Clinical Policy Title:	cobimetinib
Policy Number:	RxA.361
Drug(s) Applied:	Cotellic®
Original Policy Date:	03/06/2020
Last Review Date:	09/14/2021
Line of Business Policy Applies to:	All lines of business

Background

Cobimetinib (Cotellic®) is a kinase inhibitor. It is indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
cobimetinib (Cotellic®)	Melanoma	60 mg (three tablets) orally once daily for 21 days, then off for 7 days (28-day cycle).	60 mg/day

Dosage Forms

- Tablet: 20 mg

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Metastatic or Unresectable Melanoma (must meet all)**:**

1. Diagnosis of metastatic or unresectable melanoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is positive for the BRAF V600E or V600K mutation;
5. Prescribed in combination with Zelboraf®;
6. Dose does not exceed 60 mg/day (3 tablets) per day, for the first 21 days of each 28-day cycle.

Approval duration
Commercial: 12 months
Medicaid: 6 months

B. Central Nervous System (CNS) Cancers (off -label) (must meet all):

1. Member has BRAF V600E mutation-positive disease;

2. Prescribed by or in consultation with an oncologist;
3. Age 18 ≥ years;
4. Used as adjuvant treatment in combination with vemurafenib;
5. Patient has incomplete resection, biopsy, or surgically inaccessible location;
6. Patient has one of the following: (a, b or c):
   a. Pilocytic astrocytoma;
   b. Pleomorphic xanthoastrocytoma (PXA);
   c. Ganglioglioma;
7. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).
   *Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration
Commercial: 6 months
Medicaid: 6 months

C. Cutaneous Melanoma (off -label) (must meet all):
1. Member has BRAF V600 mutation-positive disease as detected by an FDA approved or CLIA compliant test;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Patient has unresectable or metastatic disease;
5. Request is for one of the following (a, b or c):
   a. Used in combination with atezolizumab and vemurafenib as first-line therapy;
   b. Used in combination with vemurafenib as (i or ii):
      i. Initial therapy or subsequent therapy;
      ii. As re-induction therapy for patients who experience disease control (i.e., complete response, partial response, or stable disease) from prior MEK inhibitor therapy, but subsequently have disease progression/relapse >3 months after treatment discontinuation;
   c. Used as adjuvant therapy in combination with vemurafenib in patients with unacceptable toxicities to dabrafenib/trametinib (i or ii):
      i. Patient has lymph node involvement following complete resection, complete lymph node dissection (CLND), therapeutic lymph node dissection (TLND), or nodal basin ultrasound surveillance;
      ii. Patient has clinical satellite/in-transit metastases or local satellite/in-transit recurrence with no evidence of disease (NED) after complete excision to clear margins:
6. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).
   *Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration
Commercial: 6 months
Medicaid: 6 months

D. Histiocytic Neoplasms - Langerhans Cell Histiocytosis (off -label) (must meet all):
1. Diagnosis of Langerhans Cell Histiocytosis;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;

4. Request is for one of the following (a or b):
   a. As preferred first-line or subsequent therapy for mitogen-activated protein (MAP) kinase pathway mutation;
   b. As a single agent for non-detectable mutation, or testing not available for one of the following (i, ii, iii, iv, or v):
      i. Multisystem Langerhans Cell Histiocytosis (LCH) with symptomatic or impending organ dysfunction;
      ii. Pulmonary LCH;
      iii. Multifocal single system bone disease not responsive to treatment with a bisphosphonate and >2 lesions (useful in certain circumstances);
      iv. CNS lesions;
      v. Relapsed/refractory disease;
5. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).
   *Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration
Commercial: 6 months
Medicaid: 6 months

E. Histiocytic Neoplasms- Erdheim-Chester Disease (off -label) (must meet all):
1. Diagnosis of Erdheim-Chester Disease;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Request is for one of the following (a or b):
   a. As preferred first-line or subsequent therapy for mitogen-activated protein (MAP) kinase pathway mutation;
   b. As a single agent for non detectable mutation, or testing not available for one of the following (i or ii):
      i. Erdheim-Chester Disease (ECD) with symptomatic disease;
      ii. Relapsed/refractory disease;
5. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).
   *Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration
Commercial: 6 months
Medicaid: 6 months

F. Histiocytic Neoplasms - Rosai-Dorfman Disease (off -label) (must meet all):
1. Diagnosis of Rosai-Dorfman Disease;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years of age or older;
4. Request is for one of the following (a or b):
   a. As preferred first-line or subsequent therapy for mitogen-activated protein (MAP) kinase pathway mutation;
   b. As a single agent for non detectable mutation, or testing not available for one of the following (i, ii or iii):

i. Symptomatic unresectable (bulky/site of disease) unifocal disease;
ii. Symptomatic multifocal disease;
iii. Relapsed/refractory disease;

5. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).
*Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. All indications in section I (must meet all)**:**

1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets (a or b):*
   a. If request is for a dose increase, new dose does not exceed 60 mg/day (3 tablets) per day for the first 21 days of each cycle.
   b. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

***Prescribed regimen must be FDA-approved or recommended by NCCN.Approval duration**
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
BRAF: B-Raf proto-oncogene serine/threonine kinase
FDA: Food and Drug Administration
WHO: World Health Organisation
PXA: Pleomorphic xanthoastrocytoma
LCH: Langerhans Cell Histiocytosis
CNS: Central Nervous System
MAP: Mitogen-Activated Protein
MAPK: Mitogen-Activated Protein Kinase
ECD: Erdheim-Chester Disease
ERK: extracellular signal related kinase

APPENDIX B: Therapeutic Alternatives

- Not applicable.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - None reported.

- Boxed warning(s):
  - None reported.

APPENDIX D: General Information

- Cobimetinib 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. BRAF V600E and K mutations result in constitutive activation of the BRAF pathway which includes MEK1 and MEK2. In mice implanted with tumor cell lines expressing BRAF V600E, cobimetinib inhibited tumor cell growth.
- Cobimetinib and vemurafenib target two different kinases in the RAS/RAF/MEK/ERK pathway. Compared to either drug alone, coadministration of cobimetinib and vemurafenib resulted in increased apoptosis in vitro Reference ID: 4212951 12 and reduced tumor growth in mouse implantation models of tumor cell lines harboring BRAF V600E mutations. Cobimetinib also prevented vemurafenib-mediated growth enhancement of a wild-type BRAF tumor cell line in an in vivo mouse implantation model.

References

1. Cotellic® Prescribing Information. South San Francisco, CA: Genentech; January 2018. Available at: https://www.gene.com/download/pdf/cotellic_prescribing.pdf. Accessed June 24, 2021.
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3. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed June 24, 2021.
4. National Comprehensive Cancer Network. Cutaneous Melanoma Version 3.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. Accessed June 24, 2021.
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6. National Comprehensive Cancer Network. Histiocytic Neoplasms Version 1.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/histiocytic_neoplasms.pdf. Accessed June 24, 2021.
7. National Comprehensive Cancer Network. Cutaneous Melanoma Version 2.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. Accessed June 24, 2021.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	03/06/2020
Policy was reviewed. 1. Policy title table was updated 2. Line of Business policy was updated to 'All lines of business'. 3. Continued therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance..." 4. Initial therapy criteria I.A.6 clarified dosing is limited to the first 21 days of each 28-day cycle. 5. Continued therapy approval duration for Medicaid updated to 12 months.	07/14/2020	09/14/2020

6. Approval duration for commercial was updated from length of benefit to 12 months. 7. Reference reviewed and updated.		
Policy was reviewed: 1. Statement about provider sample ‘‘The provision of provider samples does not guarantee coverage…” was added to Clinical Policy. 2. Initial Approval Criteria I.A was updated from “Melanoma” to "Metastatic or Unresectable Melanoma.” 3. Initial Approval Criteria I.B was updated to include off-label indication, “Central Nervous System (CNS) Cancers (off -label).” 4. Initial Approval Criteria I.C was updated to include off-label indication, “Cutaneous Melanoma (off-label).” 5. Initial Approval Criteria I.D was updated to include off-label indication, “Histiocytic Neoplasms - Langerhans Cell Histiocytosis (off -label).” 6. Initial Approval Criteria I.E was updated to include off-label indication, “Histiocytic Neoplasms- Erdheim-Chester Disease (off -label).” 7. Initial Approval Criteria I.F was updated to include off-0lable indication, “Histiocytic Neoplasms - Rosai-Dorfman Disease (off -label).” 8. Continued Therapy Approval Criteria II.A was updated from “Melanoma” to “All Indications in Section I.” 9. Continued Therapy Approval Criteria II.A.1 was rephrased to “Member is currently receiving medication that has been authorized by RxAdvance…” 10. Continued Therapy Approval Criteria II.A.3.b was updated to include, “Dose is within FDA maximum limit for any FDA-approved indication or is supported…”.. 11. Appendix A was updated to include abbreviations WHO, PXA, LCH, CNS, MAP, MAPK, ERK and ECD. 12. Appendix D was updated to include “Cobimetinib is a reversible inhibitor of	06/24/2021	09/14/2021

mitogen-activated protein kinase…" and "Cobimetinib and vemurafenib target two different kinases in the RAS/RAF/MEK/ERK pathway…". 13. References were reviewed and updated.		