AUSTRALIAN PRODUCT INFORMATION
Cotellic® (cobimetinib fumarate)

1. NAME OF THE MEDICINE
Cobimetinib fumarate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains cobimetinib hemifumarate equivalent to 20 mg cobimetinib.

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

For the full list of excipients, see section 6.1 List of excipients.

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

4.2 DOSE AND METHOD OF ADMINISTRATION
Dosage

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

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

Please also refer to the full Product Information for Zelboraf, which is used in combination with Cotellic.

Standard Dosage
The recommended dose of Cotellic is 60 mg (three 20 mg tablets) once daily for 21 days in 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 Pharmacokinetic properties). Cotellic tablets should be swallowed whole with water.

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

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

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

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

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

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

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

Table 1 below gives general Cotellic dose modification advice.

Table 1. Recommended Cotellic Dose Modifications

Grade (CTC-AE)*	Recommended Cotellic dosage
Grade 1 or Grade 2 (tolerable)	No dose reduction
Grade 2 (intolerable) or Grade 3/4	
1st appearance	Interrupt treatment until Grade ≤1, restart treatment at 40 mg once daily
2nd appearance	Interrupt treatment until Grade ≤1, restart treatment at 20mg once daily
3rd appearance	Consider permanent discontinuation

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

Dose Modification Advice for Specified Adverse Drug Reactions

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

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

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	Not applicable	Not applicable
	< 40% (or 40 – 49% and ≥ 10% absolute decrease from baseline)	Interrupt treatment for 2 weeks	< 10% absolute decrease from baseline	1st occurrence: 40mg
				2nd occurrence: 20mg
				3rd occurrence: permanent discontinuation
			< 40% (or ≥ 10% absolute decrease from baseline)	Permanent discontinuation
Symptomatic	Not applicable	Interrupt treatment for 4 weeks	Asymptomatic and < 10% absolute decrease from baseline	1st occurrence: 40mg
				2nd occurrence: 20mg
				3rd occurrence: permanent discontinuation
			Asymptomatic and < 40% (or ≥ 10% absolute decrease from baseline)	Permanent discontinuation
			Symptomatic regardless of LVEF	Permanent discontinuation

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

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

Asymptomatic CPK elevations

Grade ≤ 3: Cotellic dosing does not need to be modified or interrupted to manage asymptomatic Grade ≤ 3 creatine phosphokinase elevations (see section 4.8 Adverse effects (Undesirable effects) Laboratory Abnormalities).

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

Liver Laboratory Abnormalities

- Grade ≤ 2: Cotellic and Zelboraf should be continued at the prescribed dose.
- Grade 3: Continue Cotellic at the prescribed dose. The dose of Zelboraf may be reduced as clinically appropriate. Please refer to the full Product Information for Zelboraf.
- Grade 4: Interrupt Cotellic treatment and Zelboraf treatment. If liver laboratory abnormalities improve to Grade ≤ 1 within 4 weeks, restart Cotellic at a dose reduced by 20 mg and Zelboraf at a clinically appropriate dose; please refer to the full Product Information for Zelboraf. 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 Zelboraf treatment.

Photosensitivity

- Grade ≤ 2 (tolerable): manage with supportive care.
- Grade 2 (intolerable) or Grade ≥ 3: Cotellic and Zelboraf should be interrupted until resolution to Grade ≤ 1. Treatment can be restarted with no change in Cotellic dose. Zelboraf dosing should be reduced, please refer to the full Product Information for Zelboraf.

Rash

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

- *Grade ≤ 2 (tolerable)*: manage with supportive care.
- Grade 2 (intolerable) or Grade ≥ 3:
    - *Acneiform rash*: Follow general dose modification recommendations in Table 1 for Cotellic. Zelboraf 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). Zelboraf dosing may be either temporarily interrupted and/or reduced, please refer to the full Product Information for Zelboraf.

Special Dosage Instructions

Elderly

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

Children

The safety and efficacy of Cotellic in children and adolescents (< 18 years) has 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 Pharmacokinetic properties). 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 Pharmacokinetic properties). Liver laboratory abnormalities can occur when Cotellic is used in combination with Zelboraf (see section 4.4 Special warnings and precautions for use).

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 Product Information for Zelboraf, which is used in combination with Cotellic.

Haemorrhage
Haemorrhage, including major haemorrhages defined as symptomatic bleeding in a critical area or organ, can occur with Cotellic (see section 4.8 Adverse effects (Undesirable effects)).

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).

Prescribers should follow the dose modification guidance for haemorrhage management (see section 4.2 Dose and method of administration).

Serous Retinopathy
Serous retinopathy (fluid accumulation within the layers of the retina) has been observed in patients treated with MEK inhibitors, including Cotellic (see section 4.8 Adverse effects (Undesirable effects)). The majority of events were reported as chorioretinopathy or retinal detachment.

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

For patients reporting any symptoms of new or worsening visual disturbances, prompt 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 Dose and method of administration).

Left Ventricular Dysfunction
Decrease in left ventricular ejection fraction (LVEF) from baseline has been reported in patients receiving Cotellic (see section 4.8 Adverse effects (Undesirable effects)). 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 Dose and method of administration).

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 Zelboraf and when Zelboraf is used as a single agent (please refer to the full Product Information for Zelboraf).

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 Zelboraf (see section 4.8 Adverse effects (Undesirable effects)).

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 Zelboraf. Manage Grade 4 liver laboratory abnormalities with dose interruption, reduction or discontinuation of treatment of both Cotellic and Zelboraf (see section 4.2 Dose and method of administration).

Rhabdomyolysis and CPK elevations

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

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 Dose and method of administration).

Grade 3 or 4 CPK elevations, including asymptomatic elevations over baseline, have been reported in patients receiving Cotellic with Zelboraf in clinical trials (see section 4.8 Adverse effects (Undesirable effects)). 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, evaluate 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 Dose and method of administration).

Dermatological reactions
Severe rash and other skin reactions can occur with Cotellic see section 4.8 Adverse effects (Undesirable effects). Prescribers should follow the dosage modification recommendations for rash if events occur (see section 4.2 Dose and method of administration).

Photosensitivity
Photosensitivity, including severe cases, can occur with Cotellic, when used with Zelboraf (see section 4.8 Adverse effects (Undesirable effects)).

Advise patients to avoid sun exposure, wear protective clothing and use a broad spectrum UVA/UVB sun screen and lip balm (SPF ≥ 30+) when outdoors. Manage photosensitivity with dose modification (see section 4.2 Dose and method of administration).

Use in patients who have progressed on a BRAF inhibitor
There are limited data in patients taking the combination of Cotellic with Zelboraf 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 Pharmacodynamic properties, Clinical trials). Use of Cotellic in this population should be guided by careful benefit-risk assessment of the treatment and disease.

Use in the Elderly
Age does not have a clinically significant effect on the exposure of cobimetinib, based on a population pharmacokinetic analysis (see section 5.2 Pharmacokinetic properties).

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

Use in 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 Pharmacokinetic properties).

Use in Hepatic Impairment
No dose adjustment is recommended in patients with hepatic impairment (see section 5.2 Pharmacokinetic properties). Liver laboratory abnormalities can occur when Cotellic is used in combination with Zelboraf (see section 4.4 Special warnings and precautions for use).

Effect of Gender
Gender does not have an effect on Cotellic exposure (see section 5.2 Pharmacokinetic properties).

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effects of Concomitant Medications on cobimetinib

CYP3A Inhibitors/Inducers

Cobimetinib is metabolised by CYP3A. Cobimetinib AUC increased approximately 7-fold in the presence of a potent CYP3A inhibitor (itraconazole) in healthy subjects. Since cobimetinib is a sensitive substrate of CYP3A, it is likely that cobimetinib exposures will be significantly lower in the presence of CYP3A inducers. Therefore, concomitant administration of potent CYP3A inducers and inhibitors is not recommended. Use of cobimetinib in the presence of moderate CYP3A inhibitors or inducers should be avoided where possible. Caution should be exercised when cobimetinib must be co-administered with moderate CYP3A inducers and inhibitors (see section 4.2 Dose and method of administration for advice about reducing dose on the basis of adverse events).

Acid-Reducing Agents

Cobimetinib was administered in the presence of rabeprazole (a proton pump inhibitor) in healthy subjects to determine the effect of increased gastric pH. Cobimetinib pharmacokinetics were not altered and thus, gastric pH elevations do not affect cobimetinib absorption.

Effects of cobimetinib on Concomitant Medications

CYP Substrates

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

Other Anti-Cancer Agents

Zelboraf

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

Interactions Mediated by Drug Transport Systems

In vitro studies show that cobimetinib is a substrate but not an inhibitor of P-glycoprotein (P-gp). *In vitro* studies also show that cobimetinib is not a substrate of breast cancer resistance protein (BCRP) but is a weak to moderate inhibitor of BCRP.

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

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

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

In toxicology studies, degenerative changes were observed in reproductive tissues including increased apoptosis/necrosis of corpora lutea and seminal vesicle, epididymal and vaginal epithelial cells and follicular cysts of ovaries in rats, and apoptosis/necrosis of epididymal epithelial cells in dogs at exposure ≥ 3 times the expected clinical exposure based on AUC. The effect of cobimetinib on human fertility is unknown.

Use in Pregnancy – Category D
Cotellic is not recommended during pregnancy.

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

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

When administered to pregnant rats, cobimetinib caused embryolethality and foetal malformations of the great vessels and skull, and decreased ossification sites at clinically relevant exposures (systemic exposures approximately 0.9 to 1.4 times the human clinical plasma AUC exposure).

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

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
No studies on the effects on the ability to drive and to use machines have been performed.

Visual disturbances have been reported in some patients treated with Cotellic during clinical trials (see sections 4.4 Special warnings and precautions for use and 4.8 Adverse effects (Undesirable effects)). Patients should be advised not to drive or use machines without first consulting with their prescriber if their vision is impaired.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)
The safety of Cotellic in combination with Zelboraf has been evaluated in 247 patients with advanced BRAF V600 mutated melanoma in the Phase III study GO28141. The median time to onset of first Grade ≥ 3 adverse events was 0.6 months in the Cotellic-plus-Zelboraf arm vs. 0.8 months in the placebo-plus-Zelboraf control arm.

The safety of Cotellic in combination with Zelboraf has also been evaluated in 129 patients with advanced BRAF V600 mutated melanoma in the Phase Ib study NO25395. The safety profile of Cotellic in NO25395 was consistent with that observed in study GO28141.

The table below 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 Zelboraf in the GO28141 study. The following categories of frequency have been used: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), very rare (< 1/10,000).

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

ADRs	Phase III study: GO28141				Frequency[a] (All Grades)
	Cotellic + Zelboraf (n = 247)		Placebo + Zelboraf (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
Vision Blurred	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
Dermatitis acneiform rash	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

ADRs (all grades) Reported with < 5% Greater Incidence in the Cotellic-Plus- Zelboraf Arm than the Placebo-Plus-Zelboraf Control Arm in Study GO28141

Eye disorders: visual impairment (3% in the Cotellic arm vs. 0% in the control arm) (see section 4.4 Special warnings and precautions for use).

Metabolism and nutrition disorders: hyperglycemia (3% in the Cotellic arm vs. 1% in the control arm), hypophosphatemia (4% in the Cotellic arm vs 1% in the control arm).

Respiratory, thoracic and mediastinal disorders: pneumonitis (1% in the Cotellic arm vs. < 1% in the control arm).

Skin and subcutaneous tissue disorders: rash (40% in the Cotellic arm vs. 38% in the control arm).

Further Information on Selected Adverse Reactions

Haemorrhage

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

The majority of events were Grade 1 or 2 and non-serious (12% of patients in the Cotellic arm vs. 7% patients in the control arm). Most events resolved or were resolving with no change in Cotellic dose.

Grade 3 to 4 events were experienced by 1% of patients in each arm (see section 4.4 Special warnings and precautions for use).

Photosensitivity

Photosensitivity has been observed with a higher frequency in the Cotellic arm vs. the control 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 arm vs. 0% in the control arm.

There were no apparent trends in the time of onset of Grade ≥ 3 events. Grade ≥ 3 photosensitivity events in the Cotellic arm were treated with primary topical medication in conjunction with dose interruptions of both Cotellic and Zelboraf (see section 4.2 Dose and method of administration).

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

Laboratory Abnormalities

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

Test*	**Cotellic + Zelboraf (n = 247) (%)**		**Placebo + Zelboraf (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
Haematology				
Anaemia	69	2	57	3
Lymphopenia	67	9	50	7
Thrombocytopenia	18	0	10	0
Other Laboratory Abnormalities				
Increased 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

Table 5. Post-Marketing Experience

System Organ Class (SOC)	**Adverse Drug Reaction (ADR)**
Musculoskeletal and connective tissue disorders	Rhabdomyolysis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents, ATC code: L01XE38

Mechanism of Action

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

Cobimetinib is an orally available inhibitor of MEK1 and MEK2 tyrosine-threonine kinases. It has shown high inhibitory potency in biochemical and cell based assays, as well as anti-tumour activity *in vivo* in xenograft tumour models mutated for BRAF. Cobimetinib also showed efficacy in some KRAS mutant models.

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

In pre-clinical studies, 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 signaling 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 signaling, greater tumour cell apoptosis and enhanced tumour responses in pre-clinical models than vemurafenib alone.

Clinical trials

Study GO28141 (coBRIM)

Study GO28141 is a multicentre, randomised, double-blind, placebo-controlled, Phase III study to evaluate the safety and efficacy of Cotellic in combination with Zelboraf® compared to Zelboraf plus placebo, in patients with previously untreated BRAF V600 mutation-positive unresectable locally advanced (stage IIIC) or metastatic melanoma (stage IV). Patients with abnormal liver function tests, history of acute coronary syndrome within 6 months, evidence of Class II or greater congestive heart failure (New York Heart Association), active central nervous system lesions, or evidence of retinal pathology were excluded from the study.

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

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

- Cotellic 60 mg once daily on Days 1 − 21 of each 28-day treatment cycle and 960 mg Zelboraf twice daily on Days 1−28.
- Placebo once daily on Days 1 − 21 of each 28-day treatment cycle and 960 mg Zelboraf 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 and PFS as assessed by an independent review facility (IRF).

Efficacy results are summarised in Table 6.

Table 6. Efficacy results from Study GO28141

	Cotellic + Zelboraf n = 247	**Placebo + Zelboraf n = 248**
PRIMARY ENDPOINT		
Progression-free survival (Inv)[a, g]		
Median by Kaplan Meier (KM) estimate (months) (95% CI)	9.9 (9.0, NE)	6.2 (5.6, 7.4)
Hazard ratio (95% CI)	0.51 (0.39, 0.68) (*p*-value < 0.0001)	
KEY SECONDARY ENDPOINTS		
Progression-free survival (IRF)[b,c]		
Median by KM-estimate (months) (95% CI)	11.3 (8.5, NE)	6.0 (5.6, 7.5)
Hazard ratio (95% CI)	0.60 (0.45; 0.79) (*p*-value 0.0003)	
Overall survival		
Median KM estimate (months) (95% CI)	22.3 (20.3, NE)	17.4 (15.0, 19.8)
Hazard ratio (95% CI)[c]	0.70 (95% CI: 0.55, 0.90) (*p*-value = 0.0050[e])	
Objective response[a]		
Objective response rate (ORR), n (%) (95% CI[d])	167 (67.6%) (61.4%, 73.4%)	111 (44.8%) (38.5%, 51.2%)
Difference in ORR % (95% CI[f])	22.85 (14.13, 31.58) (*p*-value < 0.0001)	
Best Overall Response		
Complete Response, n (%)	25 (10.1%)	11 (4.4%)
Partial Response, n (%)	142 (57.5%)	100 (40.3%)
Stable disease, n (%)	49 (19.8%)	105 (42.3%)
Duration of response		
Median duration of response (months)	NE	7.3
95% CI for median	9.3, NE	5.8, NE

[a] Assessed and confirmed by the investigator (Inv) using RECIST v1.1; [b] Assessed and confirmed by an independent review facility (IRF) assessment using RECIST v1.1; [c] Stratified analysis by geographic region and metastasis classification (disease stage); [d] Using Clopper-Pearson method; [e] The OS *p*-value (0.0050) crossed the pre-specified boundary (*p*-value <0.0499); [f] Using Hauck-Anderson method; [g] See text for discussion of post-hoc analysis of PFS; NE = not evaluable; Note: The table represents results from the primary analysis (cut-off date 9 May 2014). The exception is the pre-planned final analysis of overall survival (cut-off date 28 August 2015)

Figure 1. Kaplan-Meier Curves of Progression-free Survival (Inv): Intent-to-Treat Population

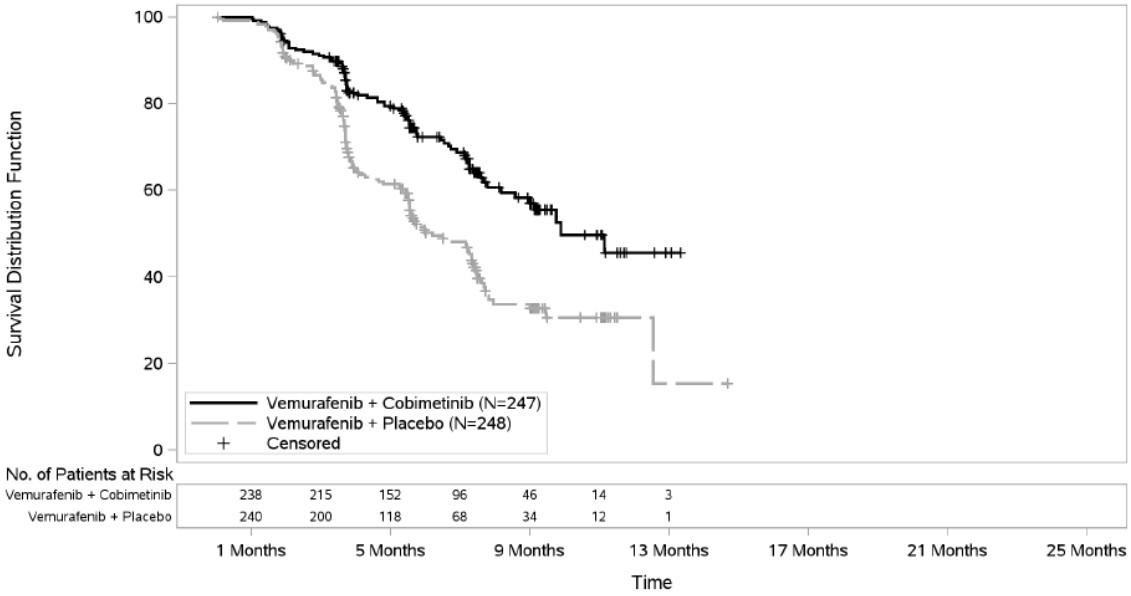


Figure 2. Kaplan-Meier Curves of Final Overall Survival: Intent-to-Treat Population

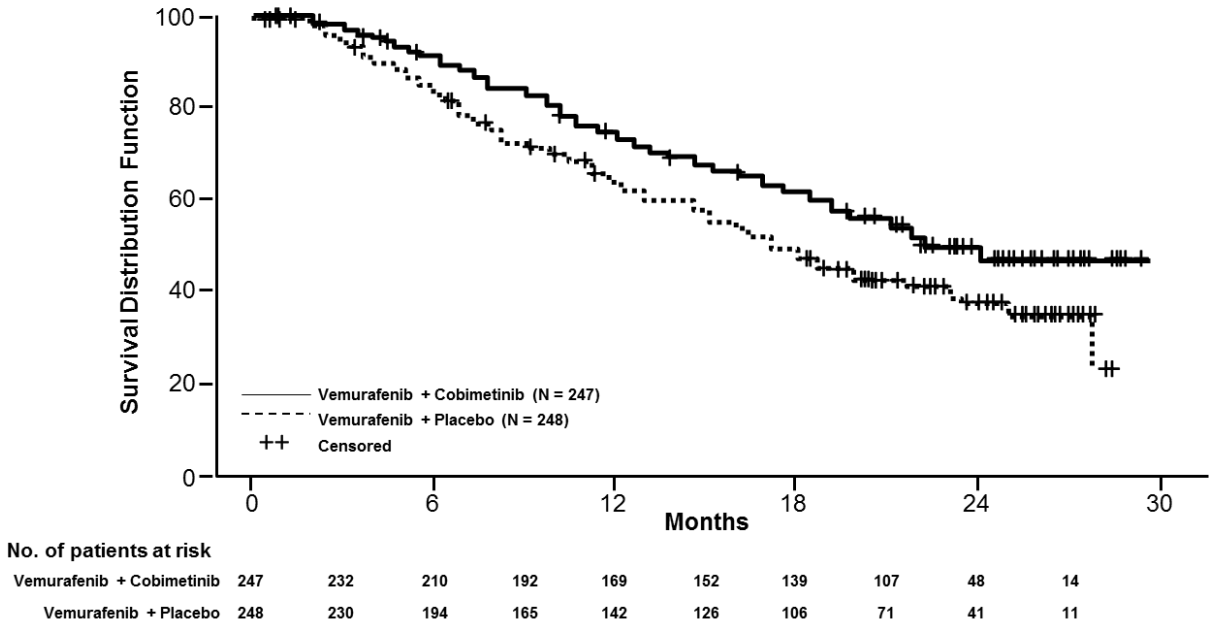
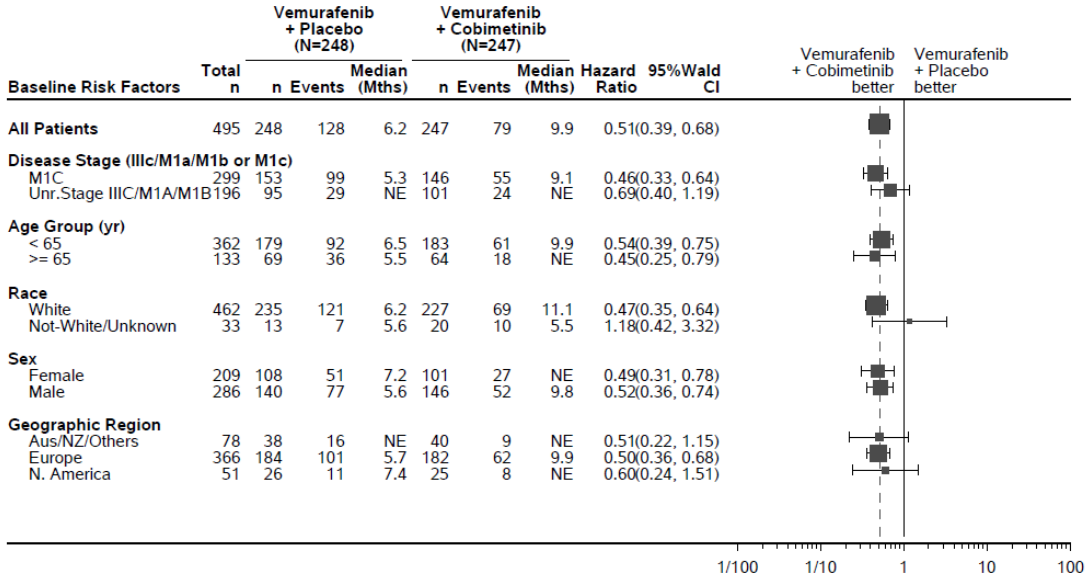


Figure 3. Forest Plots for Hazard Ratios of Progression-Free Survival Subgroup Analyses: Intent-to-Treat Population



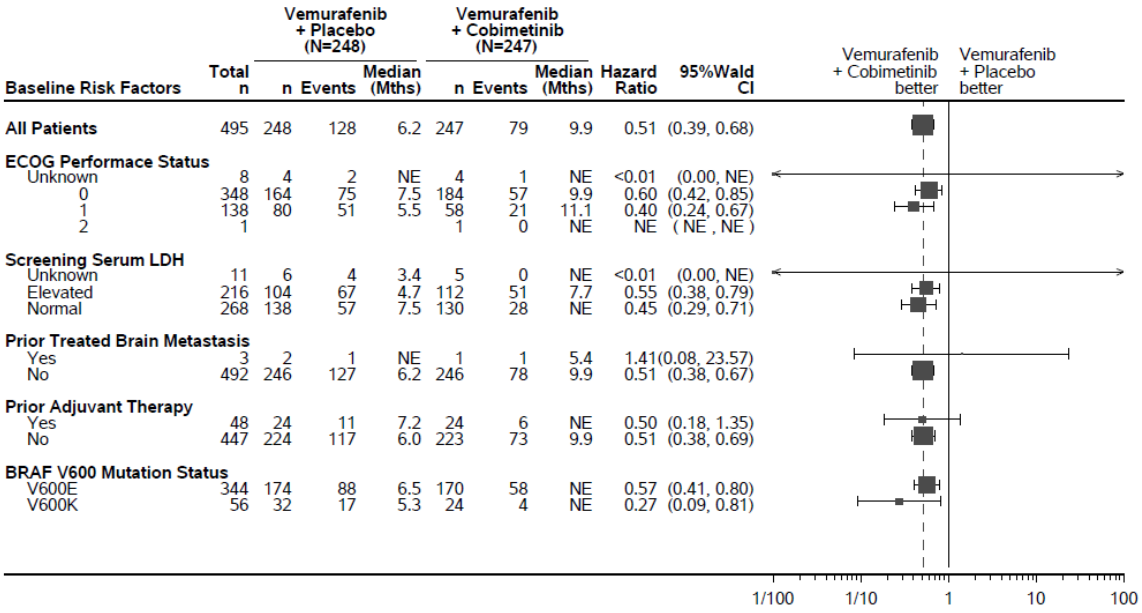
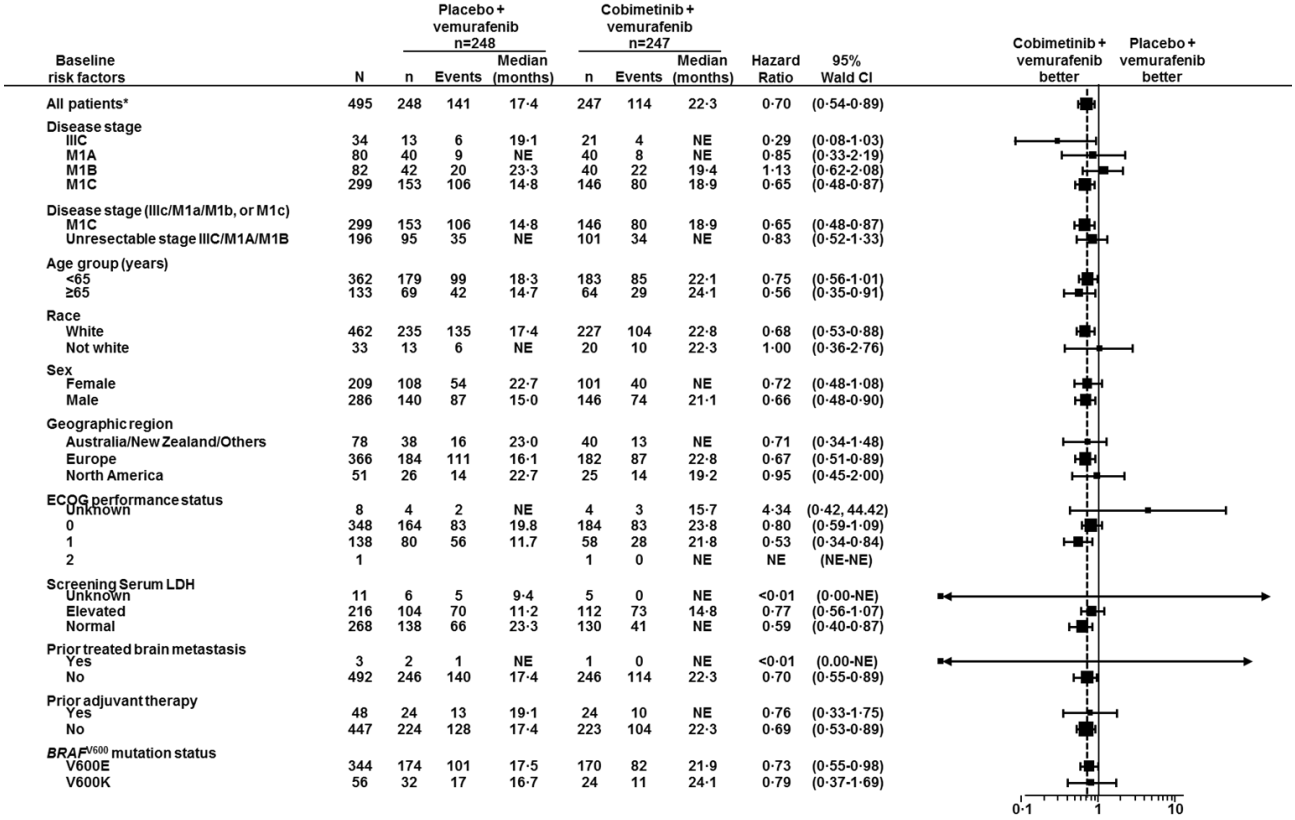


Figure 4. Forest Plot for Hazard Ratios of Final Overall Survival Subgroup Analyses: Intent-to-Treat Population



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

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

<u>Study NO25395 (BRIM7)</u>
The efficacy of Cotellic was evaluated in a Phase Ib study, NO25395, which was designed to assess the safety, tolerability, pharmacokinetics and efficacy of Cotellic when added to Zelboraf for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation (as detected by the cobas 4800 BRAF V600 Mutation Test).

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

Results of the BRAFi naïve population from study NO25395 were generally consistent with those from study GO28141. The BRAFi-naïve patients (n = 63) attained an 87% objective response rate, including a complete response in 10% of patients. The median duration of response was 12.5 months. The median PFS for BRAFi-naïve patients was 13.7 months, with median follow-up time of 12.7 months.

Among patients who had progressed on Zelboraf (n = 66), the objective response rate was 15%, the median duration of response was 6.7 months and the median PFS was 2.8 months.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral dosing of 60 mg in cancer patients, cobimetinib showed a moderate rate of absorption with a median Tmax of 2.4 hours. The mean steady-state Cmax and AUC0-24 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 (Vss) was 1050 L in healthy subjects given an intravenous (IV) dose of 2 mg. The apparent volume of distribution (Vss) was 806 L in cancer patients based on population PK analysis.

Metabolism

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.

Excretion

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.

Following IV administration of a 2 mg dose of cobimetinib, the mean plasma clearance (CL) was 10.7 L/hr. The mean CL/F following oral dosing of 60 mg in cancer patients based on a population pharmacokinetic analysis was 13.4 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 co-variates on cobimetinib clearance and volume of distribution respectively. However, sensitivity analysis suggests neither of these co-variates had a clinically significant impact on steady state exposure.

Gender

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

Elderly

Age does not have a clinically significant effect on the exposure of cobimetinib, based on a population pharmacokinetic analysis which included 133 patients ≥ 65 years of age.

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. Exposures of total cobimetinib 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 exposures ($AUC_{0-\infty}$ geometric mean ratio of 0.69 compared to healthy subjects) which is not considered to be clinically significant. Exploratory analysis of unbound cobimetinib concentrations show that exposure of unbound cobimetinib in subjects with mild and moderate hepatic impairment were similar to subjects with normal hepatic function while subjects with severe hepatic impairment had 2-fold higher exposures.

Therefore, no dose adjustment is recommended when administering Cotellic to patients with hepatic impairment (see section 4.2 Dose and method of administration).

QT Prolongation

No additive clinical effect on QT interval prolongation is observed when patients are treated with Cotellic in combination with Zelboraf. *In vitro*, cobimetinib produced moderate hERG ion channel inhibition (IC_{50} = 0.5 μM [266 ng/mL]), which is approximately 18-fold higher

than peak plasma concentrations (C_{max}) at the 60 mg dose (unbound C_{max} = 14 ng/mL [0.03 μM]).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Standard genotoxicity studies with cobimetinib were all negative. Cobimetinib was assessed for genotoxicity in *S. typhimurium* and *E. coli*, *in vitro* in primary human lymphocytes, and *in vivo* in a rat bone marrow micronucleus assay.

Carcinogenicity

No carcinogenicity studies have been conducted with Cotellic.

Other Toxicological Information

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Magnesium stearate

Tablet coating
Polyvinyl alcohol
Titanium dioxide
Macrogol 3350
Purified talc

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30 °C.

6.5 NATURE AND CONTENTS OF CONTAINER

Polyvinyl chloride/polyvinylidene chloride duplex blisters with an aluminium foil lidding containing 21 tablets.

Each pack contains 63 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

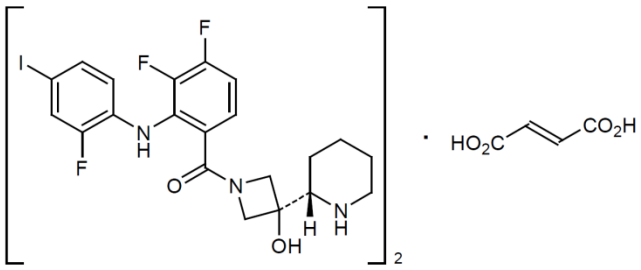
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSIOCHEMICAL PROPERTIES

Cobimetinib fumarate is described chemically as (S)-[3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl] [3-hydroxy-3-(piperidin-2-yl)azetidin-1-yl] methanone hemifumarate. It has a molecular formula of 2(C21H21F3IN3O2).C4H4O4 and a molecular weight of 1178.7 g/mol.

Cobimetinib is a white to off-white solid. The solubility of cobimetinib is high in low pH media (> 10 mg/mL at pH 1.0). The dissociation constant for cobimetinib is 8.86 (corresponding to the piperidine cation), with a distribution coefficient of 2.42 at pH 7.4.

Chemical structure



CAS number 1369665-02-0

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8. SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
Level 8, 30 – 34 Hickson Road
Sydney NSW 2000
AUSTRALIA

Medical enquiries: 1800 233 950

9. DATE OF FIRST APPROVAL

5 April 2016

10. DATE OF REVISION

12 August 2019

Summary table of changes

Section Changed	Summary of new information
All	Editorial corrections