DRUG NAME: Cobimetinib

SYNONYM(S): GDC-0973, XL518[1]

COMMON TRADE NAME(S): COTELLIC®

CLASSIFICATION: molecular targeted therapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Cobimetinib is an oral selective inhibitor of the mitogen-activated extracellular kinase (MEK) pathway. It reversibly inhibits MEK1 and MEK2. MEK proteins are components of the mitogen-activated protein kinase (MAPK) pathway involved in cellular proliferation. Mutant BRAF proteins signal through MEK1 and MEK2 and the extracellular signal-related kinase (ERK) pathway to stimulate cell growth. MEK inhibitors, in combination with other drugs targeting the MAPK pathway, increase apoptosis and reduce tumour growth.[2,3]

PHARMACOKINETICS:

Oral Absorption	45.9% bioavailability; T_{max} = 2.4 hours	
Distribution	highly bound to alpha-1 acid glycoprotein	
	cross blood brain barrier?	yes, at low levels (animal studies)
	volume of distribution	806 L
	plasma protein binding	94.8%
Metabolism	extensive hepatic metabolism via CYP3A oxidation and UGT2B7 glucuronidation	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	minimal renal elimination	
	urine[3]	18% (2% as unchanged drug)
	feces[2,3]	76.5% (7% as unchanged drug)
	terminal half life	43.6 hours
	clearance	13.8 L/h

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:
*Melanoma

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Caution:
- decreased ***left ventricular ejection fraction*** (LVEF) is reported; use with caution in patients with pre-existing conditions that impair LVEF[2]

- ***secondary malignancies,*** including ***basal cell carcinoma,*** are reported; dermatologic evaluations are recommended prior to and regularly during treatment[2]
- ***retinal vein occlusion*** (RVO) is reported; avoid cobimetinib in patients with a history of RVO and use with caution in patients with hypertension, diabetes, hypercholesterolemia, or glaucoma[2]

Special Populations: Patients 65 years or older report a higher incidence of adverse events which may lead to dose interruptions/reductions or discontinuation.[2]

Carcinogenicity: No formal carcinogenicity studies have been conducted; however, secondary malignancies have been reported.[2]

Mutagenicity: Not mutagenic in Ames test or clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[2]

Fertility: In animal studies, degenerative changes were observed in the reproductive tissue of males (e.g., seminal vesicles and epididymal epithelial cells) and females (e.g., increased apoptosis/necrosis of corpora lutea and vaginal epithelial cells) at exposures 2.5 to 8 times higher than expected human clinical plasma exposures.[2]

Pregnancy: In animal studies, cobimetinib caused embryolethality and fetal malformations of the great vessels and skull at exposures 0.9 to 1.4 times that of expected human exposures. For women of reproductive potential, two effective forms of contraception are recommended during treatment and for three months after treatment has been discontinued.[2]

Breastfeeding is not recommended due to potential secretion of cobimetinib into breast milk. Avoid breastfeeding during treatment and for 2 weeks following the last dose.[3]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[4] **Unless specified otherwise, the incidence data in the Side Effects table is based on combination therapy with vemurafenib.**

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (67%, severe 2%)
	lymphopenia (65%, severe 9%)
	thrombocytopenia (16%)
cardiac	atrial fibrillation (3%)
	cardiomyopathy (<1%); see paragraph following **Side Effects** table
eye (see paragraph following **Side Effects** table)	***retinal vein occlusion*** (<1%)
	serous retinopathy (24%, severe 1-2%)[2,3]; includes chorioretinopathy and retinal detachment
	visual impairment (3-15%, severe <1%)[2,3]; includes blurry vision, and decreased visual acuity
gastrointestinal	*emetogenic potential: low*[5]
	diarrhea (57%, severe 6%)
	hemorrhage (4%)
	nausea (39%, severe 1%)
	stomatitis (14%)[3]; includes aphthous stomatitis, mucositis, and oral mucosa ulcers
	vomiting (21%, severe 1%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
general disorders and administration site conditions	*extravasation hazard:* none[6]
	chills (10%)[3]
	fatigue (28%, severe 4%)[1]
	pyrexia (26%, severe 2%)
immune system	hypersensitivity reaction (2%, severe 1%); may require hospitalization and steroid treatment
investigations (see paragraph following **Side Effects** table)	***ALT increase*** (66%, severe 10%)
	AST increase (69%, severe 7%)
	alkaline phosphatase increase (69%, severe 7%)
	bilirubin increase (severe 2%)[3]
	creatine phosphokinase increase (65%, severe 10%)
	left ejection fraction decrease (7%, severe 1%)
	gamma-glutamyltransferase increase (60%, severe 19%)
metabolism and nutrition	dehydration (4%, severe 2%)
	hyperglycemia (4%)
	hyperkalemia (23, severe 3%)
	hypocalcemia (24%, severe 1%)
	hypokalemia (24%, severe 5%)
	hyponatremia (36%, severe 6%)
	hypophosphatemia (61%, severe 10%)
musculoskeletal and connective tissue	arthralgia (33%)
	rhabdomyolysis (<1%); see paragraph following **Side Effects** table
neoplasms (see paragraph following **Side Effects** table)	basal cell carcinoma (4%)
	cutaneous squamous cell carcinoma (3%)
	keratoacanthoma (1%)
	second primary melanoma (<1%)
nervous system disorders	cerebral hemorrhage (<1%)[7]
renal and urinary	genitourinary tract hemorrhage (2%)[3]
	hematuria (2%)[3]
reproductive system and breast disorders	reproductive system hemorrhage (2%)
respiratory, thoracic and mediastinal	pneumonitis (1%)
skin and subcutaneous tissue (see paragraph following **Side Effects** table)	alopecia (14%)
	hyperkeratosis (10%)
	dermatitis acneiform (13-16%, severe 2%)[2,3]
	photosensitivity reaction (41-47%, severe 3-4%)[2,3]; includes solar dermatitis, actinic elastosis, and sunburn
	rash (39%, severe 16%)[2,3]; includes non-acneiform, and maculopapular rash
vascular	hypertension (14-15%, severe 4%)[2,3]

Adapted from standard reference[2] unless specified otherwise.

New primary ***cutaneous malignancies*** such as cutaneous squamous cell carcinoma, basal cell carcinoma, keratoacanthoma and secondary primary melanoma have been reported. The median time to detection of ***basal cell carcinoma*** is four months, although it may be detected as early as one month following the start of cobimetinib. Perform dermatologic evaluations prior to and regularly during treatment with cobimetinib and continue for 6 months following discontinuation of treatment.[2,3,8]

Creatine phosphokinase (CPK) ***elevations*** and ***rhabdomyolysis*** have been associated with cobimetinib and may require treatment interruption, dose reduction, or discontinuation.[9]. Following elevation of CPK, evaluation for causality should include an assessment for rhabdomyolysis as well as other causes, such as cardiac injury. Rhabdomyolysis presents with muscle aches, spasm or weakness, and dark or reddish coloured urine. Hold cobimetinib for up to four weeks if patient is symptomatic or experiences any grade 4 elevation in CPK. Cobimetinib may be resumed at the next lower dose if CPK levels improve to grade 3 or lower. If there is no improvement in symptoms, permanently discontinue cobimetinib.[2,3]

Hemorrhage (all types and grades) occurs in up to 10% of patients. Hematuria and cerebral, gastrointestinal, and reproductive system hemorrhage have been reported. Hemorrhage may be managed with treatment interruption up to four weeks, followed by a dose reduction if symptoms improve to grade 1 or less. Permanently discontinue cobimetinib in the event of a grade 4 hemorrhage.[2]

Left ventricular ejection fraction (LVEF) decrease and ***cardiomyopathy*** can occur and may require dose reduction, interruption, or therapy discontinuation. LVEF should be assessed prior to starting therapy and periodically until cobimetinib is discontinued. Median time to onset of decreased LVEF is four months, although it may occur as early as one month following the start of treatment. Symptoms usually resolve within four months in the majority of patients. When restarting cobimetinib after a treatment interruption, start at a reduced dose and monitor LVEF more frequently. Permanently discontinue cobimetinib for symptomatic cardiomyopathy that does not resolve with dose interruption and/or when LVEF remains greater than 10% of baseline or is below the lower limit of normal.[2]

Ocular toxicity such as ***retinal vein occlusion*** and ***serous retinopathy*** have been reported with cobimetinib. Retinal vein occlusion (RVO) occurs suddenly and presents as blurred or reduced vision, usually affecting only one eye. Permanently discontinue cobimetinib if RVO develops. Serous retinopathy (fluid accumulation within the layers of the retina) is often asymptomatic and usually presents as chorioretinopathy or retinal detachment. Hold cobimetinib for up to four weeks for serous retinopathy. If symptoms improve to grade 1 or less, consider restarting therapy at a reduced dose. If there is no improvement within four weeks, discontinue cobimetinib. Perform ophthalmic exams at baseline, regularly during treatment, and any time a patient reports new visual disturbances.[2]

Photosensitivity may occur when cobimetinib is given in combination with other drugs such as vemurafenib. Mild to severe photosensitivity has been reported in nearly one-half of patients on combination therapy. Minimize/avoid sun exposure and use protective clothing and broad spectrum UVA/UVB sunscreen and lip balm when outdoors. Intolerable reactions may require treatment interruption. Treatment may be restarted without dose modification at the physician's discretion.[2]

Skin rash can be severe and has required hospitalization in some cases. Cobimetinib therapy may be continued without dose modification in patients with non-acneiform or maculopapular rash; however, acneiform rashes may require treatment interruption, dose reduction, or discontinuation.[2,3]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
grapefruit juice[2]	may increase plasma level of cobimetinib	may inhibit CYP 3A4 metabolism of cobimetinib in the intestinal wall	avoid grapefruit and grapefruit juice for duration of treatment
itraconazole[2]	6.7 fold increase in cobimetinib AUC	strong inhibiton of CYP 3A4 by itraconazole	avoid concurrent use

AGENT	EFFECT	MECHANISM	MANAGEMENT
rabeprazole[2]	no effects on cobimetinib pharmacokinetics		

Cobimetinib is a **CYP 3A** substrate. Avoid concurrent use of strong or moderate CYP 3A **inducers** as they may decrease cobimetinib exposure and reduce therapeutic effect. Avoid concurrent use of strong or moderate CYP 3A **inhibitors** as these may increase cobimetinib exposure and increase toxicity. If short term use (14 days or less) of **moderate CYP 3A inhibitors** cannot be avoided, consider reducing cobimetinib to 20 mg daily and monitor patients closely for toxicity. Cobimetinib may be resumed at full dose (i.e., 60 mg daily) once the moderate CYP3A inhibitor has been discontinued. However, if patients are already receiving reduced cobimetinib doses due to adverse reactions, further dose reductions are not recommended and concurrent therapy with the moderate CYP3A4 inhibitor should be avoided.[7]

Cobimetinib is a substrate of P-gp and an inhibitor of BCRP *in vitro*; clinical significance is unknown.

SUPPLY AND STORAGE:

Oral: Hoffmann-La Roche Limited supplies cobimetinib as a 20 mg film-coated tablet. Tablets contain lactose. Store at room temperature.[2]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BCCA usual dose noted in ***bold, italics***

Oral:

Cycle Length:
4 weeks[2,3]:

60 mg (range 20-60 mg) ***PO once daily for 21 consecutive days*** starting on day 1
(total dose per cycle 1260 mg [range 420-1260 mg])

Administer with food or on an empty stomach.

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"

Dosage in renal failure:

- mild to moderate impairment: no dose adjustment required[2]
- severe impairment: no information found

Dosage in hepatic failure:

- mild impairment: no dose adjustment required[3]
- moderate or severe impairment: no information found (however, as cobimetinib is metabolized and eliminated via the liver, it is expected that patients with hepatic impairment may have increased drug exposure; monitor for toxicity)

Dosage in dialysis: no information found

***Children*:** safety and effectiveness not established in children

REFERENCES:

1. Larkin J, Ascierto PA, Dréno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med 2014;371(20):1867-1876.
2. Hoffman-La Roche Ltd. COTELLIC® product monograph. Mississauga, Ontario; 22 February 2016.
3. Lexicomp Online® (database on the Internet). Cobimetinib. Lexi-Comp Inc., 16 May 2016. Available at: http://online.lexi.com. Accessed 15 June 2016.
4. Robert Tillmanns. Personal communication. BC Cancer Agency Skin & Melanoma Tumour Group; 31 Aug 2016.
5. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 Mar 2012.
6. BC Cancer Agency Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer Agency; January 2016.
7. Genentech Inc. COTELLIC® full prescribing information. South San Francisco, CA, USA; May 2016.
8. Keating GM. Cobimetinib plus Vemurafenib: a review in BRAFV600 mutation-positive unresectable or metastatic melanoma. Drugs 2016;76:605-615.
9. Hoffman-La Roche Ltd. COTELLIC® product monograph. Mississauga, Ontario; 3 February 2017.