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

----------RECENT MAJOR CHANGES----------
Dosage and Administration
Dose Modifications (2.3) ~~MM~~07/2013
Warnings and Precautions
New Primary Malignancies (5.1) ~~MM~~07/2013
Hepatotoxicity (5.6)

---------- 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)
- Do not crush or chew ZELBORAF tablets. (2.2)

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

---------- CONTRAINDICATIONS ----------
None (4)

---------- 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: 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: Monitor liver enzymes and bilirubin before initiating ZELBORAF and 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)

---------- 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: ~~06~~07/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
  2.1 Patient Selection
  2.2 Recommended Dose
  2.3 Dose Modifications
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
  5.1 New Primary Malignancies
  5.2 Tumor Promotion in BRAF Wild-Type Melanoma
  5.3 Hypersensitivity Reactions
  5.4 Dermatologic Reactions
  5.5 QT Prolongation
  5.6 Hepatotoxicity
  5.7 Photosensitivity
  5.8 Ophthalmologic Reactions
  5.9 Embryo-Fetal Toxicity
6 ADVERSE REACTIONS
  6.1 Clinical Trials Experience
7 DRUG INTERACTIONS
  7.1 Effect of Strong CYP3A4 Inhibitors or Inducers on Vemurafenib
  7.2 Effect of Vemurafenib on CYP1A2 Substrates
  7.3 Ipilimumab
8 USE IN SPECIFIC POPULATIONS
  8.1 Pregnancy
  8.3 Nursing Mothers
  8.4 Pediatric Use
  8.5 Geriatric Use
  8.6 Hepatic Impairment
  8.7 Renal Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
  12.1 Mechanism of Action
  12.3 Pharmacokinetics
  12.6 Cardiac Electrophysiology
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

*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 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 (SCC) 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-cutaneous SCC.

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 or hypotension. Permanently discontinue ZELBORAF in patients who experience a severe hypersensitivity reaction.

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 (12.6)]*. 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. Evaluate ECGs before treatment with ZELBORAF, 15 days after treatment initiation, monthly during the first 3 months of treatment, and every 3 months thereafter or more often as clinically indicated. Monitor ECG and electrolytes, including potassium, magnesium, and calcium, after dose modification of ZELBORAF for QTc prolongation.

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 laboratory abnormalities can occur with ZELBORAF (Table 2) *[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)]*.

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)]*

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
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)						

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 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, erythema nodosum, Stevens-Johnson syndrome, toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders: arthritis

Nervous system disorders: neuropathy peripheral, VIIth 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.

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

Concomitant use of ZELBORAF with drugs with a narrow therapeutic window that are predominantly metabolized by CYP1A2 is not recommended as ZELBORAF may increase concentrations of CYP1A2 substrates *[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 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]*.

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

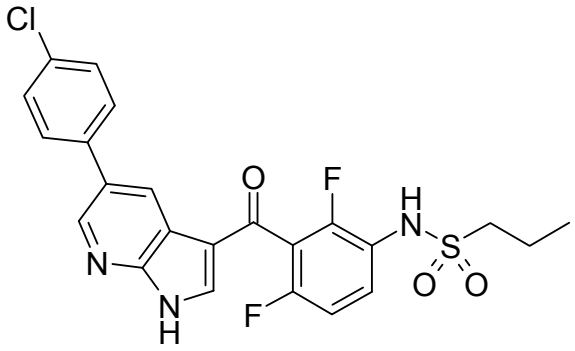
No formal clinical study has been conducted to evaluate the effect of renal impairment on the pharmacokinetics of vemurafenib. No dose adjustment is recommended for patients with mild and moderate renal impairment based on a population pharmacokinetic analysis *[see Clinical Pharmacology (12.3)]*. The 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.

12.3 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 (12.6)]*.

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).

Pharmacokinetics in Special Populations

Hepatic Impairment: The pharmacokinetics of vemurafenib were examined in patients with metastatic melanoma enrolled in the clinical trials with normal hepatic function (n=158, total bilirubin ≤ ULN) and 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, Gender, and Race: Based on the population pharmacokinetic analysis, age, body weight, and gender 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 Interactions: 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)]*.

In vitro studies suggest that vemurafenib is an inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5.

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).

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).

12.6 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).

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

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%).

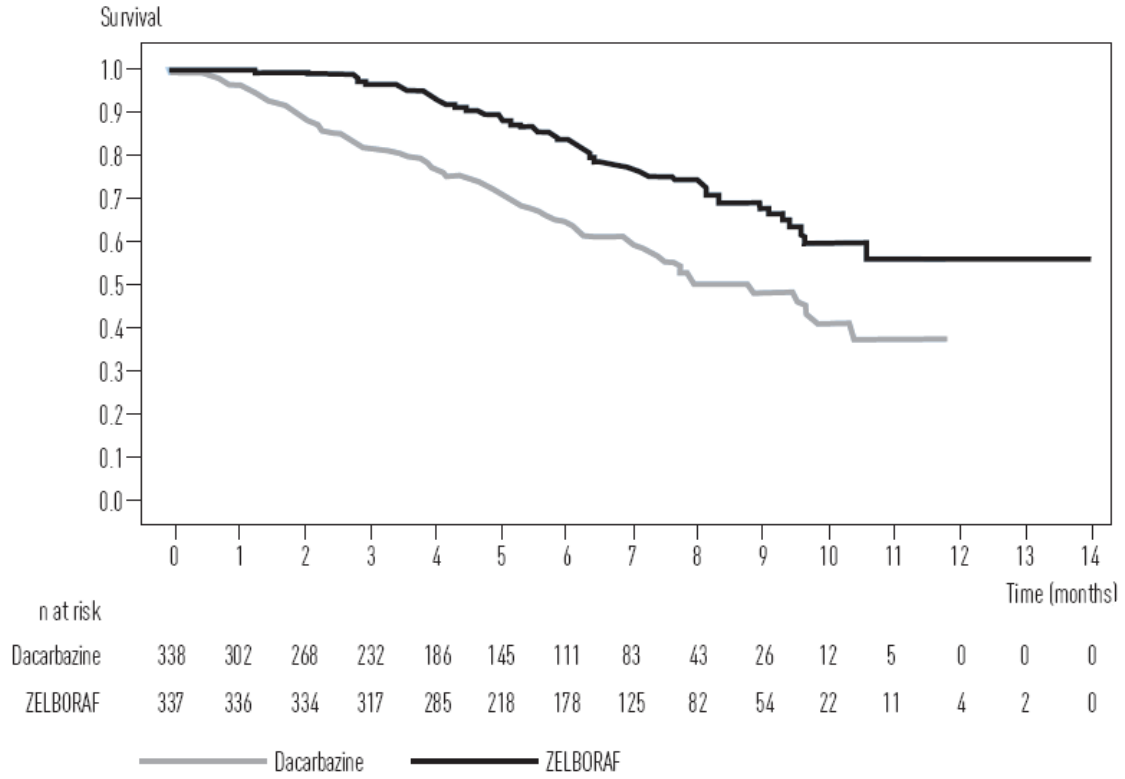
Trial 1 demonstrated statistically significant increases in overall survival and progression-free survival in the ZELBORAF arm compared to the dacarbazine control arm. Table 3 and Figure 1 summarize the efficacy results.

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

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

[a] As detected by the cobas® 4800 BRAF V600 Mutation Test
[b] Hazard ratio estimated using Cox model; a hazard ratio of < 1 favors ZELBORAF
[c] Kaplan-Meier estimate
[d] Unstratified log-rank test

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



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

Patients Who Received Prior Systemic Therapy

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 ≥ 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 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

See FDA-approved patient labeling (Medication Guide).
Health care 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 health care provider immediately of any changes in their skin *[see Warnings and Precautions (5.1)]*.
- 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)]*.
- ZELBORAF can cause mild to severe photosensitivity. Advise ZELBORAF-treated patients to avoid sun exposure, wear protective clothing, and use a broad spectrum UVA/UVB sunscreen and lip balm (SPF ≥ 30) when outdoors to help protect against sunburn *[see Warnings and Precautions (5.7)]*.

ZELBORAF is a registered trademark of Genentech, Inc.

Co-promoted by: Genentech USA, Inc. and Daiichi Sankyo, Inc.

Distributed by:

Genentech USA, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

~~Revised: JUNE 2013~~

FDA-Approved Patient Labeling

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 patients taking 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 have developed 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 start taking ZELBORAF, tell your healthcare provider if you:

- **have any heart problems, including a condition called long QT syndrome**
- **have liver or kidney problems**
- **have been told that you have low blood levels of potassium, calcium, or magnesium**
- **have any other medical conditions**
- **are pregnant or plan to become pregnant.** ZELBORAF may harm your unborn baby.
  - Females who are able to become pregnant, and males who take ZELBORAF, should use birth control during treatment and for 2 months after stopping ZELBORAF.

- Talk to your healthcare provider about birth control methods that may be right for you.
- Tell your healthcare provider right away if you become pregnant during treatment with ZELBORAF.

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

Tell your healthcare provider about all the medicines you take, including prescription and 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 ZELBORAF unless your healthcare provider tells you.
- Take ZELBORAF every 12 hours with or without a meal.
- Do not crush or chew ZELBORAF tablets.
- If you miss a dose, take it as soon as you remember. If it is within 4 hours of your next scheduled dose, just take your next dose at your regular time. Do not make up for the missed dose.
- 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 have any of these symptoms of an allergic reaction:
  - get a rash or redness all over your body
  - feel faint
  - have trouble breathing or swallowing
  - have throat tightness or hoarseness
  - have a fast heartbeat
  - have swelling of the face, lips, or tongue
- **Severe skin reactions.** Stop taking ZELBORAF and call your healthcare provider right away if you get a skin rash with any of the following symptoms, because you may have a severe skin reaction:
  - blisters on your skin
  - blisters or sores in your mouth
  - peeling of your skin
  - fever
  - redness or swelling of your face, hands, or soles of your feet

- **Changes in the electrical activity of your heart called QT prolongation. QT prolongation can cause irregular heartbeats that can be life-threatening.** Your

healthcare provider should do tests before you start taking ZELBORAF and during 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.

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

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.

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

What are the ingredients in ZELBORAF?

Active ingredient: vemurafenib
Inactive ingredients: hypromellose acetate succinate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, hydroxypropyl cellulose.
Coating: pinkish white: poly (vinyl alcohol), titanium dioxide, polyethylene glycol 3350, talc, and iron oxide red.

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

ZELBORAF is a registered trademark of Genentech, Inc.

Co-promoted by: Genentech USA, Inc. and Daiichi Sankyo, Inc.

Distributed by:

Genentech USA, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

Revised: ~~June~~ July 2013