

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr COTELLIC[®]

cobimetinib tablets

20 mg cobimetinib (as cobimetinib fumarate)

Protein Kinase Inhibitor

Hoffmann-La Roche Limited

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Pr COTELLIC®

cobimetinib tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
oral	tablet / 20 mg cobimetinib (as cobimetinib fumarate)	lactose monohydrate <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

COTELLIC® (cobimetinib) is indicated for use in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

Prior to initiation of treatment with COTELLIC in combination with vemurafenib, patients must have BRAF V600 mutation-positive melanoma tumour status confirmed by a validated test.

Clinical data supporting the effectiveness of COTELLIC in combination with vemurafenib in patients with a BRAF V600K mutation are limited (see PART II, CLINICAL TRIALS). There are no clinical data for other less common BRAF V600 mutations.

There are no clinical data to support the effectiveness of COTELLIC in combination with vemurafenib in patients with non-cutaneous malignant melanoma.

As COTELLIC is used in combination with vemurafenib, refer also to the ZELBORAF® (vemurafenib) Product Monograph.

Pediatrics (<18 years of age):

The safety and efficacy of COTELLIC in children and adolescents have not been established (see Special Populations, Pediatrics below).

CONTRAINDICATIONS

COTELLIC (cobimetinib) is contraindicated in:

- Patients with known hypersensitivity to cobimetinib or any of the excipients. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The following are clinically important adverse drug reactions, some of which were serious or life-threatening, that were identified in clinical trials conducted with COTELLIC in combination with vemurafenib.

- Left ventricular dysfunction (see Cardiovascular section below)
- Hemorrhage, including major hemorrhage (see Hematologic section below)
- Serous Retinopathy and Retinal Vein Occlusion (see Ophthalmologic section below)

COTELLIC should not be used concomitantly with a strong or moderate CYP3A inhibitor. (see Drug-Drug Interactions below, and DRUG INTERACTIONS).

COTELLIC in combination with vemurafenib should be prescribed and supervised by a qualified physician experienced in the use of anti-cancer agents.

General

COTELLIC should not be used in patients with wild-type BRAF melanoma. COTELLIC should not be used in patients with unresectable or metastatic melanoma where the BRAF mutational status is not known.

There are no clinical data to support the effectiveness of COTELLIC for the treatment of brain metastases in patients with a BRAF V600 mutation-positive melanoma. Patients with active CNS lesions were excluded from the Phase III trial, and <1% of enrolled patients had previously treated brain metastases. A tissue distribution study conducted in rats demonstrated low levels of cobimetinib in CNS tissues protected by the blood:brain barrier. COTELLIC is not recommended for patients with BRAF V600 mutation-positive melanoma who have active untreated brain metastases (see DETAILED PHARMACOLOGY, Safety Pharmacology).

Drug-Drug Interactions

Concomitant use of COTELLIC and drugs that strongly or moderately inhibit CYP3A can increase cobimetinib exposure. Strong or moderate CYP3A inhibitors should not be used while taking COTELLIC (see DRUG INTERACTIONS). If concomitant short-term use of a moderate CYP3A inhibitor is unavoidable for patients who are taking COTELLIC 60 mg, reduce COTELLIC dose to 20 mg for the duration of inhibitor use. Carefully monitor patients for safety. After discontinuation of a moderate CYP3A inhibitor, resume COTELLIC at the previous dose. For patients who are taking a reduced dose of COTELLIC (40 or 20 mg daily), do not use moderate CYP3A inhibitors (see DOSAGE AND ADMINISTRATION).

Carcinogenesis and Mutagenesis

Carcinogenicity studies have not been performed with cobimetinib (see TOXICOLOGY). In the Phase III trial, the incidence of second primary melanoma was 0.8% in the COTELLIC in combination with vemurafenib arm versus 3.3% in the placebo in combination with vemurafenib arm. The incidence of basal cell carcinoma was 6% in the COTELLIC in combination with vemurafenib arm versus 2% in the placebo in combination with vemurafenib arm.

Cardiovascular

Patients with left ventricular ejection fraction (LVEF) either below institutional lower limit of normal or below 50%, symptomatic congestive heart failure of NYHA class 2 or higher, QTcF > 450 msec, or uncontrolled hypertension \geq Grade 2 were excluded from the Phase III study (see ADVERSE REACTIONS).

Concurrent cardiac conditions, medications that affect heart rate or ECG parameters, and need for monitoring heart rate or ECGs should be considered when prescribing COTELLIC as clinically indicated.

Left Ventricular Dysfunction

The safety of COTELLIC has not been established in patients with decreased LVEF.

In the Phase III study, all patients underwent evaluation of LVEF, either by echocardiography or multiple gated ejection acquisition scan, at regular intervals during treatment. Decrease in LVEF from baseline has been reported in patients receiving COTELLIC (see ADVERSE REACTIONS). Reductions in LVEF of Grade 2 or higher severity were reported in 11% of patients in the COTELLIC in combination with vemurafenib arm versus 5% of patients in the placebo in combination with vemurafenib arm. In the COTELLIC in combination with vemurafenib arm, median time to initial onset of decreased LVEF (all grades) was 4 months (range 1-26 months). Resolution was documented in 86% of patients who experienced an event of decreased LVEF with a median time to resolution of 3 (0.1-10) months.

One patient in the Phase Ib study treated with COTELLIC in combination with vemurafenib at the therapeutic dose developed Grade 3 congestive cardiomyopathy. COTELLIC was permanently discontinued with documented improvement in LVEF from 25% to 36% approximately one month after the event.

COTELLIC is not recommended in patients with decreased LVEF (< 50% or below the institutional lower limit of normal) at baseline. COTELLIC should be used with caution in patients with conditions that could impair left ventricular function (see Monitoring and Laboratory Tests below). Decrease in LVEF from baseline can be managed using treatment interruption, dose reduction or with treatment discontinuation (see DOSAGE AND ADMINISTRATION).

Hypertension

In the Phase III study, hypertension was reported in 17% (including hypertensive crisis) of patients receiving COTELLIC in combination with vemurafenib and in 9% of patients receiving placebo in combination with vemurafenib. Hypertension was observed at similar frequencies between patients with and without pre-existing hypertension. Grade ≥ 3 hypertension events were reported in 7% of patients treated with COTELLIC in combination with vemurafenib compared with 3% of patients who received placebo in combination with vemurafenib. A greater proportion of patients in the COTELLIC in combination with vemurafenib arm compared to the placebo plus vemurafenib arm received treatment for hypertension (12% versus 5%, respectively) (see Monitoring and Laboratory Tests below).

Hematologic Hemorrhage

Hemorrhage, including major hemorrhage defined as symptomatic bleeding in a critical area or organ, can occur during treatment with COTELLIC. Severe hemorrhagic cases, including intracranial bleeding and gastrointestinal tract bleeding, have been reported in patients treated with COTELLIC in clinical trials and in the post marketing setting. In most cases, patients had additional risk factors for bleeding.

In the Phase III trial, hemorrhagic events were reported more frequently for the cobimetinib plus vemurafenib arm (14%) compared with the placebo plus vemurafenib arm (9%); of these, 1.2% and 0.8%, respectively, were grade 3. Higher frequencies in the COTELLIC in combination with vemurafenib arm were also observed for cerebral hemorrhage (1% vs. 0%), gastrointestinal tract hemorrhage (4% vs. 2%), reproductive system hemorrhage (2% vs. <1%), and hematuria (3% vs. 1%). Patients should be assessed for signs and symptoms of hemorrhagic events during treatment (see Monitoring and Laboratory Tests below).

Hemorrhage can be managed using treatment interruption, dose reduction or with treatment discontinuation (see DOSAGE AND ADMINISTRATION). Caution should be used in patients with additional risk factors for bleeding and/or in patients that use concomitant medications that may increase the risk of bleeding (including antiplatelet or anticoagulant therapy).

Hepatic

Hepatotoxicity can occur with COTELLIC. Liver laboratory test abnormalities Grade ≥ 3 were reported more frequently in the Phase III study in patients who received COTELLIC in combination with vemurafenib than in patients who received placebo in combination with vemurafenib (24% vs. 15%, respectively) (see ADVERSE REACTIONS). One patient (0.4%) treated with COTELLIC in combination with vemurafenib versus none treated with placebo plus vemurafenib, developed concurrent elevations in alanine aminotransferase (ALT) >3 times the upper limit of normal (ULN) and bilirubin >2 X ULN without evidence of cholestasis (significantly elevated serum alkaline phosphatase (ALP)). ALT and bilirubin values returned to normal with discontinuation of both drugs. Monitor liver laboratory tests before initiation of the combination treatment and monthly during treatment (see Monitoring and Laboratory Tests below).

Grade 4 liver laboratory test abnormalities can be managed using treatment interruption, dose reduction or with treatment discontinuation (see DOSAGE AND ADMINISTRATION).

Immune

Grade 3 hypersensitivity events were reported in 3 patients (1.2%) in the COTELLIC in combination with vemurafenib arm compared with no such events in the placebo plus vemurafenib arm; all events required hospitalization and treatment with steroids.

Musculoskeletal and connective tissue disorders

Rhabdomyolysis and Serum Creatine Phosphokinase (CPK) Elevations

Rhabdomyolysis and CPK elevations have been reported in patients receiving COTELLIC in clinical trials and post-marketing (see Post-Market Adverse Drug Reactions).

In the Phase III trial, increases in serum CPK levels were observed with a higher frequency in the COTELLIC in combination with vemurafenib compared with the placebo in combination with vemurafenib arm (all grades: 36% vs. 3%, Grade 3-4: 12% vs. <1%). The median time to first incidence

of Grade 3-4 CPK elevations was 0.5 (0.4 to 15) months in patients in the COTELLIC in combination with vemurafenib arm; the median time to complete resolution was 0.5 (0.2 to 27) months.

Elevation of serum CPK 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 in the COTELLIC plus vemurafenib arm and in 0.4% of patients in the placebo plus vemurafenib arm. One event of rhabdomyolysis, with concurrent increases in blood CPK, was reported in each treatment arm (Grade 4 in the COTELLIC in combination with vemurafenib arm and Grade 3 in the placebo in combination with vemurafenib arm).

Treatment interruption, dose reduction or treatment discontinuation may be required depending on severity of symptoms and grade of CPK elevation. Interrupt treatment with COTELLIC if rhabdomyolysis is diagnosed, and monitor CPK levels and other symptoms until resolution. See Monitoring and Laboratory Tests, and DOSAGE AND ADMINISTRATION.

Ophthalmologic

Patients who have a history of or evidence of retinal pathology on ophthalmologic examination that is considered a risk factor for neurosensory retinal detachment, retinal vein occlusion (RVO), or neovascular macular degeneration have not been studied.

Retinal Vein Occlusion

RVO developed in one patient (0.4%) in each arm of the Phase III study. The patient who developed RVO while on treatment with COTELLIC in combination with vemurafenib experienced blurred vision and was diagnosed with retinal ischemia. The event resolved after interruption of COTELLIC plus vemurafenib and treatment with both drugs was then permanently discontinued. Consider risk factors for RVO, including uncontrolled hypertension, diabetes, hypercholesterolemia, or glaucoma when prescribing COTELLIC.

COTELLIC is not recommended in patients with a history of RVO. If retinal vein occlusion is diagnosed, COTELLIC treatment should be permanently discontinued (see Monitoring and Laboratory Tests below; DOSAGE AND ADMINISTRATION).

Serous Retinopathy

Serous retinopathy (fluid accumulation within the layers of the retina) has been observed in patients treated with MEK-inhibitors, including COTELLIC (see ADVERSE REACTIONS). In the Phase III study, serous retinopathy developed in 27% of patients in the COTELLIC in combination with vemurafenib arm compared with 4% of patients in the placebo in combination with vemurafenib arm. The majority of events were reported as chorioretinopathy or retinal detachment. In the COTELLIC in combination with vemurafenib arm, the majority of serous retinopathy events were asymptomatic (52% of events reported were Grade 1). 13% of patients treated with COTELLIC in combination with vemurafenib experienced symptomatic (i.e. \geq Grade 2) serous retinopathy events.

In the COTELLIC in combination with vemurafenib arm, for serous retinopathy events of all grades, median time to initial onset was 1 month (range 0-9 months), and median time to documented resolution was 3 months. Most symptomatic events were resolved, or improved to asymptomatic Grade 1, within a few months following dose interruption or reduction.

Serous retinopathy can be managed with treatment interruption, dose reduction or with treatment discontinuation (see Monitoring and Laboratory Tests below; DOSAGE AND ADMINISTRATION).

Sexual Function/Reproduction

There is no clinical information on the effect of COTELLIC on human fertility. 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.

Based on findings in animals, COTELLIC may reduce fertility in females and males of reproductive potential (see TOXICOLOGY).

Skin

Photosensitivity

Severe photosensitivity has been reported in association with COTELLIC when used with vemurafenib.

In the Phase III trial, Grade ≥ 3 events occurred in 4% of patients in the COTELLIC in combination with vemurafenib arm versus no patients in the placebo in combination with vemurafenib arm (see ADVERSE REACTIONS). There were no apparent trends in the time of onset of Grade ≥ 3 events. Resolution of these events was documented for 9 of 11 patients with dose modifications and/or concomitant medications to treat the adverse events.

During treatment, all patients should be advised to avoid sun exposure, and when outdoors to wear protective clothing and to use a broad spectrum UVA/UVB sun screen and lip balm (SPF ≥ 30). Grade 2 (intolerable) or Grade ≥ 3 photosensitivity can be managed with treatment interruption, dose reduction or with treatment discontinuation (see Monitoring and Laboratory Tests below; DOSAGE AND ADMINISTRATION).

Rash

Severe rash has been reported in association with COTELLIC.

In the Phase III study, Grade 3 or 4 rash events were reported in approximately 17% of patients in both treatment arms. Grade 3 or 4 dermatitis acneiform events were reported by 2.4% vs 1.2% of patients receiving COTELLIC in combination with vemurafenib vs placebo in combination with vemurafenib, respectively. Hospitalization for rash was required in 3.2% vs 1.6% of the respective arms. The median time to onset of Grade 3 or 4 rash events in the COTELLIC in combination with vemurafenib arm was 11 days; 93% of patients who reported a rash event experienced complete resolution with a median time to resolution of approximately 23 days.

Grade ≥ 3 rash can be managed using treatment interruption, dose reduction or with treatment discontinuation (see Monitoring and Laboratory Tests below; DOSAGE AND ADMINISTRATION).

Ability to Drive and Use Machines

No studies on the effects on the ability to drive and to use machines have been performed.

Visual disturbances have been reported in some patients treated with COTELLIC during clinical trials (see Ophthalmologic and ADVERSE REACTIONS: Clinical Trial Adverse Drug Reactions). Patients should be advised not to drive or operate machines if they experience visual disturbances or any other adverse effects that may affect their ability.

Special Populations

Pregnant Women: COTELLIC is not recommended during pregnancy. There are no data regarding the use of COTELLIC in pregnant women. Based on its mechanism of action and findings from nonclinical reproduction studies, COTELLIC may cause fetal harm when administered to a pregnant woman. When administered to pregnant rats, cobimetinib caused embryoletality and fetal malformations of the great vessels and skull at clinically relevant exposures (see TOXICOLOGY). Females of childbearing potential should use two effective forms of contraception during treatment with COTELLIC and for at least three months following treatment discontinuation. If the patient becomes pregnant while taking COTELLIC, the patient should be informed of the potential hazard to the fetus.

Nursing Women: It is not known whether COTELLIC is excreted in human breast milk. Because many drugs are excreted in human breast milk, a risk to the nursing infant cannot be excluded. A decision should be made whether to discontinue nursing or to discontinue COTELLIC therapy, taking into account the benefit of nursing for the infant and the benefit of COTELLIC for the mother.

Pediatrics (<18 years of age): The safety and efficacy of COTELLIC in children and adolescents have not been established. In a nonclinical toxicology study, at exposures lower than those reported for adult humans administered the recommended dose of 60 mg, mortality was seen in juvenile rats approximately equivalent in age to 1–2 year old humans, the cause of which was not defined (see ACTION AND CLINICAL PHARMACOLOGY; TOXICOLOGY).

Geriatrics (≥ 65 years of age): Of the 247 patients with unresectable or metastatic melanoma treated with COTELLIC in combination with vemurafenib in the Phase III study, approximately 74% were < 65, 18% were 65-74, and 8% were ≥ 75 years of age. Compared with patients < 65 years old, more patients ≥ 65 years old experienced AEs that led to discontinuation of the treatment regimen (27% versus 13%) and to dose modification of the treatment regimen (58% versus 43%). Increased sensitivity of some geriatric patients cannot be ruled out (see ADVERSE REACTIONS).

Based on the population pharmacokinetic analysis, clearance of cobimetinib was lower in older patients, however this was not considered clinically significant (see ACTION AND CLINICAL PHARMACOLOGY).

Gender: Based on the population pharmacokinetic analysis, gender does not have a clinically important effect on cobimetinib exposure (see ACTION AND CLINICAL PHARMACOLOGY).

Renal Impairment: No formal pharmacokinetic study of COTELLIC has been conducted in patients with renal impairment. Based on the population pharmacokinetic analysis, no dose adjustment is recommended in patients with mild or moderate renal impairment. The safety and efficacy of COTELLIC have not been established in patients with severe renal impairment (see ACTION AND CLINICAL PHARMACOLOGY).

Hepatic Impairment:

No dose adjustment is recommended in patients with hepatic impairment based on a pharmacokinetic study in subjects with hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY). In the hepatic impairment study, patients with total bilirubin > 6 mg/dL were excluded and patients with severe hepatic impairment had increased plasma concentrations of unbound cobimetinib compared to patients with normal hepatic function. Caution should be used in patients with hepatic impairment, as there is a lack of information with the recommended dose regimen, and because liver laboratory abnormalities can occur when COTELLIC is used in combination with vemurafenib (see DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS, HEPATIC above).

Monitoring and Laboratory Tests

Prior to initiation of treatment with COTELLIC in combination with vemurafenib, patients must have BRAF V600 mutation-positive melanoma tumour status confirmed by a validated test.

Left ventricular ejection fraction should be evaluated before initiation of treatment to establish baseline values, then after the first month of treatment and at least every 3 months or as clinically indicated until treatment discontinuation (see DOSAGE AND ADMINISTRATION). All patients restarting treatment with a dose reduction of COTELLIC should have LVEF measurements taken at approximately 2 weeks, 4 weeks, 10 weeks and 16 weeks, and then as clinically indicated.

Monitor ECG before initiating treatment and routinely during treatment with COTELLIC, when administered with vemurafenib (see also ACTION AND CLINICAL PHARMACOLOGY).

Blood pressure should be monitored at regular intervals during treatment, with control of hypertension as clinically indicated.

Ophthalmological evaluation, including retinal evaluation, should be performed before initiation of treatment and at regular intervals during treatment, if clinically indicated, and at any time that a patient reports new or worsening visual disturbances (see DOSAGE AND ADMINISTRATION).

Dermatologic evaluation should be performed before initiation of treatment and at regular intervals during treatment (see DOSAGE AND ADMINISTRATION). Patients should be instructed to inform their healthcare professionals of the occurrence of any skin changes. Dermatologic monitoring should continue for 6 months following discontinuation of treatment.

Patients should be assessed for signs and symptoms of bleeding events during treatment. Complete blood counts should be determined before initiation of treatment and periodically during treatment, or as clinically indicated (see ADVERSE REACTIONS; DOSAGE AND ADMINISTRATION).

Monitor for liver value abnormalities by liver laboratory tests before initiation of combination treatment and monthly during treatment, or more frequently as clinically indicated (see ADVERSE REACTIONS; DOSAGE AND ADMINISTRATION).

Serum CPK and creatinine levels should be measured before initiation of treatment to establish baseline values, and then monitored monthly during treatment, or as clinically indicated. For CPK elevations, evaluation of causality should include an assessment for rhabdomyolysis and other causes, including

cardiac injury (see ADVERSE REACTIONS; DOSAGE AND ADMINISTRATION).

Assess serum chemistry before initiation of treatment and periodically during treatment per institution guidelines or as clinically indicated (see ADVERSE REACTIONS).

ADVERSE REACTIONS

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Drug Reaction Overview

Study GO28141

The safety of COTELLIC in combination with vemurafenib has been evaluated in a safety population of 247 patients with previously untreated BRAF V600 mutated unresectable locally advanced or metastatic melanoma in the Phase III study GO28141 comparing COTELLIC in combination with vemurafenib to placebo in combination with vemurafenib. For patients in the COTELLIC in combination with vemurafenib arm, the median duration of COTELLIC exposure was 274 days and the median duration of vemurafenib exposure was 281 days.

The frequency of adverse events (AEs) was similar for both arms (approximately 98%). The most common AEs ($\geq 20\%$) that occurred with greater frequency in the COTELLIC in combination with vemurafenib arm were diarrhea, nausea, blood CPK increased, photosensitivity reaction, pyrexia, ALT increased, AST increased, and vomiting (see Table 1). The most common AEs ($\geq 20\%$) that occurred with greater frequency in the placebo in combination with vemurafenib arm compared with the COTELLIC in combination with vemurafenib arm, respectively, were, alopecia (31% vs 17%), and hyperkeratosis (27% vs 9%). In addition, rash (41% vs 38%), arthralgia (38% vs 42%), fatigue (37% vs 33%), decreased appetite (20% vs 20%), and GGT increased (22% vs 18%) were observed at similar frequencies in both arms.

The percentage of patients experiencing Grade ≥ 3 adverse events (AEs) was higher in the COTELLIC plus vemurafenib arm than in the placebo plus vemurafenib arm (75% vs 61%). The median time to onset of first Grade ≥ 3 AEs was 0.8 months in the COTELLIC in combination with vemurafenib arm vs. 0.8 months in the placebo in combination with vemurafenib arm.

Serious adverse events (SAEs) were reported in 37% of patients treated with COTELLIC in combination with vemurafenib compared with 28% of patients treated with placebo in combination with vemurafenib. Serious adverse drug reactions reported in $\geq 1\%$ of patients treated with COTELLIC in combination with vemurafenib included pyrexia, pneumonia, dehydration, rash, rash maculo-papular, ALT increased, AST increased, atrial fibrillation, chorioretinopathy, retinal detachment, diarrhea, small intestinal obstruction, hypersensitivity, seizure, and acute kidney injury.

Adverse events leading to permanent discontinuation of the combination were documented in 17% of patients receiving COTELLIC in combination with vemurafenib compared with 9% of patients receiving placebo in combination with vemurafenib. In patients treated with COTELLIC in combination with vemurafenib, the most common AEs resulting in permanent discontinuation of the combination were increased AST (2.0%), increased GGT (1.6%), increased ALT (1.6%), rash (1.6%), pyrexia (1.2%), and retinal detachment (1.2%).

Adverse events led to dose interruption or reduction of the combination in 47% of patients treated with COTELLIC in combination with vemurafenib versus 38% treated with placebo in combination with vemurafenib. The most common reasons cited for dose interruption or reduction of COTELLIC were diarrhea (8%), pyrexia (6%), vomiting (6%), increased blood CPK (2%), chorioretinopathy (6%), retinal detachment (3%), rash maculo-papular (5%), and rash (5%).

Geriatrics (≥ 65 years of age): Patients ≥ 65 years were more likely to have dose interruption or reduction in the COTELLIC in combination with vemurafenib arm than those < 65 years (58% vs 43%). Specific AEs led to dose modification of the combination in the elder patients were diarrhea (19%), vomiting (14%), asthenia or fatigue (16%), pyrexia (9%), dehydration (8%), blood creatinine increased (6%), AST increased (5%), CPK increased (5%), and retinal detachment (6%).

Clinical Trial Adverse Drug Reactions

The table below summarizes the adverse drug reactions (ADRs) occurring at a ≥ 5% higher incidence (All Grades) or at a ≥ 2% higher incidence (Grades 3-4) of patients treated with COTELLIC in combination with vemurafenib in the Phase III study. The following categories of frequency have been used: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000).

Table 1 Incidence of Adverse Reactions of All Grades (Incidence ≥ 5% over the control arm) or Grade 3 - 4 (Incidence ≥ 2% over the control arm)

ADRs	Phase III Study: GO28141 ^a				Frequency ^b (All Grades)
	COTELLIC + vemurafenib (n = 247)		Placebo + vemurafenib (n = 246)		
	All grades (%)	Grade 3-4 (%)	All grades (%)	Grade 3-4 (%)	
Blood and Lymphatic System Disorders					
Anemia	16	2	9	3	very common
Eye Disorders					
Chorioretinopathy	13	1	<1	0	very common
Vision Blurred	11	0	2	0	very common
Retinal Detachment	9	2	<1	0	common
Gastrointestinal disorders					
Diarrhea	61	6	33	1	very common
Nausea	43	1	26	1	very common
Vomiting	26	2	14	1	very common

ADRs	Phase III Study: GO28141 ^a				Frequency ^b (All Grades)
	COTELLIC + vemurafenib (n = 247)		Placebo + vemurafenib (n = 246)		
	All grades (%)	Grade 3-4 (%)	All grades (%)	Grade 3-4 (%)	
Stomatitis	6	0	1	0	common
General disorders and administration site conditions					
Pyrexia	29	1	24	0	very common
Chills	10	0	5	0	very common
Investigations					
Decreased Ejection Fraction	12	2	5	1	very common
Lipase Increased	4	3	2	1	common
Metabolism and nutrition disorders					
Dehydration	4	2	1	0	common
Hyponatremia	5	3	1	<1	common
Neoplasms benign, malignant and unspecified					
Basal Cell Carcinoma	6	6	2	2	common
Skin and subcutaneous tissue disorders					
Photosensitivity ^c	48	4	38	0	very common
Maculo-papular rash	15	7	15	5	very common
Acneiform Dermatitis	14	2	9	1	very common
Vascular Disorders					
Hypertension	16	6	8	3	very common

^a Data cut-off date of 30 September 2015

^b Based on the incidence rates of adverse events of all grades in the COTELLIC plus vemurafenib arm

^c Combined figure includes reports of photosensitivity reaction, sunburn, solar dermatitis, actinic elastosis

The following ADRs (all grades) were reported with <5% greater incidence in the COTELLIC arm than the control arm in study GO28141:

Cardiac disorders: Atrial fibrillation (4%)

Eye disorders: Visual impairment (3%), Detachment of retinal pigment epithelium (4%) , Macular detachment (2%)

Gastrointestinal disorders: abdominal pain (11%), dry mouth (4%), aphthous ulcer (4%)

General disorders and administration site conditions: oedema peripheral (14%)

Hematologic disorders: Hemorrhage all types and grades (14%)

Immune system disorders: Hypersensitivity (2%)

Infections and infestations: Nasopharyngitis (8%), Folliculitis (7%), Conjunctivitis (6%), Oral herpes (4%), Panniculitis (3%), Candida infection (2%)

Investigations: Blood cholesterol increased (7%), blood lactate dehydrogenase increased (5%)

Metabolism and nutrition disorders: Hyperglycemia (3%), Hypophosphatemia (4%)

Musculoskeletal and connective tissue disorders: Myalgia (15%), Muscular weakness (4%)

Nervous system disorder: Dizziness (6%)

Respiratory, thoracic and mediastinal disorders: Pneumonitis (2%), interstitial lung disease (1%)

Skin and subcutaneous tissue disorders: Rash (41%), Palmar-Plantar erythrodysesthesia syndrome (7%), Urticaria (4%), Erythema nodosum (4%), Dermatitis (3%)

Further Information on Selected Adverse Reactions

Cutaneous Squamous Cell Carcinoma, Keratoacanthoma and Hyperkeratosis

Cutaneous squamous cell carcinoma has been reported with a lower frequency in the COTELLIC plus vemurafenib vs. placebo plus vemurafenib arm (all grades: 4% vs. 13%). Keratoacanthoma has been reported with a lower frequency in the COTELLIC plus vemurafenib vs. placebo plus vemurafenib arm (all grades: 2% vs. 9%). Hyperkeratosis has been reported with a lower frequency in the COTELLIC plus vemurafenib vs. placebo plus vemurafenib arm (all grades: 10% vs. 27%).

Abnormal Hematologic and Clinical Chemistry Findings

Table 2 Incidence of Laboratory Abnormalities Occurring in $\geq 10\%$ (All Grades) or $\geq 2\%$ (Grades 3–4) of Patients in Study GO28141*

Laboratory Test	Phase III Study: GO28141			
	COTELLIC + vemurafenib		Placebo + vemurafenib	
	All Grades ^a (%)	Grades 3-4 ^a (%)	All Grades ^a (%)	Grades 3-4 ^a (%)
Chemistry				
Increased creatinine	99.6	3.3	99.6	0.8
Increased AST	74	8	45	2.1
Increased ALT	69	11	55	5
Increased alkaline phosphatase	72	7	57	3.3
Increased creatine phosphokinase ^b	81	15	18	1.4
Hypophosphatemia	71	14	41	6

Increased GGT	68	23	62	18
Decreased albumin	45	1	20	0.4
Hyperbilirubinemia	35	2	45	2
Hyponatremia	39	6	33	2.5
Hypernatremia	12	0.4	4	0
Hypokalemia	26	4.5	17	3.3
Hyperkalemia	28	2.9	17	0.4
Hypocalcemia	25	0.4	9	0.4
Hematology				
Anemia	73	2.9	59	4.1
Lymphopenia ^c	75	14	56	8
Thrombocytopenia	20	0.4	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. Data cut-off date of 30 September 2015. .

^a NCI CTCAE v4.0

^b Increased creatine phosphokinase, n=213 for COTELLIC and 217 for vemurafenib

^c Lymphopenia, n=185 for COTELLIC, and 181 for vemurafenib

Post-Market Adverse Drug Reactions

Musculoskeletal and connective tissue disorders: Rhabdomyolysis

DRUG INTERACTIONS

Overview

Cobimetinib is a substrate of CYP3A. A drug interaction was observed when cobimetinib was administered with a strong CYP3A inhibitor. Related findings and precautions are discussed further below.

Drug-Drug Interactions

Agents That May Increase Cobimetinib Plasma Concentrations

CYP3A Inhibitors:

Cobimetinib is metabolized by CYP3A. Co-administration of itraconazole (a strong CYP3A inhibitor) 200 mg once daily for 14 days with a single 10 mg cobimetinib dose administered on Day 4 increased mean cobimetinib AUC (90% CI) by 6.7-fold (5.6, 8.0) and mean C_{max} (90% CI) by 3.2-fold (2.7, 3.7). Strong CYP3A inhibitors including, but not limited to: clarithromycin, itraconazole, ketoconazole, lopinavir, posaconazole, ritonavir, and voriconazole should not be used concomitantly with COTELLIC.

Co-administration of cobimetinib with a moderate CYP3A inhibitor has not been assessed in a clinical drug interaction study. Simulations with a physiologically-based pharmacokinetics model suggest that moderate inhibitors of CYP3A could increase cobimetinib AUC by 3–4 fold and C_{max} by ~2-fold. The concomitant use of moderate CYP3A inhibitors including, but not limited to: amiodarone, delavirdine, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, miconazole, and verapamil should be avoided. If concomitant short term (14 days or less) use of a moderate CYP3A inhibitor is unavoidable for patients who are taking COTELLIC 60 mg, patients should be carefully monitored for safety and dose

should be reduced to 20 mg for the duration of inhibitor use. After discontinuation of a moderate CYP3A inhibitor, resume COTELLIC at the previous dose. For patients who are taking a reduced dose of COTELLIC (40 or 20 mg daily), do not use moderate CYP3A inhibitors (see DOSAGE AND ADMINISTRATION).

Agents That May Decrease Cobimetinib Plasma Concentrations

Effect of CYP3A Inducers:

Cobimetinib is metabolized by CYP3A and cobimetinib exposures may be lower in the presence of CYP3A inducers. Co-administration of cobimetinib with a strong or moderate CYP3A inducer has not been assessed in a clinical drug interaction study. Simulations with a physiologically-based pharmacokinetics model suggest that strong and moderate inducers of CYP3A could decrease cobimetinib AUC by 83% and 72%, respectively, and C_{max} by ~63%. The concomitant use of strong and moderate CYP3A inducers including, but not limited to: bosentan, carbamazepine, efavirenz, etravirine, modafinil, phenytoin, and rifampin should be avoided.

Acid Reducing Agents:

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.

Drugs That May Have Their Plasma Concentrations Altered by Cobimetinib

CYP Substrates:

In vitro data indicate that cobimetinib is an inhibitor of CYP3A and CYP2D6, and an inducer of CYP3A. Co-administration of cobimetinib 60 mg once daily for 13 days followed by co-administration with a single 30 mg dose of dextromethorphan (sensitive CYP2D6 substrate) and a single 2 mg dose of midazolam (sensitive CYP3A substrate) to 20 patients with solid tumors did not change dextromethorphan or midazolam systemic exposure. Therefore, cobimetinib is not an inducer or inhibitor of CYP3A or inhibitor of CYP2D6 at the clinically relevant dose.

Effects between Cobimetinib and Vemurafenib

There is no evidence of any clinically significant drug-drug interaction between cobimetinib and vemurafenib in unresectable or metastatic melanoma patients.

In vitro Studies with Drug Transporters

In vitro studies demonstrate that cobimetinib is a substrate of the efflux transporter P-glycoprotein (P-gp), but is not a substrate of the breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP1B1 or OATP1B3) or organic cation transporter OCT1. Co-administration of cobimetinib with P-gp inhibitors such as cyclosporine and verapamil may increase cobimetinib plasma concentrations.

In vitro studies indicate that cobimetinib is an inhibitor of BCRP. The relevance of this *in vitro* finding has not been investigated clinically. Cobimetinib may alter the gastrointestinal absorption of drugs which are BCRP substrates.

Cobimetinib did not inhibit the transport activities of P-gp, OATP1B1, OATP1B3, OAT1, OAT3, OCT1 or OCT2 at clinically relevant concentrations *in vitro*.

Drug-Food Interactions

Grapefruit, grapefruit juice, and products containing grapefruit extract may increase cobimetinib plasma concentrations and should be avoided.

Drug-Herb Interactions

Interactions with herbal products have not been established. St. John's wort (*Hypericum perforatum*) is an inducer of CYP3A that may decrease cobimetinib plasma concentrations and should be avoided.

DOSAGE AND ADMINISTRATION**Dosing Considerations**

Also refer to the Product Monograph for ZELBORAF[®] (vemurafenib), which is used in combination with COTELLIC.

Recommended Dose and Dosage Adjustment**Standard Dosage**

The recommended dose of COTELLIC is 60 mg (three 20 mg tablets) once daily. COTELLIC is taken on a 28 day cycle. Each COTELLIC dose consists of three 20 mg tablets (60 mg) and should be taken once daily for 21 consecutive days (days 1 to 21 - treatment period); followed by a 7 day break in COTELLIC treatment (days 22 to 28 – treatment break). Each subsequent COTELLIC treatment cycle should start after the 7-day treatment break has elapsed.

Each dose of three 20 mg tablets (60 mg) can be taken with or without food (see ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics, Absorption). COTELLIC tablets should be swallowed whole with a glass of water.

Duration of treatment

Treatment with COTELLIC should continue until the patient no longer derives benefit or until the development of unacceptable toxicity.

Missed Dose

If a dose of COTELLIC is missed, it can be taken up to 12 hours prior to the next dose to maintain the once-daily regimen. Both doses should not be taken at the same time.

Vomiting

In case of vomiting after COTELLIC administration, the patient should not take an additional dose of COTELLIC on that day, and treatment should be continued as prescribed the following day.

Dose Modification Recommendations

COTELLIC dose modification should be based on the physician's assessment of individual patient safety or tolerability. Dose modification of COTELLIC is independent of vemurafenib dose modification.

COTELLIC monotherapy should not be initiated in patients for the treatment of advanced melanoma.

If doses are omitted for toxicity; missed doses should not be replaced.

Once the dose has been reduced, it should not be increased at a later time.

Recommended COTELLIC Dose Modifications for Concomitant Drugs

If concomitant short term (14 days or less) use of a moderate CYP3A inhibitor is unavoidable for patients who are taking COTELLIC 60 mg, patients should be carefully monitored for safety and dose should be reduced to 20 mg for the duration of inhibitor use. After discontinuation of a moderate CYP3A inhibitor, resume previous dose of COTELLIC 60 mg.

Recommended COTELLIC Dose Modifications for Adverse Drug Reactions

Table 3 below gives general COTELLIC dose modification advice, and Table 4 gives COTELLIC dose modification advice for specified Adverse Drug Reactions.

Table 3 Recommended COTELLIC Dose Modifications

Grade (CTC-AE)*	Recommended COTELLIC dosage
Grade 1 or Grade 2 (tolerable)	No dose reduction
Grade 2 (intolerable) or Grade 3/4	
1 st Appearance	Interrupt treatment until grade ≤ 1 , restart treatment at 40 mg once daily [First dose reduction]
2 nd Appearance	Interrupt treatment until grade ≤ 1 , restart treatment at 20 mg once daily [Second dose reduction]
3 rd Appearance	Permanently discontinue COTELLIC

*The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events v4.0 (CTC-AE)

Table 4 Recommended COTELLIC Dose Modifications for Specified Adverse Drug Reactions (ADRs)

Adverse Drug Reaction	Dose Modification for COTELLIC	
Rhabdomyolysis or symptomatic CPK elevations	Withhold COTELLIC for up to 4 weeks <ul style="list-style-type: none"> • If improved to Grade 3 or lower, resume at the next lower dose level, if clinically indicated. • If not improved within 4 weeks, permanently discontinue. 	
Asymptomatic CPK elevations	Grade ≤ 3	COTELLIC dosing does not need to be modified or interrupted to manage asymptomatic Grade ≤ 3 creatine phosphokinase (CPK) elevations.
	Grade 4	Withhold COTELLIC for up to 4 weeks <ul style="list-style-type: none"> • If improved to Grade 3 or lower, resume at the next lower dose level, if clinically indicated. If not improved within 4 weeks, permanently discontinue.
Liver Laboratory Abnormalities and Hepatotoxicity	First Occurrence Grade 4	Withhold COTELLIC for up to 4 weeks. <ul style="list-style-type: none"> • If improved to Grade 0 or 1, then resume at the next lower dose level. • If not improved to Grade 0 or 1 within 4 weeks, permanently discontinue.

Adverse Drug Reaction	Dose Modification for COTELLIC	
	Recurrent Grade 4	Permanently discontinue COTELLIC.
Retinal vein occlusion (RVO)	Permanently discontinue COTELLIC.	
Serous Retinopathy	Withhold COTELLIC for up to 4 weeks. <ul style="list-style-type: none"> • If improved to Grade 0 or 1, then resume at the next lower dose level. • If not improved to Grade 0 or 1 within 4 weeks, permanently discontinue. 	
Photosensitivity	Grade \leq 2 (tolerable)	Should be managed with supportive care.
	Grade 2 (intolerable), Grade \geq 3	COTELLIC should be interrupted until resolution to Grade \leq 1. Treatment can be restarted with no change in COTELLIC dose.
Rash	Grade \leq 2 (tolerable) rash	Should be managed with supportive care.
	Grade 2 (intolerable) or Grade \geq 3	<i>Acneiform rash</i> : Follow general dose modification table recommendations in Table 3 for COTELLIC. <i>Non-acneiform or maculopapular rash</i> : COTELLIC dosing can be continued without modification (if clinically indicated).
Asymptomatic, absolute decrease in LVEF from baseline of greater than 10% and less than institutional lower limit of normal (LLN)	Withhold COTELLIC for 2 weeks; repeat LVEF Resume at next lower dose if all of the following are present: <ul style="list-style-type: none"> • LVEF \geq LLN and • Absolute decrease from baseline LVEF is \leq 10% Permanently discontinue if any of the following are present: <ul style="list-style-type: none"> • LVEF \leq LLN or • Absolute decrease from baseline LVEF $>$ 10% 	
Symptomatic LVEF decrease from baseline	Withhold COTELLIC for up to 4 weeks, repeat LVEF. Resume at next lower dose if all of the following are present: <ul style="list-style-type: none"> • Symptoms resolve and • LVEF is \geq LLN and • Absolute decrease from baseline LVEF is \leq 10% or less Permanently discontinue if any of the following are present: <ul style="list-style-type: none"> • Symptoms persist, or • LVEF $<$ LLN, or • Absolute decrease from baseline LVEF $>$ 10% 	
Hemorrhage	Grade 3	Withhold COTELLIC for up to 4 weeks. Resume COTELLIC at the next lower dose level if improved to Grade 0 or 1 and if clinically appropriate and improved. If not improved within 4 weeks or if clinically indicated, permanently discontinue.
	Grade 4 or cerebral hemorrhage (all grades)	Permanently discontinue COTELLIC.

Elderly:

No dose adjustment of COTELLIC is required in patients ≥ 65 years of age.

Renal Impairment:

No dose adjustment is recommended in patients with mild or moderate renal impairment, based on population pharmacokinetic analysis. The safety and efficacy of COTELLIC have not been established in patients with severe renal impairment (see ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics, Special Populations and Conditions).

Hepatic Impairment:

No dose adjustment is recommended in patients with hepatic impairment, based on a pharmacokinetic study conducted in subjects with hepatic impairment at a dose of 10 mg cobimetinib. Patients with severe hepatic impairment had increased plasma concentrations of unbound cobimetinib compared to patients with normal hepatic function (see ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics, Special Populations and Conditions). Caution should be used in patients with hepatic impairment, as there is a lack of information with the recommended dose regimen of the combination, and because liver laboratory abnormalities can occur when COTELLIC is used in combination with vemurafenib (see WARNINGS AND PRECAUTIONS).

OVERDOSAGE

There is no experience with overdose in human clinical trials. In case of suspected overdose, COTELLIC should be withheld and supportive care instituted. There is no specific antidote for overdose with COTELLIC.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The mitogen-activated protein kinase (MAPK)/ERK pathway, also known as the RAS/RAF/MEK/ERK pathway, is a signalling pathway that regulates cell proliferation, cell cycle regulation, cell survival, angiogenesis, and cell migration. The mitogen/extracellular signal-regulated kinases (MEK) proteins are upstream regulators of the extracellular signal related kinase (ERK) pathway. BRAF V600 mutations result in constitutive activation of the BRAF pathway which includes MEK1 and MEK2. COTELLIC is a selective, reversible inhibitor of MEK 1 and MEK 2. *In vitro*, COTELLIC inhibited MEK1 and MEK2 with IC50 values of 0.95 nM and 199 nM, respectively.

COTELLIC and vemurafenib target two different kinases in the MAPK/ERK pathway. Compared to either drug alone, coadministration of COTELLIC and vemurafenib resulted in increased apoptosis *in vitro* and reduced tumour growth in tumour cell lines harbouring BRAF V600E mutations.

Cardiac Electrophysiology

Serial ECG recordings were performed in 13 patients who received COTELLIC at a dose of 60 mg/day (21 days on-treatment, 7 days off-treatment) as part of a non-randomized, open-label study. ECG recordings were performed on Day 21 (pre-dose, 1.5 h, 3 h, & 6 h) of Cycle 1, and statistically significant decreases in heart rate from pretreatment baseline were observed with a maximum mean decrease of -10.7 bpm (95% CI -17.6, -3.8) at 1.5 h post-dosing. Statistically significant mean increases from baseline in the PR interval and QRS duration were observed at all time points on Day 21. The maximum mean increase in the PR interval was 15.0 ms (95% CI 6.4, 23.6) at 3 h post-dosing and the maximum mean increase in the QRS duration was 5.8 ms (95% CI 1.0, 10.7) at 1.5 h post-dosing. For the QTcF interval, the maximum mean increase from baseline was 1.2 ms (95% CI -6.2, 8.5).

Pharmacokinetics

The pharmacokinetic parameters for cobimetinib were determined in cancer patients and healthy subjects in Phase I studies.

Absorption: Following oral dosing of 60 mg in cancer patients, cobimetinib showed a moderate rate of absorption with a median T_{max} of 2.4 hours. The mean steady-state C_{max} and AUC_{0-24} were 273 ng/mL and 4340 ng.h/mL respectively. The mean accumulation ratio at steady state was approximately 2.4-fold.

Cobimetinib has linear pharmacokinetics in the dose range of ~3.5 mg to 100 mg.

The absolute bioavailability of cobimetinib was 45.9% (90% CI: 39.7%, 53.1%) in healthy subjects. A human mass balance study was conducted in healthy subjects, and showed that cobimetinib was extensively metabolized and eliminated in feces. The fraction absorbed was ~88% indicating high absorption and first pass metabolism.

Following a single dose of 20 mg cobimetinib with food (high-fat meal), median t_{max} value (6.00 hours) was extended compared to the fasted state (median t_{max} = 2.03 hours) in healthy subjects. Although absorption was slower in the fed state, exposure (AUC and C_{max}) to cobimetinib was generally similar with or without food.

Distribution: An analysis of plasma samples from healthy subjects (n=10) dosed with 10 mg cobimetinib shows that cobimetinib is 98.4% bound to plasma proteins. *In vitro*, cobimetinib is 94.8% bound to human plasma proteins and more highly bound to alpha-1 acid glycoprotein. No preferential binding to human red blood cells was observed (blood-to-plasma ratio 0.93).

The volume of distribution was 1050 L in healthy subjects given an intravenous (IV) dose of 2 mg. The apparent volume of distribution was 806 L in cancer patients based on population pharmacokinetic analysis.

Metabolism: Cobimetinib and its metabolites were characterized in a mass balance study in healthy subjects.

On average, 94% of the dose was recovered within 17 days. Cobimetinib was extensively metabolized to several metabolites, and eliminated in feces.

Oxidation by CYP3A and glucuronidation by UGT2B7 appear to be the major pathways of cobimetinib metabolism. Following oral administration of a single 20 mg radiolabeled cobimetinib dose, cobimetinib (parent compound) was the predominant moiety in plasma, followed by the glycine conjugate of the hydrolyzed cobimetinib and the glucuronide conjugate where each of them accounted for greater than 10% of the plasma radioactivity at timepoints up to 48 hour post-dose. No other metabolites greater than 10% of total circulating radioactivity or human specific metabolites were observed in plasma. Unchanged drug in feces and urine accounted for 6.6% and 1.6% of the administered dose, respectively, indicating that cobimetinib is primarily metabolized with very little renal elimination.

Excretion: Following IV administration of a 2 mg dose of cobimetinib, the mean plasma clearance (CL) was 10.7 L/hr. The mean apparent CL following oral dosing of 60 mg in cancer patients was 13.8 L/hr and the mean elimination half-life was 43.6 hours (range: 23.1 to 69.6 hours).

Following oral administration of a single 20 mg radiolabeled cobimetinib dose, 76.5% of the dose was recovered in the feces and 17.8% of the dose was recovered in the urine.

Special Populations and Conditions

Based on a population pharmacokinetic analysis, gender, race, ethnicity, baseline ECOG, mild and moderate renal impairment did not affect the pharmacokinetics of cobimetinib. Baseline age and baseline body weight were identified as statistically significant covariates on cobimetinib clearance and volume of distribution respectively. However, sensitivity analysis suggests neither of these covariates had a clinically significant impact on steady state exposure.

Pediatrics: No studies have been conducted to investigate the pharmacokinetics of cobimetinib in pediatric patients (see TOXICOLOGY).

Geriatrics: Based on the population pharmacokinetic analysis including 133 patients ≥ 65 years of age, age was a significant covariate influencing cobimetinib clearance, which decreased with increasing age, however this was not considered clinically significant.

Gender: Based on a population pharmacokinetic analysis including 210 women and 277 men, gender does not have a clinically important effect on the exposure of cobimetinib.

Hepatic Impairment: The pharmacokinetics of cobimetinib were evaluated in 6 subjects with mild hepatic impairment (Child Pugh A), 6 subjects with moderate hepatic impairment (Child Pugh B), 6 subjects with severe hepatic impairment (Child Pugh C) and 10 healthy subjects. Subjects with total bilirubin > 6 mg/dL were excluded from the study. Systemic exposures of total cobimetinib after a single dose of 10 mg cobimetinib were similar in subjects with mild or moderate hepatic impairment compared to healthy subjects; while subjects with severe hepatic impairment had 31% lower cobimetinib exposures ($AUC_{0-\infty}$ geometric mean ratio of 0.69 compared to healthy subjects) which is not considered to be clinically significant. Unbound cobimetinib exposures were similar between subjects with mild and moderate hepatic impairment compared to subjects with normal hepatic function while subjects with severe hepatic impairment had approximately 2-fold higher exposures. Longer half-life was also noted in subjects with hepatic impairment (87 h, 101 h, and 139 h in mild, moderate and severe hepatic impairment, respectively) when compared to 76 h in subjects with normal hepatic function.

Renal Impairment: Based on pre-clinical data and the human mass balance study, cobimetinib is mainly

metabolized, with minimal renal elimination. No formal pharmacokinetic study has been conducted in patients with renal impairment.

A population pharmacokinetic analysis using data from 151 patients with mild renal impairment (creatinine clearance - CRCL 60 to less than 90 mL/min), 48 patients with moderate renal impairment (CRCL 30 to less than 60 mL/min), and 286 patients with normal renal function (CRCL greater than or equal to 90 mL/min), showed that CRCL had no meaningful influence on exposure of cobimetinib.

Mild to moderate renal impairment does not influence cobimetinib exposure based on the population pharmacokinetic analysis. There are insufficient data available for patients with severe renal impairment or end stage renal disease.

STORAGE AND STABILITY

Store between 15-30°C.

Keep in a safe place out of the reach and sight of children.

SPECIAL HANDLING INSTRUCTIONS

This medicine should not be used after the expiry date (EXP) shown on the pack.

Disposal of unused/expired medicines

The release of pharmaceuticals into 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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form / Composition

Each COTELLIC film-coated tablet contains 20 mg cobimetinib (22.2 mg as cobimetinib fumarate salt). Non-medicinal ingredients (alphabetical order) include: croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The film-coating mixture includes (alphabetical order): polyethylene glycol 3350 (macrogol 3350), polyvinyl alcohol, talc, and titanium dioxide.

Packaging

COTELLIC tablets are supplied as white, round, film-coated 20 mg tablets with COB debossed on one side. COTELLIC is available in PVC/PVDC blister packs containing 63 film-coated tablets (21 tablets per blister card and 3 blister cards per carton).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

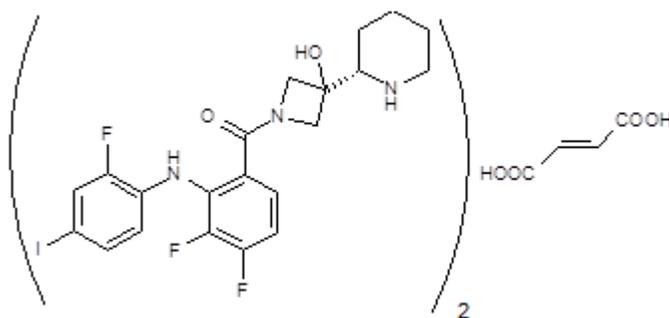
Proper name: cobimetinib fumarate

Chemical name: methanone, [3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl][3-hydroxy-3-(2*S*)-2-piperidinyl-1-azetidiny]-, (2*E*)-2-butenedioate (2:1)

Molecular formula: $C_{46}H_{46}F_6I_2N_6O_8$ ($2 C_{21}H_{21}F_3IN_3O_2 \cdot C_4H_4O_4$)

Molecular mass: 1178.71

Structural formula: cobimetinib fumarate



Physicochemical properties: Cobimetinib is a fumarate salt appearing as white to off-white solid and exhibits a pH dependent solubility. The solubility of cobimetinib in aqueous media increases with decreasing pH. In water (37°C), cobimetinib shows a solubility of 0.72 mg/mL. In 0.1 M HCl (37°C), its solubility is 48.21 mg/mL.

CLINICAL TRIALS

Study GO28141

Study Demographics and Trial Design

Study GO28141 is a multicenter, randomized, double-blind, placebo-controlled, Phase III study to evaluate the safety and efficacy of COTELLIC (cobimetinib) in combination with vemurafenib as compared to vemurafenib plus placebo, in patients with previously untreated BRAF V600 mutation-positive unresectable locally advanced (stage IIIc) or metastatic melanoma (stage IV).

Following confirmation of a BRAF V600 mutation using the cobas® 4800 BRAF V600 mutation test, 495 patients with unresectable locally advanced or metastatic melanoma were randomized to receive either:

- Placebo once daily on Days 1–21 of each 28-day treatment cycle and 960 mg vemurafenib twice daily on Days 1–28
- COTELLIC 60 mg once daily on Days 1–21 of each 28-day treatment cycle and 960 mg vemurafenib twice daily on Days 1–28

Overall, demographic characteristics and patient baseline disease characteristics were well balanced between treatment arms. Key baseline characteristics included: 58% of patients were male, 93% reported White race, median age was 55 years (range 23 - 88 years), 60% had metastatic melanoma stage M1c, Eastern Cooperative Oncology Group performance status was 0 in 72% and 1 in 28%, serum lactate dehydrogenase (LDH) was elevated in 45%, prior adjuvant therapy had been administered to 10%, and <1% had previously treated brain metastases.

Treatment continued until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurred earliest. Patients in the placebo plus vemurafenib arm were not eligible to cross over to the COTELLIC plus vemurafenib arm at disease progression.

Progression-free survival (PFS) as assessed by the investigator (Inv) using RECIST v1.1 was the primary endpoint. Secondary efficacy endpoints included overall survival (OS), objective response rate (ORR), duration of response (DoR), and PFS as assessed by an independent review facility (IRF). Global health status / health-related quality of life by patient-report, also a secondary efficacy endpoint, were measured for each treatment arm using the European Organisation for Research on the Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30).

Study Results

Overall, the median duration of follow-up for all patients was 7.3 months. 207 (41.8%) patients had experienced a PFS event at the time of the final analysis of the primary endpoint. The combination of COTELLIC and vemurafenib showed a statistically significant increase in PFS (Inv) with a hazard ratio of 0.51 (95% CI 0.39-0.68, $p < 0.0001$). The median PFS (Inv) was 9.9 months in patients receiving COTELLIC and vemurafenib versus 6.2 months in patients receiving placebo and vemurafenib. The PFS benefit in the COTELLIC plus vemurafenib arm was observed across key characteristic subgroups, specifically disease stage, age, sex, ECOG performance status, baseline lactate dehydrogenase (LDH) level, and BRAF V600 mutation E and K genotypes. In the COTELLIC plus vemurafenib arm, 67.6% of patients had an objective response (complete response or partial response) versus 44.8% in the placebo plus vemurafenib arm.

Based on the final stratified analysis of OS, the HR was 0.70 (95% CI: 0.55, 0.90; log-rank $p = 0.0050$) in favour of the COTELLIC plus vemurafenib arm. This OS p -value crossed the pre-specified boundary of 0.0499. The median OS was 22.3 months (95% CI: 20.3, upper bound not reached) in the COTELLIC plus vemurafenib arm and 17.4 months (95% CI: 15.0, 19.8) in the placebo plus vemurafenib arm. Complete efficacy results are summarized in the table below.

Table 5 Efficacy Results from Study GO28141

	COTELLIC + vemurafenib N=247	Placebo + vemurafenib N=248
Primary Endpoint with data cut-off date of 9 May 2014		
Progression Free Survival (Inv)^a		
Number of Events (%)	79 (32.0%)	128 (51.6%)
Progression	74	125
Death	5	3
Median (Kaplan-Meier estimate - months)	9.9	6.2
95% CI	(9.0, NE)	(5.6, 7.4)
Hazard ratio (95% CI)	0.51 (0.39; 0.68) (p-value < 0.0001)	
Key Secondary Endpoints		
Overall Survival (final)^b with data cut-off date of 28 August 2015		
Number of Deaths (%)	114 (46.2%)	141 (56.9%)
Median (KM-estimate – months) (95% CI)	22.3 (20.3, NE)	17.4 (15.0, 19.8)
Hazard ratio (95% CI)	0.70 (0.55, 0.90) (p-value = 0.0050 ^b)	
Objective response rate (ORR) with data cut-off date of 9 May 2014		
ORR	167 (67.6%)	111 (44.8%)
95% CI for ORR	(61.4%, 73.4%)	(38.5%, 51.2%)
Difference in ORR % (95% CI)	22.85 (14.13, 31.58) p-value < 0.0001	
Best Overall Response		
Complete Response	25 (10.1%)	11 (4.4%)
Partial Response	142 (57.5%)	100 (40.3%)
Stable disease	49 (19.8%)	105 (42.3%)
Duration of response (DoR)		
Median DoR (months)	NE	7.3
95% CI for median	9.3, NE	5.8, NE

^a Assessed by the investigator (Inv) using RECIST v1.1

^b The OS p-value (0.0050) crossed the pre-specified boundary (p value <0.0499).NE = not evaluable

The effect on PFS was also supported by analysis of PFS based on the assessment by blinded independent review.

Retrospective next generation sequencing to evaluate BRAF mutation genotypes was performed on tumour tissue from 400 of 495 patients and demonstrated that 344 (86%) tumors carried a V600E mutation and 56 (14%) had a V600K mutation. The distribution of V600E versus V600K was balanced

between treatment arms. Although limited by the low number of patients with V600K compared to patients with V600E, Inv-assessed exploratory subgroup PFS analysis by BRAF V600 mutation genotype suggests treatment benefit for V600K patients treated with COTELLIC in combination with vemurafenib.

Figure 1 Kaplan-Meier Curves of Progression-free Survival (Inv) – Intent-to-Treat Population with data cut-off date of 9 May 2014

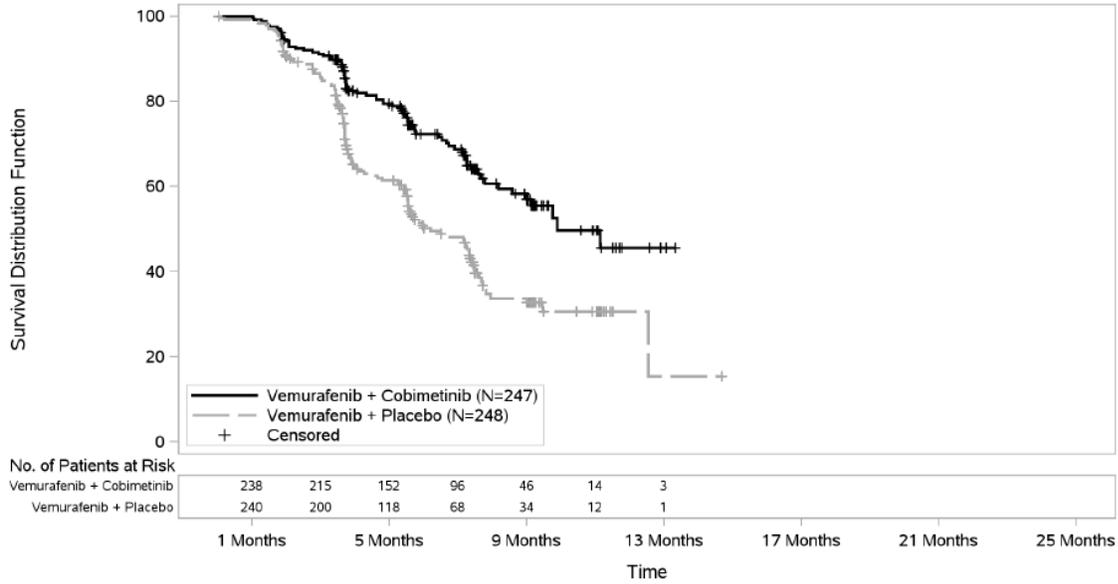
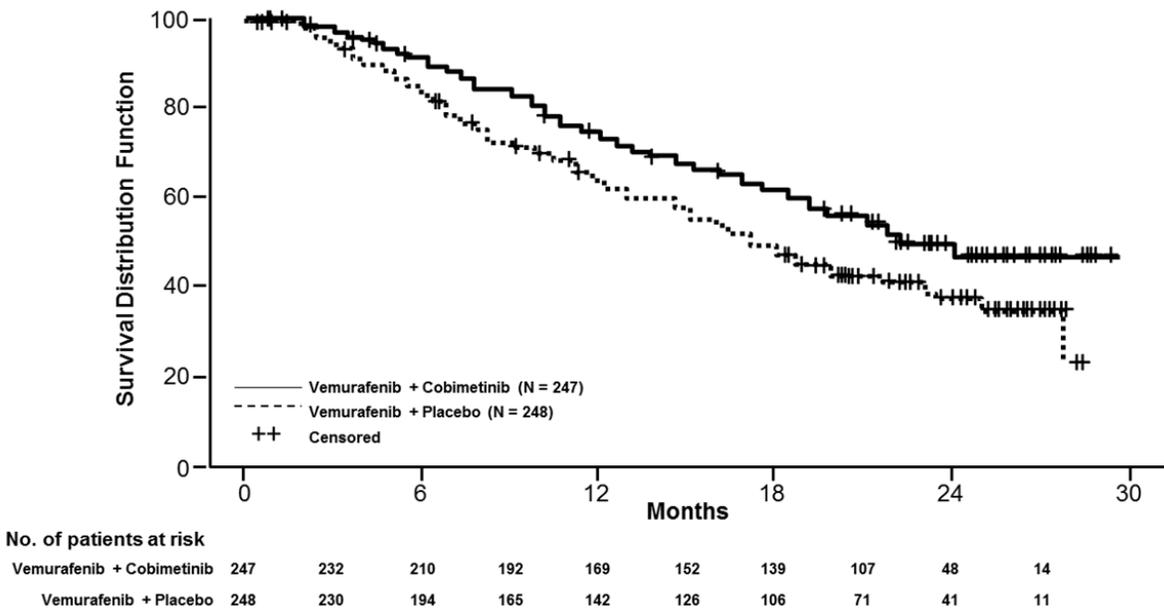


Figure 2 Kaplan-Meier Curves of Final Overall Survival – Intent-to-Treat Population with data cut-off date of 28 August 2015



Additionally, in a post hoc analysis with a data cut-off date of 16 January 2015, a median PFS of 12.3 months (95% CI 9.5, 13.4) was seen in the cobimetinib plus vemurafenib arm compared to 7.2 months (95% CI 5.6, 7.5) in the placebo plus vemurafenib arm [HR 0.58 (95% CI 0.46, 0.72)]. The median follow up of patients was 14.2 months.

Quality of Life

As measured by the EORTC QLQ-C30, all functioning domains and most symptoms (appetite loss, constipation, insomnia, nausea and vomiting, dyspnea, pain, fatigue) were similar between the two treatment arms and did not demonstrate a clinically meaningful change (≥ 10 point increase or decrease from baseline).

DETAILED PHARMACOLOGY

Safety Pharmacology

In vitro, cobimetinib was a selective inhibitor of MEK1 and MEK2 and did not inhibit other serine-threonine or tyrosine kinases ($IC_{50} > 10 \mu M$, 5310 ng/mL). In a panel of secondary pharmacological targets consisting of receptors, transporters and enzymes, the *in vitro* binding activities of the following were inhibited by $> 50\%$ at a cobimetinib concentration of $10 \mu M$ (5310 ng/mL): adrenergic β_2 receptor, muscarinic M_1 and M_2 receptors, opiate μ and κ receptors, serotonin 5-HT_{2B} receptor, σ (non-selective) receptor, somatostatin receptor, Ca^{2+} ion channel, Na^+ channel, and dopamine transporter.

In vitro, cobimetinib inhibited the human ether-à-go-go related gene (hERG) ion channel current with an IC_{50} of $0.5 \mu M$ [266 ng/mL]. In a dog cardiovascular safety pharmacology study, there were no changes in hemodynamics or ECG parameters, including QTc interval.

At clinically relevant concentrations in the rat CNS safety pharmacology study, there were no

cobimetinib-related physiological or behavioural changes.

In a tissue distribution study conducted in rats, levels of [¹⁴C]-cobimetinib-related radioactivity in the non-circumventricular CNS tissues protected by the blood:brain barrier were low.

In the respiratory safety pharmacology study conducted in the rat, the highest dose of 300 mg/kg elicited a small gradual decrease of 18% in the respiratory rate compared to pre-dose values (5-fold human clinical exposure based on unbound C_{max}). In the single dose toxicology study in the rat, a dose of 300 mg/kg led to mortality within 3 days postdose.

TOXICOLOGY

Animal Toxicology

The nonclinical toxicology profile of cobimetinib was investigated in the rat and dog in studies of up to 13 weeks in duration. Cobimetinib administration resulted in findings attributed primarily to its pharmacologic mechanism of action (inhibition of cell proliferation in tissues with high proliferative rates including gastrointestinal, integument, and hematopoietic and lymphopoietic systems). These effects occurred in animals at total systemic cobimetinib exposures generally below those achieved at the oral therapeutic dose of 60 mg/day in cancer patients (C_{max}=273 ng/mL; AUC₀₋₂₄=4340 ng hr/mL).

Repeated-dose toxicity studies in rats and dogs identified degenerative changes in the bone marrow, gastrointestinal tract, skin, thymus, adrenal gland, liver, spleen, lymph node, ovary and vagina at plasma exposures below clinical efficacious levels. These changes were generally reversible following the non-dosing recovery period, with the exception of lymphocyte depletion/necrosis and plasma cell hyperplasia in mandibular lymph nodes in rats. Dose-limiting toxicities included skin ulcerations, surface exudates, and acanthosis in the rat and chronic active inflammation and degeneration of the esophagus associated with varying degrees of gastroenteropathy in dogs.

Mortality was observed in rats and dogs at exposures below that observed in humans. In the 4-week rat study, animals treated at 1 mg/kg/day and 3 mg/kg/day survived to scheduled necropsy. Mortality was observed in animals treated at 10 mg/kg (≥0.7-fold human clinical exposure based on AUC). In the 13-week study in dogs, mortality was observed within the first 2 weeks of dosing at the dose level of 3.0 mg/kg/day (≥2.0-fold human clinical exposure based on AUC). One female dog that received 1.0 mg/kg/day was euthanized on Day 58 (~0.5 human clinical exposure based on AUC).

Carcinogenicity

No carcinogenicity studies have been conducted with COTELLIC.

Genotoxicity

Cobimetinib was not mutagenic nor did it induce structural or numerical chromosomal aberrations in vitro. Cobimetinib did not induce the formation of micronuclei in vivo in the bone marrow of rats that had been treated with cobimetinib.

Reproductive and Developmental Toxicology

No dedicated fertility studies in animals have been performed with COTELLIC.

In the repeat-dose toxicology studies, degenerative changes were observed in reproductive tissues including increased apoptosis/necrosis of corpora lutea and vaginal epithelial cells in

female rats (~2.5-fold human clinical plasma exposure based on AUC). After a single dose at higher exposures, degenerative changes were also observed in the seminal vesicles of male rats and epididymal epithelial cells of male rats and dogs (\geq 8-fold human clinical plasma exposure based on AUC).

In a repeat dose toxicity study in juvenile rats, cobimetinib systemic exposures were 2 to 11 fold higher on Day 1 than on Day 28 when exposures were similar to those in the pivotal toxicity studies in adult rats. Daily oral doses of 3 mg/kg (approximately 0.13–0.5 times the adult human AUC at the recommended dose of 60 mg) administered beginning postnatal Day 10 were associated with mortality on postnatal Day 17, the cause of which was not defined. The same dose did not lead to mortality in adult animals. In juvenile rats, cobimetinib administration resulted in similar changes as seen in the pivotal toxicity studies in adults, including reversible degenerative changes in the thymus and liver, decreased spleen and thyroid/parathyroid weights, increased phosphorus, bilirubin and red cell mass, and decreased triglycerides.

When administered to pregnant rats, cobimetinib caused embryolethality and fetal malformations of the great vessels and skull at systemic exposures approximately 0.9 to 1.4-fold human clinical plasma exposure based on AUC.

Phototoxicity

Cobimetinib was shown to be potentially phototoxic after UVA/UVB irradiation *in vitro* using cultured murine fibroblasts. There was no evidence of cutaneous or ocular phototoxicity in Long-Evans pigmented rats exposed to a single dose of cobimetinib (~7-fold human clinical plasma exposure based on AUC) and subsequent exposure to UVA and UVB radiation from a xenon lamp (to simulate sunlight).

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2. Ribas A, Gonzalez R, Pavlick A, et al. Combination of vemurafenib and cobimetinib in patients with advanced BRAF(V600)-mutated melanoma: a phase 1b study. *Lancet Oncol.* 2014;15:954-65.
3. Larkin J, Ascierto PA, Combined Vemurafenib and Cobimetinib in BRAF-Mutated Melanoma. *N Engl J Med.* 2014 ;371:1867-76.
4. Ascierto PA, McArthur GA, Dréno B, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. *Lancet Oncol.* 2016 Sep;17(9):1248-60.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

COTELLIC® cobimetinib tablets

Read this carefully before you start taking COTELLIC and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional (doctor, pharmacist or nurse) about your medical condition and treatment and ask if there is any new information about COTELLIC.

Serious Warnings and Precautions

Side effects of COTELLIC in combination with ZELBORAF® (vemurafenib), which have sometimes been serious or life-threatening, include:

- **Heart problems that can lead to inadequate pumping of the blood by your heart**
- **Bleeding problems, including bleeding in a critical area or organ of your body**
- **Eye problems**

COTELLIC should not be used with certain types of drugs that can increase the blood level of COTELLIC.

COTELLIC in combination with ZELBORAF should be prescribed and managed by a doctor who knows how to use anti-cancer drugs.

What is COTELLIC used for?

COTELLIC is used to treat adult patients with a type of skin cancer called melanoma that has spread to other parts of the body or cannot be removed by surgery.

- It is used in combination with another anti-cancer medicine called ZELBORAF. You should also read the patient medication information leaflet that comes with ZELBORAF.
- It can only be used in patients whose cancer has a specific type of change (mutation) in a gene called “BRAF”. You should have your cancer tested for this change in the “BRAF” gene before starting treatment with COTELLIC in combination with ZELBORAF.

How does COTELLIC work?

COTELLIC targets a protein called “MEK” that is important in controlling cancer cell growth. When COTELLIC is used in combination with ZELBORAF (which targets proteins made from the changed “BRAF” gene), it further slows down or stops the growth of your cancer.

What are the ingredients in COTELLIC?

Medicinal ingredients: cobimetinib fumarate

Non-medicinal ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol 3350 (macrogol 3350), polyvinyl alcohol, talc, and titanium dioxide.

COTELLIC comes in the following dosage forms:

Tablets, 20 mg

Do not use COTELLIC if:

- You are allergic to cobimetinib or any of the other ingredients in COTELLIC

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take COTELLIC. Talk about any health conditions or problems you may have, including if you:

- have melanoma cancer in your brain that has not been treated
- have any heart problems
- have high blood pressure (hypertension)
- have any health conditions or take any medicines that may increase your risk of bleeding, such as blood thinners (e.g. warfarin) and medicines that may affect blood clotting (e.g. clopidogrel, aspirin, naproxen and ibuprofen)
- have any liver problems
- have any allergies to medications
- have any muscle problems
- have any eye problems or related risk factors such as high cholesterol levels, for serious eye problems that may occur with COTELLIC
- are planning to have a child in the future. COTELLIC may reduce your fertility.
- have any previous or current skin problems, including skin cancers other than melanoma
- have high blood sugar levels (diabetes)
- have any other medical conditions
- are pregnant, think you may be pregnant, or plan on becoming pregnant. COTELLIC can harm your unborn baby.
 - Female patients who take COTELLIC should use two forms of birth control during treatment with COTELLIC and for at least 3 months after stopping COTELLIC.
 - Talk to your healthcare professional about birth control methods that may be right for you.
 - Tell your healthcare professional 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. You and your healthcare professional should decide if you will take COTELLIC or breastfeed. You should not do both.

Other warnings you should know about during treatment:

- **Driving and using machines:** COTELLIC can affect your ability to drive or use machines. Avoid driving, using tools or operating machines if you have problems with your vision or other problems that might affect your ability, e.g. if you feel dizzy or tired. Talk to your doctor if you are not sure.
- **Increased Sensitivity to Sunlight:** Avoid sunlight while you are taking COTELLIC. COTELLIC in combination with ZELBORAF can make your skin sensitive to sunlight. You may burn more easily and get severe sunburns. To help protect against sunburn:
 - When you go outside, wear clothes that protect your skin, including your head, face, hands, arms, and legs.
 - Use lip balm and a broad-spectrum sunscreen with SPF 30 or higher.

- **Lactose:** COTELLIC contains lactose (a type of sugar). If you have been told by your healthcare professional that you have intolerance to lactose, talk to your healthcare professional before taking this medicine.
- **Children and adolescents:** COTELLIC is not recommended for children and adolescents. The effects of COTELLIC in people younger than 18 years old are not known.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with COTELLIC:

Some types of medicines can affect a type of protein in the body called CYP3A. This protein breaks down COTELLIC in the body. Use of these medicines while on COTELLIC may make it more likely that you will have side effects, or may affect how COTELLIC works.

- Drugs used to treat fungal infections (itraconazole, ketoconazole, posaconazole, voriconazole, fluconazole, miconazole)
- Antibiotics used to treat infections (clarithromycin, erythromycin, rifampin)
- Drugs used to treat HIV infection (lopinavir, ritonavir, fosamprenavir, delavirdine, efavirenz, etravirine)
- Drugs used to treat heart problems (amiodarone, diltiazem, verapamil)
- Drugs used to treat seizures (fits) (carbamazepine, phenytoin)
- Bosentan, used to treat high blood pressure in the blood vessels between the heart and the lungs
- Modafinil, used to treat sleep disorders
- Imatinib, an anti-cancer drug
- Cyclosporine, used to decrease your body's immune reaction
- St. John's Wort (*Hypericum perforatum*) used to treat depression and other conditions
- You should not drink grapefruit juice, eat grapefruit or take any products containing grapefruit extract while you are on COTELLIC in combination with ZELBORAF.

How to take COTELLIC:

- Always take COTELLIC exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- Swallow COTELLIC tablets whole with a glass of water.
- COTELLIC can be taken with or without food.

Usual adult dose:

- The recommended dose of COTELLIC is 60 mg (3 tablets) taken once daily for 21 days, followed by a 7 day break with no COTELLIC treatment (28 day cycle – 3 weeks on, 1 week off).
- During the 7 day break with no COTELLIC treatment, you should keep taking ZELBORAF as directed by your healthcare professional.
- Start your next COTELLIC treatment cycle after the 7 day break.

Vomiting:

If you vomit (throw up) after taking COTELLIC, do not take an extra dose of COTELLIC on that day. Continue to take COTELLIC as normal, the next day.

Overdose:

If you think you have taken too much COTELLIC, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take COTELLIC and:

- If it is more than 12 hours before your next dose, take the missed dose as soon as you remember.
- If it is less than 12 hours before your next dose, skip the missed dose. Take the next dose at the usual time.
- Do not take a double dose to make up for a missed dose.

What are possible side effects from using COTELLIC?

These are not all the possible side effects you may feel when taking COTELLIC. Tell your healthcare professional if any of the side effects listed bothers you or does not go away. If you experience any side effects not listed here, contact your healthcare professional. Please also see the warnings above.

Very common side effects of COTELLIC – these may affect more than 1 in 10 people:

- Vomiting
- Nausea
- Abdominal pain
- Fever
- Chills
- Swelling of the arms or legs
- Skin rash with a flat discoloured area or raised bumps that looks like acne
- Muscle aches

See also the table below called *Serious side effects and what to do about them*.

Common side effects of COTELLIC – these may affect up to 1 in 10 people:

- Increased sugar level (shown in blood tests)
- Dehydration
- Dizziness
- Mouth sores, including those caused by the herpes virus (cold sores)
- Dry mouth
- Hives
- Common cold (sore throat, stuffy and / or runny nose)
- Yeast infections
- Swelling, pain and redness of the palm of hand and sole of foot
- Small red bumps or pimples around hair follicles which may be itchy or tender
- Tender and red bumps under the skin due to inflammation of the layer of fat under the skin
- Swelling, redness and itching of the eye
- Muscle weakness

See also the table below called *Serious side effects and what to do about them*.

Your healthcare professional will take blood tests while you are taking COTELLIC. The most common changes to blood tests include:

- increased blood levels of liver enzymes (GGT, ALT, or AST)
- decreased blood levels of albumin (a protein made by the liver)

- increased blood level of bilirubin (a yellow pigment in the blood)
- increased blood level of an enzyme from the pancreas called lipase
- increased blood level of an enzyme called lactate dehydrogenase
- increased blood level of enzyme from muscle [creatinine phosphokinase (CPK)]
- decreased blood level of phosphate, sodium or potassium
- increased blood level of sodium
- increased blood level of cholesterol
- increased blood level of liver or bone enzyme (alkaline phosphatase)
- decreased blood level of a type of white blood cell (lymphocyte)
- decreased blood level of red blood cells (anemia)

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	Stop taking drug and get immediate medical help
VERY COMMON		
Diarrhea: increased number of stools, loose or watery stools	✓	
Hypertension (high blood pressure): new or worsening high blood pressure, severe headache, lightheadedness, dizziness	✓	
Photosensitivity (increased sensitivity to sunlight): red, painful, itchy skin that is hot to touch (sunburn), sun rash, skin irritation, bumps or tiny papules, thickened, dry, wrinkled skin	✓	
COMMON		
Eye problems: blurred vision, distorted vision, partly missing vision, halos, any other vision changes. These problems can arise from:		
<ul style="list-style-type: none"> • Serous retinopathy (a build-up of fluid under the retina of the eye) • Separation of the retina (the area of the eye responsible for sight) from its connection at the back of the eye • Retinal vein occlusion (a blockage in a blood vessel carrying blood away from the retina): blurred or reduced vision, usually affects one eye, can occur suddenly 	✓	
Heart problems: These problems can arise from:		
<ul style="list-style-type: none"> • Left ventricular dysfunction (inadequate pumping of blood by the heart): persistent coughing or wheezing, shortness of breath, tiredness, increased heart rate, swelling of your ankles and feet • Atrial fibrillation (irregular heartbeat): feeling that your heart is racing or fluttering, weakness, decreased ability to exercise, tiredness, dizziness, lightheadedness, confusion, difficulty breathing, chest pain 	✓	
Bleeding problems: blood in the urine, unusual or excessive vaginal bleeding, bleeding of the gums, abdominal pain, red or black stools that look like tar, headache, dizziness, or feeling weak.	✓	

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	Stop taking drug and get immediate medical help
Allergic reactions: itchy rash, hives, redness of skin, swelling of the face, lips, tongue, or throat, difficulty swallowing or breathing		✓
Rash: a rash that covers a large area of your body, blisters, or peeling skin	✓	
Pneumonitis (inflammation of the lungs): difficulty breathing, may be accompanied by cough, fever or chills	✓	
Basal-cell carcinoma, cutaneous squamous cell carcinoma, and keratoacanthoma (types of skin cancer): new wart, skin sore or reddish bump that bleeds or does not heal	✓	
Abnormal liver test or liver injury: yellowing of your skin or the white of your eyes, dark or brown (tea coloured) urine, nausea or vomiting, feeling tired or weak, loss of appetite	✓	
Increased serum creatine phosphokinase (CPK) levels (increased blood levels of an enzyme from muscle) and rhabdomyolysis (a rapid breakdown of muscle): unexplained muscle aches, muscle spasms and weakness, dark, reddish-coloured urine.	✓	
UNCOMMON New primary melanoma: mole which has irregular shape, border, or colour, is growing, or changing shape or colour	✓	

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect™ (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Postal Locator 1908C
Ottawa, ON
K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect™ (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>).

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Keep out of reach and sight of children.
- Store COTELLIC between 15-30°C.

- Do not take this medicine after the expiry date which is stated on the blister pack after “EXP”. The expiry date refers to the last day of that month.
- Do not throw away any unused medicine in the garbage or down the drain or toilet. Ask your pharmacist how to best dispose of medicines that you no longer require. These measures will help to protect the environment.

If you want more information about COTELLIC:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website \(http://hc-sc.gc.ca/index-eng.php\)](http://hc-sc.gc.ca/index-eng.php); the manufacturer’s website (www.rochecanada.com), or by calling 1-888-762-4388.

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