COTELLIC®

cobimetinib

Film-coated Tablets 20 mg

Patient Safety Information Card

The marketing of Cotellic is subject to a risk management plan (RMP) including a 'Patient safety information card'. The 'Patient safety information card', emphasizes important safety information that the patient should be aware of before and during treatment. Please explain the patient the need to review the card before starting treatment.

Prescriber Guide

This product is marked with prescriber guide providing important safety information. Please ensure you are familiar with this material as it contains important safety information.

1. NAME OF THE MEDICINAL PRODUCT

Cotellic 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains cobimetinib hemifumarate equivalent to 20 mg cobimetinib.

Excipient with known effect:
Each film-coated tablet contains 36 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White, round film-coated tablets of approximately 6.6 mm diameter, with “COB” debossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Unresectable or Metastatic Melanoma
Cotellic is indicated for use in combination with vemurafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation (see sections 4.4 and 5.1).

Histiocytic Neoplasms
Cotellic as a single agent, is indicated for the treatment of adult patients with histiocytic neoplasms.

4.2 Posology and method of administration

Treatment with Cotellic in combination with vemurafenib should only be initiated and supervised by a qualified physician experienced in the use of anticancer medicinal products.

For Treatment of Melanoma

Before starting this treatment, patients must have BRAF V600 mutation-positive melanoma tumour status confirmed by a validated test (see sections 4.4 and 5.1).

Posology

The recommended dose of Cotellic is 60 mg (3 tablets of 20 mg) once daily.

Cotellic is taken on a 28 day cycle. Each 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 (Days 22 to 28-treatment break). Each subsequent Cotellic treatment cycle should start after the 7-day treatment break has elapsed.

For information on the posology of vemurafenib, please refer to its Prescribing Information.

Duration of treatment

Treatment with Cotellic should continue until the patient no longer derives benefit or until the development of unacceptable toxicity (see Table 1 below).

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 administration of Cotellic, the patient should not take an additional dose on that day and treatment should be continued as prescribed the following day.

General dose modifications

The decision on whether to reduce the dose for either or both treatments should be based on the prescriber's assessment of individual patient safety or tolerability. Dose modification of Cotellic is independent of vemurafenib dose modification.

If doses are omitted for toxicity, these doses should not be replaced. Once the dose has been reduced, it should not be increased at a later time.

Table 1 below gives general Cotellic dose modification guidance.

Table 1 Recommended Cotellic dose modifications

Grade (CTC-AE)*	Recommended Cotellic dose
Grade 1 or Grade 2 (tolerable)	No dose reduction. Maintain Cotellic at a dose of 60 mg once daily (3 tablets)
Grade 2 (intolerable) or Grade 3/4	
1st Appearance	Interrupt treatment until Grade ≤ 1, restart treatment at 40 mg once daily (2 tablets)
2nd Appearance	Interrupt treatment until Grade ≤ 1, restart treatment at 20 mg once daily (1 tablet)
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 haemorrhage

Grade 4 events or cerebral haemorrhage: Cotellic treatment should be interrupted. Cotellic treatment should be permanently discontinued for haemorrhage events attributed to Cotellic.

Grade 3 events: Cotellic treatment should be interrupted during evaluation to avoid any potential contribution to the event. There is no data on the effectiveness of Cotellic dose modification for haemorrhage events. Clinical judgment should be applied when considering restarting Cotellic treatment. Vemurafenib dosing can be continued when Cotellic treatment is interrupted, if clinically indicated.

Dose modification advice for 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.

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: 40 mg
				2nd occurrence: 20 mg
				3rd occurrence: permanent discontinuation
			< 40% (or ≥ 10% absolute decrease from baseline)	Permanent discontinuation
Symptomatic	N/A	Interrupt treatment for 4 weeks	Asymptomatic and < 10% absolute decrease from baseline	1st occurrence: 40 mg
				2nd occurrence: 20 mg
				3rd occurrence: permanent discontinuation
			Asymptomatic and < 40% (or ≥ 10% absolute decrease from baseline)	Permanent discontinuation
			Symptomatic regardless of LVEF	Permanent discontinuation

N/A = Not Applicable

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

Dose modification advice for rhabdomyolysis and creatine phosphokinase (CPK) elevations

Rhabdomyolysis or symptomatic CPK elevations

Cotellic treatment should be interrupted. If rhabdomyolysis or symptomatic CPK elevations do not improve within 4 weeks, Cotellic treatment should be permanently discontinued.
If severity is improved by at least one grade within 4 weeks, Cotellic could be restarted at a dose reduced by 20 mg, if clinically indicated. Patients should be closely monitored. Vemurafenib dosing can be continued when Cotellic treatment is modified.

Asymptomatic CPK elevations

Grade 4: Cotellic treatment should be interrupted. If CPK elevations do not improve to Grade ≤3 within 4 weeks following dose interruption, Cotellic treatment should be permanently discontinued. If CPK improves to Grade ≤3 within 4 weeks, Cotellic could be restarted, if clinically indicated, at a dose reduced by 20 mg and the patient should be closely monitored. Vemurafenib dosing can be continued when Cotellic treatment is modified.

Grade ≤3: After rhabdomyolysis has been ruled out, Cotellic dosing does not need to be modified.

Dose modification advice for Cotellic when used with vemurafenib

Liver laboratory abnormalities

For Grade 1 and 2 liver laboratory abnormalities, Cotellic and vemurafenib should be continued at the prescribed dose.

Grade 3: Cotellic should be continued at the prescribed dose. The dose of vemurafenib may be reduced as clinically appropriate. Please refer to the vemurafenib Prescribing Information.

Grade 4: Cotellic treatment and vemurafenib treatment should be interrupted. If liver laboratory abnormalities improve to Grade ≤1 within 4 weeks, Cotellic should be restarted at a dose reduced by 20 mg and vemurafenib at a clinically appropriate dose, per its Prescribing Information.

Cotellic treatment and vemurafenib treatment should be discontinued if liver laboratory abnormalities do not resolve to Grade ≤1 within 4 weeks or if Grade 4 liver laboratory abnormalities recur after initial improvement.

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 as clinically appropriate, please refer to its Prescribing Information for further information.

Rash

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

Grade ≤2 (tolerable) rash should be managed with supportive care. Cotellic dosing can be continued without modification.

Grade 2 (intolerable) or Grade ≥3 acneiform rash: General dose modification recommendations in Table 1 for Cotellic should be followed. Vemurafenib dosing can be continued when Cotellic treatment is modified (if clinically indicated).

Grade 2 (intolerable) or Grade ≥3 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 its Prescribing Information for further information.

QT prolongation

If during treatment the QTc exceeds 500 msec, please refer to the vemurafenib Prescribing Information (section 4.2) for dose modifications for vemurafenib. No dose modification of Cotellic is required when taken in combination with vemurafenib.

Special populations

Elderly patients
No dose adjustment is required in patients aged ≥65 years old.

Renal impairment
No dose adjustment is recommended in patients with mild or moderate renal impairment based on population pharmacokinetic analysis (see section 5.2). There are minimal data for Cotellic in patients with severe renal impairment, therefore an effect cannot be excluded. Cotellic should be used with caution in patients with severe renal impairment.

Hepatic impairment
No dose adjustment is recommended in patients with hepatic impairment. Patients with severe hepatic impairment may have increased plasma concentrations of unbound cobimetinib compared to patients with normal hepatic function (see section 5.2). Liver laboratory abnormalities can occur with Cotellic and caution should be used in patients with any degree of hepatic impairment (see section 4.4).

Non-Caucasian patients
The safety and efficacy of Cotellic in non-Caucasian patients have not been established.

Paediatric population
The safety and efficacy of Cotellic in children and adolescents below 18 years of age have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2, but no recommendation on posology can be made.

Method of administration
Cotellic is for oral use. The tablets should be swallowed whole with water. They can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Before taking Cotellic in combination with vemurafenib, patients must have BRAF V600 mutation-positive tumour status confirmed by a validated test.

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 5.1). 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

Limited data show that the safety of the combination of Cotellic and vemurafenib in patients with a BRAF V600 mutation-positive melanoma which has metastasised to the brain is consistent with the known safety profile of Cotellic in combination with vemurafenib. The efficacy of the Cotellic and vemurafenib combination in these patients has not been evaluated. The intracranial activity of Cotellic is unknown (see sections 5.1 and 5.2).

Haemorrhage

Haemorrhagic events, including major haemorrhagic events can occur (see section 4.8).

Caution should be used in patients with additional risk factors for bleeding, such as brain metastases, and/or in patients that use concomitant medicinal products that increase the risk of bleeding (including antiplatelet or anticoagulant therapy). For management of haemorrhage please see section 4.2.

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 4.8). 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 studies were resolved, or improved to asymptomatic Grade 1, following dose interruption or reduction.

Patients should be assessed at each visit for symptoms of new or worsening visual disturbances. If symptoms of new or worsening visual disturbances are identified, an ophthalmologic examination is recommended. If serous retinopathy is diagnosed, Cotellic treatment should be withheld until visual symptoms improve to Grade $\leq$1. Serous retinopathy can be managed with treatment interruption, dose reduction or with treatment discontinuation (see Table 1 in section 4.2).

Left ventricular dysfunction

Decrease in LVEF from baseline has been reported in patients receiving Cotellic (see section 4.8). 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 4.2).

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 with vemurafenib as a single agent (please refer to its Prescribing Information).

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 4.8).
Liver value abnormalities should be monitored by liver laboratory tests before initiation of combination treatment and monthly during treatment, or more frequently as clinically indicated (see section 4.2).

Grade 3 liver laboratory abnormalities should be managed with vemurafenib treatment interruption or dose reduction. Manage Grade 4 liver laboratory abnormalities with treatment interruption, dose reduction or with treatment discontinuation of both Cotellic and vemurafenib (see section 4.2).

Rhabdomyolysis and CPK elevations

Rhabdomyolysis has been reported in patients receiving Cotellic (see section 4.8).

If rhabdomyolysis is diagnosed, Cotellic treatment should be interrupted and CPK levels and other symptoms monitored until resolution. Depending on the severity of rhabdomyolysis, dose reduction or treatment discontinuation may be required (see section 4.2).
Grade 3 and 4 CPK elevations, including asymptomatic elevations over baseline, also occurred in patients receiving Cotellic with vemurafenib in clinical studies (see section 4.8). 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 4.2).

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 4.2).

Drug-drug interactions: CYP3A inhibitors

Concurrent use of strong CYP3A inhibitors during treatment with Cotellic should be avoided. Caution should be exercised if a moderate CYP3A inhibitor is co-administered with Cotellic. If concomitant use with a strong or moderate CYP3A inhibitor is unavoidable, patients should be carefully monitored for safety and dose modifications applied if clinically indicated (see Table 1 in section 4.2).

QT prolongation

If during treatment the QTc exceeds 500 msec, please refer to the vemurafenib Prescribing Information sections 4.2 and 4.4.

Excipients

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucosegalactose malabsorption should not take this medicine.

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on cobimetinib

CYP3A inhibitors

Cobimetinib is metabolized by CYP3A and cobimetinib AUC increased approximately 7 fold in the presence of a strong CYP3A inhibitor (itraconazole) in healthy subjects. The magnitude of interaction could potentially be lower in patients.

Strong CYP3A inhibitors (see section 4.4.)

Avoid concurrent use of strong CYP3A inhibitors during treatment with cobimetinib. Strong CYP3A inhibitors include, but are not limited to ritonavir, cobicistat, telaprevir, lopinavir, itraconazole, voriconazole, clarithromycin, telithromycin, posaconazole, nefazodone and grapefruit juice. 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.

Moderate CYP3A inhibitors (see section 4.4.)

Caution should be exercised if cobimetinib is co-administered with moderate CYP3A inhibitors. Moderate CYP3A inhibitors include, but are not limited to, amiodarone, erythromycin, fluconazole, miconazole, diltiazem, verapamil, delavirdine, amprenavir, fosamprenavir, imatinib. When cobimetinib is co-administered with a moderate CYP3A inhibitor, patients should be carefully monitored for safety.

Mild CYP3A inhibitors

Cobimetinib can be co-administered with mild inhibitors of CYP3A without dose adjustment.

CYP3A inducers

Co-administration of cobimetinib with a strong CYP3A inducer was not assessed in a clinical study, however, a reduction in cobimetinib exposure is likely. Therefore, concomitant use of moderate and strong CYP3A inducers (e.g. carbamazepine, rifampicin, phenytoin, and St. John's Wort) should be avoided. Alternative agents with no or minimal CYP3A induction should be considered. Given that cobimetinib concentrations are likely to be significantly reduced when co-administered with moderate to strong CYP3A inducers, patient's efficacy may be compromised.

P-glycoprotein inhibitors

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.

Effects of cobimetinib on other medicinal products

CYP3A and CYP2D6 substrates

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.

CYP1A2 substrates

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.

BCRP substrates

In vitro, cobimetinib is a moderate inhibitor of BCRP (Breast Cancer Resistance Protein). No clinical DDI studies have been conducted to assess this finding, and clinically relevant inhibition of intestinal BCRP cannot be ruled out.

Other anti-cancer agents

Vemurafenib

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

Effects of cobimetinib on drug transport systems

In vitro studies show that cobimetinib is not a substrate of the liver uptake transporters OATP1B1, OATP1B3 and OCT1, however, it weakly inhibits these transporters. The clinical relevance of these findings has not been investigated.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception

Women of childbearing potential should be advised to use two effective contraceptive methods, such as a condom or other barrier method (with spermicide, if available) during treatment with Cotellic and for at least three months following treatment discontinuation.

Pregnancy

There are no data from the use of Cotellic in pregnant women. Studies in animals have shown embryolethality and foetal malformations of the great vessels and skull (see section 5.3). Cotellic should not be used during pregnancy unless clearly necessary and after a careful consideration of the needs of the mother and the risk to the foetus.

Breast-feeding

It is not known whether cobimetinib is excreted in human breast milk. A risk to the newborns/infants cannot be excluded. A decision should be made whether to discontinue breast-feeding or discontinue Cotellic therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data in humans for cobimetinib. In animals, no fertility studies have been performed, but adverse effects were seen on reproductive organs (see section 5.3). The clinical relevance of this is unknown.

4.7 Effects on ability to drive and use machines

Cotellic has minor influence on the ability to drive or use machines. Visual disturbances have been reported in some patients treated with cobimetinib during clinical studies (see sections 4.4 and 4.8). Patients should be advised not to drive or use machines if they experience visual disturbances or any other adverse effects that may affect their ability.

4.8 Undesirable effects

Unresectable or Metastatic Melanoma

Summary of the safety profile

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 for the 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 Study NO25395 was consistent with that observed in Study GO28141.

In Study GO28141, the most common adverse reactions (>20%) observed with a higher frequency in the Cotellic plus vemurafenib arm were diarrhoea, rash, nausea, pyrexia, photosensitivity reaction, increased alanine aminotransferase, increased aspartate aminotransferase, increased blood creatine phosphokinase, and vomiting. The most common adverse reactions (>20%) observed with a higher frequency in the placebo plus vemurafenib arm were arthralgia, alopecia, and hyperkeratosis. Fatigue was observed at similar frequencies in both arms.

Please refer to the vemurafenib Prescribing Information for complete descriptions of all undesirable effects associated with vemurafenib treatment.

Tabulated list of adverse reactions

Adverse drug reactions (ADRs) are based on results from a multi-centre, randomised, double-blind, placebo-controlled, Phase III Study (GO28141) that evaluated the safety and efficacy of Cotellic in combination with vemurafenib as compared to vemurafenib alone in previously untreated BRAF V600 mutation-positive patients with unresectable locally advanced (Stage IIIc) or metastatic melanoma (Stage IV).

ADR frequencies are based upon the safety analysis of patients treated with cobimetinib plus vemurafenib with a median follow up of 11.2 months (data cut-off date of 19 September 2014).

ADRs which were reported in melanoma patients are listed below by MedDRA body system organ class, frequency and grade of severity. The following convention has been used for the classification of frequency:
Very common ≥ 1/10
Common ≥ 1/100 to < 1/10
Uncommon ≥ 1/1,000 to < 1/100
Rare ≥ 1/10,000 to < 1/1,000
Very rare < 1/10,000

Table 3 lists adverse reactions considered associated with the use of Cotellic. Within each frequency grouping, ADRs are presented in order of decreasing severity and were reported according to NCI-CTCAE v 4.0 (common toxicity criteria) for assessment of toxicity in Study GO28141.

Table 3 Adverse drug reactions (ADRs) in patients treated with Cotellic in combination with vemurafenib in Study GO28141^

System organ class	Very Common	Common	Uncommon
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)		Basal cell carcinoma, Cutaneous squamous cell carcinoma**, Keratoacanthoma**	
Blood and lymphatic system disorders	Anaemia		
Metabolism and nutrition disorders		Dehydration, Hypophosphataemia, Hyponatremia, Hyperglycaemia	
Eye disorders	Serous retinopathy[a], Blurred vision	Visual impairment	
Vascular disorders	Hypertension, Haemorrhage*		
Respiratory, thoracic and mediastinal disorders		Pneumonitis	
Gastrointestinal disorders	Diarrhoea, Nausea, Vomiting		
Skin and subcutaneous tissue disorders	Photosensitivity[b], Rash, Rash maculo-papular, Dermatitis acneiform, Hyperkeratosis**, Pruritus[c], Dry skin[c]		
Musculoskeletal and connective tissue disorders			Rhabdomyolysis***
General disorders and administration site conditions	Pyrexia, Chills, Oedema peripheral[c]		
Investigations	Blood CPK increased, ALT increased, AST increased, Gamma-Glutamyltransferase (GGT) increased, Blood ALP increased	Ejection fraction decreased, Blood bilirubin increased	

^ Data cut-off date of 19 September 2014

* Please refer to the paragraph *Haemorrhage* in the "Description of selected adverse reactions" section

** Please refer to the paragraph C*utaneous squamous cell carcinoma, keratoacanthoma and hyperkeratosis* in the "Description of selected adverse reactions" section.

*** Please refer to the paragraph *Rhabdomyolysis* in the "Description of selected adverse reactions" section.

[a] Includes both chorioretinopathy and retinal detachment events indicative of serous retinopathy (see section 4.4)

[b] Combined figure includes reports of photosensitivity reaction, sunburn, solar dermatitis, actinic elastosis

[c] ADRs identified in a cobimetinib monotherapy study (ML29733; US study). However, these were also reported ADRs for cobimetinib plus vemurafenib combination in clinical trials conducted in patients with unresectable or metastatic melanoma.

Histiocytic Neoplasms

The safety of Cotellic was evaluated in Study ML29733, a single-center single-arm trial in patients with histiocytic neoplasms (see section 5.1). In Study ML29733, 26 patients with histiocytic neoplasms received Cotellic 60 mg once daily for 21 days on, then 7 days off, in a 28-day treatment cycle. The median treatment duration was 10.7 months. Table 4 presents adverse reactions in at least 15% of patients reported with histiocytic neoplasms treated with Cotellic. Table 5 presents laboratory abnormalities of grades ≥ 3 reported in patients with histiocytic neoplasms treated Cotellic.

In Study ML29733, 4 patients (15%) receiving Cotellic experienced an adverse reaction that resulted in permanent discontinuation of Cotellic. One patient discontinued due to worsening of underlying dyspnea and hypoxia; one patient discontinued due to retinal vascular disorder; one patient discontinued due to hyponatremia; and the other patient discontinued due to pneumonia.

Table 4 Incidence of Adverse Reactions Reported Occurring in ≥ 15% (All Grades) or Any Percentage (Grade ≥ 3) in Patients with Histiocytic Neoplasms Treated with Cotellic in Study ML29733

Body Systems **Adverse reactions**	**All Grades* (%)** **(n=26)**	**Grades ≥3* (%)** **(n=26)**
GASTROINTESTINAL DISORDERS		
Diarrhea	62	8
Nausea	46	0
Dyspepsia[1]	27	0
Vomiting	27	0
Dry Mouth	15	0
Oral pain[2]	15	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue[3]	42	0
Edema[4]	42	4
Pain	15	0
INFECTIONS AND INFESTATIONS		
Infections[5]	62	23
Urinary tract infection	23	8
Pulmonary infections[6]	19	12
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Fall	15	4
INVESTIGATIONS		
Decreased Ejection Fraction	19	12
RENAL AND URINARY		
Acute kidney injury	15	12
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Dyspnea	27	15
Cough	15	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Acneiform dermatitis	65	0
Dry skin	31	0
Maculo-papular rash	31	0
Pruritus	31	4

VASCULAR DISORDERS		
Hemorrhage[7]	19	0
Hypertension	15	4

* NCI CTCAE v4.0.
1 Gastritis, and gastroesophageal reflux disease.
2 Oral dysesthesia and oropharyngeal pain.
3 Malaise
4 Facial edema, edema genital, edema peripheral, periorbital edema, and lymphoedema.
5 Influenza like illness, mucosal infection, paronychia, pharyngitis, pneumonia, bronchitis, sepsis, sinusitis, skin infection, tooth infection, upper respiratory tract infection., and urinary tract infection.
6 Pneumonia and bronchitis.
7 Epistaxis, contusion, purpura, hematoma, and rectal hemorrhage.

The following clinically relevant adverse reactions (all grades) of Cotellic were reported with <15% incidence in Study ML29733:
Eye disorders: Vision blurred (12%), retinal vascular disorder (4%) and retinopathy (4%).
Gastrointestinal disorders: Stomatitis (12%)
Nervous system disorders: Headache (12%)
Respiratory, thoracic, and mediastinal disorders: Hypoxia (12%), pulmonary edema (4%), and respiratory failure (8%).

Table 5 Incidence of Grade ≥ 3 Laboratory Abnormalities Occurring in Patients with Histiocytic Neoplasms Treated with Cotellic in Study ML29733*

	Grades 3–4[a] %
Chemistry	
Increased blood creatine phosphokinase	27
Hyponatremia	18
Hypokalemia	12
Increased blood creatinine	9
Increased AST	9
Hypocalcemia	9
Increased ALT	5
Hematology	
Lymphopenia	27
Leukopenia	9
Anemia	8
Neutropenia	5

AST - aspartate aminotransferase, ALT - alanine aminotransferase
*All the percentages are based on the number of patients who had a baseline result and at least one on-study laboratory test.
[a] NCI CTCAE v4.0

Description of selected adverse reactions

Haemorrhage

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%). The median time to first onset was 6.1 months in the Cotellic plus vemurafenib arm.

The majority of events were Grade 1 or 2 and non-serious. Most events resolved with no change in Cotellic dose. Major haemorrhagic events (including intracranial and gastrointestinal tract haemorrhage) were reported in the post-marketing setting. The risk of haemorrhage may be increased with concomitant use of antiplatelet or anticoagulant therapy. If haemorrhage occurs, treat as clinically indicated (see section 4.2 and 4.4).

In Study ML29733, in patients with histiocytic neoplasms, 19% of patients experienced haemorrhage events (all were of grade 1 severity).

Rhabdomyolysis

Rhabdomyolysis has been reported in the post-marketing setting. Signs or symptoms of rhabdomyolysis warrant an appropriate clinical evaluation and treatment as indicated, along with Cotellic dose modification or discontinuation according to the severity of the adverse reaction (see section 4.2 and 4.4).

Photosensitivity

Photosensitivity has been observed with a higher frequency in the Cotellic plus vemurafenib arm 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 medicinal products in conjunction with dose interruptions of both cobimetinib and vemurafenib (see section 4.2).

No evidence of phototoxicity was observed with Cotellic 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 arm vs placebo plus vemurafenib arm (all Grade: 3% vs 13%). Keratoacanthoma has been reported with a lower frequency in the Cotellic plus vemurafenib arm 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%).

Serous retinopathy

Cases of serous retinopathy have been reported in patients treated with Cotellic (see section 4.4.) For patients reporting new or worsening visual disturbances, an ophthalmologic examination is recommended. Serous retinopathy can be managed with treatment interruption, dose reduction or with treatment discontinuation (see Table 1 in section 4.2).

Left ventricular dysfunction

Decrease in LVEF from baseline has been reported in patients receiving Cotellic (see section 4.4). 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 4.2).
Laboratory abnormalities

Liver laboratory abnormalities
Liver laboratory abnormalities, specifically ALT, AST, and ALP have been observed in patients treated with Cotellic in combination with vemurafenib (see section 4.4).
Liver laboratory tests should be monitored before initiation of combination treatment and monthly during treatment, or more frequently if clinically indicated (see section 4.2).

Blood creatine phosphokinase increase
Asymptomatic increases in blood CPK levels were observed with a higher frequency in the Cotellic plus vemurafenib arm vs placebo plus vemurafenib arm in Study GO28141 (see section 4.2 and 4.4). One event of rhabdomyolysis was observed in each treatment arm of the study with concurrent increases in blood CPK.

Table 6 provides the frequency of measured liver laboratory abnormalities and elevated creatine phosphokinase for all Grades and Grades 3-4.

Table 6 Liver function and other laboratory tests observed in the Phase III Study GO28141

Changes in reported laboratory data	**Cobimetinib plus vemurafenib (n = 247) (%)**		**Placebo plus 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				
Increased blood CPK	70	12	14	<1

In Study ML29733, in patients with histiocytic neoplasms, 27% of patients experienced grade 2 CPK elevation and 27% of patients experienced grade 3-4 CPK elevation.

Special populations

Elderly patients

In the Phase III study with Cotellic in combination with vemurafenib in patients with unresectable or metastatic melanoma (n=247), 183 patients (74%) were <65 years of age, and 44 patients (18%) were 65-74 years of age, 16 (6%) were 75-84 years of age, and 4 patients (2%) were aged ≥85 years. The proportion of patients experiencing adverse events (AE) was similar in the patients aged <65 years and those aged ≥65 years. Patients ≥65 years were more likely to experience serious adverse events (SAEs) and experience AEs leading to discontinuation of cobimetinib than those <65 years.

Paediatric population

The safety of Cotellic in children and adolescents has not been fully established. The safety of Cotellic was assessed in a multi-centre, open-label, dose-escalation study in 55 paediatric patients aged 2 to 17 years with solid tumours. The safety profile of Cotellic in these patients was consistent with that in the adult population (see section 5.2).

Renal impairment

No pharmacokinetic trial in subjects with renal impairment has been conducted. Dose adjustment is not recommended for mild to moderate renal impairment based on the results of the population pharmacokinetic analysis. There are minimal data for Cotellic in patients with severe renal impairment. Cotellic should be used with caution in patients with severe renal impairment.

Hepatic impairment

No dose adjustment is recommended in patients with hepatic impairment (see section 5.2).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EE02

Mechanism of action

Cobimetinib is a reversible, selective, allosteric, oral inhibitor that blocks the mitogen-activated protein kinase (MAPK) pathway by targeting the mitogen-activated extracellular signal-regulated kinase (MEK) 1 and MEK 2 which results in inhibition of phosphorylation of the extracellular signal-regulated kinase (ERK) 1 and ERK 2. Therefore, cobimetinib blocks the cell proliferation induced by the MAPK pathway through inhibition of the MEK1/2 signalling node.

In the preclinical models, the combination of cobimetinib and vemurafenib showed that by simultaneously targeting mutated BRAF V600 proteins and MEK proteins in melanoma cells, the combination of the two products inhibits MAPK pathway reactivation through MEK1/2, resulting in a stronger inhibition of intracellular signalling and decreased tumour cell proliferation

Clinical efficacy and safety

Unresectable or Metastatic Melanoma

There is limited data on the safety and no data on efficacy of Cotellic in combination with vemurafenib in patients with central nervous system metastasis. There is no data in patients with non-cutaneous malignant melanoma.

Study GO28141 (coBRIM)

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

Only patients with ECOG performance status 0 and 1 were enrolled in Study GO28141. Patients with ECOG performance status 2 or higher were excluded from the study.

Following confirmation of a BRAF V600 mutation, using the cobas® 4800 BRAF V600 mutation test, 495 previously untreated patients with unresectable locally advanced or metastatic melanoma were randomised 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, or
- 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, duration of response (DoR) as assessed by INV and PFS as assessed by an independent review facility (IRF).

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 LDH was 46.3% in the cobimetinib plus vemurafenib arm and 43.0% in the placebo plus vemurafenib arm.

In Study GO28141, there were 89 patients (18.1%) aged 65-74, 38 patients (7.7%) aged 75-84 and 5 patients (1.0%) aged 85 years and older.

Efficacy results are summarized in Table 7.

Table 7 Efficacy results from Study GO28141 (coBRIM)

	Cotellic + vemurafenib N=247	**Placebo + vemurafenib N=248**
Primary Endpoint [a,f]		
Progression-Free Survival (PFS)		
Median (months) (95 % CI)	12.3 (9.5, 13.4)	7.2 (5.6, 7.5)
Hazard ratio (95% CI) [b]	0.58 (0.46; 0.72)	
Key Secondary Endpoints [a,f]		
Overall Survival (OS)[g]		
Median (months) (95 % CI)	22.3 (20.3, NE)	17.4 (15.0, 19.8)
Hazard ratio (95% CI)[b]	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[c]	(63.5%, 75.3%)	(43.6%, 56.4%)
Difference in ORR % (95% CI) [d]	19.6 (11.0, 28.3)	
Best Overall Response (BOR)		
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)

NE = Not evaluable

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

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

[c] Using Clopper-Pearson method

[d] Using Hauck-Anderson method

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

[f] The data cut-off date for this updated PFS analysis and the secondary endpoints of ORR, BOR and DoR is 16-January 2015. The median follow up was 14.2 months.

[g] The data cut-off date for the final OS analysis is 28 August 2015 and median follow-up was 18.5 months.

The primary analysis for Study GO28141 was conducted with a data cut-off date of 09 May 2014. Significant improvement in the primary endpoint, investigator-assessed PFS, was observed in patients assigned to the Cotellic plus vemurafenib arm compared to the placebo plus vemurafenib arm (HR 0.51 (0.39; 0.68); p-value < 0.0001). The median estimate for investigator-assessed PFS was 9.9 months for the Cotellic plus vemurafenib arm vs. 6.2 months for the placebo plus vemurafenib arm. The median estimate for independent review of PFS was 11.3 months for the Cotellic plus vemurafenib arm vs. 6.0 months for the placebo plus vemurafenib arm (HR 0.60 (0.45; 0.79); p-value = 0.0003). The objective response rate (ORR) in the Cotellic plus vemurafenib arm was 67.6% vs 44.8% in the placebo plus vemurafenib arm. The difference in ORR was 22.9 % (p-value<0.0001).

The final OS analysis for Study GO28141 was conducted with a data-cut off date of 28 August 2015. Significant improvement in OS was observed in patients assigned to the Cotellic plus vemurafenib arm compared to the placebo plus vemurafenib arm (Figure 1). The 1-year (75 %) and 2-year (48 %) OS estimates for the Cotellic plus vemurafenib arm were greater than those for placebo plus vemurafenib arm (64 % and 38 % respectively).

Figure 1 Kaplan-Meier curves of final overall survival – Intent to treat population (cut-off date: 28 August 2015)

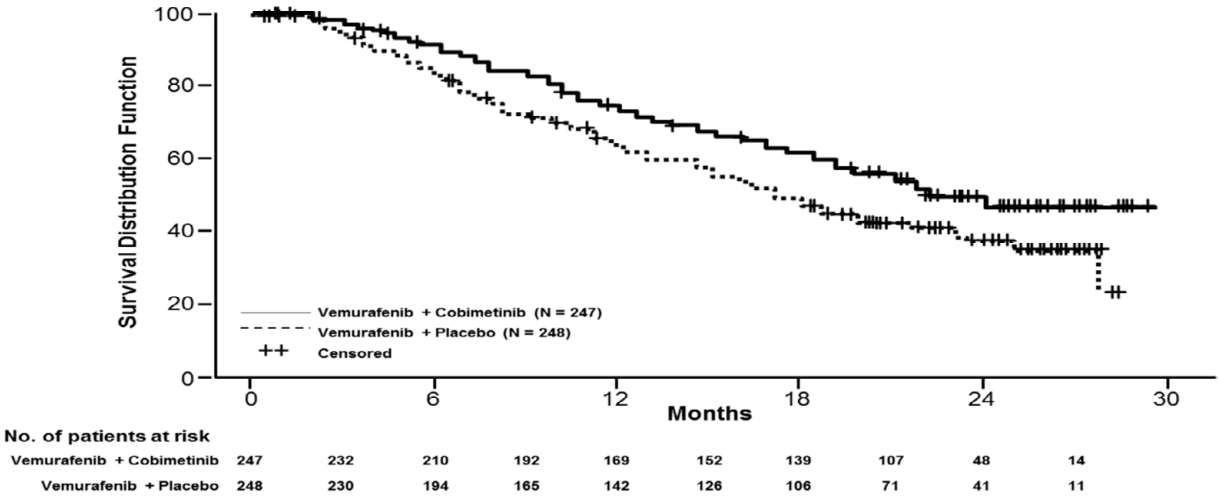
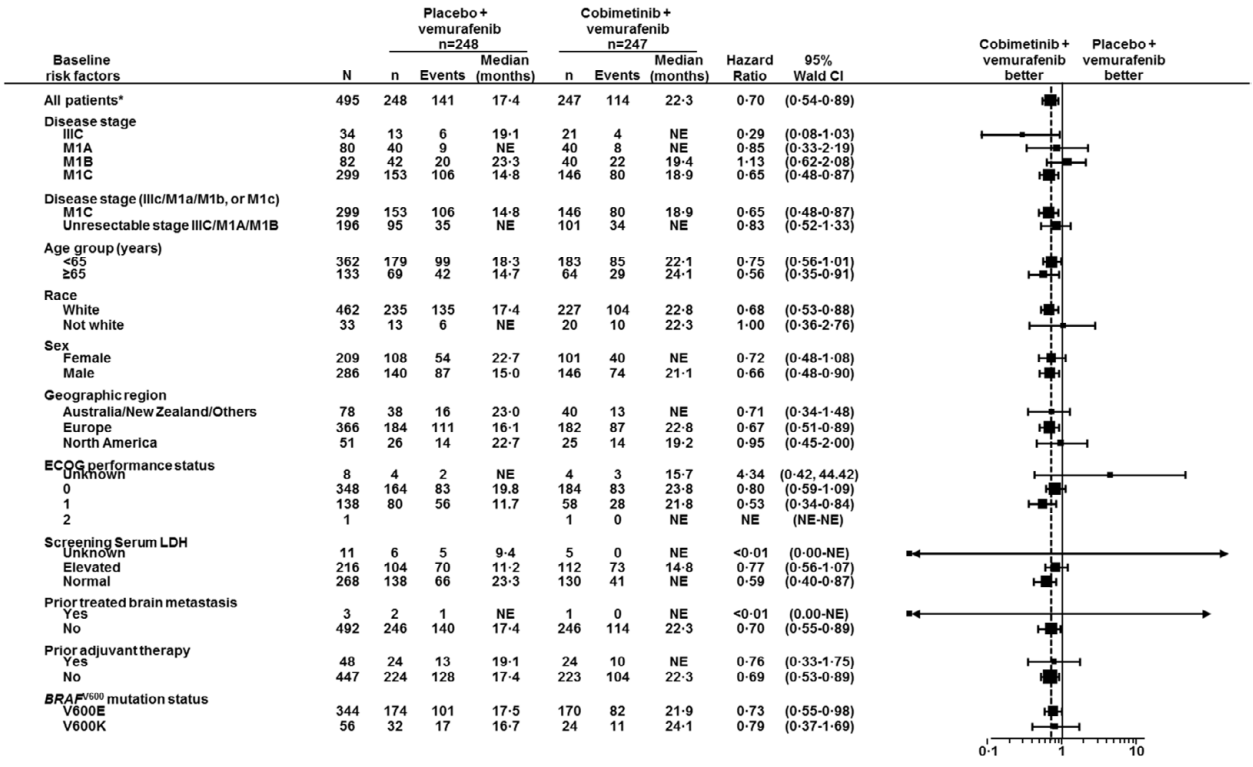


Figure 2: Forest plot for hazard ratios of final overall survival subgroup analyses – Intent to treat population (cut-off date: 28 August 2015)



Global health status / health-related quality of life by patient-report were measured using the EORTC Quality of Life Questionnaire – Core 30 (QLQ-C30). Scores for all functioning domains and most symptoms (appetite loss, constipation, nausea and vomiting, dyspnoea, 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).

Study NO25395 (BRIM7)

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 BRAFV600 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 (BRAFi) therapy naïve and 66 patients had previously progressed on prior vemurafenib therapy. Among the 63 BRAFi naïve patients, 20 patients had received prior systemic therapy for advanced melanoma with the majority (80%) being immunotherapy.

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, with median follow-up time of 8.1 months.

In patients who were naive to BRAF inhibitor therapy, the median overall survival was 28.5 months (95% CI 23.3-34.6). In patients who had progressed on BRAF inhibitor therapy, the median overall survival was 8.4 months (95% CI 6.7-11.1).

Paediatric population

A phase I/II, multi-centre, open-label, dose-escalation study was conducted in paediatric patients (< 18 years, n=55) to evaluate the safety, efficacy and pharmacokinetics of Cotellic. The study included paediatric patients with solid tumours with known or potential RAS/RAF/MEK/ERK pathway activation, for which standard therapy has proven to be ineffective or intolerable or for which no curative standard-of-care treatment options exist. Patients were treated with up to 60 mg of Cotellic orally once daily on Days 1-21 of each 28-day cycle. Overall response rate was low with only 2 partial responses (3.6%).

Histiocytic Neoplasms

A single-center, single-arm trial (Study ML29733) was conducted to evaluate the efficacy, safety, and tolerability of Cotellic as a single agent in adult patients with histologically confirmed histiocytic neoplasms of any mutational status. Patients with documented BRAF V600E mutations were enrolled if they were unable to access a BRAF inhibitor or discontinued a BRAF inhibitor due to toxicity. Enrolled patients had multi-system disease, recurrent or refractory disease, or single-system disease that is unlikely to benefit from conventional therapies, based on best available evidence.

The trial included 26 patients with histiocytic neoplasms including Langerhans Cell Histiocytosis (n=4), Rosai-Dorfman Disease (n=4), Erdheim-Chester Disease (n=13), Xanthogranuloma (n=2) and Mixed Histiocytosis (n=3). Patients with BRAF V600 mutant positive (n=6) and BRAF V600 Wild type (n=20) received Cotellic. Twenty-one patients (81%) had received prior systemic therapies. The median age was 50.5 years (range, 18 to 79 years). Sixty-five percent of patients were men (n=17) and 35% were women (n=9). The majority of patients were White (85%), 8% were Black or African American and 4% were Asian; 96% were neither Hispanic nor Latino.

Patients were treated with Cotellic 60 mg once daily for 21 days on, then 7 days off, in a 28-day treatment cycle (n=26). Eighteen patients required a dose reduction to 40 mg, and five patients required an additional dose reduction to 20 mg. The median duration of treatment following a dose reduction to 40 mg and 20 mg was 6.6 months and 3.9 months respectively.

The major efficacy outcome was best overall response rate (BORR), maintained on two occasions at least four weeks apart, as assessed by the investigator using the PET Response Criteria (PRC). Other clinical outcomes included PRC-based duration of response (DOR), and BORR maintained on two occasions at least four weeks apart, as assessed by investigator using RECIST v1.1.

The median duration of follow-up was 11.4 months (range, 0.2 to 36.8 months). The median time to PRC-based response was 2.0 (range, 0.2 to 17.3 months). The median PRC-based DOR was 31 months (range, 2 to 31 months). See Table 8 below for efficacy results.

Table 8 Efficacy of Cotellic in patients with Histiocytic neoplasms (Study ML29733)

Response	**PET Response,** [a, b] **Enrolled Patients (n=26)***	**RECIST Response, Enrolled Patients (n=26)****
Overall response rate, n (%) (95% Clopper-Pearson CI)	20 (76.9%) (56.4, 91)	12 (46.2%) (26.6, 66.6)
Best Response, n (%)		
Complete Response	16 (61.5%)	3 (11.5%)
Partial Response	4 (15.4%)	9 (34.6%)

*24 PET-evaluable patients out of 26 enrolled patients. 1 patient had missing baseline scan. 1 patient had short follow-up duration (not enrolled at least 16 weeks prior to the clinical cutoff date (CCOD)

**19 RECIST-evaluable patients out of 26 enrolled patients. 6 patients had missing baseline scans; these patients had lesions that were not measurable by RECIST 1.1 definition. 1 patient had short follow-up duration (not enrolled at least 16 weeks prior to CCOD)

[a] Complete Response by PRC was defined as a normalization of all lesions' (target and non-target) standardized uptake values (SUV) to background SUVliver (or SUVbrain for brain lesions only)

[b] Partial Response by PRC was defined as a ≥50% decrease from baseline in sum of SUV of all target lesions relative to SUVliver (or SUVbrain for brain lesions only)

5.2 Pharmacokinetic properties

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 metabolised and eliminated in faeces. 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.

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 dose of 2 mg. The apparent volume of distribution was 806 L in cancer patients based on population pharmacokinetic analysis.

Cobimetinib is a substrate of P-gp *in vitro*. The transport across the blood brain barrier is unknown.

Biotransformation

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 medicinal product in faeces and urine accounted for 6.6% and 1.6% of the administered dose, respectively, indicating that cobimetinib is primarily metabolised with minimal renal elimination. *In vitro* data indicate cobimetinib is not an inhibitor of OAT1, OAT3 or OCT2.

Elimination

Cobimetinib and its metabolites were characterised in a mass balance study in healthy subjects. On average, 94% of the dose was recovered within 17 days. Cobimetinib was extensively metabolised and eliminated in faeces.

Following intravenous 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). Therefore, it may take up to 2 weeks following treatment cessation for cobimetinib to be completely removed from systemic circulation.

Special populations

Based on a population pharmacokinetic analysis, gender, race, ethnicity, baseline ECOG, mild and moderate renal impairment did not affect the pharmacokinetic 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 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 preclinical data and the human mass balance study, cobimetinib is mainly metabolised, 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 minimal data for Cotellic in patients with severe renal impairment.

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 total cobimetinib exposures after a single dose were similar in subjects with mild or moderate hepatic impairment compared to healthy subjects, while subjects with severe hepatic impairment had lower total cobimetinib exposures (AUC0-∞ 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 (see section 4.2).

Paediatric population

The maximum tolerated dose (MTD) in paediatric patients with cancer for the tablet and suspension formulations were declared at 0.8 mg/kg/day and 1.0 mg/kg/day, respectively. The geometric mean (CV%) steady state exposures in paediatric patients at the declared MTD of 1.0 mg/kg/day (suspension formulation) was $C_{max,ss}$ 142 ng/mL (79.5%) and $AUC_{0-24,ss}$ 1862 ng.h/mL (87.0%), which is approximately 50% lower than in adults at a dose of 60 mg once daily.

5.3 Preclinical safety data

Carcinogenicity studies have not been conducted with cobimetinib. Standard genotoxicity studies with cobimetinib were negative.

No dedicated fertility studies in animals have been performed with cobimetinib. 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 clinical relevance of this is unknown.

When administered to pregnant rats, cobimetinib caused embryolethality and foetal malformations of the great vessels and skull at systemic exposures similar to human exposure at recommended dose.

Cardiovascular safety of cobimetinib in combination with vemurafenib has not been evaluated *in vivo*. *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 to be marketed dose (unbound C_{max}=14 ng/mL [0.03 μM]).

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. Dose limiting toxicities included skin ulcerations, surface exudates, and acanthosis in the rat and chronic active inflammation and degeneration of the oesophagus associated with varying degrees of gastroenteropathy in dogs.

In a repeat dose toxicity study in juvenile rats, cobimetinib systemic exposures were 2 to11 fold higher on post natal day 10 than on post natal day 38 when exposures were similar to those in adult rats. 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 blood cell mass and decreased triglycerides. Mortality occurred in juvenile animals at a dose (3 mg/kg) which did not lead to mortalities in adult animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Magnesium stearate

Film coating mixture
Polyvinyl alcohol
Titanium dioxide
Macrogol/PEG 3350
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 30℃

6.5 Nature and contents of container

Transparent PVC/PVDC blister containing 21 tablets. Each pack contains 63 tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Pharmaceuticals (Israel) Ltd. P.O.B. 6391, Hod Hasharon, 4524079.

8. MARKETING AUTHORISATION NUMBER(S)

156-38-34546-00

9. MANUFACTURER

F.Hoffmann-La Roche, Basel, Switzerland

Revised in October 2023 according to MOHs guidelines.