ZELBORAF is a prescription medicine used to treat a type of skin cancer called melanoma that has spread to other parts of the body or cannot be removed by surgery, and that has a certain type of abnormal *BRAF* gene.

Getting started with ZELBORAF

Helpful information for patients and their caregivers

Please see accompanying full Prescribing Information and Medication Guide, and pages 8-11 for additional important safety information.

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Taking an active role after your metastatic melanoma diagnosis

Finding out that you or someone you know has metastatic melanoma is very difficult. You might feel a lot of emotions. You may be afraid, anxious, hurt, or unsure of what to do next.

You are not alone.

There are many people and places you can turn to for support. You can look for comfort from friends, family, or loved ones. You can get information from doctors, nurses, and support groups, as well as from this brochure.

What next? Take an active role in your treatment.

Now that your doctor has recommended ZELBORAF for you or a loved one, it is important for you to understand this new medicine and your treatment.

By seeking support and information, you will be able to take an active role and make the most of your ZELBORAF treatment.

Please see accompanying full Prescribing Information and Medication Guide, and pages 8-11 for additional important safety information.

Introduction to ZELBORAF™ (vemurafenib)

What is ZELBORAF?

ZELBORAF is a prescription medicine used to treat a type of skin cancer called melanoma that has spread to other parts of the body or cannot be removed by surgery, and that has a certain type of abnormal *BRAF* gene. It is not known if ZELBORAF is safe and effective in children under 18 years of age.

ZELBORAF is personalized, meaning that it is designed to be used only by people whose disease has a certain characteristic, in this case a change (mutation) in the *BRAF* gene (BRAF mutation-positive melanoma). These people are the only patients in whom ZELBORAF was studied and for whom benefit has been shown. ZELBORAF is targeted to impact some forms of mutated BRAF, but it may also impact healthy cells. Therefore, ZELBORAF is known as a **personalized targeted therapy**.

ZELBORAF may cause a type of skin cancer called cutaneous squamous cell carcinoma (cuSCC). CuSCC usually does not spread to other parts of the body. Check your skin and tell your doctor about skin changes, including a new wart, a sore or bump that bleeds or does not heal, or a mole that changes size or color.

A doctor should check your skin before you start taking ZELBORAF and every 2 months while you are taking ZELBORAF to look for any new skin cancers. Your healthcare provider may continue to check your skin for 6 months after you stop taking ZELBORAF.

Important words:

BRAF (BEE-raf): in all normal and cancer cells, a gene called *BRAF* leads to the production of the BRAF protein, which is important for your body to function properly.

Mutation: a genetic change, such as a change in the *BRAF* gene.

Targeted therapy: a kind of treatment that targets certain signals needed for cancer cells to grow. ZELBORAF is designed to target some forms of mutated BRAF, but may also impact healthy cells.

BRAF mutation test: after a patient is diagnosed with metastatic melanoma, his or her doctor can order a test to check if the melanoma is BRAF mutation positive.

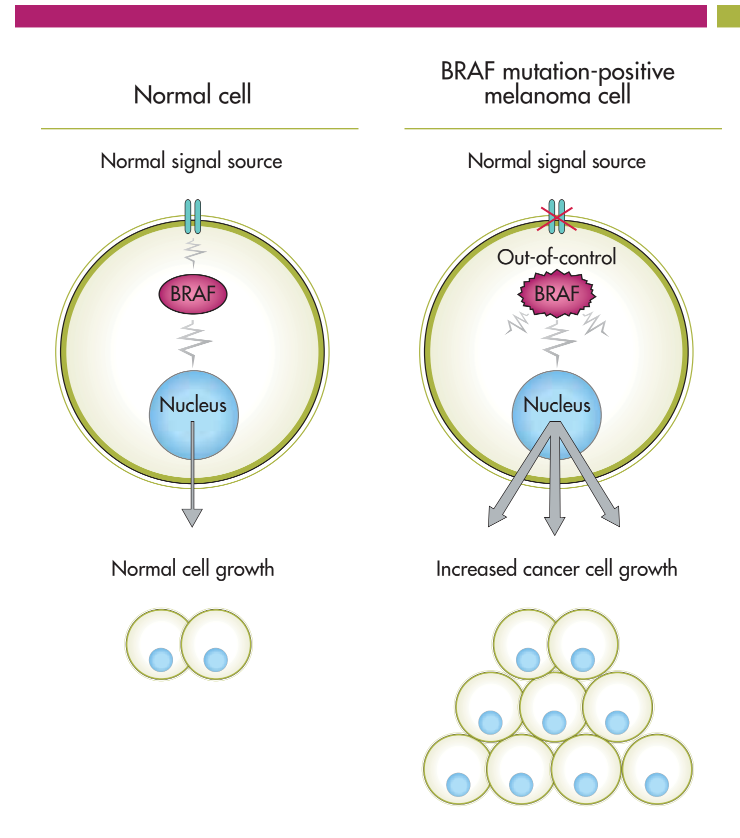
Important things to know about the BRAF mutation

ZELBORAF is used to treat a type of skin cancer called melanoma that has spread to other parts of the body or cannot be removed by surgery.

What does having the BRAF mutation mean?

ZELBORAF only works for melanoma tumors that have an abnormal *BRAF* gene. Since you have **tested positive for the BRAF mutation**, it means that your type of melanoma might be driven by a changed BRAF protein. Your doctor chose ZELBORAF for you because it targets some forms of these changed BRAF proteins and may slow down the growth of cancer.

ZELBORAF is the first FDA-approved treatment for BRAF mutation-positive metastatic melanoma.



Please see accompanying full Prescribing Information and Medication Guide, and pages 8-11 for additional important safety information.

zelboraf.com

ZELBORAF™ (vemurafenib) may extend survival

How did patients who had not been treated before do on ZELBORAF?

Results from a large study of patients who had not had any prior therapy for metastatic melanoma:

- **ZELBORAF may help you live longer:** more patients in the ZELBORAF group were still alive at the time of analysis (77%) than in the group taking a standard chemotherapy known as dacarbazine (64%)
- **ZELBORAF may cause your tumors to shrink:** almost half of the patients taking ZELBORAF had their tumors shrink compared with 5% of those taking dacarbazine
- **ZELBORAF may help control your disease:** ZELBORAF increased the time that patients lived without their cancer growing or spreading by nearly 4 months compared with those taking dacarbazine

Allergic reactions can happen while taking your ZELBORAF, and may be severe. Stop taking ZELBORAF and get medical help right away if you have any of these symptoms of an allergic reaction:

- Get a rash or redness all over your body
- Feel faint
- Have trouble breathing or swallowing
- Have throat tightness or hoarseness
- Have a fast heartbeat
- Have swelling of the face, lips, or tongue

Other possible benefits of ZELBORAF

How did previously treated patients do on ZELBORAF?

Results from a study of patients who had failed at least 1 prior therapy for metastatic melanoma:

- ZELBORAF may cause your tumors to shrink: over half of the patients taking ZELBORAF had their tumors shrink
- Patients responded quickly to ZELBORAF: on average, patients who responded to ZELBORAF did so within 1.4 months of starting treatment
- 2% of patients had their tumors disappear completely with ZELBORAF. This did not mean the cancer was cured

Stop taking ZELBORAF and call your doctor right away if you get a skin rash with any of the following symptoms, because you may have a severe skin reaction:

- 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

Please see accompanying full Prescribing Information and Medication Guide, and pages 8-11 for additional important safety information.

Possible side effects of ZELBORAF™ (vemurafenib)

What is the most important information I should know about ZELBORAF?

ZELBORAF may cause a type of skin cancer called cutaneous squamous cell carcinoma (cuSCC). CuSCC usually does not spread to other parts of the body.

Check your skin and tell your healthcare provider right away about any skin changes, including a:

- New wart
- Skin sore or reddish bump that bleeds or does not heal
- Change in size or color of a mole

A healthcare provider should check your skin before you start taking ZELBORAF, and every two months while taking ZELBORAF to look for any new skin cancers. Your healthcare provider may continue to check your skin for six months after you stop taking ZELBORAF.

See *"What are the possible side effects of ZELBORAF?"* for more information about side effects.

What should I tell my healthcare provider before taking ZELBORAF?

Before you start taking ZELBORAF, tell your healthcare provider if you:

- Have any heart problems, including a condition called long QT syndrome
- Have liver or kidney problems
- Have been told that you have low blood levels of potassium, calcium, or magnesium
- Plan to have surgery, dental, or other medical procedures
- Have any other medical conditions
- Are pregnant or plan to become pregnant. ZELBORAF may harm your unborn baby
  - Females who are able to become pregnant, and males who take ZELBORAF should use birth control during treatment and for 2 months after stopping ZELBORAF
  - Talk to your healthcare provider about birth control methods that may be right for you
  - Tell your healthcare provider right away if you become pregnant during treatment with ZELBORAF

- **Are breastfeeding or plan to breastfeed.** It is not known if ZELBORAF passes into your breast milk. You and your healthcare provider should decide if you will take ZELBORAF or breastfeed. You should not do both

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Especially, tell your healthcare provider if you take blood thinners, antifungal medicines, antibiotic medicines, HIV medicines, seizure medicines, anti-depressant medicines, or medicines to treat irregular heart beat.

Know the medicines you take. Keep a list to show your healthcare provider and pharmacist when you get a new medicine.

What should I avoid while taking ZELBORAF?

Avoid sunlight while you are taking ZELBORAF. ZELBORAF can make your skin sensitive to sunlight. You may burn more easily and get severe sunburns.

To help protect against sunburn:

- *When you go outside, wear clothes that protect your skin, including head, face, hands, arms, and legs*
- *Use lip balm and a broad-spectrum sunscreen with SPF 30 or higher*

Please see accompanying full Prescribing Information and Medication Guide, and pages 8-11 for additional important safety information.

What are the possible side effects of ZELBORAF™ (vemurafenib)?

ZELBORAF may cause serious side effects, including:

– See “What is the most important information I should know about ZELBORAF?” (on page 8)

Allergic reactions can happen while taking your ZELBORAF, and may be severe. Stop taking ZELBORAF and get medical help right away if you have any of these symptoms of an allergic reaction:

- Get a rash or redness all over your body
- Feel faint
- Have trouble breathing or swallowing
- Have throat tightness or hoarseness
- Have a fast heartbeat
- Have swelling of the face, lips, or tongue

Severe skin reactions. Stop taking ZELBORAF and call your healthcare provider right away if you get a skin rash with any of the following symptoms, because you may have a severe skin reaction:

- 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

Changes in the electrical activity of your heart called QT prolongation. QT prolongation can cause irregular heartbeats that can be life-threatening. Your healthcare provider should do tests before you start taking ZELBORAF, if your dose changes, at certain other times during treatment, and after you stop treatment with ZELBORAF, to check the levels of potassium, magnesium, and calcium in your blood, and check the electrical activity of your heart with an ECG.

Tell your healthcare provider right away if you feel faint, lightheaded, dizzy or feel your heart beating irregularly or fast while taking ZELBORAF. These may be symptoms related to QT prolongation.

Abnormal liver function tests. Your healthcare provider should do blood tests to check your liver function before you start taking ZELBORAF and during treatment. Tell your healthcare provider right

away if you get any of these symptoms of a liver problem during treatment:

- Your skin or the whites of your eyes turn yellow
- You feel tired
- Your urine turns dark or brown (tea color)
- You have nausea or vomiting
- You do not want to eat
- Pain on the right side of your stomach

Eye problems. You should have your eyes examined before and while you are taking your ZELBORAF. Tell your healthcare provider right away if you get these symptoms during treatment with ZELBORAF:

- Eye pain, swelling, or redness
- Blurred vision or other vision changes during treatment with ZELBORAF

New melanoma lesions. You may develop new melanoma lesions while taking ZELBORAF. Check your skin and tell your healthcare provider right away about any skin changes.

The most common side effects of ZELBORAF include:

- Joint pain
- Rash **(see "Severe skin reactions" on page 10)**
- Hair loss
- Tiredness
- Sunburn or sun sensitivity
- Nausea
- Itching
- Warts

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all possible side effects of ZELBORAF. For more information about side effects, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects.

You may report side effects to FDA at 1-800-FDA-1088. You may also report side effects to Genentech at 1-888-835-2555.

Taking ZELBORAF™ (vemurafenib)

How do I take ZELBORAF?

ZELBORAF is a medicine you take by mouth. You can take it at home or wherever you happen to be. You don't need to go to the doctor to take it.

- Take ZELBORAF exactly as your doctor tells you. Do not change your dose or stop ZELBORAF unless your doctor tells you
- ZELBORAF is taken in the morning and in the evening, about 12 hours apart
- Take ZELBORAF with or without a meal
- Swallow the tablets whole with a glass of water. Do not chew or crush ZELBORAF tablets
- If you take too much ZELBORAF, call your doctor right away

Dosing

How long do I take ZELBORAF?

Keep taking ZELBORAF for as long as your doctor tells you.

Why is it important to take all the doses?

It is important to keep taking ZELBORAF exactly as your doctor tells you in order for your treatment to be most effective. Do not change your dose or stop ZELBORAF unless your doctor tells you.

What if I miss a dose?

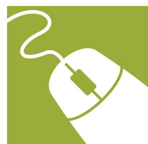
If you miss a dose, take it as soon as you remember. If it is within 4 hours of your next scheduled dose, just take your next dose at your regular time. Do not make up for the missed dose. Do not take 2 doses of ZELBORAF at the same time.

Getting support during your ZELBORAF treatment

How do I get help once I'm taking ZELBORAF?

You might need some additional support to stay on track with your treatment. The ZELBORAF Patient Partners™ program can help. This free 24/7 program is available to support you throughout your ZELBORAF therapy and can help answer any questions you may have.

You can opt in to this free 24/7 support program by calling 1-855-ZELBORAF or when you are at the doctor's office.*



For tips on how to remind yourself to take your tablets on time, please visit ***zelboraf.com****.*

Will I be able to speak to a live person?

Yes. As part of this free 24/7 support program, with your permission, a dedicated oncology nurse will call you to:

- Help manage your therapy
- Talk to you about your treatment
- Help you manage any side effects

You can call a dedicated oncology nurse 24/7 at ***1-855-ZELBORAF (1-855-935-2672)*** *whenever you have questions about your treatment.*

*With your permission, your specialty pharmacy can also enroll you in this program.

This program does not take the place of talking to your doctor about your medical condition or your treatment with ZELBORAF.

Please see accompanying full Prescribing Information and Medication Guide, and pages 8-11 for additional important safety information.

Helpful resources for patients on ZELBORAF™ (vemurafenib)

In addition to the ZELBORAF Patient Partners™ program, there are many places you can go for information and support.

Web sites for understanding your disease:

- National Cancer Institute*
  http://www.cancer.gov/cancertopics/types/melanoma
- National Comprehensive Cancer Network (NCCN) Guidelines for Patients With Melanoma*
  http://www.nccn.com/images/patient-guidelines/pdf/melanoma.pdf
- American Academy of Dermatology*
  http://www.aad.org and
  http://www.skincarephysicians.com/skincancernet

Patient support Web sites:

- Melanoma Research Foundation (MRF)*
  http://www.melanoma.org
- MRF Melanoma Patients Information Page*
  http://www.mpip.org
- AIM at Melanoma*
  http://www.aimatmelanoma.org
- Melanoma International Foundation*
  http://www.melanomaintl.org
- Skin Cancer Foundation*
  http://www.skincancer.org

*Genentech is neither affiliated with nor endorses this organization. The information provided by Genentech or this organization is meant for informational purposes only and is not meant to replace a physician's medical advice.

Notes

Please see accompanying full Prescribing Information and Medication Guide, and pages 8-11 for additional important safety information.

Assistance in getting started with your ZELBORAF treatment

How do I fill my prescription?

You are probably used to getting your medicine at your local drug store, but ZELBORAF is not sold there. Most patients can get ZELBORAF through a **specialty pharmacy**.

This specialty pharmacy delivers prescriptions primarily through the mail and sends the medicine right to your home. ZELBORAF Access Solutions® can help you receive your medication from the specialty pharmacy.

How will I be contacted?

With your permission, a ZELBORAF Access Solutions® specialist will call you when you enroll. You will then get a second call from your specialty pharmacy.
This call is to:

- Let you know when to expect your medicine
- Talk about financial or other assistance programs you might need
- Answer your questions about getting your medicine

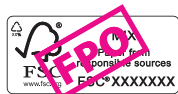
Can I get help paying for my medicine?

ZELBORAF Access Solutions® can help if you do not have insurance or have concerns about your out-of-pocket costs, such as your co-pay or co-insurance.

Your first step for getting ZELBORAF: call ***1-888-249-4918****.*

For more information about support programs, including financial assistance services, visit ***ZELBORAFAccessSolutions.com****.*

Please see accompanying full Prescribing Information and Medication Guide, and pages 8-11 for additional important safety information.



Daiichi-Sankyo

ZELBORAF™
(vemurafenib) tablets

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZELBORAF safely and effectively. See full prescribing information for ZELBORAF.

ZELBORAF™ (vemurafenib) tablet, oral
Initial U.S. Approval: 2011

-------------------------- INDICATIONS AND USAGE---------------------------

ZELBORAF™ is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with $BRAF^{V600E}$ mutation as detected by an FDA-approved test. (1, 5.10)

Limitation of Use: ZELBORAF is not recommended for use in patients with wild-type BRAF melanoma. (5.10, 14)

----------------------DOSAGE AND ADMINISTRATION----------------------

- Recommended dose: 960 mg orally twice daily. (2.1)
- Administer ZELBORAF approximately 12 hours apart with or without a meal. (2.1)
- ZELBORAF should be swallowed whole with a glass of water. ZELBORAF should not be chewed or crushed. (2.1)
- Management of symptomatic adverse drug reactions may require dose reduction, treatment interruption, or treatment discontinuation of ZELBORAF. Dose reductions resulting in a dose below 480 mg twice daily are not recommended. (2.2)

--------------------- DOSAGE FORMS AND STRENGTHS---------------------

Film-coated tablet: 240 mg (3)

----------------------------- CONTRAINDICATIONS -----------------------------

None (4)

---------------------- WARNINGS AND PRECAUTIONS-----------------------

- Cutaneous squamous cell carcinomas (cuSCC) occurred in 24% of patients. Perform dermatologic evaluations prior to initiation of therapy and every two months while on therapy. Manage with excision and continue treatment without dose adjustment. (5.1)
- Serious hypersensitivity reactions, including anaphylaxis, have been reported during and upon re-initiation of treatment. Discontinue ZELBORAF in patients who experience severe hypersensitivity reactions. (5.2)
- Severe dermatologic reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported. Discontinue treatment in patients who experience severe dermatologic reactions. (5.3)
- QT prolongation has been reported. Monitor ECG and electrolytes before treatment and after dose modification. Monitor ECGs at day 15, monthly during the first 3 months of treatment, every 3 months thereafter, or more often as clinically indicated. If the QTc exceeds 500 ms, temporarily interrupt ZELBORAF, correct electrolyte abnormalities, and control for cardiac risk factors for QT prolongation. (5.4)
- Liver laboratory abnormalities may occur. Monitor liver enzymes and bilirubin before initiation of treatment and monthly during treatment, or as clinically indicated. (5.5)
- Photosensitivity has been reported. Advise patients to avoid sun exposure while taking ZELBORAF. (5.6)
- Serious ophthalmologic reactions, including uveitis, iritis and retinal vein occlusion, have been reported. Monitor patients routinely for ophthalmologic reactions. (5.7)
- New primary malignant melanomas have been reported. Manage with excision, and continue treatment without dose modification. Perform dermatologic monitoring as outlined above. (5.8)
- Pregnancy: May cause fetal harm. Advise women of potential risk to the fetus. (5.9, 8.1)
- $BRAF^{V600E}$ testing – confirmation of $BRAF^{V600E}$ mutation using an FDA-approved test is required for selection of patients appropriate for ZELBORAF therapy. The efficacy and safety of ZELBORAF have not been studied in patients with wild-type BRAF melanoma. (5.10, 14)

----------------------------- ADVERSE REACTIONS -----------------------------

Most common adverse reactions (≥ 30%) are arthralgia, rash, alopecia, fatigue, photosensitivity reaction, nausea, pruritus and skin papilloma. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------------------------- DRUG INTERACTIONS------------------------------

- CYP Substrates: Concomitant use of ZELBORAF with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP1A2 or CYP2D6 is not recommended. If coadministration cannot be avoided, exercise caution and consider a dose reduction of the concomitant CYP1A2 or CYP2D6 substrate drug. (7.1)
- ZELBORAF may increase exposure to concomitantly administered warfarin. Exercise caution and consider additional INR monitoring when ZELBORAF is used concomitantly with warfarin. (7.1)

---------------------- USE IN SPECIFIC POPULATIONS ----------------------

- Nursing Mothers: Discontinue nursing when receiving ZELBORAF (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 08/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

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*Sections or subsections omitted from the full prescribing information are not listed

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZELBORAF™ is indicated for the treatment of patients with unresectable or metastatic melanoma with $BRAF^{V600E}$ mutation as detected by an FDA-approved test.

Limitation of Use: ZELBORAF is not recommended for use in patients with wild-type BRAF melanoma.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose of ZELBORAF is 960 mg (four 240 mg tablets) twice daily. The first dose should be taken in the morning and the second dose should be taken in the evening approximately 12 hours later. Each dose can be taken with or without a meal.

ZELBORAF tablets should be swallowed whole with a glass of water. ZELBORAF tablets should not be chewed or crushed.

Duration of treatment

It is recommended that patients are treated with ZELBORAF until disease progression or unacceptable toxicity occurs.

Missed doses

If a dose is missed, it can be taken up to 4 hours prior to the next dose to maintain the twice daily regimen. Both doses should not be taken at the same time.

2.2 Dose Modifications

Management of symptomatic adverse drug reactions or prolongation of QTc may require dose reduction, treatment interruption, or treatment discontinuation of ZELBORAF (Table 1). Dose modifications or interruptions are not recommended for cutaneous squamous cell carcinoma (cuSCC) adverse reactions *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*. Dose reductions resulting in a dose below 480 mg twice daily are not recommended.

Table 1 Dose Modification Information

Grade (CTC-AE)*	Recommended ZELBORAF Dose Modification
Grade 1 or Grade 2 (tolerable)	Maintain ZELBORAF at a dose of 960 mg twice daily.
Grade 2 (Intolerable) or Grade 3	
1st Appearance	Interrupt treatment until grade 0 – 1. Resume dosing at 720 mg twice daily.
2nd Appearance	Interrupt treatment until grade 0 – 1. Resume dosing at 480 mg twice daily.
3rd Appearance	Discontinue permanently
Grade 4	
1st Appearance	Discontinue permanently or interrupt ZELBORAF treatment until grade 0 – 1. Resume dosing at 480 mg twice daily.
2nd Appearance	Discontinue permanently

*The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events v4.0 (CTC-AE)

3 DOSAGE FORMS AND STRENGTHS

Film-coated tablet: 240 mg

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Cutaneous Squamous Cell Carcinoma (cuSCC)

Cases of cuSCC, including both SCCs of the skin and keratoacanthomas, have been reported in patients treated with ZELBORAF *[see Adverse Reactions (6.1)]*. The incidence of cuSCC in ZELBORAF-treated patients in Trial 1 was 24%. CuSCC usually occurred early in the course of treatment with a median time to the first appearance of 7 to 8 weeks. Of the patients who experienced cuSCC, approximately 33% experienced > 1 occurrence with median time between occurrences of 6 weeks. Potential risk factors associated with cuSCC in

ZELBORAF clinical studies included age (≥ 65 years), prior skin cancer, and chronic sun exposure. In the clinical trials, cases of cuSCC were managed with excision, and patients were able to continue treatment without dose adjustment.

It is recommended that all patients receive a dermatologic evaluation prior to initiation of therapy and every two months while on therapy. Any suspicious skin lesions should be excised, sent for dermatopathologic evaluation and treated as per standard of care. Monitoring should be considered for 6 months following discontinuation of ZELBORAF.

5.2 Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been reported in association with ZELBORAF and upon re-initiation of treatment. Severe hypersensitivity reactions included generalized rash and erythema or hypotension. In patients who experience a severe hypersensitivity reaction, ZELBORAF treatment should be permanently discontinued.

5.3 Dermatologic Reactions

Severe dermatologic reactions have been reported in patients receiving ZELBORAF, including one case of Stevens-Johnson syndrome and one case of toxic epidermal necrolysis in Trial 1. In patients who experience a severe dermatologic reaction, ZELBORAF treatment should be permanently discontinued.

5.4 QT Prolongation

Exposure-dependent QT prolongation was observed in an uncontrolled, open-label Phase 2 QT sub-study in previously treated patients with $BRAF^{V600E}$ mutation-positive metastatic melanoma *[see Clinical Pharmacology (12.3)]*. QT prolongation may lead to an increased risk of ventricular arrhythmias, including Torsade de Pointes. Treatment with ZELBORAF is not recommended in patients with uncorrectable electrolyte abnormalities, long QT syndrome, or who are taking medicinal products known to prolong the QT interval.

ECG and electrolytes, including potassium, magnesium, and calcium, should be monitored before treatment with ZELBORAF and after dose modification. Monitoring of ECGs should occur 15 days after treatment initiation and then monthly during the first 3 months of treatment, followed by every 3 months thereafter or more often as clinically indicated. Initiation of treatment with ZELBORAF is not recommended in patients with QTc > 500 ms. If during treatment the QTc exceeds 500 ms (CTC-AE ≥ Grade 3), ZELBORAF treatment should be temporarily interrupted, electrolyte abnormalities should be corrected, and cardiac risk factors for QT prolongation (e.g., congestive heart failure, bradyarrhythmias) should be controlled. Re-initiation of treatment should occur at a lower dose once the QTc decreases below 500 ms *[see Dosage and Administration (2.2)]*. Permanent discontinuation of ZELBORAF treatment is recommended if after correction of associated risk factors, the QTc increase meets values of both > 500 ms and > 60 ms change from pre-treatment values.

5.5 Liver Laboratory Abnormalities

Liver laboratory abnormalities have occurred with ZELBORAF (Table 3) *[see Adverse Reactions (6.1)]*. Liver enzymes (transaminases and alkaline phosphatase) and bilirubin should be monitored before initiation of treatment and monthly during treatment, or as clinically indicated. Laboratory abnormalities should be managed with dose reduction, treatment interruption, or treatment discontinuation *[see Dosage and Administration (2.2)]*.

5.6 Photosensitivity

Mild to severe photosensitivity was reported in patients treated with ZELBORAF in clinical trials *[see Adverse Reactions (6.1)]*. All patients should be advised to avoid sun exposure while taking ZELBORAF. While taking the drug, patients should be advised to wear protective clothing and use a broad spectrum UVA/UVB sunscreen and lip balm (SPF ≥ 30) when outdoors to help protect against sunburn.

For intolerable grade 2 (tender erythema covering 10 - 30% body surface area) or greater photosensitivity, dose modifications are recommended *[see Dosage and Administration (2.2)]*.

5.7 Ophthalmologic Reactions

In Trial 1, five cases of uveitis have been reported in patients treated with ZELBORAF. Treatment with steroid and mydriatic ophthalmic drops may be required to manage uveitis. Patients should be routinely monitored for signs and symptoms of uveitis. Additionally, there were five patients with blurry vision, five patients with iritis and six patients with photophobia. There was one case of retinal vein occlusion in Trial 2.

5.8 New Primary Malignant Melanoma

There were eight skin lesions in seven patients reported as new primary malignant melanoma in Trial 1. Cases were managed with excision, and patients continued treatment without dose adjustment. Monitoring for skin lesions should occur as outlined above *[see Warnings and Precautions (5.1)]*.

5.9 Use in Pregnancy

Pregnancy Category D

ZELBORAF may cause fetal harm when administered to a pregnant woman based on its mechanism of action. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.

5.10 $BRAF^{V600E}$ Testing

Confirmation of $BRAF^{V600E}$ mutation-positive melanoma as detected by an FDA-approved test is required for selection of patients for ZELBORAF therapy because these are the only patients studied and for whom benefit has been shown. For patients in ZELBORAF clinical studies, including Trial 1 and Trial 2, all enrolled patients tested positive when their tumor tissue was assessed with the cobas® 4800 BRAF V600 Mutation Test *[see Clinical Studies (14)]*. This test is designed to detect $BRAF^{V600E}$ mutations in DNA isolated from formalin-fixed, paraffin-embedded human melanoma tissue. The safety and efficacy of ZELBORAF have not been evaluated in patients whose melanoma tested negative by the cobas® 4800 BRAF V600 Mutation Test. Refer to the package inserts of FDA approved test kits, for detailed information.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in another section of the label:

- Cutaneous Squamous Cell Carcinoma *[see Warnings and Precautions (5.1)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.2)]*
- Dermatologic Reactions *[see Warnings and Precautions (5.3)]*
- QT Prolongation *[see Warnings and Precautions (5.4)]*
- Liver Laboratory Abnormalities *[see Warnings and Precautions (5.5)]*
- Photosensitivity *[see Warnings and Precautions (5.6)]*
- Ophthalmologic Reactions *[see Warnings and Precautions (5.7)]*
- New Primary Malignant Melanoma *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not predict the rates observed in a broader patient population in clinical practice.

The adverse drug reactions (ADRs) described in this section were identified from Trial 1 and Trial 2 *[see Clinical Studies (14)]*. In Trial 1, treatment naive patients with unresectable or metastatic melanoma (n=675) were allocated to ZELBORAF 960 mg orally twice daily or to dacarbazine 1000 mg/m^2 intravenously every 3 weeks. In Trial 2, (n=132) patients with metastatic melanoma and failure of at least one prior systemic therapy received treatment with ZELBORAF 960 mg orally twice daily. Adverse reactions reported in at least 10% of patients treated with ZELBORAF are presented in Table 2. The most common adverse reactions of any grade ($\geq$ 30% in either study) reported in ZELBORAF-treated patients were arthralgia, rash, alopecia, fatigue,

photosensitivity reaction, nausea, pruritus and skin papilloma. The most common (≥ 5%) Grade 3 adverse reactions were cuSCC and rash. The incidence of Grade 4 adverse reactions was ≤ 4% in both studies.

The incidence of adverse events resulting in permanent discontinuation of study medication in Trial 1 was 7% for the ZELBORAF arm and 4% for the dacarbazine arm. In Trial 2, the incidence of adverse events resulting in permanent discontinuation of study medication was 3% in ZELBORAF-treated patients. The median duration of study treatment was 4.2 months for ZELBORAF and 0.8 months for dacarbazine in Trial 1, and 5.7 months for ZELBORAF in Trial 2.

Table 2 Adverse Reactions Reported in ≥ 10% of Patients Treated with ZELBORAF*

ADRs	Trial 1: Treatment Naive Patients						Trial 2: Patients with Failure of at Least One Prior Systemic Therapy		
	ZELBORAF n= 336			Dacarbazine n= 287			ZELBORAF n= 132		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Skin and subcutaneous tissue disorders									
Rash	37	8	-	2	-	-	52	7	-
Photosensitivity reaction	33	3	-	4	-	-	49	3	-
Alopecia	45	<1	-	2	-	-	36	-	-
Pruritus	23	1	-	1	-	-	30	2	-
Hyperkeratosis	24	1	-	<1	-	-	28	-	-
Rash maculo-papular	9	2	-	<1	-	-	21	6	-
Actinic keratosis	8	-	-	3	-	-	17	-	-
Dry skin	19	-	-	1	-	-	16	-	-
Rash papular	5	<1	-	-	-	-	13	-	-
Erythema	14	-	-	2	-	-	8	-	-
Musculoskeletal and connective tissue disorders									
Arthralgia	53	4	-	3	<1	-	67	8	-
Myalgia	13	<1	-	1	-	-	24	<1	-
Pain in extremity	18	<1	-	6	2	-	9	-	-
Musculoskeletal pain	8	-	-	4	<1	-	11	-	-
Back pain	8	<1	-	5	<1	-	11	<1	-
General disorders and administration site conditions									
Fatigue	38	2	-	33	2	-	54	4	-
Edema peripheral	17	<1	-	5	-	-	23	-	-
Pyrexia	19	<1	-	9	<1	-	17	2	-
Asthenia	11	<1	-	9	<1	-	2	-	-
Gastrointestinal disorders									
Nausea	35	2	-	43	2	-	37	2	-
Diarrhea	28	<1	-	13	<1	-	29	<1	-
Vomiting	18	1	-	26	1	-	26	2	-
Constipation	12	<1	-	24	-	-	16	-	-
Nervous system disorders									
Headache	23	<1	-	10	-	-	27	-	-
Dysgeusia	14	-	-	3	-	-	11	-	-
Neoplasms benign, malignant and unspecified (includes cysts and polyps)									
Skin papilloma	21	<1	-	-	-	-	30	-	-
Cutaneous SCC[†#]	24	22	-	<1	<1	-	24	24	-

ADRs	Trial 1: Treatment Naive Patients						Trial 2: Patients with Failure of at Least One Prior Systemic Therapy		
	ZELBORAF n= 336			Dacarbazine n= 287			ZELBORAF n= 132		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Seborrheic keratosis	10	<1	-	1	-	-	14	-	-
Investigations									
Gamma-glutamyltransferase increased	5	3	<1	1	-	-	15	6	4
Metabolism and nutrition disorders									
Decreased appetite	18	-	-	8	<1	-	21	-	-
Respiratory, thoracic and mediastinal disorders									
Cough	8	-	-	7	-	-	12	-	-
Injury, poisoning and procedural complications									
Sunburn	10	-	-	-	-	-	14	-	-

[*]Adverse drug reactions, reported using MedDRA and graded using NCI-CTC-AE v 4.0 (NCI common toxicity criteria) for assessment of toxicity.

[†] Includes both squamous cell carcinoma of the skin and keratoacanthoma.

[#] All cases of cutaneous squamous cell carcinoma were to be reported as Grade 3 per instructions to study investigators and no dose modification or interruption was required.

Clinically relevant adverse events reported in < 10% of patients treated with ZELBORAF in the Phase 2 and Phase 3 studies include:

Skin and subcutaneous tissue disorders: palmar-plantar erythrodysaesthesia syndrome, keratosis pilaris, erythema nodosum, Stevens-Johnson syndrome

Musculoskeletal and connective tissue disorders: arthritis

Nervous system disorders: dizziness, neuropathy peripheral, VIIth nerve paralysis

Neoplasms benign, malignant and unspecified (includes cysts and polyps): basal cell carcinoma

Infections and infestations: folliculitis

Investigations: weight decreased

Eye disorders: retinal vein occlusion, uveitis

Vascular disorders: vasculitis

Cardiac disorders: atrial fibrillation

Table 3 shows the incidence of worsening liver laboratory abnormalities in Trial 1 summarized as the proportion of patients who experienced a shift from baseline to Grade 3 or 4.

Table 3 Change From Baseline to Grade 3/4 Liver Laboratory Abnormalities*

Parameter	Change From Baseline to Grade 3/4	
	ZELBORAF (%)	Dacarbazine (%)
GGT	11.5	8.6
AST	0.9	0.4
ALT	2.8	1.9
Alkaline phosphatase	2.9	0.4
Bilirubin	1.9	-

* For ALT, alkaline phosphatase and bilirubin, there were no patients with a change to grade 4 in either treatment arm.

7 DRUG INTERACTIONS

7.1 Effects of Vemurafenib on Drug Metabolizing Enzymes

Results from an *in vivo* drug-drug interaction study in patients with cancer demonstrated that vemurafenib is a moderate CYP1A2 inhibitor, a weak CYP2D6 inhibitor and a CYP3A4 inducer *[see Clinical Pharmacology (12.3)]*.

Coadministration of vemurafenib increased the AUC of caffeine (CYP1A2 substrate) 2.6-fold and increased the AUC of dextromethorphan (CYP2D6 substrate) by 47%, while it decreased the AUC of midazolam (CYP3A4 substrate) by 39% *[see Clinical Pharmacology (12.3)]*. Concomitant use of ZELBORAF with agents with narrow therapeutic windows that are metabolized by CYP1A2, CYP2D6 and CYP3A4 is not recommended as ZELBORAF may alter their concentrations. If coadministration cannot be avoided, exercise caution and consider a dose reduction of the concomitant CYP1A2 and CYP2D6 substrate drug.

Coadministration of vemurafenib resulted in an 18% increase in AUC of S-warfarin (CYP2C9 substrate) *[see Clinical Pharmacology (12.3)]*. Exercise caution and consider additional INR monitoring when ZELBORAF is used concomitantly with warfarin.

7.2 Drugs that Inhibit or Induce CYP3A4

Based on *in vitro* data, vemurafenib is a substrate of CYP3A4, and therefore, concomitant administration of strong CYP3A4 inhibitors or inducers may alter vemurafenib concentrations. Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) and inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) should be used with caution when coadministered with ZELBORAF.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.9)]*.

ZELBORAF may cause fetal harm when administered to a pregnant woman based on its mechanism of action.

Vemurafenib revealed no evidence of teratogenicity in rat embryo/fetuses at doses up to 250 mg/kg/day (approximately 1.3 times the human clinical exposure based on AUC) or rabbit embryo/fetuses at doses up to 450 mg/kg/day (approximately 0.6 times the human clinical exposure based on AUC). Fetal drug levels were 3-5% of maternal levels, indicating that vemurafenib has the potential to be transmitted from the mother to the developing fetus. There are no adequate and well controlled studies in pregnant women. Women of childbearing potential and men should be advised to use appropriate contraceptive measures during ZELBORAF therapy and for at least 2 months after discontinuation of ZELBORAF. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

8.3 Nursing Mothers

It is not known whether vemurafenib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from ZELBORAF in nursing infants, a decision

should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and efficacy in pediatric patients below the age of 18 have not been established.

8.5 Geriatric Use

Ninety-four (28%) of 336 patients with unresectable or metastatic melanoma treated with ZELBORAF in Trial 1 were ≥ 65 years. Elderly patients (≥ 65 years) may be more likely to experience some adverse reactions, including cutaneous squamous cell carcinoma, nausea, decreased appetite, peripheral edema, keratoacanthoma and atrial fibrillation. The effects of ZELBORAF on overall survival, progression-free survival and best overall response rate were similar in the elderly as compared to younger patients.

8.6 Gender

The Grade 3 adverse events reported more frequently in females than males were rash, arthralgia, photosensitivity and increased creatinine. The Grade 3 adverse events reported more frequently in males than females were keratoacanthoma, increased alkaline phosphatase and increased total bilirubin.

8.7 Hepatic Impairment

No adjustment to the starting dose is needed for patients with pre-existing mild and moderate hepatic impairment. In the population pharmacokinetic analysis using data from clinical trials in patients with metastatic melanoma, pre-existing mild and moderate hepatic impairment did not influence the apparent clearance of vemurafenib. Clinical and pharmacokinetic data from only three patients with pre-existing severe hepatic impairment are available from clinical trials, and based on the limited data, the potential need for starting dose adjustment cannot be determined. ZELBORAF should be used with caution in patients with pre-existing severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.8 Renal Impairment

No adjustment to the starting dose is needed for patients with pre-existing mild and moderate renal impairment. In the population pharmacokinetic analysis using data from clinical trials in patients with metastatic melanoma, pre-existing mild and moderate renal impairment did not influence the apparent clearance of vemurafenib. Clinical and pharmacokinetic data from one patient with pre-existing severe renal impairment are available from clinical trials, and based on the limited data, the potential need for starting dose adjustment cannot be determined. ZELBORAF should be used with caution in patients with pre-existing severe renal impairment *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

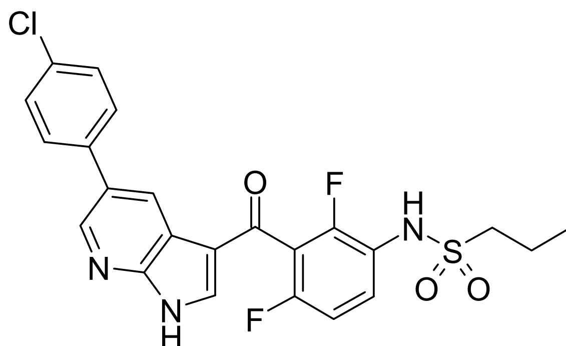
No studies on the potential for ZELBORAF to cause dependence have been performed. However, there is no evidence from the available data that ZELBORAF treatment can result in dependence.

10 OVERDOSAGE

There is no specific antidote for overdosage of ZELBORAF. Patients who develop adverse reactions should receive appropriate symptomatic treatment. In case of suspected overdose, ZELBORAF should be withheld and supportive care instituted.

11 DESCRIPTION

ZELBORAF (vemurafenib) is a kinase inhibitor available as 240 mg tablets for oral use. Vemurafenib has the chemical name propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide. It has the molecular formula $C_{23}H_{18}ClF_2N_3O_3S$ and a molecular weight of 489.9. Vemurafenib has the following chemical structure:



Vemurafenib is a white to off-white crystalline solid. It is practically insoluble in aqueous media.

Tablets of ZELBORAF are for oral administration. Each tablet contains 240 mg of vemurafenib.

The inactive ingredients of ZELBORAF are: **Tablet Core:** hypromellose acetate succinate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, and hydroxypropyl cellulose. **Coating:** pinkish white: poly(vinyl alcohol), titanium dioxide, polyethylene glycol 3350, talc, and iron oxide red.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Vemurafenib is a low molecular weight, orally available, inhibitor of some mutated forms of BRAF serine-threonine kinase, including $BRAF^{V600E}$. Vemurafenib also inhibits other kinases *in vitro* such as CRAF, ARAF, wild-type BRAF, SRMS, ACK1, MAP4K5 and FGR at similar concentrations. Some mutations in the BRAF gene including V600E result in constitutively activated BRAF proteins, which can cause cell proliferation in the absence of growth factors that would normally be required for proliferation. Vemurafenib has anti-tumor effects in cellular and animal models of melanomas with mutated $BRAF^{V600E}$.

12.3 Pharmacokinetics

The pharmacokinetics of vemurafenib were determined in patients with BRAF mutation-positive metastatic melanoma following 15 days of dosing at 960 mg twice daily with dosing approximately 12 hours apart. The population pharmacokinetic analysis pooled data from 458 patients. A one-compartment disposition model with first-order absorption and first-order elimination adequately describes the vemurafenib concentration-time profile. At steady state, vemurafenib exhibits linear pharmacokinetics within the 240 mg to 960 mg dose range.

Absorption

The bioavailability of vemurafenib has not been determined. Following oral administration of vemurafenib at 960 mg twice daily for 15 days to patients with metastatic melanoma, the median T_{max} was approximately 3 hours.

Following 15 days of dosing at 960 mg twice daily, the mean (± SD) C_{max} and AUC_{0-12} were 62 µg/mL ± 17 and 601 ± 170 µg*h/mL, respectively. The median accumulation ratio estimate from the population pharmacokinetic analysis for the twice daily regimen is 7.36, with steady state achieved at approximately 15 to 22 days following dosing at 960 mg twice daily. At steady state, the mean vemurafenib exposure in plasma is stable (concentrations before and 2-4 hours after the morning dose) as indicated by the mean ratio of 1.13.

The potential effect of food on vemurafenib absorption has not been studied. In clinical trials, vemurafenib was administered without regard to food.

Distribution

Vemurafenib is highly bound (> 99%) to human albumin and alpha-1 acid glycoprotein plasma proteins. The population apparent volume of distribution for vemurafenib in metastatic melanoma patients is estimated to be 106 L (with 66% inter-patient variability).

Metabolism

Following oral administration of ^{14}C-vemurafenib 960 mg in the tablet formulation, plasma samples were analyzed over 48 hours for vemurafenib and its metabolites. Mean data showed that vemurafenib and its metabolites represented 95% and 5% of the components in plasma, respectively.

Elimination

Following oral administration of ^{14}C-vemurafenib 960 mg in the tablet formulation, approximately 94% of the radioactive dose was recovered in feces and approximately 1% was recovered in the urine. The population apparent clearance of vemurafenib in patients with metastatic melanoma is estimated to be 31 L/day (with 32% inter-patient variability). The median of the individual elimination half-life estimates for vemurafenib is 57 hours (the 5th and 95th percentile range is 30 to 120 hours).

Pharmacokinetics in Special Populations

Hepatic Impairment: The pharmacokinetics of vemurafenib were examined in patients with metastatic melanoma enrolled in the clinical trials with normal hepatic function (n=158, total bilirubin ≤ ULN) and pre-existing mild (n=58, total bilirubin 1.0-1.5 x ULN), moderate (n=27, total bilirubin 1.5-3 x ULN), or severe (n=3, total bilirubin > 3 x ULN) hepatic impairment. Patients received vemurafenib 960 mg orally twice daily. The apparent clearance of vemurafenib in patients with pre-existing mild and moderate hepatic impairment was similar to that in patients with normal hepatic function. The potential need for dose adjustment in patients with severe hepatic impairment cannot be determined as clinical and pharmacokinetic data were available for only three patients *[see Use in Specific Populations (8.7)]*.

Renal Impairment: The pharmacokinetics of vemurafenib were examined in patients with metastatic melanoma enrolled in the clinical trials with normal renal function (CLcr ≥ 90 mL/min) and pre-existing mild (n=94, CLcr > 60 to 89 mL/min), moderate (n=11, CLcr 30 to 59 mL/min) or severe (n=1, CLcr < 29 mL/min) renal impairment. Patients received vemurafenib 960 mg orally twice daily. The apparent clearance of vemurafenib in patients with pre-existing mild and moderate renal impairment was similar to that in patients with normal renal function. The potential need for dose adjustment in patients with severe renal impairment cannot be determined as clinical and pharmacokinetic data were available for only one patient *[see Use in Specific Populations (8.8)]*.

Age: Based on the population pharmacokinetic analysis, age has no statistically significant effect on vemurafenib pharmacokinetics.

Body Weight and Gender: Based on the population pharmacokinetic analysis, there was no clinically relevant effect of body weight or gender on vemurafenib pharmacokinetics.

Race: There are insufficient data to evaluate potential differences in the pharmacokinetics of vemurafenib by race.

Pediatrics: No studies have been conducted to investigate the pharmacokinetics of vemurafenib in children.

Drug Interactions: *In vitro* studies with human hepatic microsomes showed that vemurafenib is an inhibitor of CYP1A2, 2A6, 2C9, 2C19, 2D6, and 3A4/5, with IC_{50} values of 32.5, > 50, 5.9, 22.5, 33.2, and > 50 µM, respectively.

In an *in vivo* phenotypic cocktail drug-drug interaction study in patients with cancer, a single dose of the CYP probe substrate cocktail (for CYP1A2, 2D6, 3A4, 2C19 and 2C9) was administered before and concomitantly with vemurafenib (following 15 days of dosing at 960 mg twice daily). Coadministration of vemurafenib increased the AUC of caffeine (CYP1A2 substrate) 2.6-fold and increased the C_{max} and AUC of dextromethorphan (CYP2D6 substrate) by 36% and 47%, respectively, while it decreased the C_{max} and AUC of midazolam (CYP3A4 substrate) by 35% and 39%, respectively. Coadministration of vemurafenib increased the AUC of S-warfarin (CYP2C9 substrate) by 18%. Coadministration of vemurafenib did not change the systemic exposure to omeprazole (CYP2C19 substrate) *[see Drug Interactions (7.1)]*.

In vitro studies have demonstrated that vemurafenib is both a substrate and an inhibitor of the efflux transporter P-glycoprotein (P-gp).

In vitro studies with human hepatic microsomes showed that vemurafenib is a CYP3A4 substrate. The effect of strong CYP3A4 inhibitors or strong CYP3A4 inducers on the concentrations of vemurafenib has not been evaluated *in vivo [see Drug Interactions (7.2)].*

12.4 QT Prolongation

The effect of vemurafenib 960 mg administered twice daily on QTc interval was evaluated in a multi-center, open-label, single-arm study in 132 patients with BRAF V600E mutation-positive metastatic melanoma. No large changes in mean QTc interval (i.e., >20 ms) from baseline were detected in the trial. Vemurafenib is associated with concentration-dependent QTc interval prolongation. In the first month of treatment, the largest mean change from baseline of 12.8 ms (upper boundary of the 2-sided 90% confidence interval of 14.9 ms) was observed at 2 hours post-dose on Day 15. In the first 6 months of treatment, the largest observed mean change from baseline of 15.1 ms (upper boundary of the 2-sided 90% confidence interval of 17.7 ms) was detected at a pre-dose time point.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There have been no formal studies conducted assessing the carcinogenic potential of vemurafenib. ZELBORAF increased the development of cutaneous squamous cell carcinomas in patients in clinical trials.

Vemurafenib did not cause genetic damage when tested in *in vitro* assays (bacterial mutation [AMES Assay], human lymphocyte chromosome aberration) or in the *in vivo* rat bone marrow micronucleus test.

No specific studies with vemurafenib have been conducted in animals to evaluate the effect on fertility; nevertheless, no histopathological findings were noted in reproductive organs in males and females in repeat-dose toxicology studies in rats at doses up to 450 mg/kg/day (approximately 0.6 and 1.6 times the human exposure based on AUC in males and females, respectively) and dogs at doses up to 450 mg/kg/day (approximately 0.3 times the human clinical exposure based on AUC in both males and females, respectively).

13.2 Animal Toxicology and/or Pharmacology

Consistent with the increased incidence of cutaneous squamous cell carcinomas in patients treated with vemurafenib, the treatment of mice implanted with human cuSCC cells with vemurafenib caused a dose dependent acceleration of the growth of the implanted tumors.

14 CLINICAL STUDIES

Treatment Naive Patients

The efficacy and safety of ZELBORAF in patients with treatment naive, $BRAF^{V600E}$ mutation-positive unresectable or metastatic melanoma as detected by the cobas® 4800 BRAF V600 Mutation Test were assessed in an international, randomized, open-label trial (Trial 1). The trial enrolled 675 patients; 337 were allocated to receive ZELBORAF 960 mg by mouth twice daily and 338 to receive dacarbazine 1000 mg/m^2 intravenously on Day 1 every 3 weeks. Randomization was stratified according to disease stage, lactate dehydrogenase (LDH), ECOG performance status and geographic region. Treatment continued until disease progression, unacceptable toxicity, and/or consent withdrawal. The major efficacy outcome measures of the trial were overall survival (OS) and investigator-assessed progression-free survival (PFS). Other outcome measures included confirmed investigator-assessed best overall response rate.

Baseline characteristics were balanced between treatment groups. Most patients were male (56%) and Caucasian (99%), the median age was 54 years (24% were ≥ 65 years), all patients had ECOG performance status of 0 or 1, and the majority of patients had metastatic disease (95%).

Efficacy results are summarized in Table 4 and Figure 1.

Table 4 Efficacy of ZELBORAF in Treatment Naive Patients with BRAF^{V600E} Mutation-Positive Melanoma[a]

	ZELBORAF (N=337)	Dacarbazine (N=338)	p-value[d]
Overall Survival			
Number of Deaths	78 (23%)	121 (36%)	
Hazard Ratio (95% CI)[b]	0.44 (0.33, 0.59)		<0.0001
Median Survival (months) (95 % CI)[c]	Not Reached (9.6, Not Reached)	7.9 (7.3, 9.6)	-
Median Follow-up (months) (range)	6.2 (0.4, 13.9)	4.5 (<0.1, 11.7)	
Progression-free survival			
Hazard Ratio (95% CI)[b]	0.26 (0.20, 0.33)		<0.0001
Median PFS (months) (95% CI)[c]	5.3 (4.9, 6.6)	1.6 (1.6, 1.7)	-

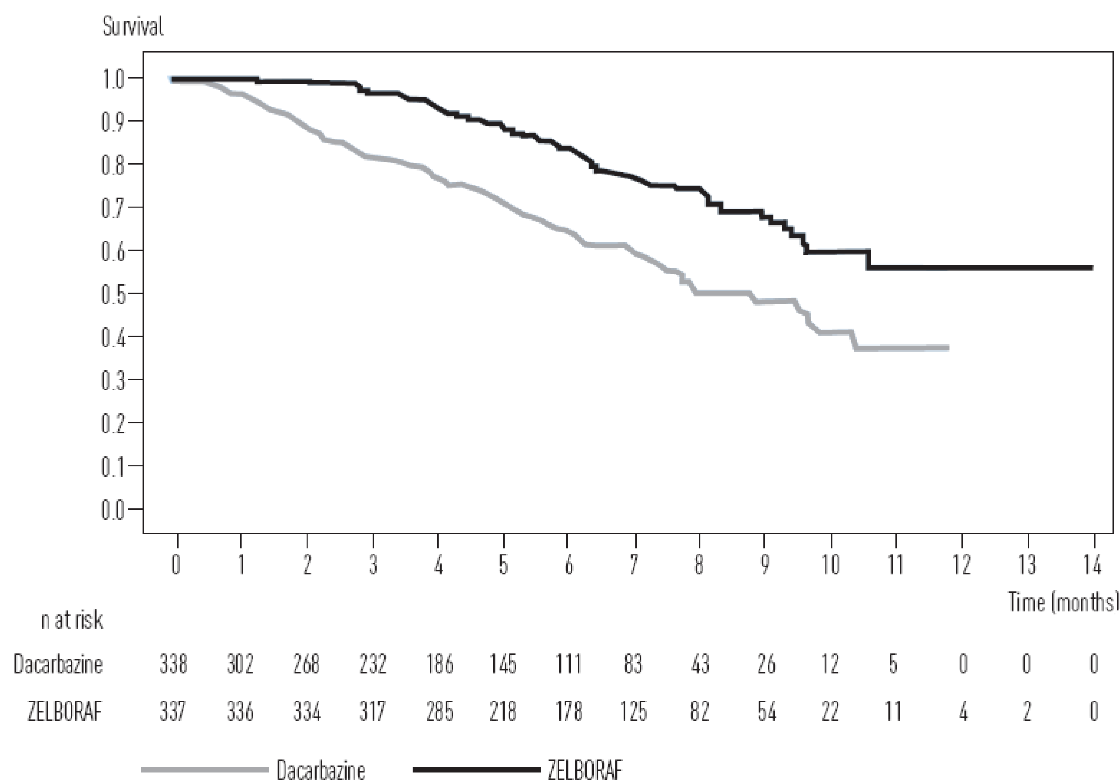
[a] As detected by the cobas® 4800 BRAF V600 Mutation Test

[b] Hazard ratio estimated using Cox model; a hazard ratio of < 1 favors ZELBORAF

[c] Kaplan-Meier estimate

[d] Unstratified log-rank test

Figure 1 Kaplan-Meier Curves of Overall Survival – Treatment Naive Patients



The confirmed, investigator-assessed best overall response rate was 48.4% (95% CI: 41.6%, 55.2%) in the ZELBORAF arm compared to 5.5% (95% CI: 2.8%, 9.3%) in the dacarbazine arm. There were 2 complete responses (0.9%) and 104 partial responses (47.4%) in the ZELBORAF arm and all 12 responses were partial responses (5.5%) in the dacarbazine arm.

Patients Who Received Prior Systemic Therapy

A single-arm, multicenter, multinational trial (Trial 2) was conducted in 132 patients with BRAF^{V600E} mutation-positive metastatic melanoma, as detected by the cobas® 4800 BRAF V600 Mutation Test, who had received at

least one prior systemic therapy. The median age was 52 years with 19% of patients being older than 65 years. The majority of patients were male (61%) and Caucasian (99%). Forty-nine percent of patients received ≥ 2 prior therapies. The median duration of follow-up was 6.87 months (range, 0.6 to 11.3).

The confirmed best overall response rate as assessed by an independent review committee (IRC) was 52% (95% CI: 43%, 61%). There were 3 complete responses (2.3%) and 66 partial responses (50.0%). The median time to response was 1.4 months with 75% of responses occurring by month 1.6 of treatment. The median duration of response by IRC was 6.5 months (95% CI: 5.6, not reached).

Patients with wild-type BRAF melanoma

ZELBORAF has not been studied in patients with wild-type BRAF melanoma.

16 HOW SUPPLIED/STORAGE AND HANDLING

ZELBORAF (vemurafenib) is supplied as 240 mg film-coated tablets with VEM debossed on one side in single bottle of 120 count. The following packaging configuration is available:

NDC 50242-090-01

Storage and Stability: Store at room temperature 20°C - 25°C (68°F - 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F), See USP Controlled Room Temperature. Store in the original container with the lid tightly closed.

Disposal of unused/expired medicines: The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established "collection systems", if available in your location.

17 PATIENT COUNSELING INFORMATION

17.1 Patient Counseling

Patients should be advised of the potential benefits and risks of ZELBORAF. Physicians should instruct their patients to read the Medication Guide before starting ZELBORAF therapy.

- **BRAF^{V600E} Testing**

  Inform patients that an assessment of BRAF^{V600E} mutation with the **cobas®** 4800 BRAF V600 Mutation Test (or other FDA approved test) is required for selection of patients appropriate for ZELBORAF therapy. These patients are the only patients studied and for whom benefit has been shown *[see Warnings and Precautions (5.10) and Clinical Studies (14)]*.

- **Cutaneous Squamous Cell Carcinoma (cuSCC)**

  Inform patients that cases of cuSCC have been reported in patients treated with ZELBORAF. Inform patients that their doctor will check their skin regularly during treatment and up to 6 months after treatment. Instruct the patient of the importance of contacting their doctor immediately of any changes in their skin *[see Warnings and Precautions (5.1)]*.

- **Photosensitivity**

  Advise patients to avoid sun exposure while taking ZELBORAF. While taking the drug, patients should be advised to wear protective clothing and use a broad spectrum UVA/UVB sunscreen and lip balm (SPF ≥ 30) when outdoors to help protect against sunburn *[see Warnings and Precautions (5.6)]*.

- **Other Common Events**

  Other commonly reported adverse events included arthralgia, rash, alopecia, fatigue, photosensitivity reactions, nausea, pruritus and skin papilloma *[see Adverse Reactions (6.1)]*.

FDA-Approved Patient Labeling

MEDICATION GUIDE

ZELBORAF™ (ZEL-bor-raf)
(vemurafenib)
tablet

Read this Medication Guide before you start taking ZELBORAF™ and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about ZELBORAF?

ZELBORAF may cause a type of skin cancer called cutaneous squamous cell carcinoma (cuSCC). CuSCC usually does not spread to other parts of the body.

Check your skin and tell your healthcare provider right away about any skin changes including a:

- new wart
- skin sore or reddish bump that bleeds or does not heal
- change in size or color of a mole

A healthcare provider should check your skin before you start taking ZELBORAF, and every two months while taking ZELBORAF to look for any new skin cancers. Your healthcare provider may continue to check your skin for six months after you stop taking ZELBORAF.

See ***"What are the possible side effects of ZELBORAF?"*** for more information about side effects.

What is ZELBORAF?

ZELBORAF is a prescription medicine used to treat a type of skin cancer called melanoma,

- that has spread to other parts of the body or cannot be removed by surgery, and
- that has a certain type of abnormal "BRAF" gene

It is not known if ZELBORAF is safe and effective in children under 18 years of age.

What should I tell my healthcare provider before taking ZELBORAF?

Before you start taking ZELBORAF, tell your healthcare provider if you:

- **have any heart problems, including a condition called long QT syndrome**
- **have liver or kidney problems**
- **have been told that you have low blood levels of potassium, calcium, or magnesium**
- **plan to have surgery, dental or other medical procedures**
- **have any other medical conditions**
- **are pregnant or plan to become pregnant.** ZELBORAF may harm your unborn baby.
  - Females who are able to become pregnant, and males who take ZELBORAF should use birth control during treatment and for 2 months after stopping ZELBORAF.
  - Talk to your healthcare provider about birth control methods that may be right for you.
  - Tell your healthcare provider right away if you become pregnant during treatment with ZELBORAF.
- **are breastfeeding or plan to breastfeed.** It is not known if ZELBORAF passes into your breast milk. You and your healthcare provider should decide if you will take ZELBORAF or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Especially, tell your healthcare provider if you take:

- the blood thinner warfarin sodium (Coumadin, Jantoven)
- antifungal medicines, such as ketoconazole (Nizoral), itraconazole (Sporanox, Onmel), or voriconazole (Vfend)

- certain antibiotic medicines, such as telithromycin (Ketek), clarithromycin (Biaxin, Biaxin XL), rifampin (Rifater, Rifimate, Rimactane, Rifadin), rifabutin (Mycobutin), rifapentine (Prifin)
- HIV medicines, such as atazanavir sulfate (Reyataz), saquinavir mesylate (Invirase), ritonavir (Kaletra), indinavir sulfate (Crixivan), nelfinavir mesylate (Viracept)
- seizure medicines, such as phenytoin (Dilantin-125, Dilantin, phenobarbital (Solfoton), or carbamazepine (Carbitrol, Equetro, Tegretol, Tegretol-XR, Teril, Epitol)
- the anti-depressant medicine nafazodone hydrochloride
- medicines to treat irregular heart beat

Know the medicines you take. Keep a list to show your healthcare provider and pharmacist when you get a new medicine.

How should I take ZELBORAF?

- Take ZELBORAF exactly as your healthcare provider tells you. Do not change your dose or stop ZELBORAF unless your healthcare provider tells you.
- ZELBORAF is taken in the morning and in the evening, about 12 hours apart.
- Take ZELBORAF with or without a meal.
- Swallow the tablets whole with a glass of water. Do not chew or crush ZELBORAF tablets.
- If you miss a dose, take it as soon as you remember. If it is within 4 hours of your next scheduled dose, just take your next dose at your regular time. Do not make up for the missed dose.
- Do not take 2 doses of ZELBORAF at the same time.
- If you take too much ZELBORAF, call your healthcare provider right away.

What should I avoid while taking ZELBORAF?

Avoid sunlight while you are taking ZELBORAF. ZELBORAF can make your skin sensitive to sunlight. You may burn more easily and get severe sunburns. To help protect against sunburn:

- When you go outside, wear clothes that protect your skin, including head, face, hands, arms, and legs.
- Use lip balm and a broad-spectrum sunscreen with SPF 30 or higher.

What are the possible side effects of ZELBORAF?

ZELBORAF may cause serious side effects, including:

- **See *"What is the most important information I should know about ZELBORAF?"***
- **Allergic reactions can happen while taking your ZELBORAF, and may be severe.** Stop taking ZELBORAF and get medical help right away if you have any of these symptoms of an allergic reaction:
    - get a rash or redness all over your body
    - feel faint
    - have trouble breathing or swallowing
    - have throat tightness or hoarseness
    - have a fast heartbeat
    - have swelling of the face, lips or tongue
- **Severe skin reactions. Stop taking ZELBORAF and call your healthcare provider right away if you get a skin rash with any of the following symptoms because you may have a severe skin reaction:**
    - 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
- **Changes in the electrical activity of your heart called QT prolongation. QT prolongation can cause irregular heartbeats that can be life-threatening.** Your healthcare provider should do tests before you start taking ZELBORAF, if your dose changes, at certain other times during treatment, and

after you stop treatment with ZELBORAF, to check the levels of potassium, magnesium, and calcium in your blood, and check the electrical activity of your heart with an ECG.

Tell your healthcare provider right away if you feel faint, lightheaded, dizzy or feel your heart beating irregularly or fast while taking ZELBORAF. These may be symptoms related to QT prolongation.

- **Abnormal liver function tests.** Your healthcare provider should do blood tests to check your liver function before you start taking ZELBORAF and during treatment. Tell your healthcare provider right away if you get any of these symptoms of a liver problem during treatment:
    - your skin or the whites of your eyes turn yellow
    - you feel tired
    - your urine turns dark or brown (tea color)
    - you have nausea or vomiting
    - you do not want to eat
    - pain on the right side of your stomach
- **Eye problems.** You should have your eyes examined before and while you are taking your ZELBORAF. Tell your healthcare provider right away if you get these symptoms during treatment with ZELBORAF:
    - eye pain, swelling, or redness,
    - blurred vision or other vision changes during treatment with ZELBORAF
- **New melanoma lesions.** You may develop new melanoma lesions while taking ZELBORAF. Check your skin and tell your healthcare provider right away about any skin changes.

The most common side effects of ZELBORAF include:

- joint pain
- rash **(see "Severe skin reactions" above)**
- hair loss
- tiredness
- sunburn or sun sensitivity
- nausea
- itching
- warts

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all possible side effects of ZELBORAF. For more information about side effects, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Genentech at 1-888-835-2555.

How should I store ZELBORAF?

- Store ZELBORAF at room temperature between 68°F to 77°F (20°C to 25°C).
- Store ZELBORAF in the original container with the lid tightly closed.
- Ask your healthcare provider or pharmacist how to safely throw away (dispose of) any unused or expired ZELBORAF.

Keep ZELBORAF and all medicine out of the reach of children.

General information about ZELBORAF

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ZELBORAF for a condition for which it was not prescribed. Do not give ZELBORAF to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about ZELBORAF. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ZELBORAF that is written for health professionals.

For more information, call Genentech at 1-888-835-2555.

What are the ingredients in ZELBORAF?

Active ingredient: vemurafenib

Inactive ingredients: hypromellose acetate succinate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, hydroxypropyl cellulose.

Coating: pinkish white: poly(vinyl alcohol), titanium dioxide, polyethylene glycol 3350, talc, and iron oxide red.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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ZELBORAF is a registered trademark of Genentech, Inc.

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