methods of non-hormonal contraception are recommended.

- Ethinylestradiol/drospirenone. Prezista may increase the risk of elevated potassium levels by drospirenone.
- Atorvastatin, pravastatin, rosuvastatin (to lower cholesterol levels). The risk of muscle tissue damage might be increased. Your doctor will evaluate which cholesterol lowering regimen is best suited for you.
- Clarithromycin (an antibiotic)
- Ciclosporin, everolimus, tacrolimus, sirolimus (for depressing the immune system) as the therapeutic effect or side effects of these medicines may be increased. Your doctor may need to do some additional tests.
- Corticosteroids including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone. These medicines are used to treat allergies, asthma, inflammatory bowel diseases, inflammatory conditions of

the eyes, joints and muscles and other inflammatory conditions. If there are no alternative treatments, they should only be used after medical evaluation and under close monitoring by the doctor for corticosteroid side effects.

- Buprenorphine/naloxone (medicines for treatment of opioid dependence)
- Salmeterol (for treatment of asthma)
- Artemether/lumefantrine (a combination medicine for treatment of malaria)
- Dasatinib, everolimus, irinotecan, nilotinib, vinblastine, vincristine (for treatment of cancer)
- Sildenafil, tadalafil, vardenafil (for treatment of erectile problems or to treat a heart and lung disorder called pulmonary hypertension)
- Glecaprevir/pibrentasvir, simeprevir (for treatment of hepatitis C)
- Fentanyl, oxycodone, tramadol (for treatment of pain)
- Fesoterodine, solifenacin (for treatment of urological problems).

The dosage of other medicines may need to be altered since either their own or Prezista's therapeutic effect or side effects may be changed when taken together:

- Alfentanil (strong and short-acting painkiller, given by injection, that is used in surgical procedures)
- Digoxin (for treatment of certain heart problems)
- Clarithromycin (an antibiotic)
- Itraconazole, isavuconazole, fluconazole, posaconazole, clotrimazole (for treatment of fungal infections); Voriconazole should only be taken following medical evaluation.
- Rifabutin (for treatment of bacterial infections)
- Sildenafil, vardenafil, tadalafil (for treatment of erectile problems or pulmonary hypertension)
- Amitriptyline, desipramine, imipramine, nortriptyline, paroxetine, sertraline,

trazodone (for treatment of depression and anxiety)

- Maraviroc (for treatment of HIV infection)
- Methadone (for treatment of opiate dependence)
- Carbamazepine, clonazepam (for prevention of seizures or for treatment of certain types of nerve pain)
- Colchicine (for treatment of gout or Familial Mediterranean Fever)
- Bosentan (for treatment of pulmonary hypertension)
- Buspirone, clorazepate, diazepam, estazolam, flurazepam, injectable midazolam, zolpidem (sedatives)
- Perphenazine, risperidone, thioridazine (for treatment of psychiatric conditions)
- Metformin (for treatment of type 2 diabetes).

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

## ! Use of the medicine and food

See section 3 – “How should the medicine be used”.

## ! Pregnancy, breast-feeding and fertility

Tell your doctor immediately if you are pregnant, planning to become pregnant or if you are breast-feeding. Do not take Prezista with ritonavir if you are pregnant or breast-feeding except with explicit permission from the doctor. Pregnant or breast-feeding mothers should not take Prezista with cobicistat.

It is recommended that HIV infected women should not breast-feed because of the possibility of infecting the baby with HIV through breast milk, and because of the unknown effects of the medicine on the baby.

## ! Driving and operating machinery

Do not drive nor operate dangerous machinery if you feel dizzy after taking Prezista.

**Important information about some of the ingredients of the medicine**

Prezista 400 mg and Prezista 600 mg Tablets contain sunset yellow FCF (E110) which may cause an allergic reaction.

## 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.**

- Take the medicine every day at the same time and always in combination with 100 mg of ritonavir, and with food. The medicine will not work properly without ritonavir and food. The type of food is not important. You must take Prezista and ritonavir within 30 minutes of eating food or any type of snack

(the type of food is not important).

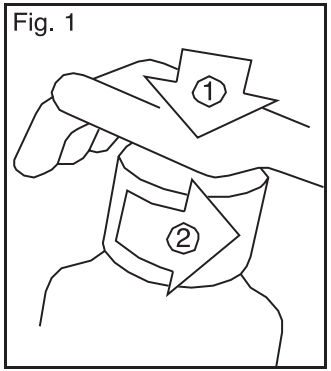
- There is no information regarding crushing/halving/chewing the tablets.
- Swallow the tablets whole with a drink such as water or milk.
- You should take the other HIV medicines that you take, according to the instructions given to you by your doctor.
- Instructions for opening the bottle:

  The bottle comes with a safety cap to prevent accidental opening by children.

  Open the bottle by pressing the cap downwards (1) while turning it counter clockwise (2).

  You should use this medicine at designated times as determined by the attending doctor.

Fig. 1




**If you accidentally took a higher dose,** immediately contact a doctor or pharmacist. If you took an overdose, or if a child has accidentally swallowed

the medicine, refer immediately to a doctor or proceed to a hospital emergency room, and bring the package of the medicine with you.

**If you forgot to take your medicine**

- If you take Prezista once a day and you forgot to take the medicine at the designated time but remembered within 12 hours from the time you were meant to take the medicine, you must take a dose as soon as you remember (together with 100 mg of ritonavir and food). If more than 12 hours have elapsed from the time you were meant to take the medicine, skip the forgotten dose. Take the next dose at the scheduled time. Under no circumstances must you take two doses together!
- If you take Prezista twice a day and you forgot to take Prezista at the designated time but remembered within 6 hours from the time you were meant to take the medicine, you must take a dose as soon as you remember (together with 100 mg of ritonavir and food). If more than 6 hours

have elapsed from the time you were meant to take the medicine, skip the forgotten dose. Take the next dose at the scheduled time. Under no circumstances must you take two doses together!

Adhere to the treatment regimen as recommended by the doctor.

Even if there is an improvement in your health, do not stop treatment with Prezista, in combination with ritonavir, without an explicit instruction from the doctor.

**Do not stop taking the medicine without consulting the doctor.**

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

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

## 4. 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 lifestyle, and in the case of blood lipids, sometimes to the HIV medicines themselves. Your doctor will test for these changes.

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

**Tell your doctor if you develop any side effect. Side effects that require particular attention:**

- Liver problems that may occasionally be severe have been reported. Your doctor should do blood tests before you start treatment with Prezista. If you have chronic hepatitis B or C infection, your doctor should perform blood

tests more often because you have an increased chance of developing liver problems.

Refer to your doctor if you notice signs and symptoms that may be indicative of liver problems, such as: yellowing of the skin or 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 your right side below your ribs.

- Skin rash (more common when used in combination with raltegravir), itching. The rash is usually of mild to moderate severity. A skin rash may also be a symptom of a rare severe condition. It is therefore important to talk to your doctor if you develop a rash. Your doctor will advise you on how to deal with the symptoms or whether to stop using Prezista.

Other severe side effects are diabetes (common) and inflammation of the pancreas (uncommon).

Very common side effects – effects that occur in more than one in ten users:

- diarrhea

Common side effects – effects that occur in 1-10 in 100 users:

- vomiting, nausea, abdominal pain or distension, indigestion, flatulence
- headache, tiredness, dizziness, drowsiness, numbness, tingling or pain in hands or feet, weakness, difficulty falling asleep

Uncommon side effects – effects that occur in 1-10 in 1,000 users:

- chest pain, changes in electrocardiogram, rapid heart rate
- decreased or abnormal skin sensitivity, pins and needles, attention disturbance, loss of memory, problems with your balance
- breathing difficulties, cough, nosebleed, throat irritation
- inflammation of the stomach or mouth, heartburn, retching, dry mouth, abdominal discomfort, constipation, belching

- kidney failure, kidney stones, urination difficulties, frequent or excessive urination, sometimes at night
- skin rash (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, discoloration of nails
- muscle pain, muscle cramps or weakness, pain in extremities, osteoporosis
- reduced 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 accumulation of fluids, malaise, irritability, pain
- symptoms of infection, herpes simplex
- erectile problems, enlargement of breasts

- sleeping problems, sleepiness, depression, anxiety, abnormal dreams, decrease in sexual drive

Rare side effects – effects that occur in 1-10 in 10,000 users:

- a reaction called DRESS: severe skin rash, which may be accompanied by fever, fatigue, swelling of the face or lymph glands, increase in eosinophils (a type of white blood cells), an effect on the liver, kidneys or lungs
- heart attack, slow heart rate, palpitations
- visual disturbances
- chills, feeling abnormal
- a feeling of confusion or disorientation, mood swings, restlessness
- fainting, epileptic fits, change in or loss of taste
- mouth sores, vomiting blood, inflammation of the lips, dry lips, coated tongue
- runny 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. This can be manifested in the results of blood and/or urine tests for specific measurements. Your doctor will explain these to you. For example: increase in some white blood cells.

The following side effects are typical for anti-HIV medicines in the same class as Prezista:

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

**If a side effect occurs, if one of the side effects worsens or if you suffer from a side effect not mentioned in the 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 should be kept in a safe place out of the reach and sight of children and/or infants in order 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.

Store at 15°C-30°C.

After first opening, you should use Prezista 400 mg and Prezista 600 mg within one month, provided that the expiry date appearing on the package has not passed.

## 6. FURTHER INFORMATION

In addition to the active ingredient the medicine also contains:

**Prezista 400 mg:**

Tablet core:

PROSOLV® SMCC HD90, crospovidone, colloidal anhydrous silica, magnesium stearate.

Tablet coating:

OPADRY® II (light) Orange 85F93377 contains: polyvinyl alcohol – partially hydrolyzed, titanium dioxide, macrogol/PEG, talc, FD&C Yellow No.6/Sunset Yellow FCF aluminum lake.

The medicine contains less than 1 mmol sodium (23 mg) per dosage unit, i.e., it is essentially “sodium-free”.

**Prezista 600 mg:**

Tablet core:

Silicified Microcrystalline cellulose, crospovidone, magnesium stearate.

Tablet coating:

OPADRY® II Orange 85F13962 contains: polyvinyl alcohol – partially hydrolyzed, macrogol/PEG, titanium dioxide, talc, FD&C Yellow No.6/Sunset Yellow FCF aluminum lake.

**What does the medicine look like and what are the contents of the pack –**

Prezista 400 mg – Film-coated, light orange, oval shaped tablet, with TMC embossed on one side, and 400MG on the other side. Each pack has a plastic bottle containing 60 tablets.

Prezista 600 mg – Film-coated, orange, oval shaped tablet, with TMC embossed on one side, and 600MG on the other side. Each pack has a plastic bottle containing 60 tablets.

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

Revised in August 2020.

Registration numbers of the medicine in the National Drug Registry of the Ministry of Health:

Prezista 400 mg: 1421231999

Prezista 600 mg: 1421332000

Prezista 400, 600 SH 08/20