PDL DRUG REVIEW

Proprietary Name: Cotellic®
Common Name: cobimetinib
PDL Category: Antineoplastics Protein Tyrosine Kinase Inhibitors

Comparable Products	Preferred Drug List Status
Mekinist	Non-Recommended with Conditions
Tafinlar	Non-Recommended with Conditions
Zelboraf	Non-Recommended with Conditions

Summary

Pharmacology/Usage: Cobimetinib fumarate, the active ingredient of Cotellic®, is a kinase inhibitor. Specifically, it is a reversible inhibitor of mitogen-activated protein kinase (MAPK)/extracellular signal regulated kinase 1 (MEK1) and MEK2. MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes cellular proliferation. Cobimetinib and vemurafenib target 2 different kinases. Compared to either drug alone, the concomitant use resulted in increased apoptosis in vitro and reduced tumor growth in mouse models of tumor cell lines harboring BRAF V600E mutations.

Indication: For the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib. Cotellic® is *not* indicated for treatment of patients with wild-type BRAF melanoma.

It is recommended to confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to starting treatment with Cotellic® with vemurafenib. Information on FDA-approved tests for the detection of BRAF V600 mutations in melanoma is available at http://www.fda.gov/CompanionDiagnostics.

There is no pregnancy category associated with this product. However, based on findings from animal reproduction studies along with its mechanism of action, Cotellic® can cause fetal harm when administered to a pregnant woman. There are no data on use in pregnant women; however, when given to pregnant rats, oral cobimetinib was teratogenic and embryotoxic at exposures that were 0.9 to 1.4 times those seen in humans at the recommended human dose. It is recommended to advise pregnant women of the potential risk to a fetus. In addition, it is recommended to use effective contraception during treatment and for 2 weeks after the final dose in females of reproductive potential. The safety and efficacy of use in the pediatric population have not been established.

Dosage Forms: Tablets: 20mg

Recommended Dosage: Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to starting treatment. The recommended daily dose is Cotellic® 60mg (taken as three 20mg tablets) PO QD for the first 21 days of each 28-day cycle until disease progression or unacceptable toxicity. Refer to the drug interactions section below for recommended dose modifications with concurrent CYP3A inhibitors. In addition, please refer to

the prescribing information for additional information regarding recommended dose modifications for Cotellic® with reported adverse events.

Dose adjustments are not required for mild to moderate renal impairment; however, a recommended dose has not been established for patients with severe renal impairment. Dose adjustments are not required for patients with mild hepatic impairment, but use has not been studied in patients with moderate to severe hepatic impairment.

Drug Interactions: It is recommended to avoid concomitant use of Cotellic® and strong or moderate CYP3A inhibitors. If concurrent short-term use (≤14 days) of moderate CYP3A inhibitors, including certain antibiotics (e.g. erythromycin, ciprofloxacin), is unavoidable for patients taking Cotellic® 60mg, it is recommended to reduce the dose to Cotellic® 20mg. After the moderate CYP3A inhibitor is discontinued, the previous dose of Cotellic® should be resumed. In addition, it is recommended to use an alternative to a strong or moderate CYP3A inhibitor in patients who are taking a reduced dose of Cotellic®. Last, it is recommended to avoid concurrent use of Cotellic® and strong or moderate CYP3A inducers (including but not limited to carbamazepine, efavirenz, phenytoin, rifampin, and St. John's Wort).

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Cotellic® plus vemurafenib) minus reported % incidence for placebo plus vemurafenib. Please note that an incidence of 0% means the incidence of the active drug was the same as or less than placebo.* The most frequently reported adverse events included diarrhea (29%), nausea (16%), vomiting (11%), stomatitis (6%), photosensitivity reaction (9%), acneiform dermatitis (5%), pyrexia (5%), chills (5%), hypertension (7%), hemorrhage (6%), vision impaired (11%), chorioretinopathy (<12%), and retinal detachment (>11%).

Lab abnormalities included increased creatinine (0%), increased AST (29%), increased ALT (13%), increased alkaline phosphatase (15%), increased creatine phosphokinase (63%), hypophosphatemia (30%), increased GGT (4%), hyponatremia (5%), hypoalbuminemia (22%), hypokalemia (8%), hyperkalemia (9%), hypocalcemia (14%), anemia (12%), lymphopenia (18%), and thrombocytopenia (8%).

Reported adverse events that can occur with Cotellic® and may require dose modifications include hemorrhage, cardiomyopathy, dermatologic reactions, serous retinopathy or retinal vein occlusion, liver laboratory abnormalities and hepatotoxicity, rhabdomyolysis and creatine phosphokinase elevations, and photosensitivity.

New primary malignancies, cutaneous and non-cutaneous, can occur with Cotellic®. It is recommended to monitor patients receiving Colletic® in combination with vemurafenib for signs or symptoms of non-cutaneous malignancies. In addition, it is recommended to perform dermatologic evaluations prior to starting therapy and every 2 months while on therapy to assess for cutaneous malignancies. Conduct dermatologic monitoring for 6 months after the discontinuation of Cotellic® given with vemurafenib.

Contraindications: There are currently no contraindications listed with this product.

Manufacturer: Genentech

Analysis: The safety and efficacy of cobimetinib was established in one multicenter, randomized, double-blinded, placebo-controlled study in previously untreated patients (N=495) with BRAF V600 mutation-positive, unresectable or metastatic melanoma. All patients received vemurafenib 960mg PO BID on days 1-28 and were randomized to Cotellic® 60mg or matching placebo on days 1-21 of an every 28-day cycle. The main efficacy outcome was investigator-assessed progression-free survival (PFS), while other outcomes assessed included investigator-assessed confirmed objective response rate (ORR), overall survival, and duration of response. Some results are included in the table below, which was adapted from the prescribing information.

Study	Cotellic® + vemurafenib	Placebo + vemurafenib
PFS (Investigator-Assessed)		
Number of Events (%)	143 (58%)	180 (73%)
Progression	131	169
Death	12	11
Median PFS, months	12.3	7.2
Hazard Ratio	0.56	
P-value	<0.001	
Overall Survival (OS)		
Number of Deaths (%)	79 (32%)	109 (44%)
Median OS, months	Not estimable	17
Hazard Ratio	0.63	
P-value	0.0019	
Objective Response Rate (ORR)		
ORR	70%	50%
Complete Response	16%	10%
Partial Response	54%	40%
P-value	<0.001	
Median Duration of Response, months	13.0	9.2

Place in Therapy: One noted reference source concludes that while 3 agents (vemurafenib, dabrafenib, and trametinib) have demonstrated significant clinical benefit for melanoma and are approved for use with BRAF mutations, the combination of a BRAF and MEK inhibitor (e.g. dabrafenib plus trametinib or vemurafenib plus cobimetinib) have demonstrated longer progression-free survival, higher objective response rate, and longer overall survival as compared with monotherapy with a BRAF inhibitor.[2]

It is recommended that Cotellic® require clinical prior authorization to verify diagnosis and concomitant use with vemurafenib (trade name Zelboraf®).

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended with Conditions**

References

[1] Cotellic [package insert]. South San Francisco, CA: Genentech USA, Inc, a member of the Roche Group; 2015.
[2] UpToDate desktop reference. Molecularly targeted therapy for metastatic melanoma. Accessed December 2015.