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

The medicine is dispensed with a doctor's prescription only

Zelboraf®
240 mg
Film-coated tablets

Composition:
Each film-coated tablet contains:
Vemurafenib 240mg (as a co-precipitate of vemurafenib and hypromellose acetate succinate)

* For information on the inactive ingredients see section 6 "Further Information".

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.

IMPORTANT INFORMATION FOR YOUR ATTENTION
- **Zelboraf®** is not intended for use among children and adolescents.
- During treatment with **Zelboraf®** you will be ordered to undergo regular blood, eye and skin tests. You may also be referred for additional tests, as needed.
- During treatment with **Zelboraf®** your skin may be more sensitive to sunlight. Therefore, direct exposure to sunlight should be avoided as much as possible.

1) WHAT IS THE MEDICINE INTENDED FOR?

Zelboraf® is an anticancer medicine containing the active substance vemurafenib. It is used to treat adults with metastatic melanoma (that has spread to other parts of the body) or that cannot be removed by surgery.

Zelboraf® is intended for use only in patients with a change (mutation) in the BRAF gene in the cancerous tumor. This change may have led to development of the melanoma.

Zelboraf® targets proteins produced by this modified gene and slows down or stops the development of the cancer.

Therapeutic group: anticancer drug, kinase inhibitor

2) BEFORE USING THE MEDICINE

Do not use Zelboraf® if:
you are sensitive (allergic) to the active ingredient vemurafenib or to any of the other ingredients of the medicine (see section 6 "Further Information").
Symptoms of allergic reactions can include swelling of the face, lips or tongue, difficulty breathing, rash, or fainting sensation.

Special warnings regarding use of this medicine
Allergic reactions
During treatment with **Zelboraf®** allergic reactions can develop that may be severe. If you have any symptoms of an allergic reaction that may include swelling of the face, lips or tongue, difficulty breathing, rash, or fainting sensation - stop taking the medicine and get medical help immediately.

Severe skin reactions
During treatment with **Zelboraf®** severe skin reactions can develop. If you get a skin rash with any of the following symptoms: blisters on your skin, blisters or sores in your mouth, peeling of your skin, fever, redness or swelling of your face, hands or soles of your feet - stop taking the medicine and refer to the doctor immediately.

Previous history of cancer
Inform the doctor if you have had another type of cancer other than melanoma, since **Zelboraf®** may cause progression in certain types of cancer.

Radiation therapy reactions
Tell the doctor if you have had, or are going to have radiotherapy, as **Zelboraf®** may worsen radiation treatment side effects.

Heart disorders
Tell the doctor if you have a heart disorder, such as an alteration of the electrical activity of your heart called "QT prolongation", seen in an E.C.G. test. The doctor will run tests to check that your heart is working properly before and during your treatment with **Zelboraf®**. If necessary, the doctor will decide to interrupt your treatment temporarily or permanently.

Eye problems
You should have your eyes examined by a doctor during treatment with **Zelboraf®**. If you have eye pain, swelling, redness, blurred vision or any vision changes in the course of treatment - refer to the doctor immediately.

Musculoskeletal/connective tissue disorders
Tell the doctor if you observe any unusual thickening of the palms of your hands accompanied by tightening of the fingers inward or any unusual thickening of the soles of your feet which may be painful.

Checks of your skin before, during and after treatment with **Zelboraf®**
If you notice any changes in your skin while under treatment with **Zelboraf®** - refer to the doctor as soon as possible.

During your treatment with **Zelboraf®** and up to 6 months after treatment, the doctor will perform regular skin tests for detection of a certain type of skin cancer called "cutaneous squamous cell carcinoma". Usually, this lesion appears on sun-damaged skin, remains local and can be cured by surgical removal. If the doctor diagnoses you with this type of skin cancer, he or she will treat it or send you to another doctor for treatment.

Additionally, the doctor will inspect your head, neck, mouth and lymph glands and will also send you for regular CT scans in order to detect squamous cell carcinoma lesions inside your body. Genital examinations for women, as well as anal examinations are also recommended before and at the end of treatment.

During treatment with **Zelboraf®**, new melanoma lesions may develop. These lesions can usually be removed by surgery and treatment with **Zelboraf®** can be continued. Monitoring of melanoma lesions will be carried out in the framework of the examinations described above to detect cutaneous squamous cell carcinoma.

Kidney or liver problems
Kidney or liver problems may affect the activity of **Zelboraf®**. If you have kidney or liver problems - tell the doctor. The doctor will perform blood tests to check liver and kidney functions before starting treatment and during treatment with **Zelboraf®**.

Sun protection
During treatment with **Zelboraf®**, you may become more sensitive to sunlight and get sunburns that can be severe.

During treatment with **Zelboraf®**, **avoid direct exposure of the skin to sunlight**. If you do plan to go into the sun, be sure to wear clothing which protects your skin, including: your head, face, arms and legs. Also use a protective preparation for your lips and body (minimum of Sun Protection Factor (SPF) 30), and apply it every 2-3 hours. These measures will help to protect you against sunburns.

Children and adolescents
Zelboraf® is not intended for use among children and adolescents. The effect of **Zelboraf®** in people younger than 18 years of age is not known.

Zelboraf® and other medicines
Before starting treatment with **Zelboraf®**, tell the doctor or pharmacist if you are taking, have recently taken or might use any other medicines, including non-prescription medicines and nutritional supplements. This is very important, as using more than one medicine at the same time can affect the way the medicines work in your body.

In particular, tell the doctor or pharmacist if you are taking:
- Medicines that affect the heart rhythm
  - Medicines for heart rhythm problems (e.g., quinidine, amiodarone)
  - Medicines for treatment of depression (e.g., amitriptyline, imipramine)
  - Antibiotics (e.g., azithromycin, clarithromycin)
  - Medicines for nausea and vomiting (e.g., ondansetron, domperidone)
- Medicines that are eliminated mainly by enzymes of the CYP1A2 type (e.g., caffeine, olanzapine, theophylline), the CYP3A4 type (e.g., some oral contraceptives) or the CYP2C8 type
- Medicines that influence a protein called P-gp or BCRP (e.g., verapamil, cyclosporine, ritonavir, quinidine, itraconazole, gefitinib)
- Medicines that could be influenced by a protein called P-gp (e.g., aliskiren, colchicine, digoxin, everolimus, fexofenadine) or by a protein called BCRP (e.g., methotrexate, mitoxantrone, rosuvastatin)
- Medicines that stimulate enzymes of the CYP3A4 type or the metabolic process called glucuronidation (e.g., rifampicin, rifabutin, carbamazepine, phenytoin, *Hypericum* [St. John's Wort])
- Medicines that strongly inhibit type CYP3A4 enzymes (e.g., ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, nefazodone, atazanavir)
- A medicine used to prevent excessive blood clotting called warfarin
- A medicine called ipilimumab, another medicine for the treatment of melanoma. The combination of this medicine with **Zelboraf®** is not recommended due to increased toxicity to the liver.

Pregnancy and breast-feeding
Use contraceptive measures during treatment with **Zelboraf®** and for at least 6 months after the end of the treatment. **Zelboraf®** may decrease the efficacy of some oral contraceptives, therefore, you should tell the doctor if you are using this type of contraception.

Zelboraf® is not recommended for use during pregnancy unless the doctor considers that the benefit for the mother outweighs the risk for the fetus. There is no information about the safety of using **Zelboraf®** in pregnant women. Tell the doctor if you are pregnant or planning to become pregnant.

It is not known whether the ingredients in **Zelboraf®** pass into human milk. Breast-feeding is not recommended during treatment with **Zelboraf®**.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to become pregnant, consult the doctor before using this medicine.

Driving and using machines
Zelboraf® has side effects that can affect your ability to drive or to operate machines. Beware of fatigue or eye problems that could be a reason for not driving.

Important information about some of the ingredients in Zelboraf®
This medicine contains less than 1 millimole of sodium (23 mg) in each tablet so it is considered 'sodium free'.

3) HOW SHOULD YOU USE THE MEDICINE?

Always use according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain. Do not exceed the recommended dose.

How many tablets should you take
The dosage and treatment regimen will be determined by the doctor only.

The recommended dosage is 4 tablets, twice a day (a total of: 8 tablets per day).

Take 4 tablets in the morning and 4 tablets in the evening.

If you experience side effects, the doctor may lower your dosage.

In case of vomiting, continue to take the medicine at the usual time and do not take an additional dose.

How to take the tablets
Do not take the medicine regularly on an empty stomach.

Swallow the tablets whole with a glass of water. Do not chew or crush the tablets.

If you accidentally take too high a dose or if a child has accidentally swallowed the medicine, refer to your doctor immediately or proceed to a hospital emergency room and bring the package of this medicine with you. Taking a higher dose than that prescribed may increase the likelihood and severity of side effects.

No cases of **Zelboraf®** overdose have been observed.

If you forgot to take the medicine
If you forgot to take the medicine at the required time:
- If more than 4 hours are left until your next scheduled dose, take the forgotten dose as soon as you remember. Take the next dose at the usual time.
- If less than 4 hours are left before the next scheduled dose, skip the missed dose. Take the next dose at the usual time.
- Do not take a double dose to make up for a forgotten dose.

If you stop using the medicine
It is very important to persevere with treatment according to the doctor's instructions. Even if there is an improvement in your health, do not stop treatment with the medicine without consulting the doctor.

If you have any further questions on the use of this medicine, consult the doctor.

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

4) SIDE EFFECTS

Like all medicines, **Zelboraf®** can cause side effects in some users. Do not be alarmed by reading the list of side effects. You may not suffer from any of them.

Serious allergic reactions: swelling of the face, lips or tongue, difficulty breathing, rash, fainting sensation. Refer to a doctor immediately if you have any of the symptoms mentioned above. Do not continue taking the medicine until clarification with the doctor.

Worsening of side effects caused by radiation therapy can occur in patients who are treated with radiation before, during, or after **Zelboraf®** treatment. This can occur on the area that was treated with radiation, such as the skin, esophagus, bladder, liver, rectum, and lungs.

Tell your doctor immediately if you experience any of the following symptoms:
- Skin rash, blistering, peeling or discoloration of the skin
- Shortness of breath, which may be accompanied by a cough, fever or chills (pneumonitis)
- Difficulty or pain when swallowing, chest pain, heartburn or acid reflux (esophagitis)

Refer to a doctor as soon as possible if you notice any changes in your skin.

Additional side effects:

Very common side effects - effects that occur in more than 1 in 10 users:
- Rash, itching, dry or scaly skin
- Skin problems including warts
- A certain type of skin cancer (cutaneous squamous cell carcinoma)
- Palmar plantar syndrome (redness, skin peeling or blisters on hands and feet)
- Hypersensitivity of the skin to sunlight, sunburns
- Loss of appetite
- Headache
- Changes in taste
- Diarrhoea
- Constipation
- Nausea, vomiting
- Hair loss
- Joint or muscle pain, musculoskeletal pain
- Pain in the extremities
- Back pain
- Fatigue
- Fever
- Swelling - usually in the legs (peripheral oedema)
- Dizziness
- Cough

Common side effects - effects that occur in up to 1 in 10 users:
- Certain types of skin cancer (basal cell carcinoma, new primary melanoma)
- Thickening of tissues underneath the skin of the palm of the hand which may cause tightening of the fingers inward; severe thickening may be disabling
- Inflammation of the eye (uveitis)
- Bell's palsy (a form of facial paralysis that is often reversible)
- Tingling or burning sensation in hands and feet
- Inflammation of joints
- Inflammation of hair roots
- Weight loss
- Inflammation of blood vessels
- Problems with the nerves that can produce pain, lack of sensation and/or muscle weakness (peripheral neuropathy)
- Changes in liver function test results (ALT, alkaline phosphatase and bilirubin increase)
- Changes in electrical activity of the heart (QT prolongation in E.C.G. tests)
- Inflammation of the fatty tissue under the skin
- Abnormal kidney function blood test results (increased creatinine levels)
- Changes in liver function test results (elevated GGT levels)
- Decreased levels of white blood cells (neutropenia)
- Low blood platelet count (thrombocytopenia)

Uncommon side effects - effects that occur in up to 1 in 100 users
- Allergic reactions that can include swelling of the face and difficulty breathing
- Blockage of blood flow to a certain part of the eye (retinal vein occlusion)
- Inflammation of the pancreas
- Change in liver laboratory test results or liver injury, including severe liver injury where liver is injured to the extent that it is not able to fully perform its function
- A certain type of skin cancer (non-cutaneous squamous cell carcinoma)
- Thickening of deep tissues underneath the skin of the soles of the feet that may be disabling if severe

Rare side effects - effects that occur in up to 1 in 1,000 users
- Progression of certain types of cancer with a RAS mutation (chronic myelomonocytic leukaemia, pancreatic adenocarcinoma)
- A type of severe skin reaction, characterized by a rash accompanied by fever and inflammation of internal organs such as the liver or kidney
- Inflammatory disease mainly affecting the skin, lung and eye (sarcoidosis)
- Types of kidney injury characterized by inflammation (acute interstitial nephritis) or damage to the tubules of the kidney (acute tubular necrosis)

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 "Reporting side effects following 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) appearing on the package and on the blisters. The expiry date refers to the last day of that month.

Storage conditions: Do not store at a temperature exceeding 30°C.

Store in the original carton to protect from moisture.

Do not discard the medicine via household waste or wastewater. Ask the pharmacist how to discard medicines you no longer need. These measures will help to protect the environment.

6) FURTHER INFORMATION

In addition to the active ingredient, the medicine also contains:
Tablet core: Croscarmellose sodium, Colloidal anhydrous silica, Magnesium stearate, Hydroxypropylcellulose

Film-coating: Polyvinyl alcohol, Titanium dioxide (E171), Macrogol 3350, Talc, Iron oxide red (E172)

What the medicine looks like and the contents of the package:
Zelboraf® 240 mg is provided as film-coated tablets colored pinkish-white to orange-white. The tablets are oval with the letters "VEM" impressed on one side.

The tablets are available in aluminium blisters; each pack contains 56 tablets.

License holder and address: Roche Pharmaceuticals (Israel) Ltd., P.O.B. 6391, Hod Hasharon, 4524079.

Manufacturer and address: F. Hoffmann-La Roche Ltd., Basel, Switzerland.

Revised in July 2023 according to MOH guidelines.

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 147.24.33558.00