PRODUCT MONOGRAPH

Pr**ZELBORAF®**

vemurafenib

Film-coated tablet, 240 mg

Professed Standard

Protein Kinase Inhibitor

Hoffmann-La Roche Limited
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Mississauga, Ontario, Canada
L5N 5M8

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PART III: CONSUMER INFORMATION

[Pr]ZELBORAF®
vemurafenib

This leaflet is part III of a three-part "Product Monograph" published when ZELBORAF was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ZELBORAF. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
ZELBORAF is used in adult patients to treat a type of skin cancer (unresectable or metastatic melanoma) that has a change (mutation) in the "BRAF" gene and that cannot be removed by surgery or has spread to other parts of the body.

Patients should have their cancer tested for this change in the "BRAF" gene before starting treatment with ZELBORAF.

What it does:
ZELBORAF targets proteins made from the mutated BRAF gene and slows down or stops the growth of cancer cells.

When it should not be used:
Do not take ZELBORAF if you are allergic (hypersensitive) to vemurafenib or any of the other ingredients of ZELBORAF. See "**What the non-medicinal ingredients are**".

What the medicinal ingredient is:
vemurafenib

What the non-medicinal ingredients are:
colloidal anhydrous silica, croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose acetate succinate (HPMC-AS), magnesium stearate, iron oxide red, macrogol 3350, polyvinyl alcohol, talc, titanium dioxide.

What dosage forms it comes in:
Film-coated tablets / 240 mg vemurafenib

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Serious side effects include:

- **Liver injury.**
- **Changes in electrical activity of the heart known as QT/QTc prolongation.**
- **Severe skin reactions (Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS], Stevens-Johnson Syndrome [SJS] and Toxic Epidermal Necrolysis [TEN]).**
- **Second cancers.**
- **Radiation injury.**

ZELBORAF should only be prescribed by a doctor who is experienced in the use of anti-cancer drugs.

ZELBORAF has not been studied in patients with severe liver impairment.

ZELBORAF has an effect on the electrical activity of the heart known as QT/QTc prolongation. This effect can be measured as a change in the electrocardiogram (ECG). Drugs with this effect on the ECG can lead to disturbances in heart rhythm (arrhythmias/dysrhythmias) that could result in dizziness, palpitations (sensation of rapid, pounding, or irregular heart beat), fainting or death. These heart rhythm disturbances are more likely in patients with risk factors, such as heart disease, or in the presence of certain interacting drugs. In general, females and people more than 65 years in age are at higher risk. It is important to follow the instructions of your doctor with regard to dosing or any special tests. You will need to have electrocardiograms (ECGs) and blood tests to measure your levels of potassium, calcium, and magnesium at regular intervals during treatment with ZELBORAF. If you experience any symptoms of a possible heart rhythm disturbance, such as dizziness, palpitations (sensation of rapid, pounding, or irregular heart beat), fainting, or seizures, you should seek immediate medical attention.

ZELBORAF may cause changes in your skin, including a new melanoma and cutaneous squamous cell carcinoma. Use of ZELBORAF may also cause a serious rash accompanied by fever and swollen glands (DRESS) or redness, pain, swelling or blistering of lips, eyes or mouth, skin peeling and flu-like symptoms (SJS/TEN). Abnormal thickening of tissues underneath the palm of the hand or underneath the sole of the feet has also been observed with ZELBORAF use. This condition can cause pain over time or be disabling. Talk to your doctor if there are any changes in your skin while taking ZELBORAF and up to six months after the last dose.

You may also become more sensitive to sunlight and get sunburns that can be severe while taking ZELBORAF. During treatment, **avoid going out in the sun** or if you go into the sun,

- wear clothing which protects your skin, including your head and face, arms and legs, including hands and feet
- use a lip balm and a broad spectrum sunscreen (minimum of SPF 30, re-applied every 2 to 3 hours).

ZELBORAF may also cause severe allergic reaction. Symptoms include swelling of the face, lips or tongue, difficulty breathing, rash, or fainting.

Based on how ZELBORAF works, it may cause certain cancers, particularly those with a mutation in another gene, called the RAS gene, to spread or get worse.

A medicine called YERVOY™ (ipilimumab) is another treatment for melanoma. Using this medicine at the same time

with ZELBORAF has shown to increase liver problems. The combination of these two drugs is not recommended.

BEFORE you use ZELBORAF talk to your doctor or pharmacist if:

- You had a prior unrelated cancer or you currently have another second cancer.
- **You have any heart disorder**, including an irregular heartbeat, an abnormal electrical signal called "prolongation of the QT interval" or a family history of QT prolongation or sudden cardiac death at <50 years.
  - you have high blood pressure.
  - you have a personal history of fainting spells.
  - you have electrolyte disturbances (e.g., low blood calcium, potassium or magnesium levels) or conditions that could lead to electrolyte disturbances (e.g., vomiting, diarrhea, dehydration).
  - you have an eating disorder or are following a strict diet.
  - you have diabetes, especially with associated nerve disorders.
- **You have liver or kidney problems.**
- **You have eye problems**.
- **You have received radiation treatment or are planning to receive radiation treatment.**
- **You are pregnant or are planning to become pregnant.** ZELBORAF may harm an unborn child. Female patients who can get pregnant must use an effective birth control method while taking ZELBORAF and for at least six months after the last dose. If you are pregnant, think you may be pregnant, or plan to get pregnant while taking ZELBORAF tell your doctor right away.
- **You are breast-feeding or plan to breast-feed.** It is not known if ZELBORAF passes into your breast milk. You and your doctor should decide if you will take ZELBORAF or breast-feed.

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

INTERACTIONS WITH THIS MEDICATION

Before starting treatment, please tell your doctor if you are taking or have recently taken any other medicines (including prescription and non-prescription medicines, vitamins, and herbal supplements). This is very important, as using more than one medicine at the same time can strengthen or weaken the effect of medicines.

In particular, please tell your doctor if you are taking:

- A specific medicine used to prevent blood clots called warfarin.
- A specific medicine for cough called dextromethorphan.
- A specific sedative used during surgery called midazolam.
- Medicines that may affect your heartbeat such as:
  - medicines for heart rhythm problems (anti-arrhythmics) such as quinidine, amiodarone.
  - medicines for depression such as amitriptyline, imipramine.
  - medicines for psychoses such as ziprasidone and haloperidol.
  - medicines for infections such as erythromycin, clarithromycin, moxifloxacin, or ketoconazole.
  - medicines for nausea and vomiting such as ondansetron, domperidone.
  - other cancer drugs such as sunitinib or nilotinib.
  - opioid painkillers.
  - asthma drugs such as formoterol or salmeterol.
  - diuretics (water pills).
  - digoxin.
- Medicines for seizures such as phenytoin or carbamazepine.
- HIV medicines such as atazanavir, saquinavir, ritonavir or indinavir.
- Other antibiotics such as rifampin or rifabutin.
- A specific medicine for relaxing muscles called tizanidine.
- A specific medicine for breathing problems called theophylline.
- A specific medicine for pain, depression and anxiety called duloxetine.

ZELBORAF may increase your body's sensitivity to radiation therapy.

You should also speak to your doctor before starting any new medication while you are on ZELBORAF.

Grapefruit, grapefruit juice, or products containing grapefruit extract should be avoided while receiving ZELBORAF.

Excessive use of caffeine should be avoided.

PROPER USE OF THIS MEDICATION

Usual dose:
The usual dose is 960 mg (4 tablets) twice a day. Take 4 tablets in the morning. Then take 4 tablets in the evening about 12 hours later. Take ZELBORAF consistently with or without food. Swallow the tablets whole with a glass of water. Do not crush or chew the tablets.

Overdose:

If you take more ZELBORAF than you should or in case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
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. Do not take 2 doses at the same time.

Vomiting
In case of vomiting, continue to take ZELBORAF as usual and do not take an additional dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

Very common side effects of ZELBORAF include:
- rash, itching, dry skin
- skin problems, including warts
- a type of skin cancer (cutaneous squamous cell carcinoma). Tell your doctor right away if you have any skin changes including a new wart, a skin sore or reddish bump, or a sore that bleeds or does not heal
- abnormal liver function (which can be severe and may cause the skin/whites of the eye to turn yellow , urine to turn dark or brown, nausea or vomiting or not wanting to eat)
- being more sensitive to sunlight, sun burn
- hair loss
- pain in joint or muscle, musculoskeletal pain
- feeling tired
- nausea, vomiting
- diarrhea
- constipation
- fever
- headache
- loss of appetite
- changes in the way things taste
- back pain
- pain in the extremities
- decrease in urine output
- abnormal kidney blood test results (creatinine increased).
- excess fluid usually in the legs
- redness, skin peeling or blisters on hand and feet (Palmar plantar syndrome)
- cough
- weight loss

Common side effects:
- a type of skin cancer (basal cell carcinoma)
- new primary melanoma
- tender red nodules just under the skin, fever, tiredness
- irregular heartbeat (atrial fibrillation)
- high blood pressure
- dizziness
- dehydration
- tingling or burning feeling in hands and feet (neuropathy peripheral)
- eye problems such as inflammation of the eye
- inflammation of hair's root

Possible serious side effects:
- **Liver injury.** Tell your doctor right away if:
  - your skin or the whites of your eyes turn yellow.
  - you feel tired.
  - your urine turns dark or brown.
  - you have nausea or vomiting.
  - you do not want to eat.
- **Kidney injury**. Tell your doctor right away if:
  - you experience decreased urine output.
  - you have fluid retention causing swelling in your legs, ankles or feet.
- **Changes in your heartbeat (called QT prolongation), very fast or abnormal heartbeats.** Seek medical attention right away if you have abnormal heartbeats, feel dizzy or faint or have seizures.
- **Allergic reactions may occur.** Tell your doctor right away if you get a rash, feel faint, have trouble breathing or have swelling of the face, lips or tongue.
- **Skin reactions.** Tell your doctor right away if you develop:
  - a serious severe rash accompanied by fever and swollen glands (DRESS) or redness, pain, swelling or blistering of lips, eyes or mouth, skin-peeling and flu-like symptoms (SJS/TEN).
  - thickening of tissue under the palm of the hand causing tightening of the fingers inward.
  - tissue thickening of the sole of feet that causes pain while walking.
- **Eye problems.** Tell your doctor right away if:
  - you have eye pain, swelling, or redness.
  - you have blurred vision or other vision changes.
- **Radiation injury.** Worsening of radiation treatment side effects has been reported 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, brain and lungs. Tell your doctor right away if:
  - you develop skin rash, blistering, peeling or discoloration of the skin
  - you have shortness of breath, which may be accompanied by a cough, fever or chills (pneumonitis)
  - you have difficulty or pain when swallowing, chest pain, heartburn or acid reflux (esophagitis)

Call your health care provider right away, if you have any of the symptoms listed above.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
Very Common	Sore skin, wart or reddish bump that bleeds or does not heal (Cutaneous squamous cell cancer including keratoacanthomas)		✓	
	Abnormal liver function tests		✓	
	If the liver tests are particularly abnormal you may experience the following: skin/whites of the eye turn yellow, feel tired, urine turns dark or brown, nausea or vomiting or not wanting to eat.			✓
	Kidney injury (decrease in urine output or abnormal kidney blood test results)		✓	
Common	Changes in heartbeat, abnormal heartbeats, feel dizzy or faint, or have seizures (QT prolongation)		✓	
	Eye problems (eye pain, swelling, or redness, or blurred vision or other vision changes)		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
Common	Reactions at sites of radiation (radiation sensitization and recall) including: - Severe skin reactions (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)		✓	
	Thickening of tissues under the palm of the hand.		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Severe allergic reactions (rash, feel faint, trouble breathing or swelling of the face, lips or tongue)			✓
	Severe skin reactions (redness, pain, swelling or blistering of lips, eyes or mouth, skin peeling and flu-like symptoms [SJS/TEN])			✓
	Thickening of tissues under the soles of the feet.		✓	
	Severe upper abdominal pain, associated with nausea and vomiting, tenderness in the abdomen		✓	
	Fever and/or infections, which may result from an abnormally low number of a type of white blood cells called neutrophils		✓	
Rare	Severe skin reactions (serious rash accompanied by fever and swollen glands [DRESS])			✓

This is not a complete list of side effects. For any unexpected effects while taking ZELBORAF, contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of the reach and sight 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 the month.

Store between 15- 30°C, in the original package. Protect from moisture.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 1908C
  Ottawa, Ontario
  K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.rochecanada.com or by contacting the sponsor, Hoffmann-La Roche Limited, at: 1-888-762-4388.

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