Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986

This medicine is dispensed with a doctor's prescription only

Xalkori® 200mg, capsules
Xalkori® 250mg, capsules

Each capsule contains **crizotinib 200 mg or 250 mg**

Inactive ingredients and allergens: see section 2 under "Important information about some of this medicine's ingredients" and section 6 "Further information".

Read the entire leaflet carefully before using this medicine. This leaflet contains concise information about this medicine. If you have any further questions, consult your doctor or pharmacist.

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

1. WHAT IS THE MEDICINE INTENDED FOR?

The medicine is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) positive for a mutation in a gene called anaplastic lymphoma kinase (ALK).
The medicine is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) positive for a mutation in a gene called ROS1.

Therapeutic group: A medicine from the protein kinase inhibitors group, antineoplastic.

2. BEFORE USING THIS MEDICINE

Do not use this medicine if:

- You are sensitive (allergic) to crizotinib or to any of the other ingredients in this medicine (see section 6).

Special warnings regarding use of the medicine
Before treatment with Xalkori, tell your doctor if:

- You have a moderate or severe liver disease.
- You have ever had any lung problems. Some lung problems may worsen during treatment with Xalkori, as Xalkori may cause inflammation of the lungs during the treatment. Symptoms may be similar to those of lung cancer. Contact your doctor immediately if you have any new or worsening symptoms including difficulty breathing, shortness of breath, or cough with or without mucus, or fever.
- You have been told that after an electrocardiogram (ECG) you have an abnormality in the ECG tracing known as prolonged QT interval (long QT syndrome).
- You have reduced heart rate.
- You have ever had gastric or intestinal problems such as perforation, or if you have conditions causing inflammation inside the abdomen (diverticulitis), or if you have disseminated cancer in the abdomen (metastasis).
- You have vision disorders (seeing flashes of light, blurred vision and double vision).
- You have a severe kidney disease.
- You are currently treated with any of the medicines listed in section "Drug interactions".

Contact your doctor immediately after having taken Xalkori:

If you are experiencing acute abdominal pain, fever, chills, shortness of breath, fast heartbeat, partial or complete loss of vision (in one or both eyes) or changes in bowel movements.

Children and adolescents
The efficacy and safety of crizotinib in children and adolescents have not been established. No information on this subject is available.

Drug interactions
If you are taking or have recently taken other medicines, including nonprescription medicines and dietary supplements, tell your doctor or pharmacist.

The following medicines in particular, may increase the risk of side effects with Xalkori:
- Clarithromycin, telithromycin, erythromycin, antibiotics used to treat bacterial infections.
- Ketoconazole, itraconazole, posaconazole, voriconazole, used to treat fungal infections.
- Atazanavir, ritonavir, cobicistat, used to treat HIV infections/AIDS.

The following medicines may reduce the effectiveness of Xalkori:
- Phenytoin, carbamazepine or phenobarbital, anti-epileptics used to treat seizures.
- Rifabutin, rifampicin, used to treat tuberculosis.
- St. John's wort (Hypericum perforatum), a herbal product used to treat depression.

Xalkori may increase the side effects associated with the following medicines:
- Alfentanil and other short acting opiates such as fentanyl (analgesics used for surgical procedures).
- Quinidine, digoxin, disopyramide, amiodarone, sotalol, dofetilide, ibutilide, verapamil, diltiazem used to treat heart problems.
- Medicines for high blood pressure called beta-blockers such as atenolol, propranolol, labetolol.
- Pimozide, used to treat mental illness.
- Metformin, used to treat diabetes.
- Procainamide, used to treat disruptions of the heart rate.
- Cisapride, used to treat stomach problems.
- Cyclosporine, sirolimus and tacrolimus used in patients who have undergone a transplant.
- Ergot derivatives (e.g., ergotamine, dihydroergotamine), used to treat migraine.
- Dabigatran, anticoagulant used to slow down blood coagulation.
- Colchicine, used to treat gout.
- Pravastatin, used to reduce cholesterol levels.
- Clonidine, guanfacine, used to treat hypertension.
- Mefloquine, used for the prevention of malaria.
- Pilocarpine, used to treat glaucoma (a severe eye disease).
- Acetylcholinesterase inhibitors, used to restore muscle function.
- Antipsychotics, used to treat mental illness.
- Moxifloxacin, used to treat bacterial infections.
- Methadone, used to treat pain and for the treatment of opioid dependence.
- Bupropion, used to treat depression and for smoking cessation.
- Efavirenz, raltegravir, used to treat HIV infection.
- Irinotecan, a chemotherapy drug used to treat colorectal cancer.
- Morphine, used to treat acute and cancer related pain.
- Naloxone, used to treat opiate drug addiction and withdrawal.

These medicines should be avoided during your treatment with Xalkori.

Oral contraceptives
If you take Xalkori while taking oral contraceptives, the oral contraceptives may be ineffective.

Using this medicine and food
You can take Xalkori with or without food; however, you should avoid drinking grapefruit juice or eating grapefruit during treatment with Xalkori as they may change the levels of Xalkori in your body.

Sun protection
Avoid spending prolonged time in sunlight. Xalkori can make your skin sensitive to the sun (photosensitivity), and you may burn more easily. You should wear protective clothing and/or use sunscreen that covers your skin to help protect against sunburn if you have to be in the sunlight during treatment with Xalkori.

Pregnancy and breastfeeding
Contact your doctor or pharmacist before taking this medicine if you are pregnant, may become pregnant or you are breastfeeding.

It is recommended to women taking the medicine and to women whose partners are taking the medicine to avoid pregnancy during treatment with Xalkori because this medicine may harm the baby. If there is any possibility that the woman taking the medicine or the partner of a man taking the medicine may become pregnant, they must use adequate contraceptives during the treatment, and for at least 90 days after completing therapy as oral contraceptives may be ineffective while taking Xalkori.

Do not breastfeed during treatment with Xalkori. Xalkori may harm the nursing baby.

If you are pregnant or breastfeeding, think you may be pregnant or you are planning to become pregnant, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
You should take special care when driving and using machines as patients taking Xalkori may experience visual disturbances, dizziness, and tiredness.

Important information about some of this medicine's ingredients
Xalkori contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per capsule, therefore it can be defined as essentially ‘sodium-free’.

3. HOW TO USE THIS MEDICINE?
Always use this preparation according to your 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 your doctor only. The standard dosage is usually one capsule of 250 mg taken twice daily (daily dose of 500 mg). Take the capsule once in the morning and once in the evening.
Take the capsule at about the same time each day.
The capsules can be taken with or without food, but always avoiding grapefruit.
Swallow the capsules whole and do not crush, dissolve or open the capsule, since this dosage form has not been tested.

If necessary, your doctor may decide to reduce the dose to 200 mg to be taken twice daily (daily dose of 400 mg), and if further dose reduction is necessary, to reduce it to 250 mg to be taken once daily. Your doctor may decide to permanently discontinue your treatment if you are unable to tolerate the dosage of Xalkori 250 mg taken orally once daily.

Do not exceed the recommended dose.

Manner of using the preparation – general instructions
Childproof caps have significantly reduced the number of poisoning cases caused by medicines annually. However, if you experience difficulties opening the package, you can ask the pharmacist to remove the safety mechanism of the cap and turn it into a regular easy to open cap.

If you have accidentally taken a higher dosage

If you have taken an overdose, or if a child has accidentally swallowed some medicine, immediately see a doctor or go to a hospital emergency room and bring the medicine package with you**.**

If you forget to take Xalkori
What to do if you forget to take a capsule depends on how long it is until your next dose.

- If your next dose is in 6 hours or more, take the missed capsule as soon as you remember. Take the next capsule at the usual time.
- If your next dose is in less than 6 hours, skip the missed capsule. Then take the next capsule at the usual time.

Tell your doctor about the missed dose at your next visit.

Do not take a double dose (two capsules at the same time) to make up for a forgotten capsule.

If you vomit after taking a dose of Xalkori, do not take an extra dose; just take the next dose at your regular time.

Adhere to the treatment as recommended by your doctor.

Even if your health improves, do not stop treatment with this medicine without consulting your doctor or pharmacist to prevent worsening of your illness.

If you stop taking Xalkori
It is important to take Xalkori every day, as long as your doctor prescribes it to you. If you are not able to take the medicine as your doctor prescribed, or you feel you do not need it anymore, contact your doctor immediately.

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

If you have any further questions about using this medicine, consult your doctor or pharmacist.

4. SIDE EFFECTS
As with any medicine, use of Xalkori may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them.

Some side effects may be serious. You should immediately contact your doctor if you experience any of the following serious side effects (see also section 2):

Liver failure
Contact your doctor immediately if you feel more tired than usual, your skin and whites of your eyes turn yellow, your urine turns dark or brown (tea color), you have nausea, vomiting, or decreased appetite, you have pain on the right side of the abdomen, you have itching, or if you bruise more easily than usual. Your doctor may perform blood tests to check your liver function,

and if the results are abnormal, your doctor may decide to reduce the dose of Xalkori or stop your treatment.

Lung inflammation
Contact your doctor immediately if you experience difficulty breathing, especially if associated with cough or fever.

Reduction in the number of white blood cells (including neutrophils)
Contact your doctor immediately if you experience fever or infection. Your doctor may instruct you to perform blood tests and if the results are abnormal, your doctor may decide to reduce the dose of Xalkori.

Dizziness, fainting, or chest discomfort
Contact your doctor immediately if you experience these symptoms, which may be signs of changes in the electrical activity (seen on electrocardiogram) or abnormal rhythm of the heart. Your doctor may perform electrocardiograms to check that there are no problems with your heart during treatment with Xalkori.

Partial or complete loss of vision in one or both eyes
Contact your doctor immediately if you experience any loss of vision or any change in vision such as visual difficulties affecting one or both eyes. Your doctor may stop treatment with Xalkori and refer you to an ophthalmologist.

Other side effects of Xalkori may include:

Very common side effects (may occur in more than 1 in 10 people)
- Visual problems (seeing flashes of light, blurred vision or double vision, often beginning immediately after starting treatment with Xalkori)
- Upset stomach, including vomiting, diarrhea, nausea
- Edema (excess fluid in body tissue, causing swelling of the hands and feet)
- Constipation
- Abnormalities in blood tests for liver function
- Decreased appetite
- Tiredness
- Dizziness
- Neuropathy (numbness or feeling of pins and needles in the joints or extremities)
- Alteration in the sense of taste
- Pain in the abdomen
- Reduction in the number of red blood cells (anemia)
- Skin rash
- Reduced heart rate

Common side effects (may occur in up to 1 in 10 people)
- Indigestion
- Increased blood levels of creatinine (may indicate that the kidneys are not functioning properly)
- Increased levels of the enzyme alkaline phosphatase in the blood (an indicator of organ malfunction or injury, particularly liver, pancreas, bone, thyroid gland, or gallbladder)
- Hypophosphatemia (low blood phosphate levels that may cause confusion or muscle weakness)
- Pouches of fluid within the kidneys (kidney cysts)
- Fainting
- Inflammation of the esophagus (swallowing tube)
- Decreased levels of testosterone, a male sex hormone
- Heart failure

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

- Hole (perforation) in the stomach or intestine
- Sensitivity to sunlight (photosensitivity).
- Increased blood levels of tests that check for muscle damage (high creatine phosphokinase levels).

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.

You can report side effects to the Ministry of Health by following the link‘ Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects or by using the link: https://sideeffects.health.gov.il.

5. HOW TO STORE THE MEDICINE?

Prevent poisoning! This and any other medicine should be kept in a closed 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 a doctor.

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

Store below 25˚C.

After first opening the plastic bottle, use the capsules within one month.

Store in the original package.

6. FURTHER INFORMATION

In addition to the active ingredient, this medicine also contains:

colloidal silicon dioxide, microcrystalline cellulose, anhydrous dibasic calcium phosphate, sodium starch glycolate, magnesium stearate, gelatin, titanium dioxide and red iron oxide

- **What the medicine looks like and contents of the pack:**

Xalkori 200 mg: a hard gelatin capsule with a pink cap and white body, with “Pfizer” printed with black ink on the capsule cap and “CRZ 200” printed with black ink on the capsule body. The capsule contains a white to light yellow powder.
Xalkori 250 mg: a hard gelatin capsule with a pink cap and body, with “Pfizer” printed with black ink on the capsule cap and “CRZ 250” printed with black ink on the capsule body. The capsule contains a white to light yellow powder.

The preparation is marketed in blister packs of 60 hard capsules and in plastic bottles of 60 hard capsules.

Not all pack types may be marketed.

- **Registration holder and address:** Pfizer Pharmaceuticals Israel Ltd., 9 Shenkar St., Herzliya Pituach 46725.
- **Registration numbers of the medicines in the National Drug Registry of the Ministry of Health:**

Xalkori 200 mg: 147-40-33588

Xalkori 250 mg: 147-41-33589

Revised in 07/2022 according to MOH guidelines.