Drug Monograph

A - Drug Name

cobimetinib

COMMON TRADE NAME(S): Cotellic™

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B - Mechanism of Action and Pharmacokinetics

Cobimetinib is a highly selective inhibitor of MEK1 and MEK2, which are signal-regulated kinases in the mitogen-activated protein kinase (MAPK) pathway. The dual targeting of the MAPK pathway with BRAF and MEK inhibitors (via 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 compared to vemurafenib alone (in pre-clinical models).

Absorption	Cobimetinib has linear pharmacokinetics in the dose range of approx 3.5 mg to 100 mg.	
	Bioavailability	45.9% in healthy subjects
	Effects with food	With or without food (Absorption is slower with food, but exposure is similar)
	Peak plasma levels	T_{max} = 2.4 hours
Distribution	Cross blood brain barrier?	Low brain penetration observed in animals
	PPB	Highly bound (94.8% *in vitro*)
Metabolism	Main enzymes involved	oxidation by CYP3A and glucuronidation by UGT2B7

	Active metabolites	Yes
	Inactive metabolites	Yes
Elimination	Feces	76.5% (6.6% as unchanged drug)
	Urine	17.8% (1.6% as unchanged drug)
	Half-life	43.6 hours (range from 23.1 to 69.6 hours)

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C - Indications and Status

Health Canada Approvals:

For the treatment of unresectable or metastatic melanoma with a BRAF V600 mutation, in combination with vemurafenib. Confirmation of BRAF V600 mutation by a validated test is required prior to initiation of treatment.

Notes:

Data supporting use in patients with BRAF V600K are limited.

There are no data to support the use of this combination in the treatment of non-cutaneous melanoma, in patients with untreated brain metastases, or in less common BRAF V600 mutations.

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D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

The following adverse reactions were reported in the Phase III study of cobimetinib in combination with vemurafenib where the incidence was higher (≥ 5% or ≥ 2% for grade 3, 4) than for vemurafenib with placebo.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Atrial fibrillation (4%)	E

	Ejection fraction decreased (12%)	E D
	Hypertension (16%) (6% severe)	E D
Dermatological	Photosensitivity (48%) (4% ≥ grade 3)	E D
	Rash (15%) (including maculopapular) (maybe severe)	E
Gastrointestinal	Dehydration (4%)	E D
	Diarrhea (61%)	E D
	GI obstruction (rare)	E
	Nausea, vomiting (43%)	I E D
General	Fever, chills (29%)	E D
Hematological	Hemorrhage (14%) (1% severe)	E D
	Myelosuppression (14%)	E D
Hepatobiliary	↑ LFTs (74%) (11% severe)	E D
	↑ Lipase (4%)	E
Hypersensitivity	Hypersensitivity (1%)	I
Metabolic / Endocrine	Abnormal electrolyte(s) (71%) (may be severe)	E D
Musculoskeletal	↑CPK (81%) (rhabdomyolysis rare)	E D
Neoplastic	Secondary malignancy (6%) (Basal Cell Carcinoma)	E D
Nervous System	Seizure (rare)	E
Ophthalmic	Retinopathy (13%) (including retinal detachment)	E D
Renal	Other (Acute kidney injury - rare)	E
Respiratory	Pneumonitis (2%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The side effects that occurred more frequently in patients treated with cobimetinib include diarrhea, rash, nausea/vomiting, increased CPK, photosensitivity reaction, fever, and elevated LFT's.

Left ventricular dysfunction has been reported in patients receiving cobimetinib and is usually reversible; one patient developed a cardiomyopathy.

Cerebral, gastrointestinal, and reproductive system **hemorrhagic events**, were reported more frequently in patients treated with cobimetinib plus vemurafenib compared to the placebo plus vemurafenib group (14% vs. 9%). The majority of patients had additional risk factors for bleeding (see Precautions section).

Serum creatinine phosphokinase (CPK) levels were elevated at a higher frequency in patients treated with cobimetinib. Rhabdomyolysis has been reported.

Serous retinopathy, including chorioretinopathy and retinal detachment, developed in 27% of patients in the cobimetinib arm (compared to 4% with placebo). Median time to initial onset was 1 month, and median time to resolution was 3 months.

Retinal vein occlusion (RVO) was reported in one patient in each arm of the study. It is recommended to consider risk factors for RVO, including uncontrolled hypertension, diabetes, hypercholesterolemia, or glaucoma, prior to initiating cobimetinib and vemurafenib.

Severe photosensitivity is possible in patients treated with the combination of cobimetinib and vemurafenib. During treatment, patients should avoid sun exposure as much as possible, wear protective clothing, and use a broad spectrum UVA/UVB sunscreen and lip balm with a minimum of SPF 30.

Cutaneous squamous cell carcinoma, keratoacanthoma and hyperkeratosis occurred in both arms of the study, but at a lower frequency in the cobimetinib plus vemurafenib group.

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Adults:

- Confirmation of BRAF V600 mutation by a validated test is required prior to initiation of treatment.
- Patients should be advised to avoid sun exposure (during treatment and for at least 5 days after stopping) and use broad spectrum sunscreen and lip balm (SPF > 30).
- Patients should have a supply of loperamide (initial dose of 4 mg followed by 2 mg every 4 hours or after every unformed stool; up to a maximum of 16 mg/day) for management at first signs of diarrhea.

Oral: 60* mg once daily on Days 1 to 21

(Available as 20 mg tablets)

Cycle duration: Repeat every 28 Days unless disease progression or unacceptable toxicity occurs

*Note: Dose for patients receiving moderate CYP3A4 inhibitors is 20 mg once daily on days 1 to 21.

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Dosage with Toxicity:

Once a dose has been reduced for toxicity, it should not be re-escalated.

Dose level reductions:

Dose level	Cobimetinib (mg/day)
-1	40
-2	20
-3	Discontinue

Table 1: Recommended Dose Modifications for Specific Adverse Effects

Adverse Effect	Severity	Action
Rhabdomyolysis or symptomatic ↑ CPK or asymptomatic grade 4		Hold for up to 4 weeks* If recovery to ≤ grade 3; restart at 1 dose level ↓ if clinically indicated.
Asymptomatic ↑ CPK	Grade 3	May continue, or consider hold until ≤ grade 2.
Liver function abnormalities and Hepatotoxicity	First occurrence Grade 4	Hold for up to 4 weeks* If recovery to ≤ grade 1, restart at 1 dose level ↓.
	Recurrent Grade 4	Permanently discontinue
Retinal vein occlusion (RVO)	Permanently discontinue	
Serous Retinopathy	Hold for up to 4 weeks*	

	If recovery to ≤ grade 1, restart at 1 dose level ↓.	
Photosensitivity	Grade ≤ 2 (tolerable)	Manage with supportive care.
	Grade 2 (intolerable), Grade ≥ 3	Hold until ≤ grade 1; restart at previous dose.
Rash	Grade ≤ 2 (tolerable)	Manage with supportive care.
	Grade 2 (intolerable), Grade ≥ 3	Acneiform rash: follow general dose modifications (see Table 2 below) Non-acneiform or maculopapular rash: continue without modification if appropriate
Asymptomatic absolute ↓ in LVEF from baseline > 10% (and < lower limit of normal (LLN)	Hold for 2 weeks; repeat LVEF[1] Restart at 1 dose level ↓ if LVEF ≥ LLN and absolute ↓ from baseline LVEF ≤ 10%. Permanently discontinue if LVEF ≤ LLN, or ↓ from baseline LVEF > 10%.	
Symptomatic LVEF ↓ from baseline	Hold for up to 4 weeks; repeat LVEF[1] Restart at 1 dose level ↓ if LVEF ≥ LLN and absolute ↓ from baseline LVEF ≤ 10% and symptoms resolve. Permanently discontinue if the symptoms persist, LVEF < LLN, or ↓ from baseline LVEF > 10%.	
Hemorrhage	Grade 3	Hold for up to 4 weeks* If recovery to ≤ grade 1; restart at 1 dose level ↓ if clinically indicated.
	Grade 4 or cerebral hemorrhage (all grades)	Permanently discontinue

*if not improved within 4 weeks, permanently discontinue

[1] LVEF should be repeated at 2, 4, 10, and 16 weeks after hold

Table 2: Recommended Dose Modifications for Other Adverse Effects

Severity	Cobimetinib Dose
Grade 1 or Grade 2 (tolerable)	No dose reduction.

Grade 2 (intolerable) or Grade 3 to 4	
1st Appearance	Hold until grade ≤1, restart at 1 dose level ↓.
2nd Appearance	Hold until grade ≤1, restart at 1 additional dose level ↓.
3rd Appearance	Permanently discontinue

Dosage with Hepatic Impairment:

- No dosage adjustment is recommended in patients with mild to moderate hepatic impairment based on a pharmacokinetic study with cobimetinib.
- Patients with severe hepatic impairment had increased plasma concentrations of unbound cobimetinib compared to those with normal hepatic function.
- Use with caution when used in combination with vemurafenib in patients with hepatic impairment.
- Refer to the dosage with toxicity table above for dose modifications for hepatotoxicity.

Dosage with Renal Impairment:

No dose adjustment recommended in patients with mild or moderate renal impairment. The safety and efficacy in patients with severe renal impairment have not been established.

Dosage in the elderly:

No dose adjustment is required. There was a higher incidence of dose modification (including discontinuation) for adverse events overall in patients ≥ 65 relative to those < 65, specifically for diarrhea, vomiting, asthenia, pyrexia, dehydration, elevated AST, chorioretinopathy, and retinal detachment.

Dosage based on gender:

Gender does not appear to have an effect on cobimetinib exposure.

Children:

Safety and efficacy in children and adolescents have not been established.

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F - Administration Guidelines

- Tablets should be swallowed whole with a glass of water with or without food.
- Avoid grapefruit, grapefruit juice, and products containing grapefruit extract.
- If a dose is missed and it is more than 12 hours before the next dose, the missed dose should be taken.
- If it is less than 12 hours before the next dose the missed dose should be skipped.
- If a patient vomits after taking a dose, they should not replace the dose that day; treatment should be continued as prescribed the following day.
- Tablets should be stored at room temperature (15-30°C).

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G - Special Precautions

Contraindications:

- Patients with known hypersensitivity to cobimetinib or any of the excipients

Other Warnings/Precautions:

- Should not be used as monotherapy.
- Should not be used in wild-type BRAF melanoma or in patients with BRAF mutational status unknown.

- Avoid concomitant use with strong or moderate CYP3A inhibitor (refer to Interactions section for dose adjustments with moderate inhibitors).
- Not recommended for use in patients with active untreated brain metastases.
- Not recommended in patients with decreased LVEF (<50% or below institutional lower limit of normal).
- Not recommended in patients with a history of retinal vein occlusion.
- Use with caution in patients with risk factors for bleeding, including patients taking concomitant medications that increase risk, such as antiplatelets and anticoagulants.

Pregnancy and Lactation:

- Embryotoxicity: Yes
- Genotoxicity: No
- Fetotoxicity: Yes
- Teratogenicity: Yes
  Cobimetinib is not recommended during pregnancy; females of childbearing potential and male patients should use two effective forms of contraception during treatment and for at least **3 months** after treatment cessation.
- Breastfeeding: Not recommended
- Fertility effects: Probable

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H - Interactions

Cobimetinib does not inhibit or induce CYP3A or inhibit CYP2D6 at the recommended dose. Co-administration with a proton pump inhibitor (rabeprazole) did not affect cobimetinib exposure. In vitro, cobimetinib is a substrate of P-gp and an inhibitor of BCRP.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ cobimetinib concentration and/or toxicity (up to 7-fold)	↓ metabolism of cobimetinib	Avoid strong inhibitors. If short term use of a moderate inhibitor is unavoidable, in patients taking 60mg daily ↓ the dose to 20mg daily for duration of inhibitor use and monitor closely. Resume previous dose when the inhibitor is stopped. For patients taking 40mg daily or

			less, avoid moderate inhibitors.
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc.)	↓ cobimetinib concentration (up to 83%) and/or efficacy	↑ metabolism of cobimetinib	Avoid use of concomitant strong or moderate inducers
P-glycoprotein inhibitors (i.e. quinidine, verapamil, cyclosporine)	May ↑ cobimetinib concentration and/or toxicity (in vitro studies only)		Caution
BCRP substrates (i.e. topotecan)	altered substrate absorption; unknown relevance	cobimetinib may inhibit BCRP	Caution

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
LVEF	Baseline, after the first month of treatment, and at least every 3 months, or as clinically indicated, until treatment discontinuation. Patients restarting treatment with a dose reduction should have LVEF measurements taken at 2 weeks, 4 weeks, 10 weeks and 16 weeks, and then as clinically indicated
Blood pressure	Baseline and at each visit
CBC	Baseline and at each visit
Liver function tests	Baseline and monthly or as clinically

	indicated
Creatinine, electrolytes, CPK levels	Baseline and monthly or as clinically indicated during treatment. Rule out rhabdomyolysis if CPK increases.
ECG	Baseline and at every second visit, as clinically indicated
Ophthalmology assessment	Baseline, at each visit, and with development of any symptoms
Clinical toxicity assessment for ocular effects, dermatologic effects, bleeding, diarrhea, nausea and vomiting, hypersensitivity, hyperglycemia, pneumonitis	Baseline and at each visit. Dermatologic monitoring should continue for 6 months following discontinuation of treatment.

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- cobimetinib - In combination with vemurafenib for the treatment of patients with previously untreated BRAF V600 mutation-positive unresectable stage III or IV melanoma, according to specific criteria

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K - References

Cobimetnib product monograph, Hoffmann-La Roche Limited. January 2018.

Larkin J, Ascierto PA, Dreno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J M ed 2014;371:1867-76.

July 2023 Added general statements on hepatitis B screening and monitoring

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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