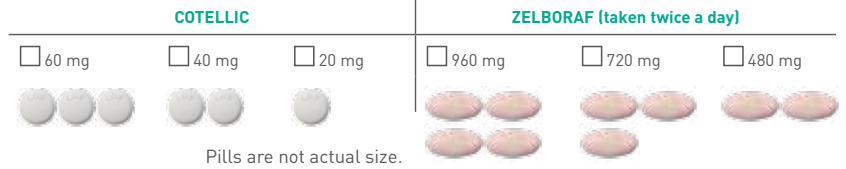


My dose of  
COTELLIC + ZELBORAF



MONTH: \_\_\_\_\_

	_____ day Date: _____	_____ day Date: _____	_____ day Date: _____	_____ day Date: _____	_____ day Date: _____	_____ day Date: _____	_____ day Date: _____
WEEK 1	☀ ZELBORAF <input type="checkbox"/>	☀ ZELBORAF <input type="checkbox"/>	☀ ZELBORAF <input type="checkbox"/>	☀ ZELBORAF <input type="checkbox"/>	☀ ZELBORAF <input type="checkbox"/>	☀ ZELBORAF <input type="checkbox"/>	☀ ZELBORAF <input type="checkbox"/>
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	COTELLIC <input type="checkbox"/>	COTELLIC <input type="checkbox"/>	COTELLIC <input type="checkbox"/>	COTELLIC <input type="checkbox"/>	COTELLIC <input type="checkbox"/>	COTELLIC <input type="checkbox"/>	COTELLIC <input type="checkbox"/>
WEEK 2	_____ day Date: _____	_____ day Date: _____	_____ day Date: _____	_____ day Date: _____	_____ day Date: _____	_____ day Date: _____	_____ day Date: _____
	☀ ZELBORAF <input type="checkbox"/>	☀ ZELBORAF <input type="checkbox"/>	☀ ZELBORAF <input type="checkbox"/>	☀ ZELBORAF <input type="checkbox"/>	☀ ZELBORAF <input type="checkbox"/>	☀ ZELBORAF <input type="checkbox"/>	☀ ZELBORAF <input type="checkbox"/>
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WEEK 3	_____ day Date: _____	_____ day Date: _____	_____ day Date: _____	_____ day Date: _____	_____ day Date: _____	_____ day Date: _____	_____ day Date: _____
	☀ ZELBORAF <input type="checkbox"/>	☀ ZELBORAF <input type="checkbox"/>	☀ ZELBORAF <input type="checkbox"/>	☀ ZELBORAF <input type="checkbox"/>	☀ ZELBORAF <input type="checkbox"/>	☀ ZELBORAF <input type="checkbox"/>	☀ ZELBORAF <input type="checkbox"/>
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WEEK 4	_____ day Date: _____	_____ day Date: _____	_____ day Date: _____	_____ day Date: _____	_____ day Date: _____	_____ day Date: _____	_____ day Date: _____
	☀ ZELBORAF <input type="checkbox"/>	☀ ZELBORAF <input type="checkbox"/>	☀ ZELBORAF <input type="checkbox"/>	☀ ZELBORAF <input type="checkbox"/>	☀ ZELBORAF <input type="checkbox"/>	☀ ZELBORAF <input type="checkbox"/>	☀ ZELBORAF <input type="checkbox"/>
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	COTELLIC <input type="checkbox"/>	COTELLIC <input type="checkbox"/>	COTELLIC <input type="checkbox"/>	NO COTELLIC THIS WEEK		COTELLIC <input type="checkbox"/>	COTELLIC <input type="checkbox"/>

Please see reverse and both accompanying Full COTELLIC Prescribing Information and Patient Information and Full ZELBORAF Prescribing Information and Medication Guide for Important Safety Information.



**Important:** If your healthcare provider prescribes ZELBORAF (vemurafenib), also read the Medication Guide that comes with ZELBORAF.

## What is COTELLIC?

COTELLIC is a prescription medicine that is used with the medicine ZELBORAF, 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 COTELLIC is right for you.

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

## How should I take COTELLIC and ZELBORAF in combination?

- Take COTELLIC and ZELBORAF exactly as your healthcare provider tells you. Do not change your dose or stop taking COTELLIC and ZELBORAF unless your healthcare provider tells you to.
- Take COTELLIC one time a day for 21 days, followed by 7 days off treatment, to complete a 28-day treatment cycle.
- Take ZELBORAF every 12 hours for every day in the 28-day cycle (no rest period).
- Do not crush or chew ZELBORAF tablets.
- Take COTELLIC and ZELBORAF with or without food.
- If you vomit after taking your dose of COTELLIC or ZELBORAF, do not take an additional dose. Take your next dose as scheduled.
- If you miss a dose of COTELLIC, take your next dose as scheduled.
- 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.

## Important Safety Information

- Avoid sunlight during treatment with COTELLIC and ZELBORAF. COTELLIC and ZELBORAF can make your skin sensitive to sunlight. You may burn more easily and get severe sunburns. 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.
- COTELLIC and ZELBORAF may cause serious side effects, including risk of new skin cancers, risk of other cancers, bleeding problems, heart problems, allergic reactions, severe rash and other severe skin reactions, eye problems, changes in the electrical activity of your heart (QT prolongation), liver problems or liver injury, muscle problems (rhabdomyolysis), skin sensitivity to sunlight (photosensitivity), worsening side effects from radiation treatment that can sometimes be severe or lead to death, kidney injury, and connective tissue disorders.
- Tell your doctor if you are pregnant or plan to become pregnant, as COTELLIC and ZELBORAF can harm your unborn baby. Females who are able to become pregnant should use effective birth control during treatment with COTELLIC and ZELBORAF and for 2 weeks after the final dose of COTELLIC or ZELBORAF (whichever is taken later).
- Do not breastfeed during treatment and for 2 weeks after the final dose of COTELLIC or ZELBORAF (whichever is taken later). 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. Some types of medicines will affect the blood levels of COTELLIC.
- Common side effects of COTELLIC in combination with ZELBORAF include diarrhea, sunburn or sun sensitivity, nausea, fever, and vomiting. COTELLIC and ZELBORAF can also cause changes in blood test results.

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 COTELLIC and ZELBORAF.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch). You may also report side effects to Genentech at (888) 835-2555.

**Please see both accompanying Full COTELLIC Prescribing Information and Patient Information and Full ZELBORAF Prescribing Information and Medication Guide for additional Important Safety Information.**

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## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use COTELLIC safely and effectively. See full prescribing information for COTELLIC.

### COTELLIC® (cobimetinib) tablets, for oral use

Initial U.S. Approval: 2015

#### INDICATIONS AND USAGE

COTELLIC® is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib. (1, 14)

#### DOSAGE AND ADMINISTRATION

- Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to initiation of COTELLIC. (2.1)
- The recommended dose is 60 mg orally once daily for the first 21 days of each 28-day cycle until disease progression or unacceptable toxicity. Take COTELLIC with or without food. (2.2)

#### DOSAGE FORMS AND STRENGTHS

Tablets: 20 mg (3)

#### CONTRAINDICATIONS

None. (4)

#### WARNINGS AND PRECAUTIONS

- **New primary malignancies, cutaneous and non-cutaneous:** Monitor patients for new malignancies prior to initiation of therapy, while on therapy, and for up to 6 months following the last dose of COTELLIC. (5.1)
- **Hemorrhage:** Major hemorrhagic events can occur with COTELLIC. Monitor for signs and symptoms of bleeding. (5.2, 2.3)
- **Cardiomyopathy:** The risk of cardiomyopathy is increased in patients receiving COTELLIC with vemurafenib compared with vemurafenib as a single agent. The safety of COTELLIC has not been established in patients with decreased left ventricular ejection fraction (LVEF). Evaluate LVEF before treatment, after one month of treatment, then every 3 months thereafter during treatment with COTELLIC. (5.3, 2.3)

- **Severe Dermatologic Reactions:** Monitor for severe skin rashes. Interrupt, reduce, or discontinue COTELLIC. (5.4, 2.3)
- **Serous Retinopathy and Retinal Vein Occlusion:** Perform an ophthalmological evaluation at regular intervals and for any visual disturbances. Permanently discontinue COTELLIC for retinal vein occlusion (RVO). (5.5, 2.3)
- **Hepatotoxicity:** Monitor liver laboratory tests during treatment and as clinically indicated. (5.6, 2.3)
- **Rhabdomyolysis:** Monitor creatine phosphokinase periodically and as clinically indicated for signs and symptoms of rhabdomyolysis. (5.7, 2.3)
- **Severe Photosensitivity:** Advise patients to avoid sun exposure. (5.8, 2.3)
- **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.9, 8.1, 8.3)

#### ADVERSE REACTIONS

Most common adverse reactions for COTELLIC (≥20%) are diarrhea, photosensitivity reaction, nausea, pyrexia, and vomiting. The most common (≥5%) Grade 3-4 laboratory abnormalities are increased GGT, increased CPK, hypophosphatemia, increased ALT, lymphopenia, increased AST, increased alkaline phosphatase, hyponatremia. (6.1)

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

#### DRUG INTERACTIONS

Avoid concomitant administration of COTELLIC with strong or moderate CYP3A inducers or inhibitors. (2.3, 7.1, 7.2)

#### USE IN SPECIFIC POPULATIONS

Lactation: Do not breastfeed while taking COTELLIC. (8.2)

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

Revised: 01/2018

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

COTELLIC® is indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Patient Selection

Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to initiation of treatment with COTELLIC with vemurafenib. 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 dosage regimen of COTELLIC is 60 mg (three 20 mg tablets) orally taken once daily for the first 21 days of each 28-day cycle until disease progression or unacceptable toxicity [see *Clinical Studies (14)*].

Take COTELLIC with or without food [see *Clinical Pharmacology (12.3)*].

If a dose of COTELLIC is missed or if vomiting occurs when the dose is taken, resume dosing with the next scheduled dose.

#### 2.3 Dose Modifications

##### Concurrent CYP3A Inhibitors

Do not take strong or moderate CYP3A inhibitors while taking COTELLIC.

If concurrent short term (14 days or less) use of moderate CYP3A inhibitors is unavoidable for patients who are taking COTELLIC 60 mg, reduce COTELLIC dose to 20 mg. After discontinuation of a moderate CYP3A inhibitor, resume previous dose of COTELLIC 60 mg [see *Drug Interactions (7.1)* and *Clinical Pharmacology (12.3)*].

Use an alternative to a strong or moderate CYP3A inhibitor in patients who are taking a reduced dose of COTELLIC (40 or 20 mg daily) [see *Drug Interactions (7.1)* and *Clinical Pharmacology (12.3)*].

##### Adverse Reactions

Review the Full Prescribing Information for vemurafenib for recommended dose modifications.

**Table 1. Recommended Dose Reductions for COTELLIC**

First Dose Reduction	40 mg orally once daily
Second Dose Reduction	20 mg orally once daily
Subsequent Modification	Permanently discontinue COTELLIC if unable to tolerate 20 mg orally once daily

**Table 2. Recommended Dose Modifications for COTELLIC for Adverse Reactions**

Severity of Adverse Reaction <sup>a</sup>	Dose Modification for COTELLIC
<i>New Primary Malignancies (cutaneous and non-cutaneous)</i>	No dose modification is required.
<i>Hemorrhage</i>	
Grade 3	Withhold COTELLIC for up to 4 weeks. <ul style="list-style-type: none"> <li>• If improved to Grade 0 or 1, resume at the next lower dose level.</li> <li>• If not improved within 4 weeks, permanently discontinue.</li> </ul>
Grade 4	Permanently discontinue.
<i>Cardiomyopathy</i>	
Asymptomatic, absolute decrease in LVEF from baseline of greater than 10% <u>and</u> less than institutional lower limit of normal (LLN)	Withhold COTELLIC for 2 weeks; repeat LVEF. Resume at next lower dose if <u>all</u> of the following are present <ul style="list-style-type: none"> <li>• LVEF is at or above LLN <u>and</u></li> <li>• Absolute decrease from baseline LVEF is 10% or less.</li> </ul> Permanently discontinue if <u>any</u> of the following are present <ul style="list-style-type: none"> <li>• LVEF is less than LLN <u>or</u></li> <li>• Absolute decrease from baseline LVEF is more than 10%.</li> </ul>
Symptomatic LVEF decrease from baseline	Withhold COTELLIC for up to 4 weeks, repeat LVEF. Resume at next lower dose if <u>all</u> of the following are present: <ul style="list-style-type: none"> <li>• Symptoms resolve <u>and</u></li> <li>• LVEF is at or above LLN <u>and</u></li> <li>• Absolute decrease from baseline LVEF is 10% or less.</li> </ul> Permanently discontinue if <u>any</u> of the following are present <ul style="list-style-type: none"> <li>• Symptoms persist, <u>or</u></li> <li>• LVEF is less than LLN, <u>or</u></li> <li>• Absolute decrease from baseline LVEF is more than 10%.</li> </ul>
<i>Dermatologic Reactions</i>	
Grade 2 (intolerable), Grade 3 or 4	Withhold or reduce dose.
<i>Serous Retinopathy or Retinal Vein Occlusion</i>	
Serous retinopathy	Withhold COTELLIC for up to 4 weeks. <ul style="list-style-type: none"> <li>• If signs and symptoms improve, resume at the next lower dose level.</li> <li>• If not improved or symptoms recur at the lower dose within 4 weeks, permanently discontinue.</li> </ul>
Retinal vein occlusion	Permanently discontinue COTELLIC.

Severity of Adverse Reaction <sup>a</sup>	Dose Modification for COTELLIC
<i>Liver Laboratory Abnormalities and Hepatotoxicity</i>	
First occurrence Grade 4	Withhold COTELLIC for up to 4 weeks. <ul style="list-style-type: none"> <li>• If improved to Grade 0 or 1, then resume at the next lower dose level.</li> <li>• If not improved to Grade 0 or 1 within 4 weeks, permanently discontinue.</li> </ul>
Recurrent Grade 4	Permanently discontinue COTELLIC.
<i>Rhabdomyolysis and Creatine Phosphokinase (CPK) elevations</i>	
<ul style="list-style-type: none"> <li>• Grade 4 CPK elevation</li> <li>• Any CPK elevation and myalgia</li> </ul>	Withhold COTELLIC for up to 4 weeks. <ul style="list-style-type: none"> <li>• If improved to Grade 3 or lower, resume at the next lower dose level.</li> <li>• If not improved within 4 weeks, permanently discontinue.</li> </ul>
<i>Photosensitivity</i>	
Grade 2 (intolerable), Grade 3 or Grade 4	Withhold COTELLIC for up to 4 weeks. <ul style="list-style-type: none"> <li>• If improved to Grade 0 or 1, resume at the next lower dose level.</li> <li>• If not improved within 4 weeks, permanently discontinue.</li> </ul>
<i>Other</i>	
<ul style="list-style-type: none"> <li>• Grade 2 (intolerable) adverse reactions</li> <li>• Any Grade 3 adverse reactions</li> </ul>	Withhold COTELLIC for up to 4 weeks. <ul style="list-style-type: none"> <li>• If improved to Grade 0 or 1, resume at the next lower dose level.</li> <li>• If not improved within 4 weeks, permanently discontinue.</li> </ul>
First occurrence of any Grade 4 adverse reaction	<ul style="list-style-type: none"> <li>• Withhold COTELLIC until adverse reaction improves to Grade 0 or 1. Then resume at the next lower dose level, <i>OR</i></li> <li>• Permanently discontinue.</li> </ul>
Recurrent Grade 4 adverse reaction	Permanently discontinue COTELLIC.

<sup>a</sup>National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0)

### 3 DOSAGE FORMS AND STRENGTHS

Tablets: 20 mg, white, round, film-coated, debossed on one side with “COB”.

### 4 CONTRAINDICATIONS

None.

### 5 WARNINGS AND PRECAUTIONS

Review the Full Prescribing Information for vemurafenib for information on the serious risks of vemurafenib.

#### 5.1 New Primary Malignancies

New primary malignancies, cutaneous and non-cutaneous, can occur with COTELLIC.

##### Cutaneous Malignancies:

In Trial 1, the following cutaneous malignancies or premalignant conditions occurred in the COTELLIC with vemurafenib arm and the vemurafenib arm, respectively: cutaneous squamous cell carcinoma (cuSCC) or keratoacanthoma (KA) (6% and 20%), basal cell carcinoma (4.5% and 2.4%), and second primary melanoma (0.8% and 2.4%). Among patients receiving COTELLIC with vemurafenib, the median time to detection of first cuSCC/KA was 4 months (range: 2 to 11 months), and the median time to detection of basal cell carcinoma was 4 months (range: 27 days to 13 months). The time to onset in the two patients with second primary melanoma was 9 months and 12 months.

Perform dermatologic evaluations prior to initiation of therapy and every 2 months while on therapy. Manage suspicious skin lesions with excision and dermatopathologic evaluation. No dose modifications are recommended for COTELLIC [see *Dosage and Administration (2.3)*]. Conduct dermatologic monitoring for 6 months following discontinuation of COTELLIC when administered with vemurafenib.

#### Non-Cutaneous Malignancies:

Based on its mechanism of action, vemurafenib may promote growth and development of malignancies [refer to the *Full Prescribing Information for vemurafenib*]. In Trial 1, 0.8% of patients in the COTELLIC with vemurafenib arm and 1.2% of patients in the vemurafenib arm developed non-cutaneous malignancies.

Monitor patients receiving COTELLIC, when administered with vemurafenib, for signs or symptoms of non-cutaneous malignancies.

### **5.2 Hemorrhage**

Hemorrhage, including major hemorrhages defined as symptomatic bleeding in a critical area or organ, can occur with COTELLIC.

In Trial 1, the incidence of Grade 3–4 hemorrhages was 1.2% in patients receiving COTELLIC with vemurafenib and 0.8% in patients receiving vemurafenib. Hemorrhage (all grades) was 13% in patients receiving COTELLIC with vemurafenib and 7% in patients receiving vemurafenib. Cerebral hemorrhage occurred in 0.8% of patients receiving COTELLIC with vemurafenib and in none of the patients receiving vemurafenib. Gastrointestinal tract hemorrhage (3.6% vs 1.2%), reproductive system hemorrhage (2.0% vs 0.4%), and hematuria (2.4% vs 0.8%) also occurred at a higher incidence in patients receiving COTELLIC with vemurafenib compared with patients receiving vemurafenib.

Withhold COTELLIC for Grade 3 hemorrhagic events. If improved to Grade 0 or 1 within 4 weeks, resume COTELLIC at a lower dose level. Discontinue COTELLIC for Grade 4 hemorrhagic events and any Grade 3 hemorrhagic events that do not improve [see *Dosage and Administration (2.3)*].

### **5.3 Cardiomyopathy**

Cardiomyopathy, defined as symptomatic and asymptomatic decline in left ventricular ejection fraction (LVEF), can occur with COTELLIC. The safety of COTELLIC has not been established in patients with a baseline LVEF that is either below institutional lower limit of normal (LLN) or below 50%.

In Trial 1, patients were assessed for decreases in LVEF by echocardiograms or MUGA at baseline, Week 5, Week 17, Week 29, Week 43, and then every 4 to 6 months thereafter while receiving treatment. Grade 2 or 3 decrease in LVEF occurred in 26% of patients receiving COTELLIC with vemurafenib and 19% of patients receiving vemurafenib. The median time to first onset of LVEF decrease was 4 months (range 23 days to 13 months). Of the patients with decreased LVEF, 22% had dose interruption and/or reduction and 14% required permanent discontinuation. Decreased LVEF resolved to above the LLN or within 10% of baseline in 62% of patients receiving COTELLIC with a median time to resolution of 3 months (range: 4 days to 12 months).

Evaluate LVEF prior to initiation, 1 month after initiation, and every 3 months thereafter until discontinuation of COTELLIC. Manage events of left ventricular dysfunction through treatment interruption, reduction, or discontinuation [see *Dosage and Administration (2.3)*]. In patients restarting COTELLIC after a dose reduction or interruption, evaluate LVEF at approximately 2 weeks, 4 weeks, 10 weeks, and 16 weeks, and then as clinically indicated.

### **5.4 Severe Dermatologic Reactions**

Severe rash and other skin reactions can occur with COTELLIC.

In Trial 1, Grade 3 to 4 rash, occurred in 16% of patients receiving COTELLIC with vemurafenib and in 17% of patients receiving vemurafenib, including Grade 4 rash in 1.6% of patients receiving COTELLIC with vemurafenib and 0.8% of the patients receiving vemurafenib. The incidence of rash resulting in hospitalization was 3.2% in patients receiving COTELLIC with vemurafenib and 2.0% in patients receiving vemurafenib. In

patients receiving COTELLIC, the median time to onset of Grade 3 or 4 rash events was 11 days (range: 3 days to 2.8 months). Among patients with Grade 3 or 4 rash events, 95% experienced complete resolution with the median time to resolution of 21 days (range 4 days to 17 months).

Interrupt, reduce the dose, or discontinue COTELLIC [*see Dosage and Administration (2.3)*].

### **5.5 Serous Retinopathy and Retinal Vein Occlusion**

Ocular toxicities can occur with COTELLIC, including serous retinopathy (fluid accumulation under layers of the retina).

In Trial 1, ophthalmologic examinations including retinal evaluation were performed pretreatment and at regular intervals during treatment. Symptomatic and asymptomatic serous retinopathy was identified in 26% of patients receiving COTELLIC with vemurafenib. The majority of these events were reported as chorioretinopathy (13%) or retinal detachment (12%). The time to first onset of serous retinopathy events ranged between 2 days to 9 months. The reported duration of serous retinopathy ranged between 1 day to 15 months. One patient in each arm developed retinal vein occlusion.

Perform an ophthalmological evaluation at regular intervals and any time a patient reports new or worsening visual disturbances. If serous retinopathy is diagnosed, interrupt COTELLIC until visual symptoms improve. Manage serous retinopathy with treatment interruption, dose reduction, or with treatment discontinuation [*see Dosage and Administration (2.3)*].

### **5.6 Hepatotoxicity**

Hepatotoxicity can occur with COTELLIC.

The incidences of Grade 3 or 4 liver laboratory abnormalities in Trial 1 among patients receiving COTELLIC with vemurafenib compared to patients receiving vemurafenib were: 11% vs. 5% for alanine aminotransferase, 8% vs. 2.1% for aspartate aminotransferase, 1.6% vs. 1.2% for total bilirubin, and 7% vs. 3.3% for alkaline phosphatase [*see Adverse Drug Reactions (6.1)*]. Concurrent elevation in ALT >3 times the upper limit of normal (ULN) and bilirubin >2 X ULN in the absence of significant alkaline phosphatase >2 X ULN occurred in one patient (0.4%) receiving COTELLIC with vemurafenib and no patients receiving single-agent vemurafenib.

Monitor liver laboratory tests before initiation of COTELLIC and monthly during treatment, or more frequently as clinically indicated. Manage Grade 3 and 4 liver laboratory abnormalities with dose interruption, reduction, or discontinuation of COTELLIC [*see Dosage and Administration (2.3)*].

### **5.7 Rhabdomyolysis**

Rhabdomyolysis can occur with COTELLIC.

In Trial 1, Grade 3 or 4 CPK elevations, including asymptomatic elevations over baseline, occurred in 14% of patients receiving COTELLIC with vemurafenib and 0.5% of patients receiving vemurafenib. The median time to first occurrence of Grade 3 or 4 CPK elevations was 16 days (range: 12 days to 11 months) in patients receiving COTELLIC with vemurafenib; the median time to complete resolution was 15 days (range: 9 days to 11 months). Elevation of serum CPK increase of more than 10 times the baseline value with a concurrent increase in serum creatinine of 1.5 times or greater compared to baseline occurred in 3.6% of patients receiving COTELLIC with vemurafenib and in 0.4% of patients receiving vemurafenib.

Obtain baseline serum CPK and creatinine levels prior to initiating COTELLIC, periodically during treatment, and as clinically indicated. If CPK is elevated, evaluate for signs and symptoms of rhabdomyolysis or other causes. Depending on the severity of symptoms or CPK elevation, dose interruption or discontinuation of COTELLIC may be required [*see Dosage and Administration (2.3)*].

### **5.8 Severe Photosensitivity**

Photosensitivity, including severe cases, can occur with COTELLIC.



In Trial 1, photosensitivity was reported in 47% of patients receiving COTELLIC with vemurafenib: 43% of patients with Grades 1 or 2 photosensitivity and the remaining 4% with Grade 3 photosensitivity. Median time to first onset of photosensitivity of any grade was 2 months (range: 1 day to 14 months) in patients receiving COTELLIC with vemurafenib, and the median duration of photosensitivity was 3 months (range: 2 days to 14 months). Among the 47% of patients with photosensitivity reactions on COTELLIC with vemurafenib, 63% experienced resolution of photosensitivity reactions.

Advise patients to avoid sun exposure, wear protective clothing and use a broad-spectrum UVA/UVB sunscreen and lip balm (SPF  $\geq$ 30) when outdoors. Manage intolerable Grade 2 or greater photosensitivity with dose modifications [*see Dosage and Administration (2.3)*].

## 5.9 Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal reproduction studies, COTELLIC can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of cobimetinib in pregnant rats during the period of organogenesis was teratogenic and embryotoxic at doses resulting in exposures [area under the curves (AUCs)] that were 0.9 to 1.4-times those observed in humans at the recommended human dose of 60 mg. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with COTELLIC, and for 2 weeks following the final dose of COTELLIC [*see Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1)*].

## 6 ADVERSE REACTIONS

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

- New Primary Cutaneous Malignancies [*see Warnings and Precautions (5.1)*]
- Hemorrhage [*see Warnings and Precautions (5.2)*]
- Cardiomyopathy [*see Warnings and Precautions (5.3)*]
- Serious Dermatologic Reactions [*see Warnings and Precautions (5.4)*]
- Serous Retinopathy and Retinal Vein Occlusion [*see Warnings and Precautions (5.5)*]
- Hepatotoxicity [*see Warnings and Precautions (5.6)*]
- Rhabdomyolysis [*see Warnings and Precautions (5.7)*]
- Severe Photosensitivity [*see Warnings and Precautions (5.8)*]

### 6.1 Clinical Trials Experience

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

The safety of COTELLIC was evaluated in Trial 1, a randomized (1:1), double-blind, active-controlled trial in previously untreated patients with BRAF V600 mutation-positive, unresectable or metastatic melanoma [*see Clinical Studies (14)*]. All patients received vemurafenib 960 mg twice daily on Days 1–28 and received either COTELLIC 60 mg once daily (n=247) or placebo (n=246) on Days 1–21 of each 28-day treatment cycle until disease progression or unacceptable toxicity. In the COTELLIC plus vemurafenib arm, 66% percent of patients were exposed for greater than 6 months and 24% of patients were exposed for greater than 1 year. Patients with abnormal liver function tests, history of acute coronary syndrome within 6 months, evidence of Class II or greater congestive heart failure (New York Heart Association), active central nervous system lesions, or evidence of retinal pathology were excluded from Trial 1. The demographics and baseline tumor characteristics of patients enrolled in Trial 1 are summarized in Clinical Studies [*see Clinical Studies (14)*].

In Trial 1, 15% of patients receiving COTELLIC experienced an adverse reaction that resulted in permanent discontinuation of COTELLIC. The most common adverse reactions resulting in permanent discontinuation were liver laboratory abnormalities defined as increased aspartate aminotransferase (AST) (2.4%), increased

gamma glutamyltransferase (GGT) (1.6%) and increased alanine aminotransferase (ALT) (1.6%); rash (1.6%); pyrexia (1.2%); and retinal detachment (2%). Among the 247 patients receiving COTELLIC, adverse reactions led to dose interruption or reductions in 55%. The most common reasons for dose interruptions or reductions of COTELLIC were rash (11%), diarrhea (9%), chorioretinopathy (7%), pyrexia (6%), vomiting (6%), nausea (5%), and increased creatine phosphokinase (CPK) (4.9%). The most common ( $\geq 20\%$ ) adverse reactions with COTELLIC were diarrhea, photosensitivity reaction, nausea, pyrexia, and vomiting.

**Table 3. Incidence of Adverse Drug Reactions Occurring in  $\geq 10\%$  (All Grades) of Patients Receiving COTELLIC with Vemurafenib and at a Higher Incidence\* than Patients Receiving Vemurafenib in Trial 1**

Adverse reactions	COTELLIC + Vemurafenib (n=247)		Placebo + Vemurafenib (n=246)	
	All Grades <sup>a</sup> (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
<b>GASTROINTESTINAL DISORDERS</b>				
Diarrhea	60	6	31	1
Nausea	41	1	25	1
Vomiting	24	1	13	1
Stomatitis <sup>b</sup>	14	1	8	0
<b>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</b>				
Photosensitivity reaction <sup>c</sup>	46	4	35	0
Acneiform dermatitis	16	2	11	1
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>				
Pyrexia	28	2	23	0
Chills	10	0	5	0
<b>VASCULAR DISORDERS</b>				
Hypertension	15	4	8	2
Hemorrhage <sup>d</sup>	13	1	7	<1
<b>EYE DISORDERS</b>				
Vision impaired <sup>e</sup>	15	<1	4	0
Chorioretinopathy	13	<1	<1	0
Retinal detachment <sup>f</sup>	12	2	<1	0

\*  $\geq 5\%$  for All Grades or  $\geq 2\%$  for Grades 3–4 incidence in patients receiving COTELLIC with vemurafenib compared with patients receiving vemurafenib as a single agent

<sup>a</sup> NCI CTCAE, v4.0.

<sup>b</sup> Includes stomatitis, aphthous stomatitis, mouth ulceration, and mucosal inflammation

<sup>c</sup> Includes solar dermatitis, sunburn, photosensitivity reaction

<sup>d</sup> Includes hemorrhage, rectal hemorrhage, melena, hemorrhoidal hemorrhage, gastrointestinal hemorrhage, hematemesis, hematochezia, gingival bleeding, metrorrhagia, uterine hemorrhage, hemorrhagic ovarian cyst, menometrorrhagia, menorrhagia, vaginal hemorrhage, hemoptysis, pulmonary, cerebral, subarachnoid hemorrhage, subgaleal hematoma, hematuria, epistaxis, contusion, traumatic hematoma, ecchymosis, purpura, nail bed bleeding, ocular, eye, conjunctival, and retinal hemorrhage

<sup>e</sup> Includes vision blurred, visual acuity reduced, visual impairment

<sup>f</sup> Includes retinal detachment, detachment of retinal pigment epithelium, detachment of macular retinal pigment epithelium

Adverse reactions of vemurafenib which occurred at a lower rate in patients receiving COTELLIC plus vemurafenib were alopecia (15%), hyperkeratosis (11%), and erythema (10%).

The following adverse reactions (all grades) of COTELLIC were reported with  $<10\%$  incidence in Trial 1:

*Respiratory, thoracic and mediastinal disorders:* Pneumonitis

**Table 4. Incidence of Laboratory Abnormalities Occurring in  $\geq 10\%$  (All Grades) or  $\geq 2\%$  (Grades 3–4) of Patients in Trial 1\***

Laboratory	COTELLIC + Vemurafenib		Placebo + Vemurafenib	
	All Grades <sup>a</sup>	Grades 3–4 <sup>a</sup>	All Grades <sup>a</sup>	Grades 3–4 <sup>a</sup>
	%	%	%	%
<b>Chemistry</b>				
Increased creatinine	99.6	3.3	99.6	0.4
Increased AST	73	8	44	2.1
Increased ALT	68	11	55	5
Increased alkaline phosphatase	71	7	56	3.3
Increased creatine phosphokinase <sup>b</sup>	79	14	16	0.5
Hypophosphatemia	68	12	38	6
Increased GGT	65	21	61	17
Hyponatremia	38	6	33	2.1
Hypoalbuminemia	42	0.8	20	0.4
Hypokalemia	25	4.5	17	3.3
Hyperkalemia	26	2.9	15	0.4
Hypocalcemia	24	0.4	10	1.7
<b>Hematology</b>				
Anemia	69	2.5	57	3.3
Lymphopenia <sup>c</sup>	73	10	55	8
Thrombocytopenia	18	0	10	0

AST - aspartate aminotransferase, ALT - alanine aminotransferase, GGT - gamma-glutamyltransferase

\*All the percentages are based on the number of patients who had a baseline result and at least one on-study laboratory test.

The laboratory results are available for a total of 233~244 patients for COTELLIC, and 232~243 for vemurafenib, except where indicated.

<sup>a</sup> NCI CTCAE v4.0.

<sup>b</sup> Increase creatine phosphokinase, n=213 for COTELLIC and 217 for vemurafenib.

<sup>c</sup> Lymphopenia, n=185 for COTELLIC, and 181 for vemurafenib.

## 7 DRUG INTERACTIONS

### 7.1 Effect of Strong or Moderate CYP3A Inhibitors on Cobimetinib

Coadministration of COTELLIC with itraconazole (a strong CYP3A4 inhibitor) increased cobimetinib systemic exposure by 6.7-fold. Avoid concurrent use of COTELLIC and strong or moderate CYP3A inhibitors. If concurrent short term (14 days or less) use of moderate CYP3A inhibitors including certain antibiotics (e.g., erythromycin, ciprofloxacin) is unavoidable for patients who are taking COTELLIC 60 mg, reduce COTELLIC dose to 20 mg. After discontinuation of a moderate CYP3A inhibitor, resume COTELLIC at the previous dose [see *Dosage and Administration (2.3) and Clinical Pharmacology (12.3)*]. Use an alternative to a strong or moderate CYP3A inhibitor in patients who are taking a reduced dose of COTELLIC (40 or 20 mg daily) [see *Dosage and Administration (2.3) and Clinical Pharmacology (12.3)*].

### 7.2 Effect of Strong or Moderate CYP3A Inducers on Cobimetinib

Coadministration of COTELLIC with a strong CYP3A inducer may decrease cobimetinib systemic exposure by more than 80% and reduce its efficacy. Avoid concurrent use of COTELLIC and strong or moderate CYP3A inducers including but not limited to carbamazepine, efavirenz, phenytoin, rifampin, and St. John's Wort [see *Clinical Pharmacology (12.3)*].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Based on findings from animal reproduction studies and its mechanism of action, COTELLIC can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology (12.1)*]. There are no available data on the use of COTELLIC during pregnancy. In animal reproduction studies, oral administration of cobimetinib in pregnant rats during organogenesis was teratogenic and embryotoxic at exposures (AUC) that were 0.9 to 1.4-times those observed in humans at the recommended human dose of 60 mg [see *Data*]. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

#### Data

##### *Animal Data*

Administration of cobimetinib to pregnant rats during the period of organogenesis resulted in increased post-implantation loss, including total litter loss, at exposures (AUC) of 0.9–1.4 times those in humans at the recommended dose of 60 mg. Post-implantation loss was primarily due to early resorptions. Fetal malformations of the great vessels and skull (eye sockets) occurred at the same exposures.

### 8.2 Lactation

#### Risk Summary

There is no information regarding the presence of cobimetinib in human milk, effects on the breastfed infant, or effects on milk production. Because of the potential for serious adverse reactions in a breastfed infant, advise a nursing woman not to breastfeed during treatment with COTELLIC and for 2 weeks after the final dose.

### 8.3 Females and Males of Reproductive Potential

#### Contraception

##### *Females*

COTELLIC can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with COTELLIC and for 2 weeks after the final dose of COTELLIC.

#### Infertility

##### *Females and Males*

Based on findings in animals, COTELLIC may reduce fertility in females and males of reproductive potential [see *Nonclinical Toxicology (13.1)*].

### 8.4 Pediatric Use

The safety and effectiveness of COTELLIC have not been established in pediatric patients.

##### *Juvenile Animal Data*

In a 4-week juvenile rat toxicology study, daily oral doses of 3 mg/kg (approximately 0.13–0.5 times the adult human AUC at the recommended dose of 60 mg) between postnatal Days 10–17 (approximately equivalent to ages 1–2 years in humans) were associated with mortality, the cause of which was not defined.

## 8.5 Geriatric Use

Clinical studies of cobimetinib did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

## 8.6 Hepatic Impairment

Adjustment in the starting dose of COTELLIC is not required in patients with mild (Child-Pugh score A), moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment [see *Clinical Pharmacology (12.3)*].

## 8.7 Renal Impairment

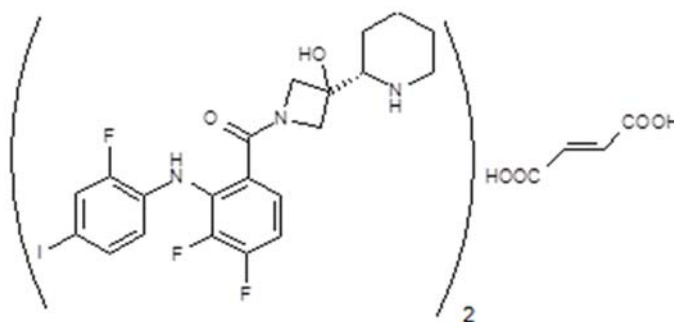
No dedicated pharmacokinetic trial in patients with renal impairment has been conducted. Dose adjustment is not recommended for mild to moderate renal impairment (CLcr 30 to 89 mL/min) based on the results of the population pharmacokinetic analysis. A recommended dose has not been established for patients with severe renal impairment [see *Clinical Pharmacology (12.3)*].

## 10 OVERDOSAGE

There is no information on overdosage of COTELLIC.

## 11 DESCRIPTION

Cobimetinib fumarate is a kinase inhibitor. The chemical name is (S)-[3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl] [3-hydroxy-3-(piperidin-2-yl)azetidin-1-yl]methanone hemifumarate. It has a molecular formula  $C_{46}H_{46}F_6I_2N_6O_8$  ( $2 C_{21}H_{21}F_3IN_3O_2 \cdot C_4H_4O_4$ ) with a molecular mass of 1178.71 as a fumarate salt. Cobimetinib fumarate has the following chemical structure:



Cobimetinib is a fumarate salt appearing as white to off-white solid and exhibits a pH dependent solubility.

COTELLIC (cobimetinib) tablets are supplied as white, round, film-coated 20 mg tablets for oral administration, debossed on one side with “COB”. Each 20 mg tablet contains 22 mg of cobimetinib fumarate, which corresponds to 20 mg of the cobimetinib free base.

The inactive ingredients of COTELLIC are: **Tablet Core:** microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate. **Coating:** polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Cobimetinib is a reversible inhibitor of mitogen-activated protein kinase (MAPK)/extracellular signal regulated kinase 1 (MEK1) and MEK2. MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes cellular proliferation. BRAF V600E and K mutations result in constitutive activation of the BRAF pathway which includes MEK1 and MEK2. In mice implanted with tumor cell lines expressing BRAF V600E, cobimetinib inhibited tumor cell growth.

Cobimetinib and vemurafenib target two different kinases in the RAS/RAF/MEK/ERK pathway. Compared to either drug alone, coadministration of cobimetinib and vemurafenib resulted in increased apoptosis in vitro

and reduced tumor growth in mouse implantation models of tumor cell lines harboring BRAF V600E mutations. Cobimetinib also prevented vemurafenib-mediated growth enhancement of a wild-type BRAF tumor cell line in an in vivo mouse implantation model.

## 12.2 Pharmacodynamics

### Cardiac Electrophysiology

Clinically relevant QT prolongation has been reported with vemurafenib, further QTc prolongation was not observed when cobimetinib 60 mg daily was co-administered with vemurafenib. Monitor ECG and electrolytes before initiating treatment and routinely during treatment with cobimetinib, when administered with vemurafenib. Review the Full Prescribing Information for vemurafenib for details.

## 12.3 Pharmacokinetics

The pharmacokinetics of cobimetinib was studied in healthy subjects and cancer patients. Cobimetinib exhibits linear pharmacokinetics in the dose range of 3.5 to 100 mg (i.e., 0.06 to 1.7 times the recommended dosage). Following oral administration of COTELLIC 60 mg once daily, steady-state was reached by 9 days with a mean accumulation ratio of 2.4-fold (44% CV).

### Absorption

Following oral dosing of 60 mg once daily in cancer patients, the median time to achieve peak plasma levels ( $T_{max}$ ) was 2.4 (range: 1–24) hours, geometric mean steady-state  $AUC_{0-24h}$  was 4340 ng·h/mL (61% CV) and  $C_{max}$  was 273 ng/mL (60% CV). The absolute bioavailability of COTELLIC was 46% (90% CI: 40%, 53%) in healthy subjects. A high-fat meal (comprised of approximately 150 calories from protein, 250 calories from carbohydrate, and 500–600 calories from fat) had no effect on cobimetinib AUC and  $C_{max}$  after a single 20 mg COTELLIC was administered to healthy subjects.

### Distribution

Cobimetinib is 95% bound to human plasma proteins in vitro, independent of drug concentration. No preferential binding to human red blood cells was observed (blood to plasma ratio of 0.93). The estimated apparent volume of distribution was 806 L in cancer patients based on a population PK analysis.

### Elimination

Following oral administration of COTELLIC 60 mg once daily in cancer patients, the mean elimination half-life ( $t_{1/2}$ ) was 44 (range: 23–70) hours and the mean apparent clearance (CL/F) was 13.8 L/h (61% CV).

### *Metabolism*

CYP3A oxidation and UGT2B7 glucuronidation were the major pathways of cobimetinib metabolism in vitro. Following oral administration of a single 20 mg radiolabeled cobimetinib dose, no oxidative metabolites >10% of total circulating radioactivity were observed.

### *Excretion*

Following oral administration of a single 20 mg radiolabeled cobimetinib dose, 76% of the dose was recovered in the feces (with 6.6% as unchanged drug) and 17.8% of the dose was recovered in the urine (with 1.6% as unchanged drug).

### Specific Populations

*Age, Sex, and Race/Ethnicity:* Based on the population pharmacokinetic analysis, age (19–88 years), sex, or race/ethnicity does not have a clinically important effect on the systemic exposure of cobimetinib.

### *Hepatic Impairment*

Following a single 10 mg COTELLIC dose, the geometric mean total cobimetinib exposure ( $AUC_{inf}$ ) values were similar in subjects with mild or moderate hepatic impairment and was decreased by 31% in subjects

with severe hepatic impairment compared to subjects with normal hepatic function. [see Use in Specific Populations (8.6)].

### *Renal Impairment*

Cobimetinib undergoes minimal renal elimination. Cobimetinib exposures were similar in 151 patients with mild renal impairment (CL<sub>cr</sub> 60 to 89 mL/min), 48 patients with moderate renal impairment (CL<sub>cr</sub> 30 to 59 mL/min) and 286 patients with normal renal function (CL<sub>cr</sub> ≥90 mL/min) [see Use in Specific Populations (8.7)].

### Drug Interaction Studies

*Vemurafenib:* Coadministration of COTELLIC 60 mg once daily and vemurafenib 960 mg twice daily resulted in no clinically relevant pharmacokinetic drug interactions.

*Effect of Strong and Moderate CYP3A Inhibitors on Cobimetinib:* In vitro studies show that cobimetinib is a substrate of CYP3A. Coadministration of itraconazole (a strong CYP3A inhibitor) 200 mg once daily for 14 days with a single 10 mg cobimetinib dose increased mean cobimetinib AUC (90% CI) by 6.7-fold (5.6, 8.0) and mean C<sub>max</sub> (90% CI) by 3.2-fold (2.7, 3.7) in 15 healthy subjects. Simulations showed that predicted steady-state concentrations of cobimetinib at a reduced dose of 20 mg administered concurrently with short-term (less than 14 days) treatment of a moderate CYP3A inhibitor were similar to observed steady-state concentrations of cobimetinib at the 60 mg dose alone [see Drug Interactions (7.1)].

*Effect of Strong and Moderate CYP3A Inducers on Cobimetinib:* Based on simulations, cobimetinib exposures would decrease by 83% when coadministered with a strong CYP3A inducer and by 73% when coadministered with a moderate CYP3A inducer [see Drug Interactions (7.2)].

*Effect of Cobimetinib on CYP Substrates:* Coadministration of cobimetinib 60 mg once daily for 15 days with a single 30 mg dose of dextromethorphan (sensitive CYP2D6 substrate) or a single 2 mg dose of midazolam (sensitive CYP3A substrate) to 20 patients with solid tumors did not change dextromethorphan or midazolam systemic exposure. In vitro data indicated that cobimetinib may inhibit CYP3A and CYP2D6. Cobimetinib at clinically relevant concentrations is not an inhibitor of CYP1A2, 2B6, 2C8, 2C9 and 2C19 or inducer of CYP1A2, 2B6 and 3A4.

*Effect of Transporters on Cobimetinib:* Cobimetinib is a substrate of efflux transporter P-glycoprotein (P-gp), but is not a substrate of Breast Cancer Resistance Protein (BCRP), Organic Anion Transporting Polypeptide (OATP1B1 or OATP1B3) or Organic Cation Transporter (OCT1) in vitro. Drugs that inhibit P-gp may increase cobimetinib concentrations.

*Effect of Cobimetinib on Transporters:* In vitro data suggest that cobimetinib at clinically relevant concentrations does not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OAT1, OAT3, or OCT2.

*Effect of Gastric Acid Reducing Drugs on Cobimetinib:* Coadministration of a proton pump inhibitor, rabeprazole 20 mg once daily for 5 days, with a single dose of 20 mg COTELLIC under fed and fasted conditions did not result in a clinically important change in cobimetinib exposure.

## **13 NONCLINICAL TOXICOLOGY**

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

Carcinogenicity studies with cobimetinib have not been conducted. Cobimetinib was not genotoxic in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells, and micronuclei in bone marrow of rats.

No dedicated fertility studies have been performed with cobimetinib in animals; however, effects on reproductive tissues observed in general toxicology studies conducted in animals suggest that there is potential for cobimetinib to impair fertility. In female rats, degenerative changes included increased apoptosis/necrosis of corpora lutea and vaginal epithelial cells at cobimetinib doses approximately twice those in humans at the clinically recommended dose of 60 mg based on body surface area. In male dogs, testicular degeneration

occurred at exposures as low as approximately 0.1 times the exposure in humans at the clinically recommended dose of 60 mg.

## 14 CLINICAL STUDIES

The safety and efficacy of cobimetinib was established in a multicenter, randomized (1:1), double-blinded, placebo-controlled trial conducted in 495 patients with previously untreated, BRAF V600 mutation-positive, unresectable or metastatic, melanoma. The presence of BRAF V600 mutation was detected using the cobas<sup>®</sup> 4800 BRAF V600 mutation test. All patients received vemurafenib 960 mg orally twice daily on days 1–28 and were randomized to receive COTELLIC 60 mg or matching placebo orally once daily on days 1–21 of an every 28-day cycle. Randomization was stratified by geographic region (North America vs. Europe vs. Australia/New Zealand/others) and disease stage (unresectable Stage IIIc, M1a, or M1b vs. Stage M1c). Treatment continued until disease progression or unacceptable toxicity. Patients randomized to receive placebo were not offered COTELLIC at the time of disease progression.

The major efficacy outcome was investigator-assessed progression-free survival (PFS) per RECIST v1.1. Additional efficacy outcomes were investigator-assessed confirmed objective response rate, overall survival, PFS as assessed by blinded independent central review, and duration of response.

The median age of the study population was 55 years (range 23 to 88 years), 58% of patients were male, 93% were White and 5% had no race reported, 60% had stage M1c disease, 72% had a baseline ECOG performance status of 0, 45% had an elevated baseline serum lactate dehydrogenase (LDH), 10% had received prior adjuvant therapy, and <1% had previously treated brain metastases. Patients with available tumor samples were retrospectively tested using next generation sequencing to further classify mutations as V600E or V600K; test results were obtained on 81% of randomized patients. Of these, 86% were identified as having a V600E mutation and 14% as having a V600K mutation.

Efficacy results are summarized in Table 5 and Figure 1.



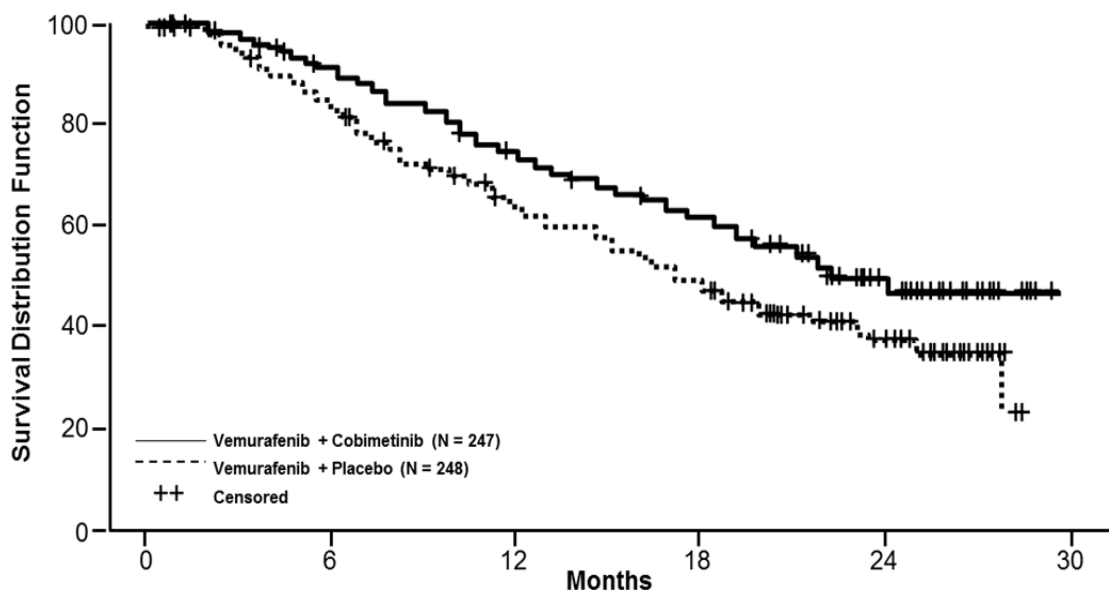
**Table 5 Efficacy Results from Trial 1**

	<b>COTELLIC + Vemurafenib (n=247)</b>	<b>Placebo + Vemurafenib (n=248)</b>
<b>Progression-Free Survival (Investigator-Assessed)</b>		
Number of Events (%)	143 (58%)	180 (73%)
Progression	131	169
Death	12	11
Median PFS, months (95% CI)	12.3 (9.5, 13.4)	7.2 (5.6, 7.5)
Hazard Ratio (95% CI)	0.56 (0.45, 0.70)	
p-value (stratified log-rank test)	<0.001	
<b>Overall Survival<sup>a</sup></b>		
Number of Deaths (%)	114 (46.2%)	141 (56.9%)
Median OS, months (95% CI)	22.3 (20.3, NE)	17.4 (15.0, 19.8)
Hazard Ratio (95% CI)	0.69 (0.54, 0.88)	
p -value (stratified log-rank test)	0.0032	
<b>Objective Response Rate</b>		
Objective Response Rate	70%	50%
(95% CI)	(64%, 75%)	(44%, 56%)
Complete Response	16%	10%
Partial Response	54%	40%
p-value	<0.001	
Median Duration of Response, months (95% CI)	13.0 (11.1, 16.6)	9.2 (7.5, 12.8)

CI - Confidence Intervals; NE - not estimable

<sup>a</sup> Based on the final overall survival analysis, conducted after 16 months from the PFS primary analysis

**Figure 1 Kaplan-Meier Curves of Overall Survival**



No. of patients at risk		0	6	12	18	24	30				
Vemurafenib + Cobimetinib	(N = 247)	247	232	210	192	169	152	139	107	48	14
Vemurafenib + Placebo	(N = 248)	248	230	194	165	142	126	106	71	41	11

The effect on PFS was also supported by analysis of PFS based on the assessment by blinded independent review. A trend favoring the cobimetinib with vemurafenib arm was observed in exploratory subgroup analyses of PFS, OS, and ORR in both BRAF V600 mutation subtypes (V600E or V600K) in the 81% of patients in this trial where BRAF V600 mutation type was determined.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

COTELLIC (cobimetinib) is supplied as 20 mg film-coated tablets debossed on one side with “COB”. COTELLIC tablets are available in bottles of 63 tablets.

NDC 50242-717-01

**Storage and Stability:** Store at room temperature below 30°C (86°F).

## 17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

Inform patients of the following:

**New primary cutaneous malignancies:** Advise patients to contact their health care provider immediately for change in or development of new skin lesions [see Warnings and Precautions (5.1)].

**Hemorrhage:** Instruct patients to contact their healthcare provider to seek immediate medical attention for signs or symptoms of unusual severe bleeding or hemorrhage [see Warnings and Precautions (5.2)].

**Cardiomyopathy:** Advise patients to report any history of cardiac disease and of the requirement for cardiac monitoring prior to and during COTELLIC administration. Instruct patients to immediately report any signs or symptoms of left ventricular dysfunction to their healthcare provider [see Warnings and Precautions (5.3)].

**Serious dermatologic reactions:** Instruct patients to contact their healthcare provider to immediately report severe skin changes [see Warnings and Precautions (5.4)].

**Serous retinopathy and retinal vein occlusion:** Instruct patients to immediately contact their healthcare

provider if they experience any changes in their vision [*see Warnings and Precautions (5.5)*].

Hepatotoxicity: Advise patients that treatment with COTELLIC requires monitoring of their liver function. Instruct patients to report any signs or symptoms of liver dysfunction [*see Warnings and Precautions (5.6)*].

Rhabdomyolysis: Instruct patients to report any signs and symptoms of muscle pain or weakness to their healthcare provider [*see Warnings and Precautions (5.7)*].

Severe photosensitivity: Advise patients to avoid sun exposure, wear protective clothing, and use broad spectrum UVA/UVB sunscreen and lip balm (SPF  $\geq$ 30) when outdoors [*see Warnings and Precautions (5.8)*].

Embryo-fetal toxicity: Advise females of reproductive potential of the potential risk to a fetus. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with COTELLIC [*see Warnings and Precautions (5.9), Use in Specific Populations (8.1)*].

Females of reproductive potential: Advise females of reproductive potential to use effective contraception during treatment with COTELLIC and for at least 2 weeks after the final dose of COTELLIC [*see Use in Specific Populations (8.3)*].

Lactation: Advise females not to breastfeed during treatment with COTELLIC and for 2 weeks after the final dose [*see Use in Specific Populations (8.2)*].

Distributed by:

**Genentech USA, Inc.**

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**PATIENT INFORMATION**  
**COTELLIC® (co-TELL-ic)**  
**(cobimetinib)**  
**tablet**

**Important:** If your healthcare provider prescribes vemurafenib, also read the Medication Guide that comes with vemurafenib.

**What is COTELLIC?**

COTELLIC is a prescription medicine that is used with the medicine vemurafenib, 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 COTELLIC is right for you.

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

**Before you take COTELLIC, tell your healthcare provider about all of your medical conditions, including if you:**

- have skin problems or history a of skin problems, other than melanoma
- have bleeding problems, any medical conditions and/or on any medications that increase your risk of bleeding
- have heart problems
- have eye problems
- have liver problems
- have muscle problems
- are pregnant or plan to become pregnant. COTELLIC can harm your unborn baby.
  - Females who are able to become pregnant should use effective birth control during treatment with COTELLIC and for 2 weeks after the final dose of COTELLIC.
  - 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 COTELLIC.
- are breastfeeding or plan to breastfeed. It is not known if COTELLIC passes into your breast milk. Do not breastfeed during treatment with COTELLIC 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. Certain medicines may affect the blood levels of COTELLIC.

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 COTELLIC?**

- Take COTELLIC exactly as your healthcare provider tells you. Do not change your dose or stop taking COTELLIC unless your healthcare provider tells you to.
- Take COTELLIC one time a day for 21 days, followed by 7 days off treatment, to complete a 28-day treatment cycle.
- Take COTELLIC with or without food.
- If you miss a dose of COTELLIC or vomit after taking your dose, take your next dose as scheduled.

**What should I avoid during treatment with COTELLIC?**

Avoid sunlight during treatment with COTELLIC. COTELLIC 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 COTELLIC?

### COTELLIC may cause serious side effects, including:

- **Risk of new skin cancers.** COTELLIC may cause new skin cancers (cutaneous squamous cell carcinoma, keratoacanthoma, or basal cell carcinoma).

#### Check your skin regularly and tell your healthcare provider right away if you have any skin changes including:

- 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 COTELLIC, and every 2 months during treatment with COTELLIC. Your healthcare provider may continue to check your skin for 6 months after you stop taking COTELLIC. Your healthcare provider should also check for cancers that may not occur on the skin. Tell our healthcare provider about any new symptoms that develop during treatment with COTELLIC and vemurafenib.

- **Bleeding problems.** COTELLIC can cause serious bleeding problems.

Call your healthcare provider and get medical attention right away if you get any signs of bleeding, including:

- red or black stools (looks like tar)
- blood in your urine
- headaches
- cough up or vomit blood
- stomach (abdominal) pain
- unusual vaginal bleeding
- dizziness or weakness

- **Heart problems.** Your healthcare provider should do tests before and during treatment to check your heart function. Tell your healthcare provider if you get any of these signs and symptoms of heart problems:

- persistent coughing or wheezing
- shortness of breath
- swelling of your ankles and feet
- tiredness
- increased heart rate

- **Severe rash.** Tell your healthcare provider right away if you get any of these symptoms:

- a rash that covers a large area of your body
- blisters
- peeling skin

- **Eye problems.** Tell your healthcare provider right away if you get any of these symptoms:

- blurred vision
- partly missing vision or loss of vision
- see halos
- any other vision changes

Your healthcare provider should check your eyes if you notice any of the symptoms above.

- **Liver problems.** Your healthcare provider should do blood tests to check your liver function before and during treatment. Tell your healthcare provider right away if you get any of these symptoms:

- yellowing of your skin or the white of your eyes
- dark or brown (tea color) urine
- nausea or vomiting
- feeling tired or weak
- loss of appetite

- **Muscle problems (rhabdomyolysis).** COTELLIC can cause muscle problems that can be severe. Treatment with COTELLIC may increase the level of an enzyme in your blood called creatine phosphokinase (CPK) and may be a sign of muscle damage. Your healthcare provider should do a blood test to check your levels of CPK before and during treatment. Tell your healthcare provider right away if you get any of these symptoms:

- muscle aches or pain
- muscle spasms and weakness
- dark, reddish urine

- **Skin Sensitivity to sunlight (photosensitivity).** Skin sensitivity to sunlight during treatment with COTELLIC is common and can sometimes be severe. Tell your healthcare provider if you get any of these symptoms:

- red, painful, itchy skin that is hot to touch
- sun rash
- skin irritation
- bumps or tiny papules
- thicken, dry, wrinkled skin

See “What should I avoid during treatment with COTELLIC?” for information on protecting your skin during treatment with COTELLIC.

The most common side effects of COTELLIC include:

- diarrhea
- nausea
- fever
- vomiting

Your healthcare provider will take blood tests during treatment with COTELLIC. The most common changes to blood tests include:

- increased blood levels of liver enzymes (GGT, ALT, or AST)
- increased blood level of enzyme from muscle (creatine phosphokinase)
- decreased blood level of phosphate, sodium or potassium
- increased blood level of liver or bone enzyme (alkaline phosphatase)
- decreased blood level of a type of white blood cell (lymphocyte)

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 COTELLIC.

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 COTELLIC?**

- Store COTELLIC at room temperature below 30°C (86°F).
- Ask your healthcare provider or pharmacist how to safely throw away (dispose of) any unused or expired COTELLIC.

**Keep COTELLIC and all medicine out of the reach of children.**

**General information about the safe and effective use of COTELLIC**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use COTELLIC for a condition for which it was not prescribed. Do not give COTELLIC to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about COTELLIC that is written for health professionals.

**What are the ingredients in COTELLIC?**

**Active ingredient:** cobimetinib fumarate

**Inactive ingredients:**

**Tablet Core:** microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate

**Coating:** polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc

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This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: May 2016

## 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

#### 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. (1.1, 2.1)
- ZELBORAF® is indicated for the treatment of patients with Erdheim-Chester Disease with BRAF V600 mutation. (1.2, 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).
- Dupuytren's Contracture and plantar fascial fibromatosis: Events should be managed with dose reduction, treatment interruption, or treatment discontinuation. (5.12).

#### ADVERSE REACTIONS

Melanoma: Most common adverse reactions ( $\geq 30\%$ ) are arthralgia, rash, alopecia, fatigue, photosensitivity reaction, nausea, pruritus, and skin papilloma. (6.1)

Erdheim-Chester Disease: Most common adverse reactions ( $>50\%$ ) are arthralgia, rash maculo-papular, alopecia, fatigue, electrocardiogram QT interval prolonged, and skin papilloma. (6.1)

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

#### DRUG INTERACTIONS

- 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: 05/2020

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Unresectable or Metastatic Melanoma

ZELBORAF<sup>®</sup> 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)*].

#### 1.2 Erdheim-Chester Disease

ZELBORAF<sup>®</sup> is indicated for the treatment of patients with Erdheim-Chester Disease (ECD) with BRAF V600 mutation.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Patient Selection for Treatment of Melanoma

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

#### 2.2 Recommended Dose

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

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

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

Do not crush or chew the tablets.

#### 2.3 Dose Modifications

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

*For Other Adverse Reactions:*

Permanently discontinue ZELBORAF for any of the following:

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

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

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

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

Do not dose reduce to below 480 mg twice daily.

#### 2.4 Dose Modification for Strong CYP3A4 Inducers

Avoid concomitant use of strong CYP3A4 inducers during treatment with ZELBORAF [see *Drug Interactions (7.1) and Clinical Pharmacology (12.3)*]. If concomitant use of a strong CYP3A4 inducer is unavoidable, increase the dose of ZELBORAF by 240 mg (one tablet) as tolerated. After discontinuation of a strong CYP3A4 inducer for two weeks, resume the ZELBORAF dose that was taken prior to initiating the strong CYP3A4 inducer.

### **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 ( $\geq 65$  years), prior skin cancer, and chronic sun exposure.

In Trial 4, in patients with ECD, the incidence of cuSCC and/or keratoacanthomas was 40.9% (9/22). The median time to first appearance of cuSCC amongst patients with at least one occurrence was 12.1 weeks.

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

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

##### *Non-Cutaneous Squamous Cell Carcinoma*

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

##### *Other Malignancies*

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

Cases of myeloid neoplasms amongst patients with ECD have been observed, including in patients who have received ZELBORAF. Monitoring complete blood count in ECD patients with co-existing myeloid malignancies is recommended.

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

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

#### **5.3 Hypersensitivity Reactions**

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

## 5.4 Dermatologic Reactions

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

## 5.5 QT Prolongation

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

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

Withhold ZELBORAF in patients who develop QTc > 500 ms (Grade 3). Upon recovery to QTc ≤ 500 ms (Grade ≤ 2), restart at a reduced dose. Permanently discontinue ZELBORAF treatment if the QTc interval remains > 500 ms and increased > 60 ms from pre-treatment values after controlling cardiac risk factors for QT prolongation (e.g., electrolyte abnormalities, congestive heart failure, and bradyarrhythmias) [see *Dosage and Administration (2.3)*].

## 5.6 Hepatotoxicity

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

### *Concurrent Administration with Ipilimumab*

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

## 5.7 Photosensitivity

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

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

## 5.8 Ophthalmologic Reactions

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

## 5.9 Embryo-Fetal Toxicity

Based on its mechanism of action, ZELBORAF can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to

use effective contraception during treatment with ZELBORAF and for 2 weeks after the final dose [see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)].

### **5.10 Radiation Sensitization and Radiation Recall**

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

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

### **5.11 Renal Failure**

Renal failure, including acute interstitial nephritis and acute tubular necrosis, can occur with ZELBORAF. In Trial 1, in patients with metastatic melanoma, 26% of ZELBORAF-treated patients and 5% of dacarbazine-treated patients experienced Grade 1-2 creatinine elevations [greater than 1 and up to 3 times upper limit of normal (ULN)]; 1.2% of ZELBORAF-treated patients and 1.1% of dacarbazine-treated patients experienced Grade 3-4 creatinine elevations (greater than 3 times ULN).

In Trial 4, in patients with ECD, 86% (19/22) of patients experienced Grade 1/2 creatinine elevations and 9.1% (2/22) of patients experienced Grade 3 creatinine elevations.

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

### **5.12 Dupuytren's Contracture and Plantar Fascial Fibromatosis**

Dupuytren's contracture and plantar fascial fibromatosis have been reported with ZELBORAF. The majority of cases were mild to moderate, but severe, disabling cases of Dupuytren's contracture have also been reported [see Dosage and Administration (2.3), Adverse Reactions (6.1, 6.2)].

## **6 ADVERSE REACTIONS**

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

- New Primary Malignancies [see Warnings and Precautions (5.1)]
- Hypersensitivity Reactions [see Warnings and Precautions (5.3)]
- Dermatologic Reactions [see Warnings and Precautions (5.4)]
- QT Prolongation [see Warnings and Precautions (5.5)]
- Hepatotoxicity [see Warnings and Precautions (5.6)]
- Photosensitivity [see Warnings and Precautions (5.7)]
- Ophthalmologic Reactions [see Warnings and Precautions (5.8)]
- Radiation Sensitization and Radiation Recall [see Warnings and Precautions (5.10)]
- Renal Failure [see Warnings and Precautions (5.11)]
- Dupuytren's Contracture and Plantar Fascial Fibromatosis [see Warnings and Precautions (5.12)]

### **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.

**Unresectable or Metastatic Melanoma with BRAF V600E Mutation** 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-naïve patients with unresectable or metastatic melanoma to receive ZELBORAF 960 mg orally twice daily or dacarbazine 1000 mg/m<sup>2</sup> 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 unresectable or metastatic melanoma patients treated with ZELBORAF. The most common adverse reactions of any grade ( $\geq 30\%$  in either study) in ZELBORAF-treated patients were arthralgia, rash, alopecia, fatigue, photosensitivity reaction, nausea, pruritus, and skin papilloma. The most common ( $\geq 5\%$ ) Grade 3 adverse reactions were cuSCC and rash. The incidence of Grade 4 adverse reactions was  $\leq 4\%$  in both studies.

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

**Table 1 Adverse Reactions Reported in  $\geq 10\%$  of Unresectable or Metastatic Melanoma 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 <sup>a</sup> (%)	All Grades (%)	Grade 3 (%)	All Grades (%)	Grade 3 <sup>a</sup> (%)
<b>Skin and subcutaneous tissue disorders</b>						
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
<b>Musculoskeletal and connective tissue disorders</b>						
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
<b>General disorders and administration site conditions</b>						
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
<b>Gastrointestinal disorders</b>						
Nausea	35	2	43	2	37	2
Diarrhea	28	< 1	13	< 1	29	< 1
Vomiting	18	1	26	1	26	2
Constipation	12	< 1	24	0	16	0
<b>Nervous system disorders</b>						
Headache	23	< 1	10	0	27	0
Dysgeusia	14	0	3	0	11	0
<b>Neoplasms benign, malignant and unspecified (includes cysts and polyps)</b>						
Skin papilloma	21	< 1	0	0	30	0
Cutaneous SCC <sup>†#</sup>	24	22	< 1	< 1	24	24
Seborrheic keratosis	10	< 1	1	0	14	0
<b>Investigations</b>						

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 <sup>a</sup> (%)	All Grades (%)	Grade 3 (%)	All Grades (%)	Grade 3 <sup>a</sup> (%)
Gamma-glutamyltransferase increased	5	3	1	0	15	6
<b>Metabolism and nutrition disorders</b>						
Decreased appetite	18	0	8	< 1	21	0
<b>Respiratory, thoracic and mediastinal disorders</b>						
Cough	8	0	7	0	12	0
<b>Injury, poisoning and procedural complications</b>						
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.

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

<sup>†</sup> Includes both squamous cell carcinoma of the skin and keratoacanthoma.

<sup>#</sup> Cases of cutaneous squamous cell carcinoma were required to be reported as Grade 3 per protocol.

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

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

*Musculoskeletal and connective tissue disorders:* arthritis, Dupuytren's contracture

*Nervous system disorders:* neuropathy peripheral, VII<sup>th</sup> 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 in Trial 1\***

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.

### *Erdheim-Chester Disease (ECD)*

This section describes adverse reactions identified from analyses of Trial 4 [see *Clinical Studies (14)*]. In Trial 4, 22 patients with BRAF V600 mutation-positive ECD received ZELBORAF 960 mg twice daily.

The median treatment duration for ECD patients in this study was 14.2 months. Table 3 presents adverse reactions reported in at least 20% of BRAF V600 mutation-positive ECD patients treated with ZELBORAF.

In Trial 4, the most commonly reported adverse reactions (> 50%) in patients with BRAF V600 mutation-positive ECD treated with ZELBORAF were arthralgia, rash maculo-papular, alopecia, fatigue, electrocardiogram QT interval prolonged, and skin papilloma. The most common ( $\geq 10\%$ ) Grade  $\geq 3$  adverse reactions were squamous cell carcinoma of the skin, hypertension, rash maculo-papular, and arthralgia.

The incidence of adverse reactions resulting in permanent discontinuation of study medication was 32%.

**Table 3 Adverse Reactions Reported in  $\geq 20\%$  of ECD Patients Treated with ZELBORAF\***

<b>Trial 4: Patients with ECD</b>		
	<b>n=22</b>	
<b>Body System Adverse Reactions</b>	<b>All Grades (%)</b>	<b>Grade 3-4 (%)</b>
<b>Skin and subcutaneous tissue disorders</b>		
Rash maculo-papular	59	18
Alopecia	55	-
Hyperkeratosis	50	5
Dry skin	45	-
Photosensitivity reaction	41	-
Palmar-plantar erythrodysesthesia syndrome	41	-
Pruritus	36	-
Actinic keratosis	32	5
Keratosis pilaris	32	-
Rash papular	23	-
<b>Musculoskeletal and connective tissue disorders</b>		
Arthralgia	82	14
<b>General disorders and administration site conditions</b>		
Fatigue	55	5
<b>Gastrointestinal disorders</b>		
Diarrhea	50	-
Nausea	32	-
Vomiting	23	-
<b>Nervous system disorders</b>		
Peripheral sensory neuropathy	36	-
<b>Neoplasms benign, malignant and unspecified (incl. cysts and polyps)</b>		
Skin papilloma	55	-
Seborrhoeic keratosis	41	-
SCC of skin <sup>#</sup>	36	36
Melanocytic nevus	23	-
<b>Cardiac disorders</b>		
Electrocardiogram QT interval prolonged	55	5
<b>Respiratory, thoracic and mediastinal disorders</b>		
Cough	36	-
<b>Vascular disorders</b>		
Hypertension	36	23
<b>Injury, poisoning and procedural complications</b>		
Sunburn	23	-

\* Adverse drug reactions, graded using NCI-CTCAE v 4.0 (NCI common toxicity criteria) for assessment of toxicity.

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

Clinically relevant adverse reactions reported in < 20% of ECD patients treated with ZELBORAF in Trial 4 include:

*Neoplasms benign, malignant and unspecified (includes cysts and polyps):* keratoacanthoma

*Musculoskeletal and connective tissue disorders:* Dupuytren's contracture

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

**Table 4 Change from Baseline to Grade 3 Liver Laboratory Abnormalities in Trial 4**

Parameter	Change From Baseline to Grade 3
	Vemurafenib (%)
AST	0
ALT	9.1
Alkaline phosphatase	4.5
Bilirubin	0

## 6.2 Postmarketing Experience

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

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

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

*Blood and lymphatic systems disorder:* Neutropenia

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

*Gastrointestinal disorders:* Pancreatitis

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

*Musculoskeletal and connective tissue disorders:* Dupuytren's contracture and plantar fascial fibromatosis [see *Warnings and Precautions (5.12)*].

## 7 DRUG INTERACTIONS

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

#### Strong CYP3A4 Inhibitors

Coadministration of a strong CYP3A4 inhibitor increased vemurafenib plasma concentrations and may lead to increased toxicity. Avoid coadministration of ZELBORAF with strong CYP3A4 inhibitors. If coadministration of a strong CYP3A4 inhibitor is unavoidable, consider dose reduction of ZELBORAF, if clinically indicated. [see *Dosage and Administration (2.3), Clinical Pharmacology (12.3)*].

#### Strong CYP3A4 Inducers



Coadministration of ZELBORAF with rifampin, a strong CYP3A4 inducer, decreased vemurafenib plasma concentrations and may result in decreased efficacy. Avoid coadministration of ZELBORAF with strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin), and replace these drugs with alternative drugs when possible. If coadministration of a strong CYP3A4 inducer is unavoidable, increase the dose of ZELBORAF by 240 mg (one tablet) as tolerated [*see Dosage and Administration (2.4), Clinical Pharmacology (12.3)*].

### **7.2 Effect of Vemurafenib on CYP1A2 Substrates**

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

### **7.3 Concurrent Ipilimumab**

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

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

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

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

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

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

#### Data

##### *Animal Data*

Vemurafenib showed no evidence of developmental toxicity in rat fetuses at doses up to 250 mg/kg/day (approximately 1.3 times the clinical exposure at 960 mg twice daily based on AUC) or rabbit fetuses at doses up to 450 mg/kg/day (approximately 0.6 times the clinical exposure at 960 mg twice daily 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.

### **8.2 Lactation**

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

### 8.3 Females and Males of Reproductive Potential

#### Contraception

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

#### 8.4 Pediatric Use

The safety and effectiveness of ZELBORAF in pediatric patients have not been established. Vemurafenib was studied in 6 adolescent patients 15 to 17 years of age with unresectable or metastatic melanoma with BRAF V600 mutation. A maximum tolerated dose was not reached with doses up to vemurafenib 960 mg twice daily. No new safety signals were observed. Vemurafenib steady-state exposure in these 6 adolescent patients was generally similar to that in adults.

#### 8.5 Geriatric Use

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

#### 8.6 Hepatic Impairment

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

#### 8.7 Renal Impairment

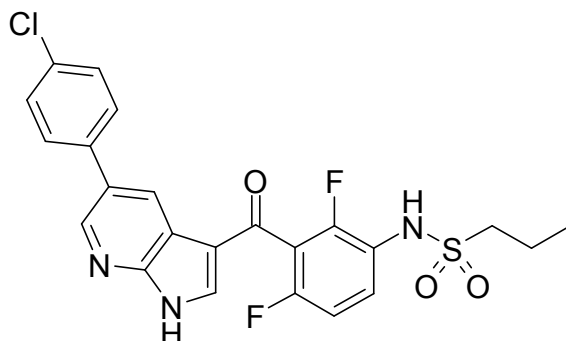
No formal clinical study has been conducted to evaluate the effect of renal impairment on the pharmacokinetics of vemurafenib. No dose adjustment is recommended for patients with mild and moderate renal impairment based on a population pharmacokinetic analysis [see *Clinical Pharmacology (12.3)*]. The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

### 10 OVERDOSAGE

There is no information on overdosage of ZELBORAF.

### 11 DESCRIPTION

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



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

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

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

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

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

### 12.2 Pharmacodynamics

#### *Cardiac Electrophysiology*

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

### 12.3 Pharmacokinetics

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

#### Absorption

The mean bioavailability of vemurafenib at steady state was 64% (56% CV). The median time to reach maximum plasma vemurafenib concentration ( $T_{max}$ ) was 3 hours following multiple doses.

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 accumulation ratio estimate from the population pharmacokinetic analysis for the twice daily regimen is 7.4, with steady-state achieved at approximately 15 to 22 days.

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

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

#### Distribution

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

#### Metabolism

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

### Specific Populations

*Hepatic Impairment:* The pharmacokinetics of vemurafenib were examined in patients with metastatic melanoma enrolled in the clinical trials with normal hepatic function ( $n=158$ , total bilirubin  $\leq$  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 ( $\text{CLcr} \geq 90$  mL/min) and mild ( $n=94$ ,  $\text{CLcr} > 60$  to 89 mL/min), moderate ( $n=11$ ,  $\text{CLcr}$  30 to 59 mL/min) or severe ( $n=1$ ,  $\text{CLcr} < 29$  mL/min) renal impairment. Patients received vemurafenib 960 mg orally twice daily. The apparent clearance of vemurafenib in patients with mild and moderate renal impairment was similar to that in patients with normal renal function. The appropriate dose for patients with severe renal impairment cannot be determined as clinical and pharmacokinetic data were available for only one patient [see Use in Specific Populations (8.7)].

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

### Drug Interaction Studies

*Effect of Strong CYP3A4 Inhibitors:* Coadministration of 960 mg ZELBORAF twice daily with once daily doses of 200 mg itraconazole, a strong CYP3A4 inhibitor, increased steady state vemurafenib  $\text{AUC}_{0-\tau}$  by 40% (90% CI: 21%, 61%) with a similar magnitude of increase in  $C_{\text{max}}$  [see Drug Interactions (7.1)].

*Effect of Strong CYP3A4 Inducers:* Coadministration of 600 mg daily doses of rifampin (a strong CYP3A inducer) with a single 960 mg dose of ZELBORAF decreased vemurafenib AUC by 40% (90% CI: 24%, 53%) with no effect on  $C_{\text{max}}$ , relative to a 960 mg dose of ZELBORAF administered alone [see Dosage and Administration (2.4), Drug Interactions (7.1)].

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

Coadministration of tizanidine 2 mg (a sensitive CYP1A2 substrate) on day 21 with vemurafenib which was administered 960 mg twice daily for 21 days increased tizanidine  $\text{AUC}_{\text{inf}}$  by 4.7-fold (90% CI: 3.6, 6.3) and  $C_{\text{max}}$  by 2.2-fold (90% CI: 1.7, 2.7) in 16 cancer patients [see Drug Interactions (7.2)]. In an in vivo phenotypic cocktail drug-drug interaction study in patients with cancer, a single dose of the CYP probe substrate cocktail (for CYP1A2, 2D6, 3A4, 2C19 and 2C9) was administered before and concomitantly with vemurafenib (following 15 days of dosing at 960 mg twice daily). Coadministration of vemurafenib increased the mean AUC of caffeine (CYP1A2 substrate) by 2.6-fold [see Drug Interactions (7.2)]. Coadministration of vemurafenib increased the mean AUC of dextromethorphan (CYP2D6 substrate) by 47% and the AUC of S-warfarin (CYP2C9 substrate) by 18%, while it decreased the mean AUC of midazolam (CYP3A4 substrate) by 39%. Coadministration of vemurafenib did not change the mean systemic exposure to omeprazole (CYP2C19 substrate).

*Effect of Vemurafenib on Transporters:* In vitro studies suggest that vemurafenib is both a substrate and an inhibitor of the efflux transporters P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP).

Administration of vemurafenib 960 mg twice daily for 22 days increased digoxin AUC by 1.8-fold (90% CI:1.6, 2.0) and C<sub>max</sub> by 1.5-fold (90% CI:1.3, 1.7) in 26 cancer patients who were coadministered a single dose of digoxin 0.25 mg (sensitive P-gp substrate) [see *Drug Interactions (7.4)*].

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

#### 13.2 Animal Toxicology and/or Pharmacology

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

### 14 CLINICAL STUDIES

#### *Treatment-Naïve Patients with BRAF V600E Mutation-Positive Unresectable or Metastatic Melanoma*

Trial 1, an international, open-label, randomized controlled trial, equally allocated 675 patients with treatment-naïve, BRAF V600E mutation-positive unresectable or metastatic melanoma, as detected by the cobas<sup>®</sup> 4800 BRAF V600 Mutation Test, to receive ZELBORAF 960 mg by mouth twice daily (n=337) or dacarbazine 1000 mg/m<sup>2</sup> 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 5 and Figure 1 summarize the efficacy results.

**Table 5 Efficacy of ZELBORAF in Treatment-Naïve Patients with BRAF V600E Mutation-Positive Melanoma<sup>a</sup>**

	ZELBORAF (n=337)	Dacarbazine (n=338)	p-value <sup>f</sup>
<b>Overall Survival</b>			
Number of Deaths <sup>b</sup>	78 (23%)	122 (36%)	
Hazard Ratio (95% CI) <sup>c</sup>	0.47 (0.35, 0.62)		< 0.0001
Updated Median Survival (months) (95 % CI) <sup>d, e</sup>	13.6 (12.0, 15.3)	10.3 (9.1, 12.8)	-

Progression-Free Survival			
Hazard Ratio (95% CI) <sup>c</sup>	0.26 (0.20, 0.33)		< 0.0001
Median PFS (months) (95% CI) <sup>d</sup>	5.3 (4.9, 6.6)	1.6 (1.6, 1.7)	-

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

<sup>b</sup> Total of 200 deaths (ZELBORAF median follow-up 6.2 months)

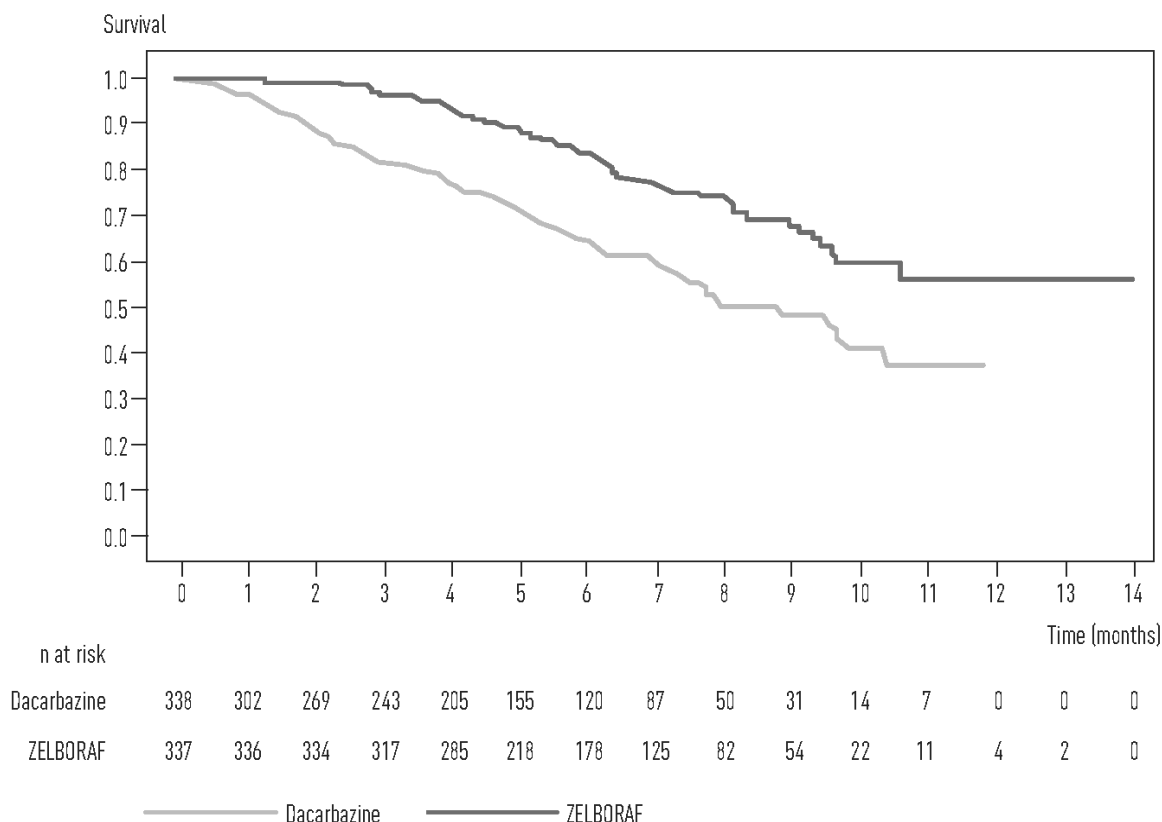
<sup>c</sup> Hazard ratio estimated using Cox model; a hazard ratio of < 1 favors ZELBORAF

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

<sup>e</sup> Updated based on 478 deaths (ZELBORAF median follow-up 13.4 months)

<sup>f</sup> Unstratified log-rank test

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



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

***Patients with BRAF V600E Mutation-Positive Metastatic Melanoma 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<sup>®</sup> 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  $\geq 2$  prior therapies. The median duration of follow-up was 6.87 months (range, 0.6 to 11.3).

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

***Patients with BRAF V600E Mutation-Positive Melanoma with Brain Metastases***

The activity of ZELBORAF for the treatment of BRAF V600E mutation-positive melanoma, metastatic to the brain was evaluated in an open-label, multicenter, single-arm, two cohort trial (Trial 3). All patients received ZELBORAF 960 mg orally twice daily until disease progression or unacceptable toxicity. Patients were required to have at least one measurable brain lesion of 0.5 cm or greater on contrast-enhanced MRI, a stable or decreasing corticosteroid dose and no prior treatment with a BRAF or MEK inhibitor. Patients in Cohort A had received no prior local therapy for brain metastases. Patients in Cohort B had received at least one prior local therapy for brain metastases (surgical resection, whole brain radiotherapy, or stereotactic radiotherapy) with CNS progression following this therapy. Patients were followed until death, disease progression, withdrawal, or up to 24 months. The primary efficacy outcome measure was the confirmed best overall response rate in the brain in Cohort A, as assessed by an independent radiology review committee using Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Secondary efficacy outcome measures included duration of response in Cohort A, and confirmed best overall response rate and duration of response in Cohort B.

A total of 146 patients (Cohort A: n=90; Cohort B: n=56) were enrolled and received at least one dose of ZELBORAF. In Cohort A, the median age of patients was 56 years, 62% were male, 47% had a pre-treatment ECOG performance status (PS) of 0, 57% had an elevated LDH value at baseline, and 20% received one or more systemic regimens for the treatment of metastatic disease. In Cohort B, the median age of patients was 53 years, 61% were male, 38% had a pre-treatment ECOG PS of 0, 55% had an elevated LDH value at baseline, and 39% received one or more systemic regimens for the treatment of metastatic disease. All patients enrolled on Trial 3 whose race was identified were White. The efficacy results are summarized in Table 6.

**Table 6 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 <sup>a</sup>	18% (11%, 27%)	18% (9%, 30%)
Complete response	2%	0
Partial response	16%	18%
Median of Duration of Response, months (95%CI <sup>b</sup> )	4.6 (2.9, 6.2)	6.6 (2.8, 10.7)

<sup>a</sup> Two-sided 95% Clopper-Pearson Confidence Interval (CI)

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

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

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

***Patients with Erdheim-Chester Disease (ECD)***

An open-label, multicenter, single-arm, multiple cohort study of ZELBORAF (Trial 4) was conducted in patients ≥ 16 years of age with non-melanoma BRAF V600 mutation-positive diseases.

The trial included 22 patients with ECD. Fifteen patients (68.2%) had received prior systemic therapies. The median age was 58.5 years (range, 34 to 77 years). Fifty-five percent of patients were men.

All 22 patients received a starting dose of 960 mg orally twice daily with or without food. For 8 patients, the dose was reduced to 720 mg twice daily. For the remaining 14 patients, the dose was ultimately reduced to 480 mg. The median duration of treatment following a dose reduction to 720 mg was 77 days (range, 4 to 1325) and to 480 mg was 236 days (range, 21 to 924). The efficacy was maintained in these patients based on the overall response rate.

The efficacy of ZELBORAF in ECD was based on best overall response rate maintained on two occasions at least four weeks apart, as assessed by the investigator using RECIST v 1.1, and is presented in Table 7 below. The median duration of follow up was 26.6 months in ECD patients (range, 3.0 to 44.3 months). The median time to response was 11 months (95% CI: 3.7, 14.6). The median DOR was not estimable.

**Table 7 Efficacy of ZELBORAF in patients with ECD (investigator assessed)**

	N=22
Overall Response	
Responders (n [%])	12 (54.5%)
(95% CI) <sup>a</sup>	(32.2, 75.6)
Complete Response (CR)	1 (4.5%)
Partial Response (PR)	11 (50%)

<sup>a</sup> 95% Confidence Interval (CI) constructed using Clopper-Pearson method

## 16 HOW SUPPLIED/STORAGE AND HANDLING

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

NDC 50242-090-01 single bottle of 120 count

NDC 50242-090-02 single bottle of 112 count

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

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

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

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

- Evidence of BRAF V600E mutation in the tumor specimen with an FDA approved test is necessary to identify patients with melanoma for whom treatment with ZELBORAF is indicated [see *Dosage and Administration (2.1)*].
- ZELBORAF increases the risk of developing new primary cutaneous malignancies. Advise patients of the importance of contacting their healthcare provider immediately for any changes in their skin [see *Warnings and Precautions (5.1)*].



- Anaphylaxis and other serious hypersensitivity reactions can occur during treatment and upon re-initiation of treatment with ZELBORAF. Advise patients to stop taking ZELBORAF and to seek immediate medical attention for symptoms of anaphylaxis or hypersensitivity [*see Warnings and Precautions (5.3)*].
- Severe dermatologic reactions can occur in patients receiving ZELBORAF. Advise patients to stop taking ZELBORAF and to contact their health-care provider for severe dermatologic reactions [*see Warnings and Precautions (5.4)*].
- ZELBORAF can prolong QT interval, which may result in ventricular arrhythmias. Advise patients of the importance of monitoring of their electrolytes and the electrical activity of their heart (via an ECG) during ZELBORAF treatment [*see Warnings and Precautions (5.5)*].
- Liver injury leading to functional hepatic impairment, including coagulopathy or other organ dysfunction, can occur with ZELBORAF. Advise patients of the importance of laboratory monitoring of their liver during ZELBORAF treatment and to contact their health-care provider for relevant symptoms [*see Warnings and Precautions (5.6)*].
- ZELBORAF can cause mild to severe photosensitivity. Advise patients to avoid sun exposure, wear protective clothing, and use a broad spectrum UVA/UVB sunscreen and lip balm (SPF  $\geq$  30) when outdoors to help protect against sunburn [*see Warnings and Precautions (5.7)*].
- Ophthalmologic reactions can occur in patients treated with ZELBORAF. Advise patients to contact their health-care provider immediately for ophthalmologic symptoms [*see Warnings and Precautions (5.8)*].

#### Embryo-fetal Toxicity

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

#### Lactation

- Advise a woman not to breastfeed during treatment with ZELBORAF and for 2 weeks after the final dose [*see Use in Specific Populations (8.2)*].
- Radiation sensitization and recall can occur in patients treated with radiation prior to, during, or subsequent to ZELBORAF treatment. Advise patients to inform their health care provider if they have had or are planning to receive radiation therapy [*see Warnings and Precautions (5.10), Adverse Reactions (6.2)*].
- Renal failure can occur in patients treated with ZELBORAF. Advise patients of the importance of monitoring serum creatinine prior to and during ZELBORAF treatment [*see Warnings and Precautions (5.11), Adverse Reactions (6.2)*].
- Advise patients to contact their health care provider for symptoms of Dupuytren's contracture or plantar fascial fibromatosis [*see Warnings and Precautions (5.12)*].

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

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