PROFESSIONAL INFORMATION

SCEHDULING STATUS

S4

1 NAME OF THE MEDICINE

Cotellic® Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 20 mg cobimetinib.

Excipients with known effect: Lactose monohydrate.

Contains sugar, i.e. 36,48 mg lactose monohydrate (see section 4.4).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White, round film-coated tablets of approximately 6,6 mm diameter, with “COB” debossed on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

Method of Administration

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

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

Please refer to the full professional information of the combination product(s).

Standard Dosage (Posology)

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

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

Each dose of three 20 mg tablets (60 mg) can be taken with or without food (see Section 5.2, 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 planned dose of Cotellic 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

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 the dose modification of any concomitant medicine used with Cotellic as combined therapy. The decision on whether to dose reduce each drug 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 and 4	
1st Appearance	Interrupt treatment until grade ≤ 1, restart treatment at 40 mg once daily
2nd Appearance	Interrupt treatment until grade ≤1, restart treatment at 20 mg 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)

Haemorrhage

Grade 4 events or cerebral haemorrhage (all grades):

Interrupt Cotellic treatment. Permanently discontinue Cotellic for haemorrhage events attributed to Cotellic.

Grade 3 events:

Interrupt Cotellic treatment. There is no data on the effectiveness of Cotellic dose modification for haemorrhage events. Clinical judgment should be applied when considering restarting Cotellic treatment. In combined therapy dosing with other product/s may be 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: 40 mg
				2nd occurrence: 20 mg
				3rd occurrence: permanent discontinuation
			< 40 % (or ≥ 10 % absolute decrease from baseline)	Permanent discontinuation
Symptomatic	Not Applicable		Asymptomatic and <10 %	1st occurrence: 40 mg

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

Combination product 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. In combined therapy, dosing with other product/s may 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 4.8).

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. Combined therapy 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.

Dose modification advice for Cotellic when used with vemurafenib

Liver laboratory abnormalities

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: 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.

Special Dosage Instructions

Geriatric Use:

Age does not have an effect on Cotellic exposure. 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 5.2, Special Populations).

Hepatic impairment:

No dose adjustment is recommended in patients with hepatic impairment (see Section 5.2, Special Populations). Liver laboratory abnormalities can occur when Cotellic is used in combination with vemurafenib (see Section 4.4).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Please also refer to the full prescribing information for products used in combination with Cotellic.

New primary malignancies

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

Cutaneous Malignancies:

In Trial 1, the following cutaneous malignancies or premalignant conditions occurred in the Cotellic with vemurafenib arm and the vemurafenib arm, respectively: cutaneous squamous cell carcinoma (cuSCC) or keratoacanthoma (KA) (6 % and 20 %), basal cell carcinoma (4,5 % and 2,4 %), and second primary melanoma (0,8 % and 2,4 %). Among patients receiving Cotellic with vemurafenib, the median time to detection of first cuSCC/KA was 4 months (range: 2 to 11 months), and the median time to detection of basal cell carcinoma was 4 months (range: 27 days to 13 months). The time to onset in the two patients with second primary melanoma was 9 months and 12 months.

Perform dermatologic evaluations prior to initiation of therapy and every 2 months while on therapy. Manage suspicious skin lesions with excision and dermatopathologic evaluation. No dose modifications are recommended for Cotellic (see Section 4.2). Conduct dermatologic monitoring for 6 months following discontinuation of Cotellic when administered with vemurafenib.

Non-Cutaneous Malignancies:

Based on its mechanism of action, vemurafenib may promote growth and development of malignancies (*please refer to the full professional information for vemurafenib*). In Trial 1, 0,8 % of patients in the Cotellic with vemurafenib arm and 1,2 % of patients in the vemurafenib arm developed non-cutaneous malignancies.

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

Severe Dermatologic Reactions

Severe rash and other skin reactions can occur with Cotellic.

In Trial 1, Grade 3 to 4 rash, occurred in 16 % of patients receiving Cotellic with vemurafenib and in 17 % of patients receiving vemurafenib, including Grade 4 rash in 1,6 % of patients

receiving Cotellic with vemurafenib and 0,8 % of the patients receiving vemurafenib. The incidence of rash resulting in hospitalisation was 3,2 % in patients receiving Cotellic with vemurafenib and 2,0 % in patients receiving vemurafenib. In patients receiving Cotellic, the median time to onset of Grade 3 or 4 rash events was 11 days (range: 3 days to 2,8 months). Among patients with Grade 3 or 4 rash events, 95 % experienced complete resolution with the median time to resolution of 21 days (range 4 days to 17 months).

Interrupt, reduce the dose, or discontinue Cotellic (see Section 4.2).

Haemorrhage

Haemorrhage, including major haemorrhages defined as symptomatic bleeding in a critical area or organ, can occur with Cotellic (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 medications that increase the risk of bleeding (including antiplatelet or anticoagulant therapy).

For haemorrhage management, (see Section 4.2).

Serous retinopathy

Serous retinopathy (fluid accumulation within the layers of the retina) has been observed in 26 % of patients treated with MEK-inhibitors, including Cotellic (see Section 4.8). The majority of events were reported as chorioretinopathy (13 %) or retinal detachment (12 %).

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 4.2).

Left ventricular dysfunction

Clinically significant decrease in left ventricular ejection fraction (LVEF) from baseline has been reported in 27,1 % of 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.

Hepatotoxicity

Hepatotoxicity can occur with Cotellic.

The incidences of Grade 3 or 4 liver laboratory abnormalities in Trial 1 among patients receiving Cotellic with vemurafenib compared to patients receiving vemurafenib were: 11 % vs. 5 % for alanine aminotransferase, 8 % vs. 2,1 % for aspartate aminotransferase, 1,6 % vs. 1,2 % for total bilirubin, and 7 % vs. 3,3 % for alkaline phosphatase (See Section 4.8). Concurrent elevation in ALT > 3 times the upper limit of normal (ULN) and bilirubin > 2 X ULN in the absence of significant alkaline phosphatase > 2 X ULN occurred in one patient (0,4 %) receiving Cotellic with vemurafenib and no patients receiving single-agent vemurafenib.

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 professional 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 4.8).

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 4.2).

Rhabdomyolysis and Creatine phosphokinase (CPK) elevations

Rhabdomyolysis has been reported in patients receiving Cotellic (See Section 4.8).

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 4.2).

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

Severe Photosensitivity

Photosensitivity, including severe cases, can occur with Cotellic.

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

Advise patients to avoid sun exposure, wear protective clothing and use a broad-spectrum UVA/UVB sunscreen and lip balm (SPF ≥ 30) when outdoors. Manage intolerable Grade 2 or greater photosensitivity with dose modifications (see Section 4.2).

Effect of other medicinal products on cobimetinib

As cobimetinib is a sensitive substrate of CYP3A, the concomitant administration of CYP3A inhibitors or inducers may alter cobimetinib concentrations. Concomitant administration of potent CYP3A inhibitors and inducers is not recommended. Moderate CYP3A inhibitors and inducers should be used with caution when co-administered with Cotellic (see Section 4.5).

Sugars

Cotellic contains lactose monohydrate. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take Cotellic.

Cotellic contains lactose monohydrate which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

Effects of concomitant medications on Cotellic

CYP3A Inhibitors/Inducers:

Cotellic is metabolised by CYP3A and Cotellic AUC increased approximately 7-fold in the presence of a potent CYP3A inhibitor (itraconazole) in healthy subjects. Since Cotellic is a sensitive substrate of CYP3A, it is likely that Cotellic exposures will be lower in the presence of CYP3A inducers. Therefore concomitant administration of potent CYP3A inducers and inhibitors is not recommended. Caution should be exercised when Cotellic is co-administered with moderate CYP3A inducers and inhibitors.

Acid Reducing Agents:

Cotellic pharmacokinetics are not altered by the co-administration of a proton pump inhibitor.

Cotellic 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 Cotellic absorption.

Effects of Cotellic on concomitant medicines

CYP Substrates:

In vitro data indicate that Cotellic 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 Cotellic. Therefore Cotellic can be co-administered with medications that are substrates of CYP3A and CYP2D6.

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 patients.

Effects of transporters on Cotellic

In vitro studies show that Cotellic is a substrate of P-glycoprotein (P-gp).

In vitro studies also show that Cotellic is not a substrate of breast cancer resistance protein (BCRP).

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

Effects of Cotellic on transporters

In vitro data suggest that Cotellic 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.

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

A woman must take two effective forms of contraception during treatment with Cotellic and for at least three months following treatment discontinuation.

Pregnancy

Cotellic is not recommended during pregnancy.

There are no data regarding the use of Cotellic in pregnant women.

When administered to pregnant rats, Cotellic caused embryolethality and foetal malformations of the great vessels and skull at clinically relevant exposures.

Breastfeeding

Mothers receiving Cotellic must not breastfeed their infants.

Fertility

The effect of Cotellic on human fertility is unknown. No dedicated fertility studies in animals have been performed with Cotellic.

4.7 Effects on ability to drive and use machines

Cotellic may have a minor influence on the ability to drive and use machines. Chorioretinopathy, blurred vision, or retinal detachment may occur during treatment with Cotellic (see Section 4.8).

4.8 Undesirable effects

Clinical trials

Summary of the safety profile

A total of 376 patients with unresectable or metastatic melanoma with BRAF V600 mutation have received Cotellic in combination with vemurafenib.

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

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.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions (ADRs) from clinical trials (Tables 3 and 4) are listed by MedDRA system organ class. Table 3 summarises 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.

Table 4 summarises ADRs occurring at a <5 % higher incidence (All Grades) of patients treated with Cotellic in combination with vemurafenib in the Phase III Study. The corresponding frequency category for each adverse drug reaction is based on the following convention: 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 Summary of ADRs occurring at a ≥ 5% higher incidence (All Grades) or at a ≥ 2% higher incidence (Grades 3-4) in the Cotellic arm than the control arm in patients with unresectable or metastatic melanoma

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					
Anaemia	13	2	8	2	very common
Eye Disorders					

Chorioretinopathy	13	<1	<1	-	very common
Blurred Vision	10	-	2	-	very common
Retinal Detachment	9	2	<1	-	common
Gastrointestinal disorders					
Diarrhoea	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

Table 4: Summary of ADRs (all grades) reported with <5 % greater incidence in the Cotellic arm than the control arm in patients with unresectable or metastatic melanoma:

ADRs	**Phase III Study: GO28141**		**Frequency category: Cotellic + vemurafenib arm (All grades)**
	Cotellic plus vemurafenib arm (All grades)	**placebo plus vemurafenib arm (All grades)**	
Eye disorders			
Visual impairment[1]	3 %	-	common
General disorders and administration site conditions			
Peripheral oedema	15,3 %	11,4 %	very common
Metabolism and nutrition disorders			
Hyperglycaemia	3 %	1 %	common
Hypophosphatemia	4 %	1 %	common
Respiratory, thoracic and mediastinal disorders			
Pneumonitis	1 %	<1 %	common
Skin and subcutaneous tissue disorders			

Rash	40 %	38 %	very common
Pruritus	20,6 %	19,2 %	very common
Dry skin	14,9 %	16,7 %	very common
Vascular disorders			
Cerebral haemorrhage	1 %	-	common
Gastrointestinal (GI) tract haemorrhage	4 %	1 %	common
Reproductive system haemorrhage	2 %	<1 %	common
Haematuria	3 %	1 %	common

[1]*See sections 4.4 Warnings and Precautions, and 4.7 Ability to Drive and Use Machines*

Description of selected adverse reactions from clinical trials

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 %). Higher frequencies seen in the Cotellic plus vemurafenib arm are given in table 4.

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). 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 4.4).

Photosensitivity

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 4.2, Dose modification advice for specified adverse drug reactions (ADRs), Photosensitivity).

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

Cutaneous squamous cell carcinoma, Keratoacanthoma and Hyperkeratosis

In patients with unresectable or metastatic melanoma 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 grades: 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 %).

Laboratory Abnormalities

Table 5 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

Post Marketing Experience

Table 6 Adverse Drug Reactions reported from post marketing experience

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Report Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There is no specific antidote for overdosage with Cotellic. Stop the Cotellic and administer symptomatic and supportive treatment. Electrocardiographic monitoring is needed to identify any QTc interval changes.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC code: L01EE02– Antineoplastic agents / Other Antineoplastic agents / Mitogen-activated protein kinase inhibitors.

Mechanism of Action:

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

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

Cobimetinib 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-tumour activity *in vivo* in xenograft tumour models, including those that are mutated for BRAF and KRAS. Treatment of MAPK-dysregulated cancer cells and tumours with cobimetinib 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. Cobimetinib therefore opposes the pro-mitogenic and oncogenic activity induced by the MAPK pathway through inhibition of the MEK1/2 signalling node.

By simultaneously targeting BRAF and MEK the combination of vemurafenib and cobimetinib inhibits MAPK pathway reactivation through MEK1/2 resulting in stronger inhibition of signalling, greater tumour cell apoptosis.

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 1 050 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.

Metabolism: 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; 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 faeces and urine accounted for 6,6 % and 1,6 % of the administered dose, respectively, indicating that cobimetinib is primarily metabolised with very little renal elimination.

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).

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.

Paediatric Population

The pharmacokinetics of cobimetinib were assessed in a phase I/II, multi-centre, open-label, dose-escalation study that was conducted in paediatric (<18 years, n=55) and young adult patients (18-30 years, n=1). Patients received either the commercially-available 20-mg tablet formulation or an investigational suspension formulation in the dose escalation stage. All patients received suspension formulation in the expansion phase.

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 mean steady state exposures in paediatric patients at 1,0 mg/kg dose of cobimetinib suspension were approximately 50 % lower compared with those in adult patients when single agent cobimetinib at the approved 60 mg/day dose was administered. Doses above 1,0 mg/kg suspension were not tolerated in paediatric patients and hence it was not possible to administer higher doses to paediatric patients.

Geriatric Population

Data obtained in 133 geriatric patients ≥ 65 show that age does not have an effect on the exposure of cobimetinib.

Renal Impairment

Based on pre-clinical data and the human mass balance study, cobimetinib is mainly metabolised, 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 cobimetinib to patients with hepatic impairment (see Section 4.2 and Section 4.4).

Gender

Data obtained from 210 women and 277 men show that gender does not have an effect on the exposure of cobimetinib.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients – tablet core: croscarmellose sodium (E468), lactose monohydrate, magnesium stearate (E470b) and microcrystalline cellulose (E460).

Excipients – film-coating: macrogol 3350, polyvinyl alcohol, talc (E553b), titanium dioxide (E171) and purified water.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

60 months

6.4 Special precautions for storage

Store at or below 30 °C.

Keep in carton until required for use.

Keep out of reach of children.

6.5 Nature and contents of container

Transparent PVC/PVDC blisters containing 21 tablets. Each pack contains 63 tablets (3 x blisters of 21 tablets), placed in an outer carton.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

90 Bekker Road, Hertford Office Park

Building E, Vorna Valley, Midrand,

Johannesburg 1686

South Africa

Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

8. REGISTRATION NUMBER(S)

51/32.16/0871

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

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