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

The medicine is dispensed with a doctor's prescription only

| Kaletra 200 mg/50 mg Tablets | Kaletra 100 mg/25 mg Tablets | Kaletra Oral Solution |
|---|---|---|

**Kaletra 200 mg/50 mg:** Each tablet contains the following active ingredients:
lopinavir 200 mg
ritonavir 50 mg
**Kaletra 100 mg/25 mg:** Each tablet contains the following active ingredients:
lopinavir 100 mg
ritonavir 25 mg
**Kaletra Oral Solution:** Each ml contains the following active ingredients:
lopinavir 80 mg
ritonavir 20 mg

Inactive ingredients: see section 6 in the leaflet.

**Read this 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.

**The medicine is intended for adults and children above 6 months of age.**

**What is the most important information I should know about Kaletra?**
**Kaletra may cause onset of serious side effects, including:**

- **Interactions with other medicines. It is important to know which medicines should not be taken together with Kaletra.** For further information, see section 2.1 "Do not take Kaletra if you are being concomitantly treated with".
- **Side effects may occur in babies taking Kaletra Oral Solution.** Kaletra Oral Solution contains alcohol (ethanol) and propylene glycol. Refer to the doctor immediately if your baby appears too sleepy/drowsy or their breathing changes.
- **Pancreatitis.** Kaletra can cause pancreatitis, which may be serious and may lead to death. People who have high levels of certain fats in the blood (triglycerides) have a risk for developing pancreatitis. If you have advanced HIV-1 disease, you may have an increased risk of high blood triglyceride levels and pancreatitis. If you have suffered from pancreatitis in the past, you may have an increased risk of getting pancreatitis again during treatment with Kaletra. Tell your doctor if you have any signs or symptoms of pancreatitis including:
  - nausea
  - vomiting
  - stomach-area (abdominal) pain
- **Liver problems.** Liver problems, including death, can occur in patients who take Kaletra. Your doctor will perform blood tests before and during treatment with Kaletra to check your liver function. If you have Hepatitis B or Hepatitis C, or other liver problems, you may have an increased risk of developing new problems or worsening of existing liver problems while taking Kaletra. Tell your doctor immediately if you have any of the following signs and symptoms of liver problems including:
  o loss of appetite
  o yellow skin and whites of the eyes (jaundice)
  o dark-colored urine
  o pale-colored stools
  o itchy skin
  o stomach-area (abdominal) pain
- **Changes in your heart rhythm and the electrical activity of your heart.** These changes may appear on an ECG (electrocardiogram) and can lead to serious heart problems. The risk of suffering from these problems may be higher if:
  o you have suffered in the past from an irregular heart rhythm or certain heart diseases.
  o you are taking other medicines that may affect your heart rhythm while you are being treated with Kaletra.

Tell your doctor immediately if you are suffering from any of the following effects:
- dizziness
- lightheadedness
- fainting
- sensation of irregular heartbeats

**See "Side effects" section for further information about serious side effects.**

## 1. WHAT IS THE MEDICINE INTENDED FOR?

Kaletra is intended, in combination with other anti-retroviral preparations, for the treatment of adults and children aged 6 months and above, who are HIV-1 carriers.

HIV is the virus that causes AIDS (acquired immune deficiency syndrome).

**Therapeutic group:** lopinavir, ritonavir – HIV protease enzyme inhibitors.

## 2. BEFORE USING THE MEDICINE

**2.1 Do not use the medicine if:**
- **you are sensitive (allergic)** to the active ingredients or any of the additional ingredients contained in the medicine (see section 6 in the leaflet).

**☒ Do not take Kaletra if you are being concomitantly treated with:**
- alfuzosin – used in men to treat symptoms of a benign prostatic hyperplasia
- apalutamide – a medicine to treat cancer
- cisapride – for relief of certain gastric problems
- colchicine – to treat gout, in patients with kidney or liver problems
- dronedarone – to treat atrial fibrillation after restoring normal heart rhythm
- elbasvir/grazoprevir – to treat hepatitis C virus
- ergot-containing medicines – to treat headaches, including:
  o ergotamine tartrate
  o dihydroergotamine mesylate
  o methylergonovine
- lovastatin – to lower blood cholesterol
- oral midazolam – for sleep and/or sedation
- lurasidone – to treat schizophrenia
- pimozide – to treat schizophrenia
- ranolazine – to treat chronic angina pectoris
- rifampicin – to treat tuberculosis
- rifampin – antibacterial
- sildenafil – when used for the treatment of pulmonary arterial hypertension
- simvastatin – to lower blood cholesterol
- lomitapide – to lower blood cholesterol
- compounds containing Hypericum perforatum (St. John's wort)
- triazolam – to treat sleep disturbances and/or ease anxiety

Serious problems may arise if you or your child take one of the above-mentioned medicines with Kaletra.

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

**❗ Before and during treatment with Kaletra, tell the doctor if:**
- you have any heart problems, including a problem called Congenital Long QT Syndrome
- you have or had pancreatic problems
- you have liver problems, including viral hepatitis B or C
- you have diabetes
- you have high cholesterol level in your blood
- you have hemophilia. Kaletra may cause increased bleeding
- you have a low potassium level in your blood
- you are pregnant or planning a pregnancy. See information in the "Pregnancy, breastfeeding and fertility" section 2.5
- you are breastfeeding or plan to breastfeed. See information in the "Pregnancy, breastfeeding and fertility" section 2.5

**2.3 Drug interactions**

**❗ If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. Kaletra interacts with many medicines.**
- **Keep a list of all your medicines to show your doctor and pharmacist.**
- You can ask your doctor or pharmacist for a list of medicines that interact with Kaletra.
- **Do not start taking a new medicine without informing the pharmacist or your doctor.** Your doctor can tell you if it is safe to take Kaletra with other medicines. Your doctor may need to change the dosages of other medicines while you are taking Kaletra.

**Do not** take Kaletra on a 1 time each day dosing schedule if you also take carbamazepine, phenobarbital, phenytoin, efavirenz, nevirapine, or nelfinavir.

**Especially inform your doctor or pharmacist if you are taking:**
- medicines to treat HIV
- estrogen-based contraceptives (birth control pills and patches) e.g., ethinyl estradiol. Kaletra may reduce the effectiveness of estrogen-based birth control pills. During treatment with Kaletra, you should use an additional or different type of birth control. Consult your doctor about the types of birth control you can use to prevent pregnancy while taking Kaletra (**see "Pregnancy, breastfeeding and fertility" section 2.5**)
- sedatives/hypnotics: midazolam, not for oral use, oral midazolam - (see section 2.1: "Do not take Kaletra if you are being concomitantly treated with")
- a medicine to treat men with benign prostatic hyperplasia-related symptoms - alfuzosin - (see section 2.1: "Do not take Kaletra if you are being concomitantly treated with")
- a medicine to treat chronic angina pectoris - ranolazine - (see section 2.1: "Do not take Kaletra if you are being concomitantly treated with")
- a medicine to treat atrial fibrillation after normalization of heart rate - dronedarone - (see section 2.1: "Do not take Kaletra if you are being concomitantly treated with")
- medicines to treat cancer: apalutamide - (see section 2.1: "Do not take Kaletra if you are being concomitantly treated with"), abemaciclib, encorafenib, ivosidenib, vinblastine, vincristine, nilotinib, dasatinib, venetoclax, ibrutinib, neratinib
- medicines for regulating heart rhythm: amiodarone, bepridil, lidocaine, quinidine
- medicines to lower cholesterol: atorvastatin, rosuvastatin. In addition, simvastatin, lovastatin, lomitapide - (see section 2.1: "Do not take Kaletra if you are being concomitantly treated with")
- a medicine to treat parasites: atovaquone
- medicines to treat impotence: avanafil, tadalafil, or vardenafil. In addition, sildenafil
- anti-tuberculosis medicines: bedaquiline
- antivirals to treat hepatitis C virus: glecaprevir/pibrentasvir, boceprevir, simeprevir, ombitasvir/paritaprevir/ritonavir and dasabuvir, sofosbuvir/velpatasvir/voxilaprevir
- compounds that contain Hypericum perforatum (St. John's wort) - (see section 2.1: "Do not take Kaletra if you are being concomitantly treated with")
- ergot-containing medicines to treat headaches: ergotamine tartrate, dihydroergotamine mesylate, methylergonovine - (see section 2.1: "Do not take Kaletra if you are being concomitantly treated with")
- a medicine to relieve certain stomach problems: cisapride - (see section 2.1: "Do not take Kaletra if you are being concomitantly treated with")
- a medicine to treat pain associated with endometriosis: elagolix
- protease inhibitors: tipranavir, saquinavir, indinavir, fosamprenavir
- steroids: betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, methylprednisolone, mometasone, prednisone, triamcinolone
- antiepileptics: carbamazepine, lamotrigine, phenobarbital, phenytoin, valproate
- antibiotics: clarithromycin, metronidazole, rifabutin. In addition, rifampicin, rifampin - (see section 2.1: "Do not take Kaletra if you are being concomitantly treated with")
- gout treatment: colchicine (see section 2.1: "Do not take Kaletra if you are being concomitantly treated with")
- disulfiram
- calcium channel blockers: felodipine, nicardipine, nifedipine
- antifungals: itraconazole, ketoconazole, voriconazole, isavuconazonium
- narcotic painkillers: methadone, fentanyl
- medicines to treat schizophrenia: pimozide, lurasidone - (see section 2.1: "Do not take Kaletra if you are being concomitantly treated with")
- antipsychotics: quetiapine
- a medicine for the treatment of sleep disturbances and/or to relieve anxiety: triazolam
- anticoagulants: rivaroxaban, warfarin
- medicines to treat asthma: salmeterol
- medicines that affect the immune system: cyclosporin, tacrolimus, sirolimus (rapamycin)
- a medicine to treat low platelet levels arising from a chronic autoimmune disease (chronic immune thrombocytopenia): fostamatinib
- antidepressants: trazodone, bupropion
- medicines used to treat pulmonary arterial hypertension: bosentan, tadalafil or vardenafil. In addition, sildenafil - (see section 2.1: "Do not take Kaletra if you are being concomitantly treated with")

**2.4 Use of the medicine and food**
- Kaletra Tablets: Kaletra Tablets can be taken without regard to meals.
- Kaletra Oral Solution: Take Kaletra Oral Solution with food to increase absorption.

**2.5 Pregnancy, breastfeeding and fertility**
- Tell the doctor if you are pregnant or are planning a pregnancy. It is not known if Kaletra will harm your unborn baby.
  - Kaletra Oral Solution contains alcohol (ethanol) and propylene glycol. It is not advisable to take Kaletra Oral Solution during pregnancy as there is no safe level of alcohol exposure during pregnancy. Tell your doctor if you become pregnant while taking Kaletra.
  - Kaletra may reduce the effectiveness of hormonal contraceptives. Women who may become pregnant need to use another or additional effective contraception during the course of treatment with Kaletra.
- Tell the doctor if you are breastfeeding or are planning to breastfeed. **Do not breastfeed if you are taking Kaletra.**
  - It is not recommended to breastfeed if you are an HIV-1 carrier, since there is a risk of passing HIV-1 to your baby.
  - Talk to your doctor about the best way to feed your baby.

**2.6 Important information about some of the ingredients of Kaletra Oral Solution**
**Each 1 ml of medicine contains:**
**356.3 mg ethanol (alcohol 42.4% v/v)**, 168.6 mg high fructose corn syrup, 152.7 mg propylene glycol (15.3% w/v), 10.2 mg castor oil, 4.1 mg acesulfame K.
**Total content of ethanol (alcohol) per bottle: 25.44 ml.**

For full list of inactive ingredients, refer to section 6.

## 3. HOW SHOULD YOU USE THE MEDICINE?

Always use the preparation according to the doctor's instructions.
Check with the doctor or pharmacist if you are uncertain regarding the preparation dosage and treatment regimen.
The dosage and treatment regimen will be determined by the doctor only.

**Do not exceed the recommended dose.**
- Take Kaletra every day exactly according to the doctor's instructions.
- Stay under the care of your doctor during treatment with Kaletra.
- It is important to set up a dosing schedule and follow it every day.
- Do not change or stop treatment without first consulting with the attending doctor.
- Kaletra Tablets: Swallow the tablets whole. Do not chew, break or crush.
- Kaletra Oral Solution: Care should be taken to measure the dose using the syringe provided.
- If you take Kaletra and didanosine:
  - didanosine can be taken with **Kaletra tablets**, without food
  - take didanosine either one hour before or two hours after taking **Kaletra Oral Solution**
- If you are pregnant:
  - During pregnancy, **do not take** Kaletra Tablets on a 1 time each day dose schedule.
  - Avoid use of **Kaletra Oral Solution** during pregnancy.
- If your child was prescribed Kaletra:
  - Tell the doctor if your child's weight changes. A 1 time each day dose schedule of Kaletra **should not be given to children**, rather, doses divided according to the doctor's instructions. When giving Kaletra to your child, give exactly as determined by the doctor.
  - To administer the Kaletra Oral Solution dosage prescribed for your child, measure the dose with the provided syringe.
- Kaletra Oral Solution contains propylene glycol and a large amount of alcohol (ethanol). If you plan to take or administer Kaletra Oral Solution through a feeding tube, talk to the doctor. Kaletra Oral Solution contains propylene glycol and alcohol (ethanol), and is therefore not recommended for use in certain feeding tubes.
- There may have a greater chance of getting diarrhea when taking Kaletra once a day than when taking twice a day.
- **Do not forget** to take a dose of the medicine. This could make the virus harder to treat.
- **If you forget to take Kaletra**, take the missed dose as soon as you remember. If it is almost time for the next dose, **do not take** the forgotten dose. Instead, continue with the regular dosing schedule by taking your next dose at its regular time. **Do not take** more than one dose of Kaletra at one time.

**If you or your child accidentally 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.**
**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 the use of the medicine, consult the doctor or pharmacist.**

## 4. SIDE EFFECTS:

As with any medicine, use of Kaletra 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.

**Kaletra can cause serious side effects, including:**
- **See section "What is the most important information I should know about Kaletra?", in the beginning of the leaflet.**
- **Inflammation of the pancreas (pancreatitis).** Some patients who take Kaletra may develop pancreatitis which may be serious and cause death. If you have suffered from pancreatitis in the past, you have a higher chance of developing pancreatitis again. Tell your doctor if you have nausea, vomiting, or abdominal pain while taking Kaletra. These may be signs of pancreatitis.
- **Liver problems.** Liver problems, including death, can occur in patients who take Kaletra. Your doctor will perform blood tests before and during treatment with Kaletra to check your liver function. Patients with liver problems, such as hepatitis B and C, who take Kaletra, may experience worsening of these problems. Tell your doctor immediately if you have any of the following signs and symptoms of liver problems:
  o loss of appetite
  o yellowing of the skin and whites of the eyes (jaundice)
  o dark-colored urine
  o pale-colored stools
  o itchy skin
  o stomach-area (abdominal) pain
- **Diabetes and high blood sugar levels (hyperglycemia).** You may develop new diabetes, worsening of your diabetes, or have high blood sugar levels during treatment with Kaletra. Tell your doctor if you notice any of the following signs or symptoms:
  - increased urination
  - increased hunger or thirst
  - unusual weight loss
  - increased level of blood sugar

  The attending doctor may need to prescribe a new medicine for you to treat high blood sugar levels, or change the diabetes medicines you are taking.
- **Changes in your immune system** may occur when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your doctor immediately if you start developing new symptoms after starting treatment with your HIV-1 medicine.
- **Increases in certain fat (triglycerides and cholesterol) levels in your blood.** Large increases in triglycerides and cholesterol can be seen in blood test results of some patients who take Kaletra. Your doctor will perform blood tests to check your cholesterol and triglyceride levels before you start taking Kaletra and during your treatment.
- **Changes in body fat** may occur in some patients who take antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck, chest and around the trunk. Loss of fat from the legs, hands and face may also occur. The cause and long-term health implications of these effects are not known at this time.
- **Increased bleeding in patients with hemophilia.** Some patients with hemophilia have increased bleeding when taking Kaletra or similar medicines.
- **Skin rash, which can be severe,** can appear in patients who take Kaletra. Tell your doctor if you had a rash when you took another medicine to treat HIV-1 infection, or if you notice any kind of rash while taking Kaletra.
- **Kidney stones.**

**Very common side effects** - effects that occur in more than one user in ten:
- Diarrhea
- Nausea
- Upper respiratory tract infection

**Common side effects** - effects that occur in 1-10 in 100 users:
- Pancreatitis
- Vomiting, enlarged abdomen, pain in the upper and lower abdominal area, flatulence, indigestion, decreased appetite, reflux from the stomach to the esophagus which may cause pain
- Swelling or inflammation of the stomach and intestines
- Increased cholesterol level in the blood, increased triglycerides level in the blood, high blood pressure
- Decreased ability of the body to regulate sugar, including: diabetes, weight loss
- Low level of red blood cells, low level of white blood cells that fight infection
- Rash, eczema, accumulation of scales of greasy skin
- Dizziness, anxiety, sleeping difficulties
- Tiredness, lack of strength and energy, headache including migraine
- Hemorrhoids
- Inflammation of the liver, including increased liver enzymes, abnormally high level of bilirubin (a pigment produced from the breakdown of red blood cells) in the blood
- Kidney failure
- Allergic reactions, including hives/urticaria and inflammation in the mouth
- Changes in face or body shape due to changes in body fat distribution
- Lower respiratory tract infection
- Enlargement of the lymph nodes
- Impotence, abnormally heavy or extended menstrual bleeding or absence of menstruation
- Muscle problems, such as: muscle weakness, muscle spasms, pain in the joints, muscles and back
- Damage to nerves of the peripheral nervous system
- Night sweats, itching, rash including swelling of the skin, infection of the skin, inflammation of the skin or hair pores, edema

**Uncommon side effects** - effects that occur in 1-10 in 1,000 users:
- Abnormal dreams
- Change or loss of sense of taste
- Hair loss
- Change in ECG called atrioventricular block
- Plaque that builds up in the arteries that may cause a heart attack and stroke
- Inflammation of the blood vessels and capillaries
- Inflammation of the bile duct
- Convulsions
- Constipation
- Deep vein inflammation that is related to blood clots
- Dry mouth
- Lack of control of intestinal sphincters
- Inflammation of the upper part of the small intestine, after the stomach. Wound or ulcer in the digestive tract, bleeding from the digestive tract or from the rectum
- Red blood cells in the urine
- Fatty liver, enlarged liver
- Hypofunctioning of the sex glands (testicles or ovaries)
- Flare-up of immune system symptoms related to an inactive infection in the body
- Increased appetite
- Decreased libido
- Inflammation of the kidney
- Bone destruction caused by poor blood supply to the area
- Oral sore or ulcers, inflammation in the stomach and intestine, inflammation in the mouth
- Breakdown of muscle fibers that leads to release of muscle fiber content (myoglobin) to the bloodstream
- A sound in one or both ears, such as: buzzing, ringing or whistling
- Tremor
- Abnormal closure of a heart valve
- Vertigo (spinning sensation)
- Eye problems, abnormal vision
- Weight gain
- Lactic acidosis

**Side effects of unknown frequency (effects whose frequency has not been determined):**
- Yellowing of the skin and whites of the eyes (jaundice)
- Severe or life-threatening skin blisters and rash (Stevens-Johnson syndrome, erythema multiforme [inflammatory skin rash]).
- Kidney stones.

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

**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.
- Kaletra 100 mg/25 mg Tablets: Store at a temperature below 25°C.
- Kaletra 200 mg/50 mg Tablets: This medicine does not require any special storage conditions. It is recommended to store it at room temperature.
- Kaletra Oral Solution: Store in refrigerator (2-8°C) until dispensed to the patient. After the medicine is dispensed to the patient, it can be kept outside of the refrigerator, at a temperature below 25°C and should be used within 42 days.
- Store in the original package. Do not transfer the tablets to a different container.
- Do not discard medicines in wastewater or household waste. Ask the pharmacist how to get rid of medicines you no longer need. Taking these measures will help preserve the environment.

## 6. FURTHER INFORMATION

- In addition to the active ingredients, the medicine also contains the following inactive ingredients:

| Kaletra Tablets 200 mg/50 mg | Kaletra Tablets 100 mg/25 mg |
|---|---|
| Copovidone, Sorbitan laurate, Colloidal anhydrous silica, Hypromellose, Sodium stearyl fumarate, Titanium dioxide, Macrogol type 400, Hydroxypropyl cellulose, Talc, Red ferric oxide E172, Macrogol type 3350, Polysorbate 80. | Copovidone ,Sorbitan laurate, Colloidal anhydrous silica, Sodium stearyl fumarate, Polyvinyl alcohol, Titanium dioxide, Macrogol type 3350, Talc, Yellow ferric oxide E172. |
| **Kaletra Oral Solution** | |
| Dehydrated Alcohol, Corn syrup high fructose, Propylene glycol, Purified water, Glycerol, Povidone, Flavor Magnasweet, Flavour vanilla natural & artificial, Flavour cotton candy artificial, Polyoxyl 40 hydrogenated castor oil, Saccharin sodium, Acesulfame potassium, Sodium chloride, Oil peppermint, Sodium citrate, Anhydrous citric acid, levomenthol. | |

- **What the medicine looks like and the contents of the package:**
Kaletra 100 mg/25 mg Tablets: Light yellow-colored tablets. The tablets are provided in plastic bottles which contain 60 tablets.
Kaletra 200 mg/50 mg Tablets: Red-colored tablets. The tablets are provided in plastic bottles which contain 120 tablets.
Kaletra Oral Solution: One package contains five bottles, which contain 60 ml solution, and five 5 ml measuring syringes.
- **License holder and address:** AbbVie Biopharmaceuticals Ltd., 4 Haharash St., Hod Hasharon, Israel.
- **Manufacturer name and address:** AbbVie Deutschland GmbH & Co. KG, Knollstrasse 67061, Ludwigshafen, Germany.
- Revised in January 2022 according to MOH guidelines.
- **Registration number of the medicine in the National Drug Registry of the Ministry of Health:**
Kaletra Tablets 100 mg/25 mg: 141 07 32003
Kaletra Tablets 200 mg/50 mg: 137 96 31542
Kaletra Oral Solution: 122 05 30210