**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 for oral use**
**Initial U.S. Approval: 2011**

**----------RECENT MAJOR CHANGES----------**

| | |
|---|---|
| Warnings and Precautions | |
| Radiation Sensitization and Radiation Recall (5.10) | 05/2016 |
| Renal Failure (5.11) | 05/2016 |

**---------- 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, 2.1)

Limitation of Use: ZELBORAF is not indicated for treatment of patients with wild-type BRAF melanoma. (2.1, 5.2)

**----------DOSAGE AND ADMINISTRATION----------**
- Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with ZELBORAF. (2.1)
- Recommended dose: 960 mg orally twice daily taken approximately 12 hours apart with or without a meal. (2.2)

**---------- DOSAGE FORMS AND STRENGTHS----------**
Tablet: 240 mg (3)

**---------- CONTRAINDICATIONS ----------**
None

**---------- WARNINGS AND PRECAUTIONS----------**
- New Primary Cutaneous Malignancies: Perform dermatologic evaluations prior to initiation of therapy, every 2 months while on therapy, and for up to 6 months following discontinuation of ZELBORAF. Manage with excision and continue treatment without dose adjustment. (5.1)
- New Non-Cutaneous Squamous Cell Carcinoma: Evaluate for symptoms or clinical signs of new non-cutaneous SCC before initiation of treatment and periodically during treatment. (5.1)
- Other Malignancies: Monitor patients receiving ZELBORAF closely for signs or symptoms of other malignancies (5.1).
- Tumor Promotion in BRAF Wild-Type Melanoma: Increased cell proliferation can occur with BRAF inhibitors (5.2).
- Serious Hypersensitivity Reactions including anaphylaxis and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS Syndrome): Discontinue ZELBORAF for severe hypersensitivity reactions. (5.3)
- Severe Dermatologic Reactions, including Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: Discontinue ZELBORAF for severe dermatologic reactions. (5.4)
- QT Prolongation: Monitor ECG and electrolytes before and during treatment. Withhold ZELBORAF for QTc of 500 ms or greater. Correct electrolyte abnormalities and control for cardiac risk factors for QT prolongation. (5.5)
- Hepatotoxicity: Measure liver enzymes and bilirubin before initiating ZELBORAF and monitor monthly during treatment. (5.6)
- Photosensitivity: Advise patients to avoid sun exposure. (5.7)
- Serious Ophthalmologic Reactions: Monitor for signs and symptoms of uveitis. (5.8)
- Embryo-Fetal Toxicity: May cause fetal harm. Advise women of potential risk to the fetus. (5.9, 8.1)
- Radiation Sensitization and Radiation Recall: Severe cases have been reported. (5.10).
- Renal Failure: Measure serum creatinine before initiating ZELBORAF and monitor periodically during treatment (5.11).

**---------- 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----------**
- Avoid concomitant administration of ZELBORAF with strong CYP3A4 inhibitors or inducers. (7.1)
- CYP1A2 Substrates: ZELBORAF can increase concentrations of CYP1A2 substrates. Avoid concomitant use of ZELBORAF with CYP1A2 substrates with a narrow therapeutic window. If coadministration cannot be avoided, monitor closely for toxicities and consider dose reduction of CYP1A2 substrates. (7.2).

**---------- 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: 05/2016**

**FULL PRESCRIBING INFORMATION: CONTENTS***



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

# 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 indicated for treatment of patients with wild-type BRAF melanoma *[see Warnings and Precautions (5.2)]*.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Patient Selection

Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with ZELBORAF *[see Warnings and Precautions (5.2)]*. Information on FDA-approved tests for the detection of BRAF V600 mutations in melanoma is available at http://www.fda.gov/CompanionDiagnostics.

### 2.2 Recommended Dose

The recommended dose of ZELBORAF is 960 mg (four 240 mg tablets) orally every 12 hours with or without a meal. A missed dose can be taken up to 4 hours prior to the next dose.

Treat patients with ZELBORAF until disease progression or unacceptable toxicity occurs.

Do not take an additional dose if vomiting occurs after ZELBORAF administration, but continue with the next scheduled dose.

Do not crush or chew the tablets.

### 2.3 Dose Modifications

*For New Primary Cutaneous Malignancies:* No dose modifications are recommended.

*For Other Adverse Reactions:*

Permanently discontinue ZELBORAF for any of the following:

- Grade 4 adverse reaction, first appearance (if clinically appropriate) or second appearance
- QTc prolongation > 500 ms and increased by > 60 ms from pre-treatment values [*see Warnings and Precautions (5.5)*]

Withhold ZELBORAF for NCI-CTCAE (v4.0) intolerable Grade 2 or greater adverse reactions.

Upon recovery to Grade 0–1, restart ZELBORAF at a reduced dose as follows:

- 720 mg twice daily for first appearance of intolerable Grade 2 or Grade 3 adverse reactions
- 480 mg twice daily for second appearance of Grade 2 (if intolerable) or Grade 3 adverse reactions or for first appearance of Grade 4 adverse reaction (if clinically appropriate)

Do not dose reduce to below 480 mg twice daily.

## 3 DOSAGE FORMS AND STRENGTHS

Tablet: 240 mg.

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 New Primary Malignancies

*Cutaneous Malignancies*

Cutaneous squamous cell carcinoma, keratoacanthoma, and melanoma occurred at a higher incidence in patients receiving ZELBORAF compared to those in the control arm in Trial 1. The incidence of cutaneous squamous cell carcinomas (cuSCC) and keratoacanthomas in the ZELBORAF arm was 24% compared to <

1% in the dacarbazine arm *[see Adverse Reactions (6.1)]*. The median time to the first appearance of cuSCC was 7 to 8 weeks; approximately 33% of patients who developed a cuSCC while receiving ZELBORAF experienced at least one additional occurrence with median time between occurrences of 6 weeks. Potential risk factors associated with cuSCC observed in clinical studies using ZELBORAF included age (≥ 65 years), prior skin cancer, and chronic sun exposure.

In Trial 1, new primary malignant melanoma occurred in 2.1% (7/336) of patients receiving ZELBORAF compared to none of the patients receiving dacarbazine.

Perform dermatologic evaluations prior to initiation of therapy and every 2 months while on therapy. Manage suspicious skin lesions with excision and dermatopathologic evaluation. Consider dermatologic monitoring for 6 months following discontinuation of ZELBORAF.

*Non-Cutaneous Squamous Cell Carcinoma*

Non-cutaneous squamous cell carcinomas (non-cuSCC) of the head and neck can occur in patients receiving ZELBORAF *[see Adverse Reactions (6.1)]*. Monitor patients receiving ZELBORAF closely for signs or symptoms of new non-cuSCC.

*Other Malignancies*

Based on mechanism of action, ZELBORAF may promote malignancies associated with activation of RAS through mutation or other mechanisms *[see Warnings and Precautions (5.2)]*. Monitor patients receiving ZELBORAF closely for signs or symptoms of other malignancies.

### 5.2 Tumor Promotion in BRAF Wild-Type Melanoma

In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells that are exposed to BRAF inhibitors. Confirm evidence of BRAF V600E mutation in tumor specimens prior to initiation of ZELBORAF *[see Indications and Usage (1) and Dosage and Administration (2.1)]*.

### 5.3 Hypersensitivity Reactions

Anaphylaxis and other serious hypersensitivity reactions can occur during treatment and upon re-initiation of treatment with ZELBORAF. Severe hypersensitivity reactions included generalized rash and erythema, hypotension, and drug reaction with eosinophilia and systemic symptoms (DRESS syndrome). Permanently discontinue ZELBORAF in patients who experience a severe hypersensitivity reaction *[see Adverse Reactions (6.2)]*.

### 5.4 Dermatologic Reactions

Severe dermatologic reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, can occur in patients receiving ZELBORAF. Permanently discontinue ZELBORAF in patients who experience a severe dermatologic reaction *[see Adverse Reactions (6.1)]*.

### 5.5 QT Prolongation

Concentration-dependent QT prolongation occurred in an uncontrolled, open-label QT sub-study in previously treated patients with BRAF V600E mutation-positive metastatic melanoma *[see Clinical Pharmacology (12.2)]*. QT prolongation may lead to an increased risk of ventricular arrhythmias, including Torsade de Pointes.

Do not start treatment in patients with uncorrectable electrolyte abnormalities, QTc > 500 ms, or long QT syndrome, or in patients who are taking medicinal products known to prolong the QT interval. Prior to and following treatment initiation or after dose modification of ZELBORAF for QTc prolongation, evaluate ECG and electrolytes (including potassium, magnesium, and calcium) after 15 days, monthly during the first 3 months, and then every 3 months thereafter or more often as clinically indicated.

Withhold ZELBORAF in patients who develop QTc > 500 ms (Grade 3). Upon recovery to QTc ≤ 500 ms (Grade ≤ 2), restart at a reduced dose. Permanently discontinue ZELBORAF treatment if the QTc interval

remains > 500 ms and increased > 60 ms from pre-treatment values after controlling cardiac risk factors for QT prolongation (e.g., electrolyte abnormalities, congestive heart failure, and bradyarrhythmias) *[see Dosage and Administration (2.3)]*.

### 5.6 Hepatotoxicity

Liver injury leading to functional hepatic impairment, including coagulopathy or other organ dysfunction, can occur with ZELBORAF *[see Adverse Reactions (6.1)]*. Monitor transaminases, alkaline phosphatase, and bilirubin before initiation of treatment and monthly during treatment, or as clinically indicated. Manage laboratory abnormalities with dose reduction, treatment interruption, or treatment discontinuation *[see Dosage and Administration (2.3)]*.

*Concurrent Administration with Ipilimumab*

The safety and effectiveness of ZELBORAF in combination with ipilimumab have not been established *[see Indications and Usage (1)]*. In a dose-finding trial, Grade 3 increases in transaminases and bilirubin occurred in a majority of patients who received concurrent ipilimumab (3 mg/kg) and vemurafenib (960 mg BID or 720 mg BID) *[see Drug Interactions (7.3)]*.

### 5.7 Photosensitivity

Mild to severe photosensitivity can occur in patients treated with ZELBORAF *[see Adverse Reactions (6.1)]*. Advise patients to avoid sun exposure, wear protective clothing and use a broad spectrum UVA/UVB sunscreen and lip balm (SPF ≥ 30) when outdoors.

Institute dose modifications for intolerable Grade 2 or greater photosensitivity *[see Dosage and Administration (2.2)]*.

### 5.8 Ophthalmologic Reactions

Uveitis, blurry vision, and photophobia can occur in patients treated with ZELBORAF. In Trial 1, uveitis, including iritis, occurred in 2.1% (7/336) of patients receiving ZELBORAF compared to no patients in the dacarbazine arm. Treatment with steroid and mydriatic ophthalmic drops may be required to manage uveitis. Monitor patients for signs and symptoms of uveitis.

### 5.9 Embryo-Fetal Toxicity

ZELBORAF can 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 Radiation Sensitization and Radiation Recall

Radiation sensitization and recall, in some cases severe, involving cutaneous and visceral organs have been reported in patients treated with radiation prior to, during, or subsequent to vemurafenib treatment. Fatal cases have been reported in patients with visceral organ involvement. *[see Adverse Reactions (6.2)]*.

Monitor patients closely when vemurafenib is administered concomitantly or sequentially with radiation treatment.

### 5.11 Renal Failure

Renal failure, including acute interstitial nephritis and acute tubular necrosis, can occur with ZELBORAF. Twenty-six percent of ZELBORAF-treated patients and 5% of dacarbazine-treated patients experienced Grade 1-2 creatinine elevations [greater than 1 and up to 3 times upper limit of normal (ULN)]; 1.2% of ZELBORAF-treated patients and 1.1% of dacarbazine-treated patients experienced Grade 3-4 creatinine elevations (greater than 3 times ULN).

Measure serum creatinine before initiation of ZELBORAF and periodically during treatment.

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- New Primary Malignancies *[see Warnings and Precautions (5.1)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.3)]*
- Dermatologic Reactions *[see Warnings and Precautions (5.4)]*
- QT Prolongation *[see Warnings and Precautions (5.5)]*
- Hepatotoxicity *[see Warnings and Precautions (5.6)]*
- Photosensitivity *[see Warnings and Precautions (5.7)]*
- Ophthalmologic Reactions *[see Warnings and Precautions (5.8)]*
- Radiation Sensitization and Radiation Recall *[see Warnings and Precautions (5.10)]*
- Renal Failure *[see Warnings and Precautions (5.11)]*

### 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.

This section describes adverse drug reactions (ADRs) identified from analyses of Trial 1 and Trial 2 *[see Clinical Studies (14)]*. Trial 1 randomized (1:1) 675 treatment-naive patients with unresectable or metastatic melanoma to receive ZELBORAF 960 mg orally twice daily or dacarbazine 1000 mg/m$^2$ intravenously every 3 weeks. In Trial 2, 132 patients with metastatic melanoma and failure of at least one prior systemic therapy received treatment with ZELBORAF 960 mg orally twice daily.

Table 1 presents adverse reactions reported in at least 10% of patients treated with ZELBORAF. The most common adverse reactions of any grade (≥ 30% in either study) 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 1 Adverse Reactions Reported in ≥ 10% of Patients Treated with ZELBORAF***

| ADRs | Trial 1: Treatment-Naïve 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[a] (%) | All Grades (%) | Grade 3 (%) | All Grades (%) | Grade 3[a] (%) |
| **Skin and subcutaneous tissue disorders** | | | | | | |
| Rash | 37 | 8 | 2 | 0 | 52 | 7 |
| Photosensitivity reaction | 33 | 3 | 4 | 0 | 49 | 3 |
| Alopecia | 45 | < 1 | 2 | 0 | 36 | 0 |
| Pruritus | 23 | 1 | 1 | 0 | 30 | 2 |
| Hyperkeratosis | 24 | 1 | < 1 | 0 | 28 | 0 |
| Rash maculo-papular | 9 | 2 | < 1 | 0 | 21 | 6 |
| Actinic keratosis | 8 | 0 | 3 | 0 | 17 | 0 |
| Dry skin | 19 | 0 | 1 | 0 | 16 | 0 |
| Rash papular | 5 | < 1 | 0 | 0 | 13 | 0 |
| Erythema | 14 | 0 | 2 | 0 | 8 | 0 |

| ADRs | Trial 1: Treatment-Naïve 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[a] (%) | All Grades (%) | Grade 3 (%) | All Grades (%) | Grade 3[a] (%) |
| **Musculoskeletal and connective tissue disorders** | | | | | | |
| Arthralgia | 53 | 4 | 3 | < 1 | 67 | 8 |
| Myalgia | 13 | < 1 | 1 | 0 | 24 | < 1 |
| Pain in extremity | 18 | < 1 | 6 | 2 | 9 | 0 |
| Musculoskeletal pain | 8 | 0 | 4 | < 1 | 11 | 0 |
| 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 | 0 | 23 | 0 |
| Pyrexia | 19 | < 1 | 9 | < 1 | 17 | 2 |
| Asthenia | 11 | < 1 | 9 | < 1 | 2 | 0 |
| **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 | 0 | 16 | 0 |
| **Nervous system disorders** | | | | | | |
| Headache | 23 | < 1 | 10 | 0 | 27 | 0 |
| Dysgeusia | 14 | 0 | 3 | 0 | 11 | 0 |
| **Neoplasms benign, malignant and unspecified (includes cysts and polyps)** | | | | | | |
| Skin papilloma | 21 | < 1 | 0 | 0 | 30 | 0 |
| Cutaneous SCC[†#] | 24 | 22 | < 1 | < 1 | 24 | 24 |
| Seborrheic keratosis | 10 | < 1 | 1 | 0 | 14 | 0 |
| **Investigations** | | | | | | |
| Gamma-glutamyltransferase increased | 5 | 3 | 1 | 0 | 15 | 6 |
| **Metabolism and nutrition disorders** | | | | | | |
| Decreased appetite | 18 | 0 | 8 | < 1 | 21 | 0 |
| **Respiratory, thoracic and mediastinal disorders** | | | | | | |
| Cough | 8 | 0 | 7 | 0 | 12 | 0 |
| **Injury, poisoning and procedural complications** | | | | | | |
| Sunburn | 10 | 0 | 0 | 0 | 14 | 0 |

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

[a] Grade 4 adverse reactions limited to gamma-glutamyltransferase increased (< 1% in Trial 1 and 4% in Trial 2).

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

[#] Cases of cutaneous squamous cell carcinoma were required to be reported as Grade 3 per protocol.

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

*Skin* and *subcutaneous tissue disorders:* palmar-plantar erythrodysesthesia syndrome, keratosis pilaris, panniculitis, erythema nodosum, Stevens-Johnson syndrome, toxic epidermal necrolysis

*Musculoskeletal and connective tissue disorders:* arthritis

*Nervous system disorders:* neuropathy peripheral, VII[th] nerve paralysis

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

*Infections and infestations:* folliculitis

*Eye disorders:* retinal vein occlusion

*Vascular disorders:* vasculitis

*Cardiac disorders:* atrial fibrillation

Table 2 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 2 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 | 0 |

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

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of ZELBORAF. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Neoplasms benign, malignant and unspecified (incl. cysts and polyps):* Progression of pre-existing chronic myelomonocytic leukemia with NRAS mutation *[see Warnings and Precautions (5.1)]*.

*Skin and subcutaneous tissue disorders:* Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) *[see Warnings and Precautions (5.3)]*.

*Blood and lymphatic systems disorder:* Neutropenia

*Injury, poisoning and procedural complications:* Radiation sensitization and recall *[see Warnings and Precautions (5.10)]*.

*Gastrointestinal disorders:* Pancreatitis

*Renal and urinary disorders: Acute interstitial nephritis, acute tubular necrosis [see Warnings and Precautions (5.11)]*.

# 7 DRUG INTERACTIONS

## 7.1 Effect of Strong CYP3A4 Inhibitors or Inducers on Vemurafenib

Vemurafenib is a substrate of CYP3A4 based on in vitro data; therefore, coadministration of strong CYP3A4 inhibitors or inducers may alter vemurafenib concentrations *[see Clinical Pharmacology (12.3)]*. Avoid coadministration of ZELBORAF with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or strong inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital), and replace these drugs with alternative drugs when possible.

### 7.2 Effect of Vemurafenib on CYP1A2 Substrates

Coadministration of ZELBORAF with tizanidine, a sensitive CYP1A2 substrate, increased tizanidine systemic exposure by 4.7-fold. Avoid concomitant use of ZELBORAF with drugs having a narrow therapeutic window that are predominantly metabolized by CYP1A2 *[see Clinical Pharmacology (12.3)]*. If coadministration cannot be avoided, monitor closely for toxicities and consider a dose reduction of concomitant CYP1A2 substrates.

### 7.3 Concurrent Ipilimumab

Increases in transaminases and bilirubin occurred in a majority of patients who received concurrent ipilimumab and ZELBORAF *[see Warnings and Precautions Section 5.6]*.

### 7.4 Effect of Vemurafenib on P-gp Substrates

Coadministration of ZELBORAF with digoxin, a sensitive P-glycoprotein (P-gp) substrate, increased digoxin systemic exposure by 1.8-fold. Avoid concurrent use of P-gp substrates known to have narrow therapeutic indices. If use of these medications is unavoidable, consider dose reduction of P-gp substrates with narrow therapeutic indices.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

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

ZELBORAF can 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

Clinical studies of ZELBORAF did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

### 8.6 Hepatic Impairment

No formal clinical study has been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of vemurafenib. No dose adjustment is recommended for patients with mild and moderate hepatic impairment based on a population pharmacokinetic analysis *[see Clinical Pharmacology (12.3)]*. The appropriate dose of ZELBORAF has not been established in patients with severe hepatic impairment.

### 8.7 Renal Impairment

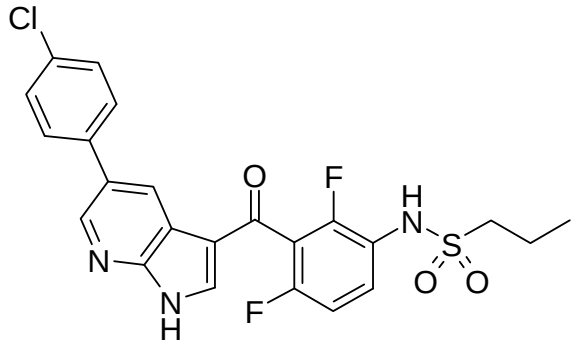
No formal clinical study has been conducted to evaluate the effect of renal impairment on the pharmacokinetics of vemurafenib. No dose adjustment is recommended for patients with mild and moderate renal impairment based on a population pharmacokinetic analysis *[see Clinical Pharmacology (12.3)]*. The appropriate dose of ZELBORAF has not been established in patients with severe renal impairment.

## 10 OVERDOSAGE

There is no information on overdosage of ZELBORAF.

## 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.

### 12.2 Pharmacodynamics

***Cardiac Electrophysiology***

In a multi-center, open-label, single-arm study in 132 patients with BRAF V600E mutation-positive metastatic melanoma, patients administered vemurafenib 960 mg orally twice daily did not experience large changes in mean QTc interval (i.e., > 20 ms) from baseline. Vemurafenib is associated with concentration-dependent QTc interval prolongation. The largest mean change from baseline in the first month of treatment occurred at 2 hours post-dose on Day 15—an increase of 12.8 ms (upper boundary of the two-sided 90% confidence interval of 14.9 ms). In the first 6 months of treatment, the largest observed mean change from baseline occurred at a pre-dose time point—an increase of 15.1 ms (upper boundary of the two-sided 90% confidence interval of 17.7 ms).

### 12.3 Pharmacokinetics

The pharmacokinetics of vemurafenib were determined in patients with BRAF mutation-positive metastatic melanoma following 15 days of 960 mg twice daily with dosing approximately 12 hours apart. The population pharmacokinetic analysis pooled data from 458 patients. 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. The median $T_{max}$ was approximately 3 hours following multiple doses.

The mean (± SD) $C_{max}$ and $AUC_{0-12}$ were 62 ± 17 µg/mL and 601 ± 170 µg*h/mL, respectively. The median accumulation ratio estimate from the population pharmacokinetic analysis for the twice daily regimen is 7.4, with steady-state achieved at approximately 15 to 22 days.

In clinical trials, vemurafenib was administered without regard to food. A food effect study has demonstrated that a single dose of vemurafenib administered with a high-fat meal increased AUC by approximately 5-fold, increased $C_{max}$ by 2.5-fold, and delayed $T_{max}$ by approximately 4 hours as compared to the fasted state.

QTc prolongation may occur with increased exposures as vemurafenib is associated with concentration-dependent QTc interval prolongation *[see Clinical Pharmacology (12.2)]*.

Distribution

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

Metabolism

Following oral administration of 960 mg of $^{14}$C-vemurafenib, mean data showed that vemurafenib and its metabolites represented 95% and 5% of the components in plasma over 48 hours, respectively.

Elimination

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

Specific 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 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 mild and moderate hepatic impairment was similar to that in patients with normal hepatic function. The appropriate dose for patients with severe hepatic impairment cannot be determined as clinical and pharmacokinetic data were available for only three patients *[see Use in Specific Populations (8.6)]*.

*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 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 mild and moderate renal impairment was similar to that in patients with normal renal function. The appropriate dose for patients with severe renal impairment cannot be determined as clinical and pharmacokinetic data were available for only one patient *[see Use in Specific Populations (8.7)]*.

*Age, Body Weight, Sex, and Race:* Based on the population pharmacokinetic analysis, age, body weight, and sex do not have a clinically important effect on the exposure of vemurafenib. 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 pediatric patients.

Drug Interaction Studies

*Effect of Strong CYP3A4 Inhibitors or Inducers on Vemurafenib:* In vitro studies have demonstrated that vemurafenib is a CYP3A4 substrate. The effect of strong CYP3A4 inhibitors or strong CYP3A4 inducers on the systemic exposure of vemurafenib has not been evaluated in vivo *[see Drug Interactions (7.1)]*.

*Effect of Vemurafenib on CYP Substrates:* In vitro studies suggest that vemurafenib is an inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5.

Coadministration of tizanidine 2 mg (a sensitive CYP1A2 substrate) on day 21 with vemurafenib which was administered 960 mg twice daily for 21 days increased tizanidine $AUC_{inf}$ by 4.7-fold (90% CI: 3.6, 6.3) and $C_{max}$ by 2.2-fold (90% CI: 1.7, 2.7) in 16 cancer patients *[see Drug Interactions (7.2)]*. 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 mean AUC of caffeine (CYP1A2 substrate) by 2.6-fold *[see Drug Interactions (7.2)]*. Coadministration of vemurafenib increased the mean AUC of dextromethorphan (CYP2D6 substrate) by 47% and the AUC of S-warfarin (CYP2C9 substrate) by 18%, while it decreased the mean AUC of midazolam (CYP3A4 substrate) by 39%. Coadministration of vemurafenib did not change the mean systemic exposure to omeprazole (CYP2C19 substrate).

*Effect of Vemurafenib on Transporters:* In vitro studies suggest that vemurafenib is both a substrate and an inhibitor of the efflux transporters P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP). Administration of vemurafenib 960 mg twice daily for 22 days increased digoxin AUC by 1.8-fold (90% CI:1.6, 2.0) and $C_{max}$ by 1.5-fold (90% CI:1.3, 1.7) in 26 cancer patients who were coadministered a single dose of digoxin 0.25 mg (sensitive P-gp substrate) *[see Drug Interactions (7.4)]*.

## 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-Naïve Patients***

Trial 1, an international, open-label, randomized controlled trial, equally allocated 675 patients with treatment-naive, BRAF V600E mutation-positive unresectable or metastatic melanoma, as detected by the cobas® 4800 BRAF V600 Mutation Test, to receive ZELBORAF 960 mg by mouth twice daily (n=337) or dacarbazine 1000 mg/m$^2$ intravenously on Day 1 every 3 weeks (n=338). Randomization stratification factors were 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%).

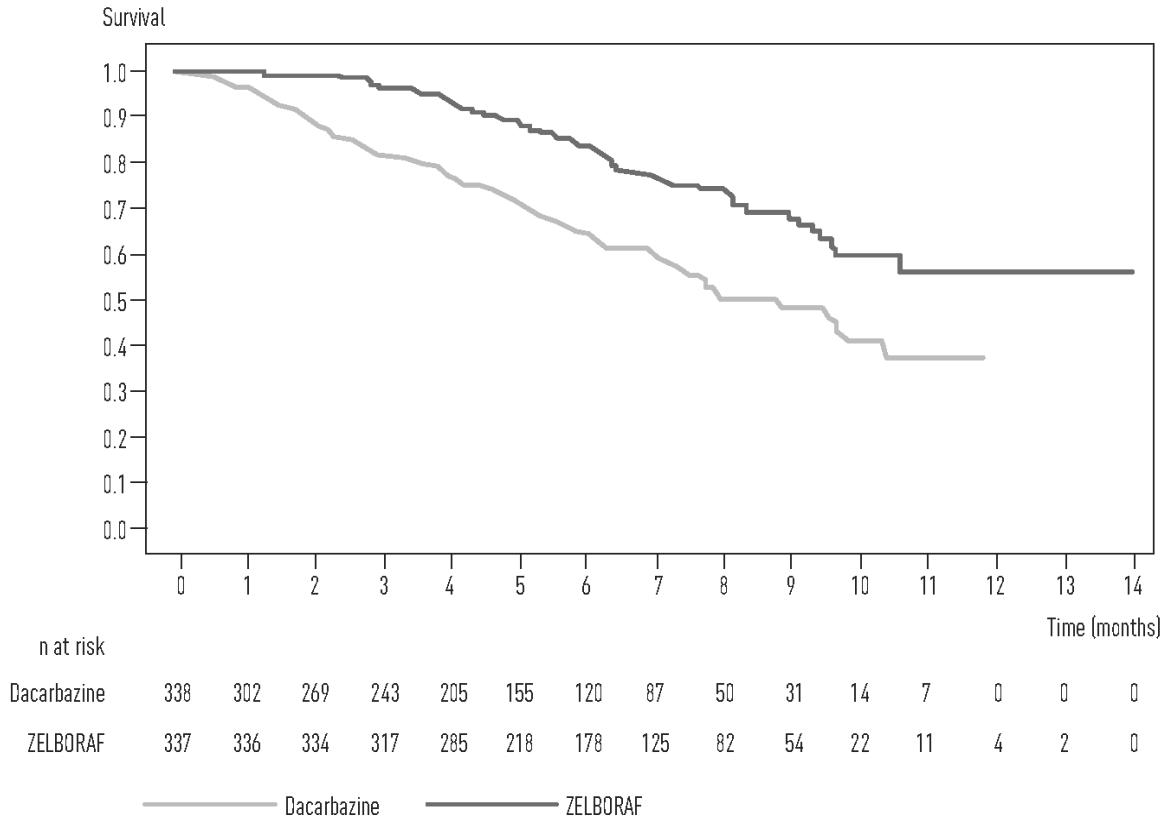
Trial 1 demonstrated statistically significant increases in overall survival and progression-free survival in the ZELBORAF arm compared to the dacarbazine control arm. Table 3 and Figure 1 summarize the efficacy results.

**Table 3 Efficacy of ZELBORAF in Treatment-Naïve Patients with BRAF V600E Mutation-Positive Melanoma[a]**

| | ZELBORAF (n=337) | Dacarbazine (n=338) | p-value[f] |
|---|---|---|---|
| **Overall Survival** | | | |
| Number of Deaths[b] | 78 (23%) | 122 (36%) | |
| Hazard Ratio (95% CI)[c] | 0.47 (0.35, 0.62) | | < 0.0001 |
| Updated Median Survival (months) (95 % CI)[d, e] | 13.6 (12.0, 15.3) | 10.3 (9.1, 12.8) | - |
| **Progression-Free Survival** | | | |
| Hazard Ratio (95% CI)[c] | 0.26 (0.20, 0.33) | | < 0.0001 |
| Median PFS (months) (95% CI)[d] | 5.3 (4.9, 6.6) | 1.6 (1.6, 1.7) | - |

[a] As detected by the cobas® 4800 BRAF V600 Mutation Test
[b] Total of 200 deaths (Zelboraf median follow-up 6.2 months)
[c] Hazard ratio estimated using Cox model; a hazard ratio of < 1 favors ZELBORAF
[d] Kaplan-Meier estimate
[e] Updated based on 478 deaths (Zelboraf median follow-up 13.4 months)
[f] Unstratified log-rank test

**Figure 1 Kaplan-Meier Curves of Overall Survival – Treatment-Naïve 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***

In a single-arm, multicenter, multinational trial (Trial 2), 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, received ZELBORAF 960 mg by mouth twice daily. 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 $\geqslant$ 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 *[see Warnings and Precautions (5.2)]*.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

ZELBORAF (vemurafenib) is supplied as 240 mg film-coated tablets with VEM debossed on one side. The following packaging configurations are available:

NDC 50242-090-01 single bottle of 120 count

NDC 50242-090-02 single bottle of 112 count

**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

See FDA-approved patient labeling (Medication Guide).

Healthcare providers should advise patients of the potential benefits and risks of ZELBORAF and instruct their patients to read the Medication Guide before starting ZELBORAF therapy. Inform patients of the following:

- Evidence of BRAF V600E mutation in the tumor specimen with an FDA approved test is necessary to identify patients for whom treatment with ZELBORAF is indicated *[see Dosage and Administration (2.1)]*.
- ZELBORAF increases the risk of developing new primary cutaneous malignancies. Advise patients of the importance of contacting their healthcare provider immediately for any changes in their skin *[see Warnings and Precautions (5.1)]*.
- Anaphylaxis and other serious hypersensitivity reactions can occur during treatment and upon re-initiation of treatment with ZELBORAF. Advise patients to stop taking ZELBORAF and to seek immediate medical attention for symptoms of anaphylaxis or hypersensitivity *[see Warnings and Precautions (5.3)]*.
- Severe dermatologic reactions can occur in patients receiving ZELBORAF. Advise patients to stop taking ZELBORAF and to contact their health-care provider for severe dermatologic reactions *[see Warnings and Precautions (5.4)]*.
- ZELBORAF can prolong QT interval, which may result in ventricular arrhythmias. Advise patients of the importance of monitoring of their electrolytes and the electrical activity of their heart (via an ECG) during ZELBORAF treatment *[see Warnings and Precautions (5.5)]*.
- Liver injury leading to functional hepatic impairment, including coagulopathy or other organ dysfunction, can occur with ZELBORAF. Advise patients of the importance of laboratory monitoring of their liver during ZELBORAF treatment and to contact their health-care provider for relevant symptoms *[see Warnings and Precautions (5.6)]*.
- ZELBORAF can cause mild to severe photosensitivity. Advise patients to avoid sun exposure, wear protective clothing, and use a broad spectrum UVA/UVB sunscreen and lip balm (SPF $\geq$ 30) when outdoors to help protect against sunburn *[see Warnings and Precautions (5.7)]*.
- Ophthalmologic reactions can occur in patients treated with ZELBORAF. Advise patients to contact their health-care provider immediately for ophthalmologic symptoms *[see Warnings and Precautions (5.8)]*.
- ZELBORAF can cause fetal harm when administered to a pregnant woman based on its mechanism of action. Advise women of childbearing potential and men to use appropriate contraceptive measures during ZELBORAF therapy and for at least 2 months after discontinuation of ZELBORAF. Advise patients to contact their health-care provider immediately if they become pregnant *[see Warnings and Precautions (5.9) and Use in Special Populations (8.1)]*.
- Radiation sensitization and recall can occur in patients treated with radiation prior to, during, or subsequent to ZELBORAF treatment. Advise patients to inform their health care provider if they

have had or are planning to receive radiation therapy *[see Warnings and Precautions (5.10), Adverse Reactions (6.2)]*.

- Renal failure can occur in patients treated with ZELBORAF. Advise patients of the importance of monitoring serum creatinine prior to and during ZELBORAF treatment *[see Warnings and Precautions (5.11), Adverse Reactions (6.2)]*.

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**MEDICATION GUIDE**
**ZELBORAF® (ZEL-bor-raf)**
**(vemurafenib)**
**tablet**

**What is the most important information I should know about ZELBORAF?**
**ZELBORAF can cause serious side effects, including:**
**Risk of cancers.** ZELBORAF may cause a type of skin cancer called cutaneous squamous cell carcinoma (cuSCC). New melanoma lesions have occurred in people who take ZELBORAF. ZELBORAF may also cause another type of cancer called non-cutaneous squamous cell carcinoma (SCC). Talk with your healthcare provider about your risk for these cancers.
**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

Your healthcare provider should check your skin before you start taking ZELBORAF, and every 2 months while 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.

Your healthcare provider should also check for cancers that may not occur on the skin. Tell your healthcare provider about any new symptoms that you get while 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.

Your healthcare provider will perform a test to make sure that ZELBORAF is right for you.
- ZELBORAF is not used to treat melanoma with a normal 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 take ZELBORAF, tell your healthcare provider if you:**
- have any heart problems, including a condition called long QT syndrome
- have liver or kidney problems
- have had or are planning to receive radiation therapy
- have been told that you have low blood levels of potassium, calcium, or magnesium
- have any other medical conditions
- are pregnant or plan to become pregnant. ZELBORAF can harm your unborn baby.
  - Females who are able to become pregnant, and males who take ZELBORAF, should use birth control during treatment and for at least 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 over-the-counter medicines, vitamins, and herbal supplements. Know the medicines you take. Keep a list of them 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 taking ZELBORAF unless your healthcare provider tells you to.
- Take ZELBORAF every 12 hours with or without a meal.
- Do not crush or chew ZELBORAF tablets.
- Do not take an additional dose of ZELBORAF if you vomit after taking your scheduled dose. Take your next dose at your regular time.
- If you miss a dose of ZELBORAF, 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.
- If you take too much ZELBORAF, call your healthcare provider or go the nearest hospital emergency room 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 your 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 ZELBORAF and can be severe.** Stop taking ZELBORAF and get medical help right away if you get any of these symptoms of an allergic reaction:
  - o rash or redness all over your body
  - o trouble breathing or swallowing
  - o swelling of the face, lips, or tongue
  - o throat tightness or hoarseness
  - o feel faint
  - o a fast heartbeat
- **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:
  - o blisters on your skin
  - o blisters or sores in your mouth
  - o peeling of your skin
  - o fever
  - o 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 and during your treatment with ZELBORAF to check the electrical activity of your heart.
  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.
- **Liver injury.** 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:
  - o yellowing of your skin or the white part of your eyes
  - o dark or brown (tea color) urine
  - o nausea or vomiting
  - o loss of appetite
  - o pain on the right side of your stomach
- **Eye problems.** Tell your healthcare provider right away if you get any of these symptoms during treatment with ZELBORAF:
  - o eye pain, swelling, or redness
  - o blurred vision or other vision changes
- **Worsening side effects from radiation treatment.** Tell your healthcare provider if you have had or are planning to receive radiation therapy.
- **Kidney injury**. Your healthcare provider should do blood tests to check your kidney function before you start taking ZELBORAF and during treatment.

**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 the 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.

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.

**What are the ingredients in ZELBORAF?**

**Active ingredient:** vemurafenib

**Inactive ingredients: Tablet Core:** 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.

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 For more information, go to www.ZELBORAF.com or call 1-877-436-3683.

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