

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: Can cause fetal harm. Advise females of the potential risk to the fetus and to use effective contraception. (5.9, 8.1, 8.3)
- 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**-----

- Lactation: Do not breastfeed while taking Zelboraf. (8.2)

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

Revised: 08/2016

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1 **FULL PRESCRIBING INFORMATION**

2 **1 INDICATIONS AND USAGE**

3 ZELBORAF[®] is indicated for the treatment of patients with unresectable or metastatic melanoma with
4 BRAF V600E mutation as detected by an FDA-approved test.

5 Limitation of Use: ZELBORAF is not indicated for treatment of patients with wild-type BRAF melanoma
6 [*see Warnings and Precautions (5.2)*].

7 **2 DOSAGE AND ADMINISTRATION**

8 **2.1 Patient Selection**

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

12 **2.2 Recommended Dose**

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

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

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

18 Do not crush or chew the tablets.

19 **2.3 Dose Modifications**

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

21 *For Other Adverse Reactions:*

22 Permanently discontinue ZELBORAF for any of the following:

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

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

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

- 28 • 720 mg twice daily for first appearance of intolerable Grade 2 or Grade 3 adverse reactions
29 • 480 mg twice daily for second appearance of Grade 2 (if intolerable) or Grade 3 adverse reactions or
30 for first appearance of Grade 4 adverse reaction (if clinically appropriate)

31 Do not dose reduce to below 480 mg twice daily.

32 **3 DOSAGE FORMS AND STRENGTHS**

33 Tablet: 240 mg.

34 **4 CONTRAINDICATIONS**

35 None.

36 **5 WARNINGS AND PRECAUTIONS**

37 **5.1 New Primary Malignancies**

38 *Cutaneous Malignancies*

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

42 1% in the dacarbazine arm [see *Adverse Reactions (6.1)*]. The median time to the first appearance of cuSCC
43 was 7 to 8 weeks; approximately 33% of patients who developed a cuSCC while receiving ZELBORAF
44 experienced at least one additional occurrence with median time between occurrences of 6 weeks. Potential
45 risk factors associated with cuSCC observed in clinical studies using ZELBORAF included age (≥ 65
46 years), prior skin cancer, and chronic sun exposure.

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

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

52 *Non-Cutaneous Squamous Cell Carcinoma*

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

56 *Other Malignancies*

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

60 **5.2 Tumor Promotion in BRAF Wild-Type Melanoma**

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

65 **5.3 Hypersensitivity Reactions**

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

71 **5.4 Dermatologic Reactions**

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

75 **5.5 QT Prolongation**

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

80 Do not start treatment in patients with uncorrectable electrolyte abnormalities, QTc > 500 ms, or long QT
81 syndrome, or in patients who are taking medicinal products known to prolong the QT interval. Prior to and
82 following treatment initiation or after dose modification of ZELBORAF for QTc prolongation, evaluate
83 ECG and electrolytes (including potassium, magnesium, and calcium) after 15 days, monthly during the first
84 3 months, and then every 3 months thereafter or more often as clinically indicated.

85
86 Withhold ZELBORAF in patients who develop QTc > 500 ms (Grade 3). Upon recovery to QTc \leq 500 ms
87 (Grade \leq 2), restart at a reduced dose. Permanently discontinue ZELBORAF treatment if the QTc interval

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

91 **5.6 Hepatotoxicity**

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

97 *Concurrent Administration with Ipilimumab*

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

102 **5.7 Photosensitivity**

103 Mild to severe photosensitivity can occur in patients treated with ZELBORAF [*see Adverse Reactions*
104 *(6.1)*]. Advise patients to avoid sun exposure, wear protective clothing and use a broad spectrum UVA/UVB
105 sunscreen and lip balm (SPF \geq 30) when outdoors.

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

108 **5.8 Ophthalmologic Reactions**

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

113 **5.9 Embryo-Fetal Toxicity**

114 Based on its mechanism of action, ZELBORAF can cause fetal harm when administered to a pregnant
115 woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to
116 use effective contraception during treatment with ZELBORAF and for 2 weeks after the final dose [*see Use*
117 *in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)*].

118 **5.10 Radiation Sensitization and Radiation Recall**

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

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

124 **5.11 Renal Failure**

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

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

131

132 **6 ADVERSE REACTIONS**

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

- 134 • New Primary Malignancies [see Warnings and Precautions (5.1)]
- 135 • Hypersensitivity Reactions [see Warnings and Precautions (5.3)]
- 136 • Dermatologic Reactions [see Warnings and Precautions (5.4)]
- 137 • QT Prolongation [see Warnings and Precautions (5.5)]
- 138 • Hepatotoxicity [see Warnings and Precautions (5.6)]
- 139 • Photosensitivity [see Warnings and Precautions (5.7)]
- 140 • Ophthalmologic Reactions [see Warnings and Precautions (5.8)]
- 141 • Radiation Sensitization and Radiation Recall [see Warnings and Precautions (5.10)]
- 142 • Renal Failure [see Warnings and Precautions (5.11)]

144 **6.1 Clinical Trials Experience**

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

148 This section describes adverse drug reactions (ADRs) identified from analyses of Trial 1 and Trial 2 [see
 149 *Clinical Studies (14)*]. Trial 1 randomized (1:1) 675 treatment-naïve patients with unresectable or metastatic
 150 melanoma to receive ZELBORAF 960 mg orally twice daily or dacarbazine 1000 mg/m² intravenously
 151 every 3 weeks. In Trial 2, 132 patients with metastatic melanoma and failure of at least one prior systemic
 152 therapy received treatment with ZELBORAF 960 mg orally twice daily.

153 Table 1 presents adverse reactions reported in at least 10% of patients treated with ZELBORAF. The most
 154 common adverse reactions of any grade ($\geq 30\%$ in either study) in ZELBORAF-treated patients were
 155 arthralgia, rash, alopecia, fatigue, photosensitivity reaction, nausea, pruritus, and skin papilloma. The most
 156 common ($\geq 5\%$) Grade 3 adverse reactions were cuSCC and rash. The incidence of Grade 4 adverse
 157 reactions was $\leq 4\%$ in both studies.

158 The incidence of adverse events resulting in permanent discontinuation of study medication in Trial 1 was
 159 7% for the ZELBORAF arm and 4% for the dacarbazine arm. In Trial 2, the incidence of adverse events
 160 resulting in permanent discontinuation of study medication was 3% in ZELBORAF-treated patients. The
 161 median duration of study treatment was 4.2 months for ZELBORAF and 0.8 months for dacarbazine in Trial
 162 1, and 5.7 months for ZELBORAF in Trial 2.

163 **Table 1 Adverse Reactions Reported in $\geq 10\%$ 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

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

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

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

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

169

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

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

174 *Musculoskeletal and connective tissue disorders:* arthritis

175 *Nervous system disorders:* neuropathy peripheral, VIIth nerve paralysis

176 *Neoplasms benign, malignant and unspecified (includes cysts and polyps):* basal cell carcinoma,
 177 oropharyngeal squamous cell carcinoma
 178 *Infections and infestations:* folliculitis
 179 *Eye disorders:* retinal vein occlusion
 180 *Vascular disorders:* vasculitis
 181 *Cardiac disorders:* atrial fibrillation

182 Table 2 shows the incidence of worsening liver laboratory abnormalities in Trial 1 summarized as the
 183 proportion of patients who experienced a shift from baseline to Grade 3 or 4.

184 **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

185 * For ALT, alkaline phosphatase, and bilirubin, there were no patients with a change to Grade 4 in either treatment arm.
 186
 187

188 6.2 Postmarketing Experience

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

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

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

196 *Blood and lymphatic systems disorder:* Neutropenia

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

199 *Gastrointestinal disorders:* Pancreatitis

200 *Renal and urinary disorders:* Acute interstitial nephritis, acute tubular necrosis [see Warnings and
 201 Precautions (5.11)].
 202

203 7 DRUG INTERACTIONS

204 7.1 Effect of Strong CYP3A4 Inhibitors or Inducers on Vemurafenib

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

211 7.2 Effect of Vemurafenib on CYP1A2 Substrates

212 Coadministration of ZELBORAF with tizanidine, a sensitive CYP1A2 substrate, increased tizanidine
 213 systemic exposure by 4.7-fold. Avoid concomitant use of ZELBORAF with drugs having a narrow

214 therapeutic window that are predominantly metabolized by CYP1A2 [see *Clinical Pharmacology (12.3)*]. If
215 coadministration cannot be avoided, monitor closely for toxicities and consider a dose reduction of
216 concomitant CYP1A2 substrates.

217 **7.3 Concurrent Ipilimumab**

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

220 **7.4 Effect of Vemurafenib on P-gp Substrates**

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

225 **8 USE IN SPECIFIC POPULATIONS**

226 **8.1 Pregnancy**

227 Risk Summary

228 Based on its mechanism of action, ZELBORAF can cause fetal harm when administered to a pregnant
229 woman [see *Clinical Pharmacology 12.1*]. There are no available data on the use of ZELBORAF in
230 pregnant women to determine the drug-associated risk; however, placental transfer of vemurafenib to a fetus
231 has been reported. Exposure to vemurafenib could not be achieved in animals at levels sufficient to fully
232 address its potential toxicity in pregnant women. Advise pregnant women of the potential harm to a fetus.

233
234 The estimated background risks of major birth defects and miscarriage for the indicated population(s) are
235 unknown. In the U.S. general population, the estimated background risk of major birth defects and
236 miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

237

238 Data

239 *Animal Data*

240 Vemurafenib showed no evidence of developmental toxicity in rat fetuses at doses up to 250 mg/kg/day
241 (approximately 1.3 times the clinical exposure at 960 mg twice daily based on AUC) or rabbit fetuses at
242 doses up to 450 mg/kg/day (approximately 0.6 times the clinical exposure at 960 mg twice daily based on
243 AUC). Fetal drug levels were 3–5% of maternal levels, indicating that vemurafenib has the potential to be
244 transmitted from the mother to the developing fetus.

245 **8.2 Lactation**

246 There is no information available regarding the presence of vemurafenib in human milk, effects on the
247 breastfed infant, or effects on milk production. Because of the potential for serious adverse reactions in a
248 breastfed infant, including malignancy, severe dermatologic reactions, QT prolongation, hepatotoxicity,
249 photosensitivity, and ophthalmologic toxicity, [see *Warnings and Precautions (5)*], advise women not to
250 breastfeed during treatment with ZELBORAF and for 2 weeks after the final dose.

251 **8.3 Females and Males of Reproductive Potential**

252 Contraception

253 Based on its mechanism of action, ZELBORAF can cause fetal harm when administered to a pregnant
254 woman [see *Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective
255 contraception during treatment with ZELBORAF and for 2 weeks after the final dose.

256 **8.4 Pediatric Use**

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

258 **8.5 Geriatric Use**

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

261 **8.6 Hepatic Impairment**

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

266 **8.7 Renal Impairment**

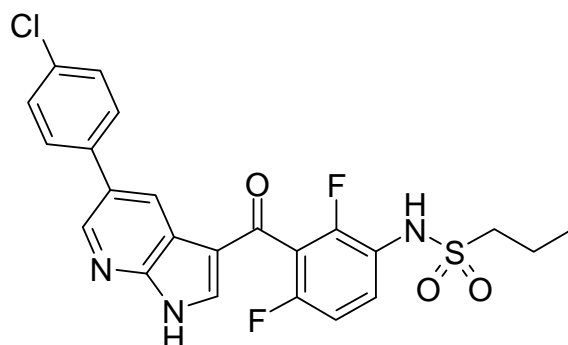
267 No formal clinical study has been conducted to evaluate the effect of renal impairment on the
268 pharmacokinetics of vemurafenib. No dose adjustment is recommended for patients with mild and moderate
269 renal impairment based on a population pharmacokinetic analysis [see *Clinical Pharmacology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

271 **10 OVERDOSAGE**

272 There is no information on overdosage of ZELBORAF.

273 **11 DESCRIPTION**

274 ZELBORAF (vemurafenib) is a kinase inhibitor available as 240 mg tablets for oral use. Vemurafenib has
275 the chemical name propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-
276 2,4-difluoro-phenyl}-amide. It has the molecular formula $C_{23}H_{18}ClF_2N_3O_3S$ and a molecular weight of
277 489.9. Vemurafenib has the following chemical structure:



278

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

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

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

284 **12 CLINICAL PHARMACOLOGY**

285 **12.1 Mechanism of Action**

286 Vemurafenib is an orally available inhibitor of some mutated forms of BRAF serine-threonine kinase,
287 including BRAF V600E. Vemurafenib also inhibits other kinases in vitro such as CRAF, ARAF, wild-type
288 BRAF, SRMS, ACK1, MAP4K5, and FGR at similar concentrations. Some mutations in the BRAF gene
289 including V600E result in constitutively activated BRAF proteins, causing cell proliferation in the absence
290 of growth factors normally required for proliferation. Vemurafenib demonstrated anti-tumor effects in
291 cellular and animal models of melanomas with mutated BRAF V600E.

292 **12.2 Pharmacodynamics**

293 **Cardiac Electrophysiology**

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

302 **12.3 Pharmacokinetics**

303 The pharmacokinetics of vemurafenib were determined in patients with BRAF mutation-positive metastatic
304 melanoma following 15 days of 960 mg twice daily with dosing approximately 12 hours apart. The
305 population pharmacokinetic analysis pooled data from 458 patients. At steady-state, vemurafenib exhibits
306 linear pharmacokinetics within the 240 mg to 960 mg dose range.

307 Absorption

308 The bioavailability of vemurafenib has not been determined. The median T_{max} was approximately 3 hours
309 following multiple doses.

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

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

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

319 Distribution

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

322 Metabolism

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

325 Elimination

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

330 Specific Populations

331 *Hepatic Impairment:* The pharmacokinetics of vemurafenib were examined in patients with metastatic
332 melanoma enrolled in the clinical trials with normal hepatic function (n=158, total bilirubin \leq ULN) and
333 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,
334 total bilirubin > 3 x ULN) hepatic impairment. Patients received vemurafenib 960 mg orally twice daily.
335 The apparent clearance of vemurafenib in patients with mild and moderate hepatic impairment was similar
336 to that in patients with normal hepatic function. The appropriate dose for patients with severe hepatic
337 impairment cannot be determined as clinical and pharmacokinetic data were available for only three patients
338 [*see Use in Specific Populations (8.6)*].

339 *Renal Impairment:* The pharmacokinetics of vemurafenib were examined in patients with metastatic
340 melanoma enrolled in the clinical trials with normal renal function ($CL_{Cr} \geq 90$ mL/min) and mild (n=94,
341 $CL_{Cr} > 60$ to 89 mL/min), moderate (n=11, CL_{Cr} 30 to 59 mL/min) or severe (n=1, $CL_{Cr} < 29$ mL/min)
342 renal impairment. Patients received vemurafenib 960 mg orally twice daily. The apparent clearance of
343 vemurafenib in patients with mild and moderate renal impairment was similar to that in patients with normal
344 renal function. The appropriate dose for patients with severe renal impairment cannot be determined as
345 clinical and pharmacokinetic data were available for only one patient [see *Use in Specific Populations*
346 (8.7)].

347 *Age, Body Weight, Sex, and Race:* Based on the population pharmacokinetic analysis, age, body weight, and
348 sex do not have a clinically important effect on the exposure of vemurafenib. There are insufficient data to
349 evaluate potential differences in the pharmacokinetics of vemurafenib by race.

350 *Pediatrics:* No studies have been conducted to investigate the pharmacokinetics of vemurafenib in pediatric
351 patients.

352 Drug Interaction Studies

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

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

358 Coadministration of tizanidine 2 mg (a sensitive CYP1A2 substrate) on day 21 with vemurafenib which was
359 administered 960 mg twice daily for 21 days increased tizanidine AUC_{inf} by 4.7-fold (90% CI: 3.6, 6.3) and
360 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
361 phenotypic cocktail drug-drug interaction study in patients with cancer, a single dose of the CYP probe
362 substrate cocktail (for CYP1A2, 2D6, 3A4, 2C19 and 2C9) was administered before and concomitantly with
363 vemurafenib (following 15 days of dosing at 960 mg twice daily). Coadministration of vemurafenib
364 increased the mean AUC of caffeine (CYP1A2 substrate) by 2.6-fold [see *Drug Interactions (7.2)*].
365 Coadministration of vemurafenib increased the mean AUC of dextromethorphan (CYP2D6 substrate) by
366 47% and the AUC of S-warfarin (CYP2C9 substrate) by 18%, while it decreased the mean AUC of
367 midazolam (CYP3A4 substrate) by 39%. Coadministration of vemurafenib did not change the mean
368 systemic exposure to omeprazole (CYP2C19 substrate).

369 *Effect of Vemurafenib on Transporters:* In vitro studies suggest that vemurafenib is both a substrate and an
370 inhibitor of the efflux transporters P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP).
371 Administration of vemurafenib 960 mg twice daily for 22 days increased digoxin AUC by 1.8-fold (90%
372 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
373 dose of digoxin 0.25 mg (sensitive P-gp substrate) [see *Drug Interactions (7.4)*].

374

375 **13 NONCLINICAL TOXICOLOGY**

376 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

379 Vemurafenib did not cause genetic damage when tested in vitro (bacterial mutation [AMES Assay]; human
380 lymphocyte chromosome aberration assay) or in vivo (rat bone marrow micronucleus test).

381 No specific studies with vemurafenib have been conducted in animals to evaluate the effect on fertility;
382 however, in repeat-dose toxicity studies, no adverse histopathological findings were noted in the
383 reproductive organs of rats at doses up to 450 mg/kg/day (approximately 0.6 and 1.6 times the human

384 exposure based on AUC in males and females, respectively) or of dogs at doses up to 450 mg/kg/day
385 (approximately 0.3 times the human exposure based on AUC).

386 13.2 Animal Toxicology and/or Pharmacology

387 Consistent with the increased incidence of cutaneous squamous cell carcinomas in vemurafenib-treated
388 patients, vemurafenib caused dose-dependent acceleration of tumor growth in mice implanted with human
389 cuSCC cells.

390 14 CLINICAL STUDIES

391 Treatment-Naïve Patients

392 Trial 1, an international, open-label, randomized controlled trial, equally allocated 675 patients with
393 treatment-naïve, BRAF V600E mutation-positive unresectable or metastatic melanoma, as detected by the
394 cobas[®] 4800 BRAF V600 Mutation Test, to receive ZELBORAF 960 mg by mouth twice daily (n=337) or
395 dacarbazine 1000 mg/m² intravenously on Day 1 every 3 weeks (n=338). Randomization stratification
396 factors were disease stage, lactate dehydrogenase (LDH), ECOG performance status, and geographic region.
397 Treatment continued until disease progression, unacceptable toxicity, and/or consent withdrawal. The major
398 efficacy outcome measures of the trial were overall survival (OS) and investigator-assessed progression-free
399 survival (PFS). Other outcome measures included confirmed investigator-assessed best overall response
400 rate.

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

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

407 **Table 3 Efficacy of ZELBORAF in Treatment-Naïve Patients with BRAF V600E Mutation-Positive**
408 **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)	-

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

410 ^b Total of 200 deaths (Zelboraf median follow-up 6.2 months)

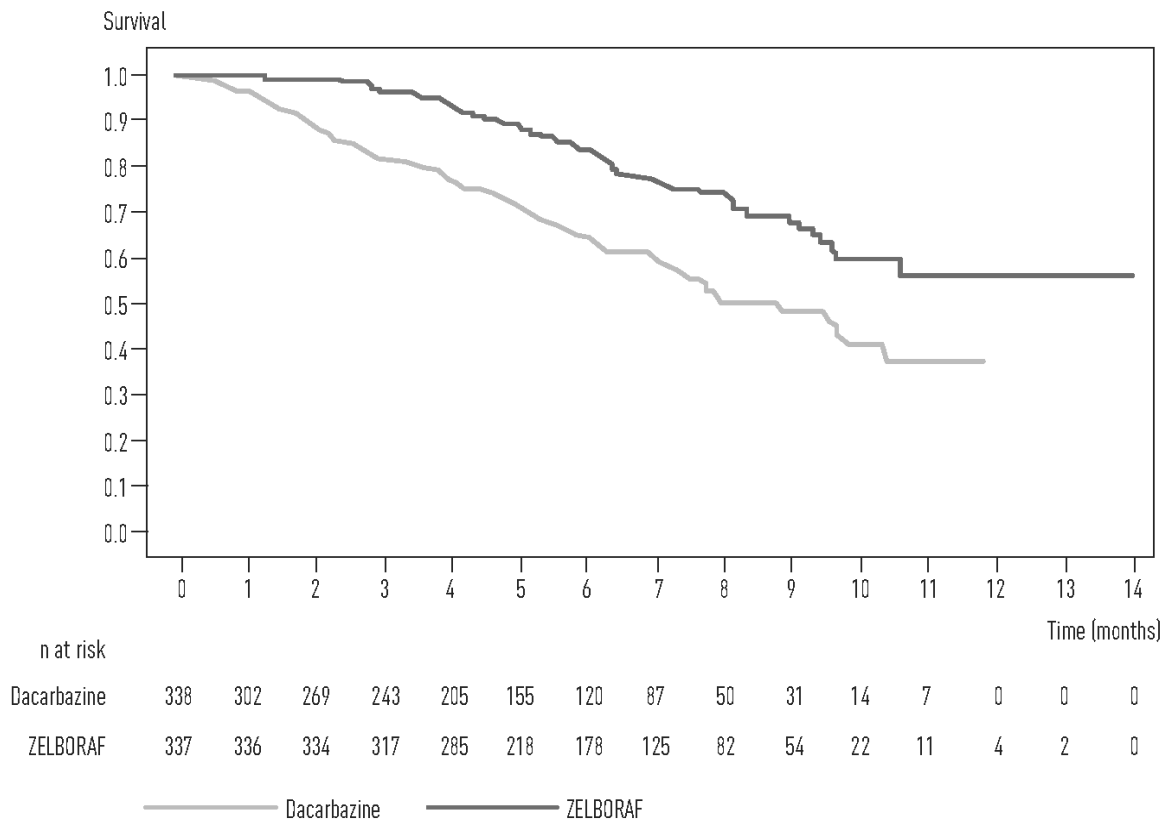
411 ^c Hazard ratio estimated using Cox model; a hazard ratio of < 1 favors ZELBORAF

412 ^d Kaplan-Meier estimate

413 ^e Updated based on 478 deaths (Zelboraf median follow-up 13.4 months)

414 ^f Unstratified log-rank test

415



417
418
419

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

424 ***Patients Who Received Prior Systemic Therapy***

425 In a single-arm, multicenter, multinational trial (Trial 2), 132 patients with BRAF V600E mutation-positive
426 metastatic melanoma, as detected by the cobas[®] 4800 BRAF V600 Mutation Test, who had received at least
427 one prior systemic therapy, received ZELBORAF 960 mg by mouth twice daily. The median age was 52
428 years with 19% of patients being older than 65 years. The majority of patients were male (61%) and
429 Caucasian (99%). Forty-nine percent of patients received ≥ 2 prior therapies. The median duration of
430 follow-up was 6.87 months (range, 0.6 to 11.3).

431 The confirmed best overall response rate as assessed by an independent review committee (IRC) was 52%
432 (95% CI: 43%, 61%). There were 3 complete responses (2.3%) and 66 partial responses (50.0%). The
433 median time to response was 1.4 months with 75% of responses occurring by month 1.6 of treatment. The
434 median duration of response by IRC was 6.5 months (95% CI: 5.6, not reached).

435 ***Patients with Brain Metastases***

436 The activity of ZELBORAF for the treatment of BRAF V600E mutation-positive melanoma, metastatic to
437 the brain was evaluated in an open-label, multicenter, single-arm, two cohort trial (Trial 3). All patients
438 received Zelboraf 960 mg orally twice daily until disease progression or unacceptable toxicity. Patients
439 were required to have at least one measurable brain lesion of 0.5 cm or greater on contrast-enhanced MRI, a
440 stable or decreasing corticosteroid dose and no prior treatment with a BRAF or MEK inhibitor. Patients in
441 Cohort A had received no prior local therapy for brain metastases. Patients in Cohort B had received at least
442 one prior local therapy for brain metastases (surgical resection, whole brain radiotherapy, or stereotactic

443 radiotherapy) with CNS progression following this therapy. Patients were followed until death, disease
444 progression, withdrawal, or up to 24 months. The primary efficacy outcome measure was the confirmed best
445 overall response rate (BORR) in the brain in Cohort A, as assessed by an independent radiology review
446 committee using Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Secondary efficacy
447 outcome measures included duration of response in Cohort A, and confirmed BORR and duration of
448 response in Cohort B.

449

450 A total of 146 patients (Cohort A: n=90; Cohort B: n=56) were enrolled and received at least one dose of
451 Zelboraf. In Cohort A, the median age of patients was 56 years, 62% were male, 47% had a pre-treatment
452 ECOG performance status (PS) of 0, 57% had an elevated LDH value at baseline, and 20% received one or
453 more systemic regimens for the treatment of metastatic disease. In Cohort B, the median age of patients was
454 53 years, 61% were male, 38% had a pre-treatment ECOG PS of 0, 55% had an elevated LDH value at
455 baseline, and 39% received one or more systemic regimens for the treatment of metastatic disease. All
456 patients enrolled on Trial 3 whose race was identified were White. The efficacy results are summarized in
457 Table 4.

458

459 **Table 4 Efficacy Results in Patients with BRAF V600E Melanoma Brain Metastases**

	Cohort A (n=90)	Cohort B (n=56)
Confirmed Best Overall Response Rate in Brain, 95%CI ^a	18% (11%, 27%)	18% (9%, 30%)
Complete response	2%	0
Partial response	16%	18%
Median of Duration of Response, months (95%CI ^b)	4.6 (2.9, 6.2)	6.6 (2.8, 10.7)

460 ^a Two-sided 95% Clopper-Pearson Confidence Interval (CI)

461 ^b Kaplan-Meier estimate

462

463 ***Patients with Wild-Type BRAF Melanoma***

464 ZELBORAF has not been studied in patients with wild-type BRAF melanoma [see *Warnings and*
465 *Precautions (5.2)*].

466

467 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

470 NDC 50242-090-01 single bottle of 120 count

471 NDC 50242-090-02 single bottle of 112 count

472 **Storage and Stability:** Store at room temperature 20°C–25°C (68°F–77°F); excursions permitted between
473 15°C and 30°C (59°F and 86°F), See USP Controlled Room Temperature. Store in the original container
474 with the lid tightly closed.

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

478 **17 PATIENT COUNSELING INFORMATION**

479 See FDA-approved patient labeling (Medication Guide).

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

- 483 • Evidence of BRAF V600E mutation in the tumor specimen with an FDA approved test is necessary
484 to identify patients for whom treatment with ZELBORAF is indicated [*see Dosage and*
485 *Administration (2.1)*].
- 486 • ZELBORAF increases the risk of developing new primary cutaneous malignancies. Advise patients
487 of the importance of contacting their healthcare provider immediately for any changes in their skin
488 [*see Warnings and Precautions (5.1)*].
- 489 • Anaphylaxis and other serious hypersensitivity reactions can occur during treatment and upon re-
490 initiation of treatment with ZELBORAF. Advise patients to stop taking ZELBORAF and to seek
491 immediate medical attention for symptoms of anaphylaxis or hypersensitivity [*see Warnings and*
492 *Precautions (5.3)*].
- 493 • Severe dermatologic reactions can occur in patients receiving ZELBORAF. Advise patients to stop
494 taking ZELBORAF and to contact their health-care provider for severe dermatologic reactions [*see*
495 *Warnings and Precautions (5.4)*].
- 496 • ZELBORAF can prolong QT interval, which may result in ventricular arrhythmias. Advise patients
497 of the importance of monitoring of their electrolytes and the electrical activity of their heart (via an
498 ECG) during ZELBORAF treatment [*see Warnings and Precautions (5.5)*].
- 499 • Liver injury leading to functional hepatic impairment, including coagulopathy or other organ
500 dysfunction, can occur with ZELBORAF. Advise patients of the importance of laboratory
501 monitoring of their liver during ZELBORAF treatment and to contact their health-care provider for
502 relevant symptoms [*see Warnings and Precautions (5.6)*].
- 503 • ZELBORAF can cause mild to severe photosensitivity. Advise patients to avoid sun exposure, wear
504 protective clothing, and use a broad spectrum UVA/UVB sunscreen and lip balm (SPF \geq 30) when
505 outdoors to help protect against sunburn [*see Warnings and Precautions (5.7)*].
- 506 • Ophthalmologic reactions can occur in patients treated with ZELBORAF. Advise patients to contact
507 their health-care provider immediately for ophthalmologic symptoms [*see Warnings and*
508 *Precautions (5.8)*].

509 Embryo-fetal Toxicity

- 510 • Advise pregnant women and females of reproductive potential of the potential risk to a fetus [*see*
511 *Warnings and Precautions (5.9) and Use in Special Populations (8.1)*].
- 512 • Advise females of reproductive potential to use effective contraception during treatment with
513 ZELBORAF and for 2 weeks after the final dose [*see Warnings and Precautions (5.9) and Use in*
514 *Special Populations (8.1, 8.3)*].
- 515 • Advise female patients to contact their health-care provider immediately with a known or suspected
516 pregnancy [*see Warnings and Precautions (5.9) and Use in Special Populations (8.1, 8.3)*].

517 Lactation

- 518 • Advise a woman not to breastfeed during treatment with ZELBORAF and for 2 weeks after the final
519 dose. [*see Use in Specific Populations (8.2)*].
- 520
- 521 • Radiation sensitization and recall can occur in patients treated with radiation prior to, during, or
522 subsequent to ZELBORAF treatment. Advise patients to inform their health care provider if they

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

- 525 • Renal failure can occur in patients treated with ZELBORAF. Advise patients of the importance of
526 monitoring serum creatinine prior to and during ZELBORAF treatment [see *Warnings and*
527 *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 should use effective birth control during ZELBORAF treatment and for 2 weeks after the final dose.
 - 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 or think you are pregnant during treatment with ZELBORAF.
- are breastfeeding or plan to breastfeed. It is not known if ZELBORAF passes into your breast milk. Do not breastfeed during treatment with ZELBORAF and for 2 weeks after the final dose. Talk to your healthcare provider about the best way to feed your baby during this time.

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:
 - rash or redness all over your body
 - throat tightness or hoarseness
 - trouble breathing or swallowing
 - feel faint
 - swelling of the face, lips, or tongue
 - 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:
 - blisters on your skin
 - fever
 - blisters or sores in your mouth
 - redness or swelling of your face, hands, or soles of your feet
 - peeling of your skin
- **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:
 - yellowing of your skin or the white part of your eyes
 - dark or brown (tea color) urine
 - nausea or vomiting
 - loss of appetite
 - 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
- **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.

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

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

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