TAB-COT-2017 10

COTELLIC FILM-COATED TABLET 20MG

Cobimetinib

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1. DESCRIPTION

1.1 THERAPEUTIC / PHARMACOLOGIC CLASS OF DRUG

Cobimetinib is a small molecule that is a potent and highly selective targeted inhibitor of MEK1 and MEK2 tyrosine-threonine kinases

ATC code: L01XE38

1.2 TYPE OF DOSAGE FORM

Film-coated tablet

1.3 ROUTE OF ADMINISTRATION

Oral

1.4 STERILE / RADIOACTIVE STATEMENT

Not applicable

1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Cobimetinib

Each film-coated tablet contains 20 mg cobimetinib (22.20 mg as cobimetinib hemifumarate salt). Cobimetinib tablets 20 mg, are round, white, film-coated tablets with "COB" debossed on one side.

Excipients:

Core: Lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate

Film coat: polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc

2. CLINICAL PARTICULARS

2.1 THERAPEUTIC INDICATION(S)

Cotellic is indicated for use in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation.

2.2 DOSAGE AND ADMINISTRATION

General

Cotellic therapy should only be initiated and supervised by a healthcare professional experienced in the treatment of patients with cancer.

Patients treated with Cotellic in combination with vemurafenib must have BRAF V600 mutation-positive melanoma tumor status confirmed by a validated test.

Please also refer to the full prescribing information for vemurafenib, which is used in combination with Cotellic.

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 (60mg) 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 dose of three 20 mg tablets (60 mg) can be taken with or without food (*see Section 3.2.1 Absorption*). Cotellic tablets should be swallowed whole with water.

Duration of treatment

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

Delayed or Missed doses

If a dose is missed, it can be taken up to 12 hours prior to the next dose to maintain the once-daily regimen.

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

General

Cotellic dose modification should be based on the prescriber's assessment of individual patient safety or tolerability.

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.

Dose modification of Cotellic is independent of vemurafenib dose modification. The decision on whether to dose reduce either or both drugs should be based on clinical assessment.

Table 1 below gives general Cotellic dose modification advice.

Table 1 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	
1st Appearance	Interrupt treatment until grade ≤1, restart treatment at 40mg once daily
2nd Appearance	Interrupt treatment until grade ≤1, restart treatment at 20mg once daily
3rd Appearance	Consider permanent discontinuation

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

Dose modification advice for specified adverse drug reactions(ADRs)

Hemorrhage

Grade 4 events or cerebral hemorrhage (all grades):
Interrupt Cotellic treatment. Permanently discontinue Cotellic for hemorrhage events attributed to Cotellic.

Grade 3 events:
Interrupt Cotellic treatment. There is no data on the effectiveness of Cotellic dose modification for hemorrhage events. Clinical judgment should be applied when considering restarting Cotellic treatment. Vemurafenib dosing can be continued when Cotellic treatment is interrupted, if clinically indicated.

Left ventricular dysfunction

Permanent discontinuation of Cotellic treatment should be considered if cardiac symptoms are attributed to Cotellic and do not improve after temporary interruption of Cotellic.

Table 2 Recommended dose modifications for Cotellic in patients with left ventricular ejection fraction (LVEF) decrease from baseline

Patient	LVEF value	Recommended Cotellic Dose Modification	LVEF value following treatment break	Recommended Cotellic daily dose
Asymptomatic	≥ 50% (or 40 – 49% and <10% absolute decrease from baseline)	Continue at current dose	N/A	N/A
	< 40% (or 40 – 49% and ≥ 10% absolute decrease from baseline)	Interrupt treatment for 2 weeks	<10% absolute decrease from baseline	1st occurrence: 40mg
				2nd occurrence: 20mg
				3rd occurrence: permanent discontinuation
			< 40% (or ≥ 10% absolute decrease from baseline)	Permanent discontinuation
Symptomatic	Not Applicable	Interrupt treatment for 4 weeks	Asymptomatic and <10% absolute decrease from baseline	1st occurrence: 40mg
				2nd occurrence: 20mg
				3rd occurrence: permanent discontinuation
			Asymptomatic and < 40% (or ≥ 10% absolute decrease from baseline)	Permanent discontinuation
			Symptomatic regardless of LVEF	Permanent discontinuation

Vemurafenib treatment can be continued when Cotellic treatment is modified (if clinically indicated).

Rhabdomyolysis and Creatine phosphokinase (CPK) elevations

Rhabdomyolysis or symptomatic CPK elevations:
Interrupt Cotellic treatment. If severity is improved by at least one grade within 4 weeks, restart Cotellic at a dose reduced by 20 mg, if clinically indicated. Vemurafenib dosing can be continued when Cotellic treatment is modified, if clinically indicated.

If rhabdomyolysis or symptomatic CPK elevations do not improve within 4 weeks, permanently discontinue Cotellic treatment.

Asymptomatic CPK elevations:
Grade ≤ 3: Cotellic dosing does not need to be modified or interrupted to manage asymptomatic Grade ≤ 3 creatine phosphokinase (CPK) elevations (*see section 2.6 Undesirable Effects, Clinical Trials, Laboratory Abnormalities*).

Grade 4: Interrupt Cotellic treatment. If improved to Grade ≤ 3 within 4 weeks, restart Cotellic at a dose reduced by 20 mg, if clinically indicated. Vemurafenib dosing can be continued when Cotellic treatment is modified, if clinically indicated. If CPK elevations do not improve to Grade ≤3 within 4 weeks following dose interruption, permanently discontinue Cotellic treatment.

Liver laboratory abnormalities

For Grade ≤ 2 liver laboratory abnormalities, Cotellic and vemurafenib should be continued at the prescribed dose.

Grade 3: Continue Cotellic at the prescribed dose. The dose of vemurafenib may be reduced as clinically appropriate. Please refer to the full prescribing information for vemurafenib.

Grade 4:

Interrupt Cotellic treatment and vemurafenib treatment. If liver laboratory abnormalities improve to Grade ≤1 within 4 weeks, restart Cotellic at a dose reduced by 20 mg and vemurafenib at a clinically appropriate dose; please refer to the full prescribing information for vemurafenib.

If liver laboratory abnormalities do not resolve to Grade ≤1 within 4 weeks or if Grade 4 liver laboratory abnormalities recur, discontinue Cotellic treatment and vemurafenib treatment.

Photosensitivity

Grade ≤ 2 (tolerable) photosensitivity should be managed with supportive care.

Grade 2 (intolerable) or Grade ≥ 3 photosensitivity: Cotellic and vemurafenib should be interrupted until resolution to Grade ≤ 1. Treatment can be restarted with no change in Cotellic dose. Vemurafenib dosing should be reduced; please refer to the full prescribing information for vemurafenib.

Rash

Rash events may occur with either Cotellic or vemurafenib treatment. The dose of Cotellic and/or vemurafenib may be either interrupted and/or reduced as clinically indicated. Additionally:

Grade ≤ 2 (tolerable) rash should be managed with supportive care.

Grade 2 (intolerable) or Grade ≥ 3 rash:

Acneiform rash: Follow general dose modification table recommendations in Table 1 for Cotellic. Vemurafenib dosing can be continued when Cotellic treatment is modified (if clinically indicated).

Non-acneiform or maculopapular rash: Cotellic dosing can be continued without modification (if clinically indicated). Vemurafenib dosing may be either temporarily interrupted and/or reduced, please refer to the full prescribing information for vemurafenib.

QT prolongation

If during treatment the QTc exceeds 500 msec, please refer to the vemurafenib product insert for dose modifications for vemurafenib. No dose modification of Cotellic is required when taken in combination with vemurafenib.

2.2.1 Special Dosage Instructions

Elderly: No dose adjustment of Cotellic is required in patients ≥ 65 years of age.

Children: The safety and efficacy of Cotellic in children and adolescents (<18 years) have not been established.

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 section 3.2.5 Pharmacokinetics in Special Populations*).

Hepatic impairment: No dose adjustment is recommended in patients with hepatic impairment (*see section 3.2.5 Pharmacokinetics in Special Populations*). Cotellic should be used with caution in patients with moderate to severe hepatic impairment. Liver laboratory abnormalities can occur when Cotellic is used in combination with vemurafenib (*see section 2.4 Warnings and Precautions, General*).

2.3 CONTRAINDICATIONS

Cotellic is contraindicated in patients with known hypersensitivity to cobimetinib or any of the excipients.

2.4 WARNINGS AND PRECAUTIONS

2.4.1 General

Please also refer to the full prescribing information for vemurafenib, which is used in combination with Cotellic.

Hemorrhage

Hemorrhage, including major hemorrhages defined as symptomatic bleeding in a critical area or organ, can occur with Cotellic (*see section 2.6 Undesirable Effects, Clinical Trials*).

Bleeding events have been reported more frequently in the Cotellic plus vemurafenib arm than in the placebo plus vemurafenib arm (all types and grades: 13% vs 7%) in Study GO28141 (see section 2.6 *Undesirable Effects*). Higher frequencies in the Cotellic plus vemurafenib arm were observed for cerebral hemorrhage (1% vs 0%), GI tract hemorrhage (4% vs 2%), reproductive system hemorrhage (2% vs 1%), and hematuria (3% vs 1%).
The majority of events were Grade 1 or 2 and non-serious (12% of patients in the Cotellic plus vemurafenib arm vs 7% patients in the placebo plus vemurafenib arm). Grade 3-5 events were experienced by 1% of patients in each arm. Most events resolved or were resolving with no change in Cotellic dose. Grade 3-4 events were experienced by 1% of patients in each arm.

Based on post marketing surveillance and safety from other clinical trials, additional cases of severe hemorrhage cases have been identified, including intracranial and gastrointestinal tract bleeds. Many of these patients had other risk factors for bleeding including prior medical history, or concurrent medications such as anticoagulants or antiplatelet therapy.

Caution should be used in patients with additional risk factors for bleeding, such as brain metastases, and/or in patients that use concomitant medications that increase the risk of bleeding (including antiplatelet or anticoagulant therapy).

Please refer to section 2.2 for hemorrhage management (*see Dose modification advice for specified adverse drug reactions (ADRs), Hemorrhage*).

Cotellic in combination with vemurafenib in patients who have progressed on a BRAF inhibitor

There are limited data in patients taking the combination of Cotellic with vemurafenib who have progressed on a prior BRAF inhibitor. These data show that the efficacy of the combination will be lower in these patients (see section 3.1.2). Therefore other treatment options should be considered before treatment with the combination in this prior BRAF inhibitor treated population. The sequencing of treatments following progression on a BRAF inhibitor therapy has not been established.

Cotellic in combination with vemurafenib in patients with brain metastases

The safety and efficacy of the combination of Cotellic and vemurafenib have not been evaluated in patients with a BRAF V600 mutation-positive melanoma which has metastasised to the brain. The intracranial activity of cobimetinib is currently unknown (see sections 3.1.2).

Serous retinopathy

Serous retinopathy (fluid accumulation within the layers of the retina) has been observed in patients treated with MEK-inhibitors, including Cotellic (*see section 2.6 Undesirable Effects, Clinical Trials*). The majority of events were reported as chorioretinopathy or retinal detachment.

Median time to initial onset of serous retinopathy events was 1 month (range 0 - 9 months). Most events observed in clinical trials were resolved, or improved to asymptomatic grade 1, following dose interruption or reduction.

For patients reporting new or worsening visual disturbances, an ophthalmologic examination is recommended. If serous retinopathy is diagnosed, Cotellic treatment should be withheld until visual symptoms improve to Grade ≤1. Serous retinopathy can be managed with treatment interruption, dose reduction or with treatment discontinuation (*see section 2.2 Dosage and Administration, Dose Modification Recommendations: Table 1*).

Left ventricular dysfunction

Decrease in left ventricular ejection fraction (LVEF) from baseline has been reported in patients receiving Cotellic (*see section 2.6 Undesirable Effects, Clinical Trials*). Median time to initial onset of events was 4 months (1 - 13 months).

LVEF 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. Decrease in LVEF from baseline can be managed using treatment interruption, dose reduction or with treatment discontinuation (*see section 2.2 Dosage and Administration, Dose modification advice for specified adverse drug reactions (ADRs), Left ventricular dysfunction*).
All patients restarting treatment with a dose reduction of Cotellic should have LVEF measurements taken after approximately 2 weeks, 4 weeks, 10 weeks and 16 weeks, and then as clinically indicated.

Patients with a baseline LVEF either below institutional lower limit of normal (LLN) or below 50% have not been studied.

Liver laboratory abnormalities

Liver laboratory abnormalities can occur when Cotellic is used in combination with vemurafenib, and when vemurafenib is used as a single agent (*please refer to the full prescribing information for vemurafenib*).

Liver laboratory abnormalities, specifically increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP), have been observed in patients treated with Cotellic plus vemurafenib (*see section 2.6 Undesirable Effects, Clinical Trials, Laboratory Abnormalities*).

Monitor for liver value abnormalities by liver laboratory tests before initiation of combination treatment and monthly during treatment, or more frequently as clinically indicated.

Manage Grade 3 liver laboratory abnormalities with treatment interruption or dose reduction of vemurafenib. Manage Grade 4 liver laboratory abnormalities with dose

interruption, reduction or discontinuation of treatment of both Cotellic and vemurafenib (*see section 2.2 Dosage and Administration, Dose modification recommendations*).

Rhabdomyolysis and CPK elevations

Rhabdomyolysis has been reported in patients receiving Cotellic (*see section 2.6 Undesirable Effects, Post-Marketing*).

Interrupt treatment with Cotellic if rhabdomyolysis is diagnosed, and monitor CPK levels and other symptoms until resolution. Depending on the severity of rhabdomyolysis, dose reduction or treatment discontinuation may be required (*see section 2.2 Dosage and Administration, Dose modification advice for specified adverse drug reactions (ADRs), Rhabdomyolysis and Creatine phosphokinase (CPK) elevations*).

Grade 3 and 4 CPK elevations, including asymptomatic elevations over baseline, also occurred in patients receiving Cotellic with vemurafenib in clinical trials (*see section 2.6 Undesirable Effects, Clinical Trials, Laboratory Abnormalities*). The median time to first occurrence of Grade 3 or 4 CPK elevations was 16 days (range: 11 days to 10 months); the median time to complete resolution was 16 days (range: 2 days to 15 months).

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. If serum CPK is elevated, check for signs and symptoms of rhabdomyolysis or other causes. Depending on the severity of symptoms or CPK elevation, treatment interruption, dose reduction or treatment discontinuation may be required (*see section 2.2 Dosage and Administration, Dose modification advice for specified adverse drug reactions (ADRs), Rhabdomyolysis and Creatine phosphokinase (CPK) elevations*).

Diarrhoea

Cases of Grade ≥3 and serious diarrhoea have been reported in patients treated with Cotellic. Diarrhoea should be managed with anti-diarrhoeal agents and supportive care. For Grade ≥3 diarrhoea that occurs despite supportive care, Cotellic and vemurafenib should be withheld until diarrhoea has improved to Grade ≤1. If Grade ≥3 diarrhoea recurs, the dose of Cotellic and vemurafenib should be reduced (see section 2.6).

2.4.2 Drug Abuse and Dependence

No data to report.

2.4.3 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 section 2.4 Warnings and Precautions, General, Serous retinopathy*

and 2.6 Undesirable Effects, Clinical Trials). Patients should be advised not to drive or use machines without first consulting with their prescriber if their vision is impaired.

2.4.4 Laboratory Tests

See sections 2.4 Warnings and Precautions, General, and 2.6, Undesirable Effects

2.4.5 Interactions with other Medicinal Products and other Forms of Interaction

Effects of concomitant medications on cobimetinib

CYP3A Inhibitors/Inducers:

Cobimetinib is metabolized by CYP3A and cobimetinib AUC increased approximately 7-fold in the presence of a potent CYP3A inhibitor (itraconazole) in healthy subjects. Since cobimetinib is a sensitive substrate of CYP3A, it is likely that cobimetinib exposures will be lower in the presence of CYP3A inducers. Therefore concomitant administration of potent CYP3A inducers and inhibitors is not recommended. If concomitant use of a strong CYP3A inhibitor is unavoidable, patients should be carefully monitored for safety. For strong CYP3A inhibitors used short-term (7 days or less), consider interrupting cobimetinib therapy during the duration of inhibitor use. Caution should be exercised when cobimetinib is co-administered with moderate CYP3A inducers and inhibitors.

Acid Reducing Agents:

Cobimetinib pharmacokinetics are not altered by the co-administration of a proton pump inhibitor. Cobimetinib was administered in the presence of rabeprazole (a proton pump inhibitor) in healthy subjects to determine the effect of increased gastric pH. Thus, gastric pH elevations do not affect cobimetinib absorption.

Effects of cobimetinib on concomitant medications

CYP Substrates:

In vitro data indicate that cobimetinib is an inhibitor of CYP3A and CYP2D6. A clinical drug-drug interaction (DDI) Study in cancer patients showed that plasma concentrations of midazolam (a sensitive CYP3A substrate) and dextromethorphan (a sensitive CYP2D6 substrate) were not altered in the presence of cobimetinib. Therefore cobimetinib can be co-administered with medications that are substrates of CYP3A and CYP2D6.

In vitro, cobimetinib is a potential inducer of CYP1A2 and may therefore reduce the exposure of substrates of this enzyme e.g., theophylline. No clinical DDI studies have been conducted to assess the clinical relevance of this finding.

Other anti-cancer agents

Vemurafenib:

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

Effects of transporters on cobimetinib

In vitro studies show that cobimetinib is a substrate of P-glycoprotein (P-gp). Concomitant administration of P-gp inhibitors such as ciclosporin and verapamil may have the potential to increase plasma concentrations of cobimetinib.

In vitro studies also show that cobimetinib is not a substrate of breast cancer resistance protein (BCRP). No clinical DDI studies have been conducted to assess this finding, and clinically relevant inhibition of intestinal BCRP cannot be ruled out.

In vitro studies show that cobimetinib is not a substrate of the liver uptake transporters OATP1B1, OATP1B3, and OCT1.

Effects of cobimetinib on transporters

In vitro data suggest that cobimetinib is a weak to moderate inhibitor of BCRP, and a weak inhibitor of OATP1B1, OATP1B3 and OCT1. The clinical relevance of these findings has not been investigated.

Cobimetinib is not an inhibitor of P-gp, OAT1, OAT3 or OCT2. It is unlikely that cobimetinib would alter the hepatic uptake or renal excretion of drugs that are substrates of these transporters.

2.5 USE IN SPECIAL POPULATIONS

2.5.1 Pregnancy

Cotellic is not recommended during pregnancy.

There are no data regarding the use of Cotellic in pregnant women. When administered to pregnant rats, cobimetinib caused embryolethality and fetal malformations of the great vessels and skull at clinically relevant exposures (see section 3.3.4 Teratogenicity).

Use two effective forms of contraception during treatment with Cotellic and for at least three months following treatment discontinuation.

2.5.2 Labor and Delivery

The safe use of Cotellic during labor and delivery has not been established.

2.5.3 Nursing Mothers

It is not known whether Cotellic is excreted in human breast milk. A risk to newborns/infants cannot be excluded. A decision should be made whether to recommend breast-feeding or to administer the drug, taking into account the importance of the drug to the mother.

2.5.4 Pediatric Use

The safety and efficacy of Cotellic in children and adolescents (<18 years) have not yet been established.

2.5.5 Geriatric Use

Age does not have an effect on Cotellic exposure (*see Section 3.2.5 Pharmacokinetics in Special Populations*).

2.5.6 Gender

Gender does not have an effect on Cotellic exposure (*see Section 3.2.5 Pharmacokinetics in Special Populations*).

2.5.7 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 Section 3.2.5 Pharmacokinetics in Special Populations*).

2.5.8 Hepatic Impairment

No dose adjustment is recommended in patients with hepatic impairment (*see section 3.2.5 Pharmacokinetics in Special Populations*). Liver laboratory abnormalities can occur when Cotellic is used in combination with vemurafenib (*see section 2.4 Warnings and Precautions, General*).

2.5.9 Ethnicity

The effect of race could not be assessed due to limited data available in non-Caucasian ethnic groups (see Section 3.1.2 Clinical/Efficacy Studies).

2.6 UNDESIRABLE EFFECTS

2.6.1 Clinical Trials

The safety of Cotellic in combination with vemurafenib has been evaluated in 247 patients with advanced BRAF V600 mutated melanoma in Study GO28141.

The median time to onset of first Grade ≥ 3 adverse events was 0.6 months in the Cotellic plus vemurafenib arm vs 0.8 months in the placebo plus vemurafenib arm.

The safety of Cotellic in combination with vemurafenib has also been evaluated in 129 patients with advanced BRAF V600 mutated melanoma in Study NO25395. The safety profile of NO25395 was consistent with that observed in Study GO28141.

The table below summarizes the 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 3 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				Frequency[a] (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	13	2	8	2	very common
Eye Disorders					
Chorioretinopathy	13	<1	<1	-	very common
Vision Blurred	10	-	2	-	very common
Retinal Detachment	9	2	<1	-	common
Gastrointestinal disorders					
Diarrhea	60	6	31	1	very common
Nausea	41	1	25	1	very common
Vomiting	24	1	13	1	very common
General disorders and administration site conditions					
Pyrexia	28	2	23	-	very common
Chills	10	-	5	-	very common
Investigations					
Decreased Ejection Fraction	9	2	4	1	common
Metabolism and nutrition disorders					
Dehydration	4	2	1	-	common
Hyponatremia	5	2	1	<1	common
Neoplasms benign, malignant and unspecified					
Basal Cell Carcinoma	4	4	2	2	common
Skin and subcutaneous tissue disorders					
Photosensitivity[b]	47	4	35	-	very common
Maculo−papular rash	15	7	15	5	very common
Acneiform Dermatitis	14	2	9	1	very common
Vascular Disorders					
Hypertension	15	4	8	2	very common

[a] Based on the Phase III Study GO28141 adverse events of all grades
[b] 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:

Eye disorders; Visual impairment (3% in Cotellic plus vemurafenib arm vs 0% in the placebo plus vemurafenib arm) (*see sections 2.4 Warnings and Precautions, General, Serous retinopathy, and 2.4.3 Ability to Drive and Use Machines*)

Metabolism and nutrition disorders: Hyperglycemia (3% in the Cotellic plus vemurafenib arm vs 1% in the placebo plus vemurafenib arm), Hypophosphatemia (4% in the Cotellic plus vemurafenib arm vs 1% in the placebo plus vemurafenib arm)

Respiratory, thoracic and mediastinal disorders: Pneumonitis (1% in the Cotellic plus vemurafenib arm vs <1% in the placebo plus vemurafenib arm)

Skin and subcutaneous tissue disorders: Rash (40% in the Cotellic plus vemurafenib arm vs 38% in the placebo plus vemurafenib arm)

Further information on selected adverse reactions

Hemorrhage

Bleeding events have been reported more frequently in the Cotellic plus vemurafenib arm than in the placebo plus vemurafenib arm (all types and grades: 13% vs 7%). Higher frequencies in the Cotellic plus vemurafenib arm were observed for cerebral hemorrhage (1% vs 0%), gastrointestinal (GI) tract hemorrhage (4% vs 1%), reproductive system hemorrhage (2% vs <1%), and hematuria (3% vs 1%).

The majority of events were Grade 1 or 2 and non-serious (12% of patients in the Cotellic plus vemurafenib arm vs 7% patients in the placebo plus vemurafenib arm). Grade 3-4 events were experienced by 1% of patients in each arm. Most events resolved or were resolving with no change in Cotellic dose.

Grade 3-4 events were experienced by 1% of patients in each arm (*see section 2.4 Warnings and Precautions, General*).

Photosensitivity

Photosensitivity has been observed with a higher frequency in the Cotellic plus vemurafenib vs. placebo plus vemurafenib arm (47% vs. 35%). The majority of events

were Grades 1 or 2, with Grade ≥ 3 events occurring in 4% of patients in the Cotellic plus vemurafenib arm vs. 0% in the placebo plus vemurafenib arm.

There were no apparent trends in the time of onset of Grade ≥ 3 events. Grade ≥ 3 photosensitivity events in the Cotellic plus vemurafenib arm were treated with primary topical medication in conjunction with dose interruptions of both Cotellic and vemurafenib (*see section 2.2 Dosage and Administration, Dose modification recommendations: Table 1*).

No evidence of phototoxicity was observed with cobimetinib as a single agent.

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 grade: 3% vs. 13%). Keratoacanthoma has been reported with a lower frequency in the Cotellic plus vemurafenib vs. placebo plus vemurafenib arm (all grade: 2% vs. 9%). Hyperkeratosis has been reported with a lower frequency in the Cotellic plus vemurafenib vs. placebo plus vemurafenib arm (all grade: 11% vs. 30%).

2.6.1.1 Laboratory Abnormalities

Table 4 Liver function and other laboratory tests observed in the phase III Study GO28141

Test*	Cotellic + vemurafenib (n = 247) (%)		Placebo + vemurafenib (n = 246) (%)	
	All Grades	**Grades 3-4**	**All Grades**	**Grades 3-4**
Liver Function Test				
Increased ALP	69	7	55	3
Increased ALT	67	11	54	5
Increased AST	71	7	43	2
Increased GGT	62	20	59	17
Increased blood bilirubin	33	2	43	1
Other Laboratory Abnormalities				
Increase blood CPK	70	12	14	<1

*based on reported laboratory data

ALP - alkaline phosphatase, ALT - alanine aminotransferase, AST - aspartate aminotransferase, GGT - gamma-glutamyltransferase, CPK - creatine phosphokinase

2.6.2 Post Marketing

Table 5 Adverse Drug Reactions reported in the post marketing setting

System Organ Class (SOC)	ADR
Musculoskeletal and connective tissue disorders	Rhabdomyolysis

2.6.2.1 Laboratory Abnormalities

Not applicable

2.7 OVERDOSE

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

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 PHARMACODYNAMIC PROPERTIES

3.1.1 Mechanism of Action

The mitogen-activated protein kinase (MAPK)/extracellular signal regulated kinase (MEK) pathway is a key signaling pathway that regulates cell proliferation, cell cycle regulation, cell survival, angiogenesis, and cell migration.

Cotellic is an orally available, highly selective allosteric inhibitor that targets MEK1/2. It has shown high inhibitory potency in biochemical and cell based assays, as well as broad anti-tumor activity *in vivo* in xenograft tumor models, including those that are mutated for BRAF and KRAS.

In biochemical and structural studies, Cotellic has been shown to interact with MEK in a manner that is less susceptible to the dynamic conformational changes seen with the phosphorylation state of MEK. As a result Cotellic maintains binding affinity and inhibitory activity when MEK becomes phosphorylated. Due to this distinct allosteric mechanism of inhibition, Cotellic has shown the strongest activity in cancer cell lines and tumors with high phosphorylated MEK levels, as is frequently observed in BRAF mutant tumors.

In pre-clinical studies, treatment of MAPK-dysregulated cancer cells and tumors with Cotellic results in inhibition of phosphorylation of ERK1/2, the only known substrates of MEK1/2. Functional mediation of the MAPK pathway is dependent upon ERK1/2 activity that phosphorylates protein targets in the cytoplasm and nucleus that induce cell-cycle progression, cell proliferation, survival and migration. Cotellic therefore opposes

the pro-mitogenic and oncogenic activity induced by the MAPK pathway through inhibition of the MEK1/2 signaling node.

By simultaneously targeting BRAF and MEK the combination of vemurafenib and Cotellic inhibits MAPK pathway reactivation through MEK1/2 resulting in stronger inhibition of signaling, greater tumor cell apoptosis and enhanced tumor responses in pre-clinical models than vemurafenib alone.

3.1.2 Clinical / Efficacy Studies

Study GO28141

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

Key baseline characteristics included: 58% of patients were male, median age was 55 years (range 23 to 88 years), 60% had metastatic melanoma stage M1c and the proportion of patients with elevated lactate dehydrogenase (LDH) was 46.3% in the Cotellic plus vemurafenib arm and 43.0% in the placebo plus vemurafenib arm.

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

Progression-free survival (PFS) as assessed by the investigator (Inv) was the primary endpoint. Secondary efficacy endpoints included overall survival (OS), objective response rate (ORR), duration of response and PFS as assessed by an independent review facility (IRF).

Efficacy results are summarized in the table below.

Table 6: Efficacy results from Study GO28141-Cut-off date 16 January 2015

	Cotellic + vemurafenib N=247	**Placebo + vemurafenib N=248**
Primary Endpoint		
Progression-Free Survival (PFS)[a,g]		
Median (months) 95 % CI	12.3 (9.5, 13.4)	7.2 (5.6, 7.5)
Hazard ratio (95% CI) [c]	0.58 (0.46; 0.72)	
Key Secondary Endpoints		
PFS (IRF)[b,c]		
Median (KM-estimate - months) 95% CI	11.3 (8.5, NE)	6.0 (5.6, 7.5)
Hazard ratio (95% CI)	0.60 (0.45; 0.79) (p-value = 0.0003)	
OS		
Median (KM-estimate - months) 95% CI	22.3 (20.3, NE)	17.4 (15.0, 19.8)
Hazard ratio (95% CI)[c]	0.70 (95% CI: 0.55, 0.90) (p-value = 0.0050[e])	
Objective response rate (ORR)	172 (69.6%)	124 (50.0%)
95% CI for ORR[d]	(63.5%, 75.3%)	(43.6%, 56.4%)
Difference in ORR % (95% CI) [f]	19.6 (11.0, 28.3)	
Best Overall Response		
Complete Response	39 (15.8%)	26 (10.5%)
Partial Response	133 (53.8%)	98 (39.5%)
Stable disease	44 (17.8%)	92 (37.1%)
Duration of Response (DoR)		
Median DoR (months) 95% CI for median	13 (11.1, 16.6)	9.2 (7.5, 12.8)

[a] Assessed and confirmed by the investigator (Inv) using RECIST v1.1

[b] Assessed and confirmed by an independent review facility (IRF) assessment using RECIST v1.1

[c] Stratified analysis by geographic region and metastasis classification (disease stage)

[d] Using Clopper-Pearson method

[e] The OS p-value (0.0050) crossed the pre-specified boundary (p value <0.0499)

[f] Using Hauck-Anderson method

[g] See text for discussion of post-hoc analysis of PFS

Figure 1: Kaplan-Meier Curves of Progression-free Survival (Inv) – Intent-to-Treat Population (cut-off date: 16 January 2015)

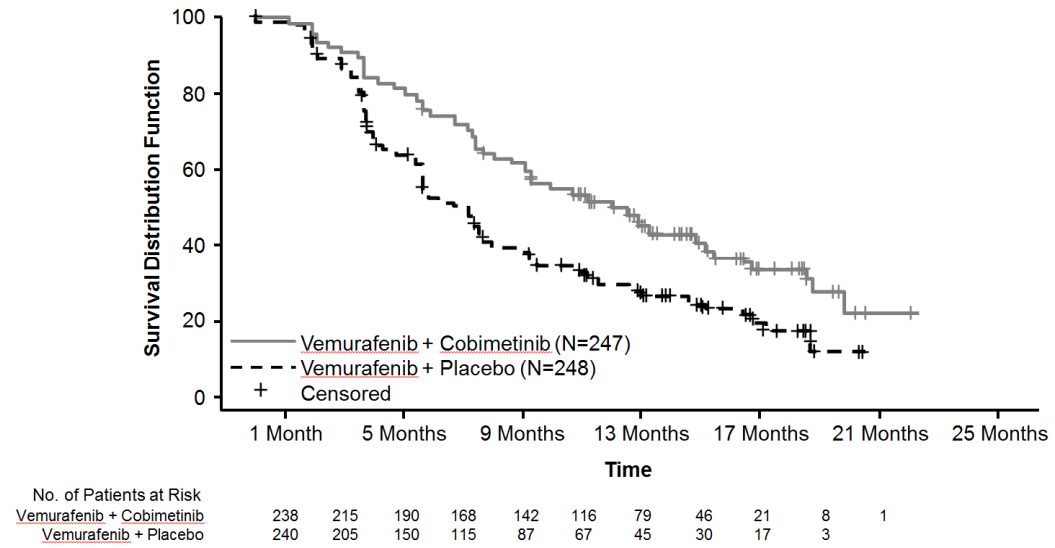


Figure 2: Kaplan-Meier Curves of Final Overall Survival – Intent-to-Treat Population

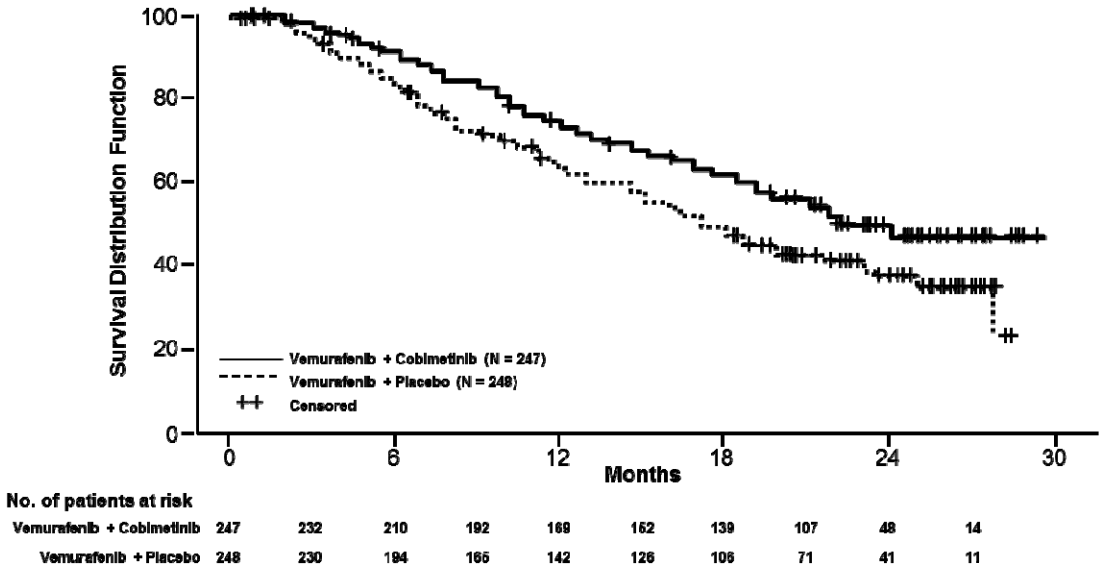


Figure 3: Forest Plots for Hazard Ratios of Progression-Free Survival Subgroup Analyses – Intent-to-Treat Population (cut-off date: 16 January 2015)

Baseline Risk Factors	Total n	Placebo + vemurafenib (n=248) n	Events	Median (months)	Cobimetinib + vemurafenib (n=247) n	Events	Median (Months)	Hazard Ratio	95%Wald CI
All Patients	495	248	180	7.2	247	143	12.3	0.59	(0.47, 0.73)
Disease Stage (IIIc/M1a/M1b, or M1c)									
M1c	299	153	128	5.5	146	94	9.5	0.52	(0.40, 0.68)
Unresectable Stage IIIc/M1a/M1b	196	95	52	11.0	101	49	13.4	0.73	(0.49, 1.08)
Age Group (yr)									
< 65	362	179	128	7.2	183	107	12.6	0.61	(0.47, 0.79)
≥ 65	133	69	52	5.6	64	36	11.2	0.52	(0.34, 0.80)
Sex									
Female	209	108	72	7.5	101	52	12.9	0.57	(0.40, 0.82)
Male	286	140	108	5.7	146	91	11.1	0.58	(0.44, 0.77)
Geographic Region									
Australia/New Zealand/Others	78	38	26	7.4	40	20	13.3	0.57	(0.32, 1.03)
Europe	366	184	138	6.0	182	107	11.2	0.58	(0.45, 0.75)
N. America	51	26	16	7.5	25	16	11.2	0.57	(0.28, 1.17)
ECOG Performance Status									
0	348	164	110	7.6	184	100	12.9	0.65	(0.49, 0.85)
1	138	80	66	5.5	58	41	10.0	0.53	(0.35, 0.78)
Screening Serum LDH									
Elevated	216	104	85	5.4	112	78	8.2	0.57	(0.42, 0.78)
Normal	268	138	90	7.8	130	65	13.4	0.59	(0.43, 0.81)
Prior Adjuvant Therapy									
Yes	48	24	16	7.2	24	12	16.5	0.60	(0.28, 1.27)
No	447	224	164	7.2	223	131	11.2	0.59	(0.47, 0.74)
BRAF^{V600} Mutation Status									
V600E	344	174	126	7.2	170	102	10.6	0.64	(0.49, 0.83)
V600K	56	32	24	6.0	24	14	12.4	0.52	(0.27, 1.02)

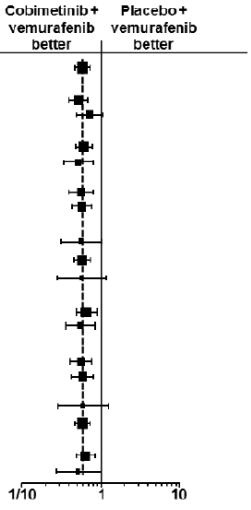
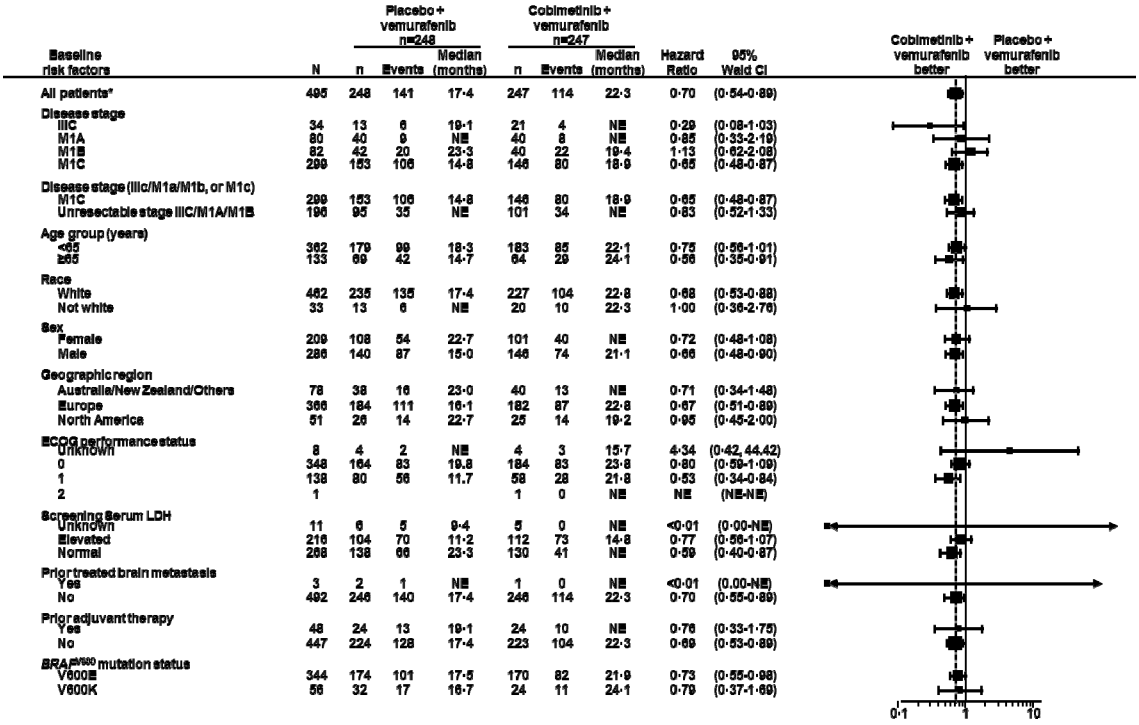


Figure 4: Forest Plot for Hazard Ratios of Final Overall Survival Subgroup Analyses – Intent-to-Treat Population



Additionally, in a post hoc analysis, a median PFS benefit 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 (0.46, 0.72)]. The median follow up of patients was 14.2 months.

Global health status / health-related quality of life, symptom severity, and functional interference of symptoms by patient-report were measured for each treatment arm using the EORTC QLQ-C30 questionnaire. Scores for all functioning domains (cognitive, emotional, social, role, and physical), and most symptoms (appetite loss, constipation, nausea and vomiting, dyspnea, pain, fatigue) showed that the mean change from baseline was similar between the two treatment arms and did not demonstrate a clinically meaningful change (all scores were < 10 point change from baseline) and were similar between the two treatment arms. Patients in the Cotellic plus vemurafenib arm reported significant worsening of diarrhea from baseline at only Cycle 1 Day 15 and Cycle 2 Day 15 as measured by the EORTC QLQ-C30; but not at subsequent timepoints.

Study NO25395

The efficacy of Cotellic was evaluated in Phase Ib Study, NO25395, which was designed to assess the safety, tolerability, pharmacokinetics and efficacy of Cotellic when added to vemurafenib for the treatment of patients with BRAF V600 mutation-positive (as detected by the cobas 4800 BRAF V600 Mutation Test) unresectable or metastatic melanoma.

This Study treated 129 patients with Cotellic and vemurafenib: 63 were BRAF inhibitor therapy naïve (BRAFi) and 66 patients had previously progressed on prior vemurafenib therapy. Within the BRAFi naïve patient population (n = 63), there were 20 patients (32%) who had received prior systemic therapy.

Results of the BRAFi naïve population from Study NO25395 were generally consistent with those from Study GO28141. The BRAFi-naïve patients (n=63) attained an 87% objective response rate, including a complete response in 16% of patients. The median duration of response was 14.3 months. The median PFS for BRAFi-naïve patients was 13.8 months, with median follow-up time of 20.6 months.

Among patients who had progressed on vemurafenib (n=66), the objective response rate was 15%. The median duration of response was 6.8 months. The median PFS for patients who had progressed on vemurafenib was 2.8 months.

3.2 PHARMACOKINETIC PROPERTIES

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

3.2.1 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.

The pharmacokinetics of cobimetinib are not altered when administered in the fed state (high-fat meal) compared with the fasted state in healthy subjects. Since food does not alter the pharmacokinetics of cobimetinib, it can be administered with or without food.

3.2.2 Distribution

Cobimetinib is 94.8% bound to human plasma proteins *in vitro*. 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 PK analysis. Cobimetinib is a substrate of P-gp in vitro. The transport across the blood brain barrier is unknown.

3.2.3 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 and eliminated in feces; no single metabolite was predominant.

Oxidation by CYP3A and glucuronidation by UGT2B7 appear to be the major pathways of cobimetinib metabolism. Cobimetinib is the predominant moiety in plasma. No oxidative 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. In vitro data indicate cobimetinib is not an inhibitor of OAT1, OAT3 or OCT2.

3.2.4 Elimination

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.

The mean elimination half-life following oral dosing of cobimetinib was 43.6 hours (range: 23.1 to 69.6 hours).

3.2.5 Pharmacokinetics in Special Populations

Based on a population pharmacokinetic analysis, gender, race, ethnicity, baseline ECOG, mild and moderate renal impairment did not affect the PK 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.

Gender: Gender does not have an effect on the exposure of cobimetinib, based on a population pharmacokinetic analysis including 210 women and 277 men.

Elderly: Age does not have an effect on the exposure of cobimetinib, based on a population pharmacokinetic analysis including 133 patients ≥ 65 years of age.

Renal Impairment: Based on pre-clinical data and the human mass balance Study, cobimetinib is mainly metabolized, with minimal renal elimination. No formal PK Study has been conducted in patients with renal impairment.

A population PK 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 PK analysis. The potential need for dose adjustment in patients with severe renal impairment cannot be determined due to limited data.

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. Systemic exposures after a single dose of cobimetinib were similar in subjects with mild or moderate hepatic impairment compared to healthy subjects; while subjects with severe hepatic impairment had lower cobimetinib exposures ($AUC_{0-\infty}$ geometric mean ratio of 0.69 compared to healthy subjects) which is not considered to be clinically significant. Therefore, no dose adjustment is recommended when administering Cotellic to patients with hepatic impairment (*see Section 2.2.1 Special Dosage Instructions and 2.4 Warnings and Precautions, General, Liver laboratory abnormalities*).

3.3 PRECLINICAL SAFETY

3.3.1 Carcinogenicity

No carcinogenicity studies have been conducted with Cotellic.

3.3.2 Mutagenicity

Standard genotoxicity studies with cobimetinib were all negative.

3.3.3 Impairment of Fertility

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

In toxicology studies, degenerative changes were observed in reproductive tissues including increased apoptosis/necrosis of corpora lutea and seminal vesicle, epididymal and vaginal epithelial cells in rats, and epididymal epithelial cells in dogs. The effect of cobimetinib on human fertility is unknown.

3.3.4 Teratogenicity

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 times the human clinical plasma AUC exposure.

3.3.5 Other

QT Prolongation

No additive clinical effect on QT interval prolongation is observed when patients are treated with Cotellic in combination with vemurafenib. *In vitro*, cobimetinib produced moderate hERG ion channel inhibition (IC_{50} = 0.5 μM [266 ng/mL]), which is approximately 18-fold higher than peak plasma concentrations (C_{max}) at the 60 mg dose (unbound C_{max} = 14 ng/mL [0.03 μM]).

General toxicity assessment

Toxicity studies in rats and dogs identified generally reversible degenerative changes in the bone marrow, gastrointestinal tract, skin, thymus, adrenal gland, liver, spleen, lymph node, kidney, heart, ovary, and vagina at plasma exposures below clinical efficacious levels.

Non-clinical studies revealed no other special hazard for humans based on conventional studies of safety pharmacology and genotoxicity.

4. PHARMACEUTICAL PARTICULARS

4.1 STORAGE

Shelf-life: as registered locally; store at or below 30°C.

4.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

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.

4.3 PACKS

Film-coated tablets 20 mg 63 Tablets

Medicine: keep out reach of children

Current at Oct 2017

Roche

Product owner: F.Hoffmann-La Roche Ltd,
Grenzacherstrasse 124, CH-4070 Basel,
Switzerland