

**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<sup>V600E</sup> 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<sup>V600E</sup> testing – confirmation of BRAF<sup>V600E</sup> 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](http://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\***

1	INDICATIONS AND USAGE
2	DOSAGE AND ADMINISTRATION
2.1	Recommended Dose
2.2	Dose Modifications
3	DOSAGE FORMS AND STRENGTHS
4	CONTRAINDICATIONS
5	WARNINGS AND PRECAUTIONS
5.1	Cutaneous Squamous Cell Carcinoma (cuSCC)
5.2	Hypersensitivity Reactions
5.3	Dermatologic Reactions
5.4	QT Prolongation
5.5	Liver Laboratory Abnormalities
5.6	Photosensitivity
5.7	Ophthalmologic Reactions
5.8	New Primary Malignant Melanoma
5.9	Use in Pregnancy
5.10	BRAF <sup>V600E</sup> Testing
6	ADVERSE REACTIONS
6.1	Clinical Trials Experience
7	DRUG INTERACTIONS
7.1	Effects of Vemurafenib on Drug Metabolizing Enzymes
7.2	Drugs that Inhibit or Induce CYP3A4
8	USE IN SPECIFIC POPULATIONS

8.1	Pregnancy
8.3	Nursing Mothers
8.4	Pediatric Use
8.5	Geriatric Use
8.6	Gender
8.7	Hepatic Impairment
8.8	Renal Impairment
9	DRUG ABUSE AND DEPENDENCE
10	OVERDOSAGE
11	DESCRIPTION
12	CLINICAL PHARMACOLOGY
12.1	Mechanism of Action
12.3	Pharmacokinetics
12.4	QT Prolongation
13	NONCLINICAL TOXICOLOGY
13.1	Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2	Animal Toxicology and/or Pharmacology
14	CLINICAL STUDIES
16	HOW SUPPLIED/STORAGE AND HANDLING
17	PATIENT COUNSELING INFORMATION
17.1	Patient Counseling

\*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<sup>V600E</sup> 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
<b>Grade 1 or Grade 2 (tolerable)</b>	Maintain ZELBORAF at a dose of 960 mg twice daily.
<b>Grade 2 (Intolerable) or Grade 3</b>	
1 <sup>st</sup> Appearance	Interrupt treatment until grade 0 – 1. Resume dosing at 720 mg twice daily.
2 <sup>nd</sup> Appearance	Interrupt treatment until grade 0 – 1. Resume dosing at 480 mg twice daily.
3 <sup>rd</sup> Appearance	Discontinue permanently
<b>Grade 4</b>	
1 <sup>st</sup> Appearance	Discontinue permanently or interrupt ZELBORAF treatment until grade 0 – 1. Resume dosing at 480 mg twice daily.
2 <sup>nd</sup> 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 ( $\geq 65$  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<sup>V600E</sup> 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  $\geq$  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  $\geq 30$ ) 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<sup>V600E</sup> Testing

Confirmation of BRAF<sup>V600E</sup> 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<sup>®</sup> 4800 BRAF V600 Mutation Test [*see Clinical Studies (14)*]. This test is designed to detect BRAF<sup>V600E</sup> 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<sup>®</sup> 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<sup>2</sup> 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 (≥ 30% in either study) reported in ZELBORAF-treated patients were arthralgia, rash, alopecia, fatigue,

photosensitivity reaction, nausea, pruritus and skin papilloma. The most common ( $\geq 5\%$ ) Grade 3 adverse reactions were cuSCC and rash. The incidence of Grade 4 adverse reactions was  $\leq 4\%$  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  $\geq 10\%$  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 (%)
<b>Skin and subcutaneous tissue disorders</b>									
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	-	-
<b>Musculoskeletal and connective tissue disorders</b>									
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	-
<b>General disorders and administration site conditions</b>									
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	-	-
<b>Gastrointestinal disorders</b>									
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	-	-
<b>Nervous system disorders</b>									
Headache	23	<1	-	10	-	-	27	-	-
Dysgeusia	14	-	-	3	-	-	11	-	-
<b>Neoplasms benign, malignant and unspecified (includes cysts and polyps)</b>									
Skin papilloma	21	<1	-	-	-	-	30	-	-
Cutaneous SCC <sup>†#</sup>	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	-	-
<b>Investigations</b> Gamma-glutamyltransferase increased	5	3	<1	1	-	-	15	6	4
<b>Metabolism and nutrition disorders</b> Decreased appetite	18	-	-	8	<1	-	21	-	-
<b>Respiratory, thoracic and mediastinal disorders</b> Cough	8	-	-	7	-	-	12	-	-
<b>Injury, poisoning and procedural complications</b> 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 erythrodysesthesia syndrome, keratosis pilaris, erythema nodosum, Stevens-Johnson syndrome

*Musculoskeletal and connective tissue disorders:* arthritis

*Nervous system disorders:* dizziness, neuropathy peripheral, VII<sup>th</sup> 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  $\geq 65$  years. Elderly patients ( $\geq 65$  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**

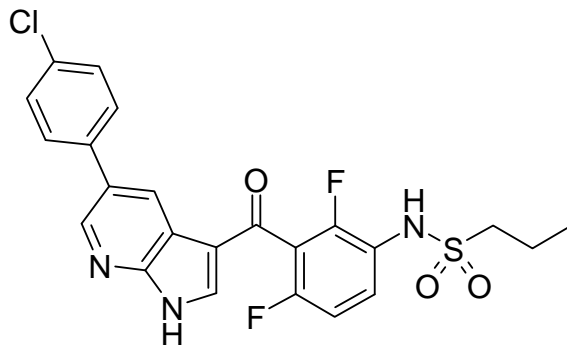
No studies on the potential for ZELBORAF to cause dependence have been performed. However, there is no evidence from the available data that ZELBORAF treatment can result in dependence.

### **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<sup>V600E</sup>. 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<sup>V600E</sup>.

### 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<sub>max</sub> was approximately 3 hours.

Following 15 days of dosing at 960 mg twice daily, the mean ( $\pm$  SD) C<sub>max</sub> and AUC<sub>0-12</sub> were 62  $\mu$ g/mL  $\pm$  17 and 601  $\pm$  170  $\mu$ g\*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  $^{14}\text{C}$ -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  $^{14}\text{C}$ -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  $\leq$  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  $\geq$  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<sub>50</sub> values of 32.5,  $>$  50, 5.9, 22.5, 33.2, and  $>$  50  $\mu\text{M}$ , 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<sub>max</sub> and AUC of dextromethorphan (CYP2D6 substrate) by 36% and 47%, respectively, while it decreased the C<sub>max</sub> 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<sup>V600E</sup> mutation-positive unresectable or metastatic melanoma as detected by the cobas<sup>®</sup> 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<sup>2</sup> 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<sup>V600E</sup> Mutation-Positive Melanoma<sup>a</sup>**

	ZELBORAF (N=337)	Dacarbazine (N=338)	p-value <sup>d</sup>
<b>Overall Survival</b>			
Number of Deaths	78 (23%)	121 (36%)	
Hazard Ratio (95% CI) <sup>b</sup>	0.44 (0.33, 0.59)		<0.0001
Median Survival (months) (95 % CI) <sup>c</sup>	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)	
<b>Progression-free survival</b>			
Hazard Ratio (95% CI) <sup>b</sup>	0.26 (0.20, 0.33)		<0.0001
Median PFS (months) (95% CI) <sup>c</sup>	5.3 (4.9, 6.6)	1.6 (1.6, 1.7)	-

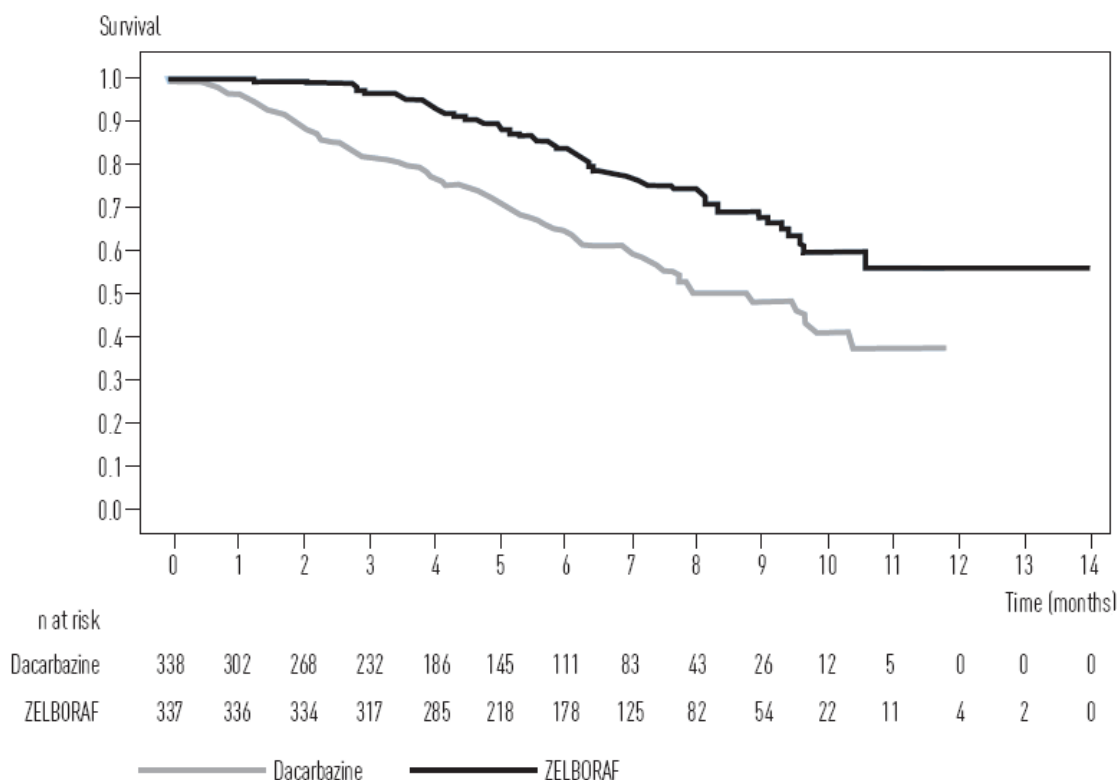
<sup>a</sup> As detected by the cobas<sup>®</sup> 4800 BRAF V600 Mutation Test

<sup>b</sup> Hazard ratio estimated using Cox model; a hazard ratio of < 1 favors ZELBORAF

<sup>c</sup> Kaplan-Meier estimate

<sup>d</sup> 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<sup>V600E</sup> mutation-positive metastatic melanoma, as detected by the cobas<sup>®</sup> 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  $\geq 2$  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<sup>V600E</sup> Testing**

Inform patients that an assessment of BRAF<sup>V600E</sup> mutation with the **cobas**<sup>®</sup> 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  $\geq 30$ ) 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**