Package leaflet: Information for the user

Zelboraf 240 mg film-coated tablets
vemurafenib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zelboraf is and what it is used for

Zelboraf is an anticancer medicine that contains the active substance vemurafenib. It is used to treat adult patients with melanoma that has spread to other parts of the body or cannot be removed by surgery.

It can only be used in patients whose cancer has a change (mutation) in the "BRAF" gene. This change may have led to the development of melanoma.

Zelboraf targets proteins made from this modified gene and slows down or stops the development of your cancer.

2. What you need to know before you take Zelboraf

Do not take Zelboraf:
- If you are **allergic** to vemurafenib or any of the other ingredients of this medicine (listed in section 6 of this leaflet). Symptoms of allergic reactions may include swelling of the face, lips or tongue, difficulty breathing, rash, or fainting sensation.

Warnings and precautions
Talk to your doctor before taking Zelboraf.

Allergic reactions
- **Allergic reactions can happen while taking Zelboraf and may be severe.** Stop taking Zelboraf and get medical help immediately if you have any symptoms of an allergic reaction such as swelling of the face, lips or tongue, difficulty breathing, rash, or fainting sensation.

Severe skin reactions
- **Severe skin reactions can happen while taking Zelboraf.** Stop taking Zelboraf and talk to your doctor immediately 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.

Previous history of cancer

- **Tell your doctor if you have had a different type of cancer than melanoma**, as Zelboraf may cause progression of certain types of cancers.

Radiation therapy reactions

- **Tell your doctor if you have had, or are going to have radiotherapy**, as Zelboraf may worsen radiation treatment side effects.

Heart disorder

- **Tell your doctor if you have a heart disorder, such as an alteration of the electrical activity of your heart called "QT prolongation".** Your doctor will run tests to check that your heart is working properly before and during your treatment with Zelboraf. If necessary, your doctor may decide to interrupt your treatment temporarily or stop it altogether.

Eye problems

- **You should have your eyes examined by your doctor while you are taking Zelboraf.** Tell your doctor immediately if you get eye pain, swelling, redness, blurred vision or other vision changes during your treatment.

Musculoskeletal/Connective Tissue disorder

- **Tell your 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

- **If you notice any changes in your skin while taking this medicine, please talk to your doctor as soon as possible.**
- Regularly during your treatment and up to 6 months after your treatment, your doctor needs to check your skin for a type of cancer called "cutaneous squamous cell carcinoma".
- Usually, this lesion appears on sun-damaged skin, remains local and can be cured by surgical removal.
- If your doctor finds this type of skin cancer, he or she will treat it or send you to another doctor for treatment.
- Additionally, your doctor needs to inspect your head, your neck, your mouth, your lymph glands and you will undergo CT scans regularly. This is a precautionary measure in case a squamous cell carcinoma lesion would develop inside your body. Genital examinations (for women) and anal examinations are also recommended before and at the end of your treatment.
- You may develop new melanoma lesions while taking Zelboraf. These lesions are usually removed by surgery and patients continue their treatment. Monitoring of these lesions occurs as outlined above for cutaneous squamous cell carcinoma.

Kidney or liver problems

- **Tell your doctor if you have kidney or liver problems.** This may affect the activity of Zelboraf. Your doctor will also do some blood tests to check your liver and kidney functions before you start taking Zelboraf and during treatment.

Sun protection

- If you are taking Zelboraf, you may become more sensitive to sunlight and get sunburns that can be severe. During treatment, **avoid exposing your skin to direct sunlight.**
- If you do plan to go into the sun:
  - wear clothing which protects your skin, including your head and face, arms and legs;
  - use a lip balm and a broad spectrum sunscreen (minimum of Sun Protection Factor (SPF) 30, re-applied every 2 to 3 hours).
- This will help to protect you against sunburn.

Children and adolescents
Zelboraf is not recommended for children and adolescents. The effects of Zelboraf in people younger than 18 years old are not known.

Other medicines and Zelboraf
Before starting treatment, tell your doctor if you are taking, have recently taken or might use any other medicines (including those you have bought for yourself from a pharmacy, supermarket or health store). This is very important, as using more than one medicine at the same time can strengthen or weaken the effect of medicines.

In particular, tell your doctor if you are taking:
- Medicines that are known to affect the way your heart beats:
  - medicines for heart rhythm problems (e.g. quinidine, amiodarone)
  - medicines for depression (e.g. amitriptyline, imipramine)
  - medicines for bacterial infections (e.g. azithromycin, clarithromycin)
  - medicines for nausea and vomiting (e.g. ondansetron, domperidone).
- Medicines that are mainly eliminated by metabolising proteins called CYP1A2 (e.g caffeine, olanzapine, theophylline), CYP3A4 (e.g. some oral contraceptives) or called CYP2C8.
- 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 a protein called BCRP (e.g. methotrexate, mitoxantrone, rosuvastatin).
- Medicines that stimulate the metabolising proteins called CYP3A4 or a metabolising process called glucuronidation (e.g. rifampicin, rifabutin, carbamazepine, phenytoin or St John's Wort).
- Medicines that strongly inhibit the metabolising protein called CYP3A4 (e.g. ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, nefazodone, atazanavir).
- A medicine used to prevent blood clots 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.

If you are taking any of these medicines (or if you are not sure), please talk to your doctor before taking Zelboraf.

Pregnancy and breast-feeding
- **Use an appropriate method of contraception during your treatment** and for at least 6 months after the end of your treatment. Zelboraf may decrease the efficacy of some oral contraceptives. Please tell your doctor if you are taking an oral contraceptive.
- Zelboraf is not recommended for use during pregnancy unless your doctor considers that the benefit for the mother outweighs the risk for the baby. There is no information about the safety of Zelboraf in pregnant women. Tell your 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 have a baby, ask your doctor for advice before taking 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 of Zelboraf
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Zelboraf

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

How many tablets should you take
- The recommended dose is 4 tablets twice a day (a total of 8 tablets).
- Take 4 tablets in the morning. Then take 4 tablets in the evening.
- If you experience side effects, your doctor may decide to carry on your treatment but lower your dose. Always take Zelboraf exactly as your doctor has told you.
- In case of vomiting, continue to take Zelboraf as usual and do not take an additional dose.

Taking your tablets
- Do not take Zelboraf regularly on an empty stomach.
- Swallow the tablets whole with a glass of water. Do not chew or crush the tablets.

If you take more Zelboraf than you should
If you take more Zelboraf than you should, talk to your doctor immediately. Taking too much Zelboraf may increase the likelihood and severity of side effects. No cases of overdose have been observed with Zelboraf.

If you forget to take Zelboraf
- If you forget a dose and it is more than 4 hours before your next dose, just take your dose as soon as you remember it. Take the next dose at the usual time.
- If it is less than 4 hours before your next dose, skip the missed dose. Then take the next dose at the usual time.
- Do not take a double dose to make up for a forgotten dose.

If you stop taking Zelboraf
It is important to keep taking Zelboraf for as long as your doctor prescribes it for you. If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, Zelboraf can cause side effects, although not everybody gets them.

Serious allergic reactions
If you get any of these:
- Swelling of the face, lips or tongue
- Difficulty breathing
- Rash
- Fainting sensation.

Call a doctor immediately. Do not use any more Zelboraf until you have spoken to a doctor.

Worsening of radiation treatment side effects 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).

Please talk to your doctor as soon as possible if you notice any changes in your skin.

Side effects are listed below by frequency:

Very common (may affect more than 1 in 10 people):
- Rash, itching, dry or scaly skin
- Skin problems including warts
- A type of skin cancer (cutaneous squamous cell carcinoma)
- Palmar plantar syndrome (i.e. redness, skin peeling or blisters on hands and feet)
- Sunburn, being more sensitive to sunlight
- Loss of appetite
- Headache
- Changes in the way things taste
- Diarrhoea
- Constipation
- Feeling sick (nausea), vomiting
- Hair loss
- Joint or muscle pain, musculoskeletal pain
- Pain in the extremities
- Back pain
- Feeling tired (fatigue)
- Dizziness
- Fever
- Swelling usually in the legs (peripheral oedema)
- Cough.

Common (may affect up to 1 in 10 people):
- Types of skin cancers (basal cell carcinoma, new primary melanoma)
- Thickening of tissues underneath the palm of the hand which may cause tightening of the fingers inward; it can be disabling if severe
- Inflammation of the eye (uveitis)
- Bell's palsy (a form of facial paralysis that is often reversible)
- Tingling or burning feelings in hands and feet
- Inflammation of joints
- Inflammation of hair's roots
- Weight loss
- Inflammation of blood vessels
- Problem with the nerves that can produce pain, loss of sensation and/or muscle weakness (neuropathy peripheral)
- Change in liver tests results (ALT, alkaline phosphatase and bilirubin increase)
- Changes in electrical activity of the heart (QT prolongation)
- Inflammation of the fatty tissue under the skin
- Abnormal kidney blood test results (creatinine increased).
- Change in liver tests results (GGT increase)
- Decreased white blood cells (neutropenia).
- Low blood platelet count (thrombocytopenia)
- Sore mouth or mouth ulcers, inflammation of mucous membranes (stomatitis)

Uncommon (may affect up to 1 in 100 people):
- Allergic reactions that may include swelling of the face and difficulty breathing
- Blockage of blood flow to part of the eye (retinal vein occlusion)

- Inflammation of the pancreas
- Change in liver laboratory tests 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 type of cancer (non-cutaneous squamous cell carcinoma**)**
- Thickening of deep tissues underneath the sole of the feet that may be disabling if severe

Rare (may affect up to 1 in 1,000 people)

- Progression of a type of pre-existing cancers with RAS mutations (Chronic Myelomonocytic Leukaemia, Pancreatic adenocarcinoma)
- A type of severe skin reaction characterised by rash accompanied by fever and inflammation of internal organs such as liver and kidney
- Inflammatory disease mainly affecting the skin, lung and eye (sarcoidosis)
- Types of kidney injury characterised by inflammation (acute interstitial nephritis) or damage to the tubules of the kidney (acute tubular necrosis).

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly (see details below). By reporting side effects you can help provide more information on the safety of this medicine.

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

5. How to store Zelboraf

Keep this medicine out of the sight and reach of children.

Do not use Zelboraf after the expiry date which is stated on the carton and the blister after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Zelboraf contains
- The active substance is vemurafenib. Each film-coated tablet contains 240 milligrams (mg) of vemurafenib (as a co-precipitate of vemurafenib and hypromellose acetate succinate).
- The other ingredients are:
  - Tablet core: colloidal anhydrous silica, croscarmellose sodium, hydroxypropyl cellulose and magnesium stearate
  - Film-coating: iron oxide red, macrogol 3350, polyvinyl alcohol, talc and titanium dioxide.

What Zelboraf looks like and contents of the pack
Zelboraf 240 mg film-coated tablets are pinkish white to orange white. They are oval with “VEM” engraved on one side.
They are available in aluminium perforated unit dose blisters in packs of 56 x 1 tablets.

Marketing Authorisation Holder and Manufacturer
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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