Prescriber guide

COTELLIC®
cobimetinib

Cotellic® (cobimetinib)
Film-coated tablets, 20 mg
Prescriber Brochure

For your attention:

- This caregiver brochure contains important information about Cotellic®.
  For any further information, please refer to Cotellic® and vemurafenib Prescribing Information as approved by the Israeli MoH.
- There is a patient card available for distribution that contains important information to the patient, prior and during treatment with Cotellic®.

Therapeutic indications

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.

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. 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.

Haemorrhage

Haemorrhagic events, including major haemorrhagic events can occur.

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).

Serous retinopathy:
Serous retinopathy (fluid accumulation within the layers of the retina) has been observed in patients treated with MEK-inhibitors, including Cotellic. 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 ≤1. Serous retinopathy can be managed with treatment interruption, dose reduction or with treatment discontinuation.

Left ventricular dysfunction:
Decrease in LVEF from baseline has been reported in patients receiving Cotellic.
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.
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.
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.
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. 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.

Rhabdomyolysis and CPK elevations

Rhabdomyolysis has been reported in patients receiving Cotellic.

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.

Grade 3 and 4 CPK elevations, including asymptomatic elevations over baseline, also occurred in patients receiving Cotellic with vemurafenib in clinical studies. 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.

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.

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.

QT prolongation:
If during treatment the QTc exceeds 500 msec, please refer to the vemurafenib Prescribing Information sections.

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'.

Interaction with other medicinal products

Effects of other medicinal products on Cotellic

CYP3A inhibitors: Cotellic is metabolized by CYP3A and Cotellic 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: Avoid concurrent use of strong CYP3A inhibitors during treatment with Cotellic. 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 Cotellic therapy during the duration of inhibitor use.

Moderate CYP3A inhibitors: Caution should be exercised if Cotellic 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 Cotellic is co-administered with a moderate CYP3A inhibitor, patients should be carefully monitored for safety.

Mild CYP3A inhibitors: Cotellic can be co-administered with mild inhibitors of CYP3A without dose adjustment.

CYP3A inducers: Co-administration of Cotellic with a strong CYP3A inducer was not assessed in a clinical study; however, a reduction in Cotellic 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 Cotellic 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: Cotellic 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 Cotellic.

Effects of Cotellic 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 Cotellic.

CYP1A2 substrates: In vitro, Cotellic 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, Cotellic 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.

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 Cotellic during clinical studies.
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.

Undesirable effects –

Table 1: Adverse events in patients treated with Cotellic and vemurafenib (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**		
Musculoskeletal and connective tissue disorders			Rhabdomyolysis***
General disorders and administration site conditions	Pyrexia, Chills		
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
* For further information please refer to the paragraph *Haemorrhage* in the "Description of selected adverse reactions" section in the updated Prescribing Information.
** For further information please refer to the paragraph C*utaneous squamous cell carcinoma, keratoacanthoma and hyperkeratosis* in the "Description of selected adverse reactions" section in the updated Prescribing Information.
*** 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

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 2 below gives general Cotellic dose modification guidance.

Table 2 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 3 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	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 vemorafenib

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 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 2 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 for dose modifications for vemurafenib. No dose modification of Cotellic is required when taken in combination with vemurafenib.

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. 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.

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

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.

No dose adjustment is recommended in patients with mild or moderate renal impairment based on population pharmacokinetic analysis. 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. Liver laboratory abnormalities can occur with Cotellic and caution should be used in patients with any degree of hepatic impairment.

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. No data are available.

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.
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 Cotellic 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 Cotellic. In animals, no fertility studies have been performed, but adverse effects were seen on reproductive organs. The clinical relevance of this is unknown.

Contraindications

Hypersensitivity to the active substance (Cotellic) or to any of the excipients:

Tablet core:
Microcrystalline cellulose, Lactose monohydrate, Croscarmellose sodium, Magnesium stearate.

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

Posology and method of administration

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.

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.

Method of administration

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

Reporting of suspected adverse reactions
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using the portal:https://sideeffects.health.gov.il/

Or by referring to Roche Pharmaceuticals Israel Drug Safety in the following mail:
israel.drugsafety@roche.com

This brochure format and content has been checked and approved by the Ministry of Health in Aug 2020.

לקבלת מידע נוסף ניתן לפנות לחברה:
רוש פרמצבטיקה (ישראל) בע"מ
רחוב החרש 6, ת.ד. 6391, הוד השרון 4524079
www.roche.co.il

CODE