Braftovi® (encorafenib)
(Oral)

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I. Length of Authorization [1,9]

Coverage is provided for 6 months and may be renewed (unless otherwise specified).

- Coverage for the adjuvant treatment of melanoma is up to a maximum of 1 year of therapy.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Braftovi 75 mg capsules: 6 capsules per day

B. Max Units (per dose and over time) [HCPCS Unit]:

- Cutaneous Melanoma: 450 mg daily
- Colorectal Cancer: 300 mg daily

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

- Patient is at least 18 years of age; **AND**
- Patient has not received prior therapy with BRAF and/or MEK inhibitors (e.g., vemurafenib, dabrafenib, cobimetinib, trametinib, etc.) unless otherwise specified; **AND**

Universal Criteria [1]

- Patient will avoid concomitant therapy with all of the following:
  - Coadministration with strong or moderate CYP3A4 inhibitors (e.g., fluconazole, itraconazole, grapefruit juice, etc.), or if therapy is unavoidable, the patient will be monitored closely for adverse reactions and/or dose modifications will be implemented; **AND**
  - Coadministration with strong or moderate CYP3A4 inducers (e.g., rifampin, carbamazepine, St. John's Wort, phenobarbital, etc.); **AND**

- Coadministration with drugs known to prolong the QT/QTc interval (e.g., amitriptyline, amiodarone, etc.); **AND**

Cutaneous Melanoma † ‡ [1,4]

- Patient has BRAF V600 mutation-positive disease as detected by an FDA approved or CLIA compliant test*; **AND**
  - Patient has unresectable or metastatic** disease; **AND**
    - Used in combination with binimetinib or as a single-agent if BRAF/MEK inhibitor combination contraindications exist; **AND**
      - Used as first-line or subsequent therapy; **OR**
      - Used as re-induction therapy for patients who experience disease control *(i.e., complete response, partial response, or stable disease)* from prior BRAF inhibitor therapy, but subsequently have disease progression/relapse >3 months after treatment discontinuation; **OR**
  - Patient has limited resectable disease; **AND**
    - Used as initial treatment in combination with binimetinib; **AND**
    - Patient has unacceptable toxicities to dabrafenib/trametinib or on the basis of agent side effect profiles; **AND**
      - Patient has stage III disease with clinical satellite/in-transit metastases; **OR**
      - Patient has local satellite/in-transit recurrence; **OR**
  - Used as adjuvant therapy in combination with binimetinib in patients with unacceptable toxicities to dabrafenib/trametinib or on the basis of agent side-effect profiles; **AND**
    - Patient has lymph node involvement following complete resection, complete lymph node dissection (CLND), therapeutic lymph node dissection (TLND), or nodal basin ultrasound surveillance; **OR**
    - 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

***Metastatic disease includes stage III unresectable/borderline resectable disease with clinically positive node(s) or clinical satellite/in transit metastases, as well as unresectable local satellite/in-transit recurrence, unresectable nodal recurrence, and widely disseminated distant metastatic disease.*

Colorectal Cancer † ‡ [1,4]

- Patient has BRAF V600E mutation-positive disease as detected by an FDA approved or CLIA compliant test*; **AND**
- Used in combination with cetuximab or panitumumab; **AND**
  - Used as primary treatment for unresectable metastatic disease after previous adjuvant FOLFOX or CapeOX within the past 12 months; **OR**

- Used as subsequent therapy for progression of advanced or metastatic disease after at least one prior line of treatment in the advanced or metastatic disease setting

Appendiceal Adenocarcinoma – Colon Cancer ‡ [4]

- Patient has BRAF V600E mutation-positive disease as detected by an FDA approved or CLIA compliant test*; **AND**
- Used in combination with cetuximab or panitumumab; **AND**
- Used as subsequent therapy for progression of advanced or metastatic disease after at least one prior line of treatment in the advanced or metastatic disease setting

** If confirmed using an immunotherapy assay-http://www.fda.gov/CcompanionDiagnostics*

† FDA Approved Indication(s); ‡ Compendia Recommended Indication(s); Φ Orphan Drug

IV. Renewal Criteria [1]

Coverage can be renewed based upon the following criteria:

- Patient continues to meet universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: major hemorrhagic events, QTc prolongations (i.e., QTc > 500 ms), uveitis, new primary malignancies, etc.; **AND**

Adjuvant treatment of Cutaneous Melanoma [8]

- Treatment has not exceeded 1 year of therapy

Cutaneous Melanoma (re-induction therapy) [4,8]

- *Refer to Section III for criteria (see Cutaneous Melanoma – Used as re-induction therapy)*

V. Dosage/Administration [1,9]

Indication	Dose
Cutaneous Melanoma	Administer 450 mg (6 capsules) orally once daily, in combination with binimetinib, until disease progression or unacceptable toxicity *(for adjuvant treatment of melanoma treat until disease recurrence or unacceptable toxicity for up to 1 year)*.
Colorectal Cancer and Appendiceal Adenocarcinoma	Administer 300 mg (4 capsules) orally once daily, in combination with cetuximab or panitumumab, until disease progression or unacceptable toxicity

VI. Billing Code/Availability Information

HCPCS Code:

- J8999 – Prescription drug oral, chemotherapeutic, Not Otherwise Specified
- C9399 – Unclassified drugs or biologics (Hospital Outpatient Use Only)

NDC:

- Braftovi 75 mg oral capsule: 70255-0025-xx

VII. References

1. Braftovi [package insert]. Boulder, CO; Array BioPharma; February 2022. Accessed September 2022.
2. Flaherty KT, Infante JR, Daud A, at al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med. 2012 Nov; 367(18):1694-703. doi: 10.1056/NEJMoa1210093. Epub 2012 Sep 29.
3. Long GV, Stroyakovksy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Eng J Med 2014 Sep 29, {Epub ahead of print]
4. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) encorafenib. National Comprehensive Cancer Network, 2022. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed September 2022.
5. Dummer R, Asciedrto PA, Gogas H, et al. Overall survival in COLUMBUS: A phase 3 trial of encorafenib (ENCO) plus binimetinib (BINI) vs vemurafenib (VEM) or enco in BRAF-mutant melanoma (Abstract 9504). American Society of Clinical Oncology 2018 annual meeting.
6. Van Cutsem E, Huijberts S, Grothey A, et al. Binimetinib, Encorafenib, and Cetuximab Triplet Therapy for Patients With BRAF V600E-Mutant Metastatic Colorectal Cancer: Safety Lead-In Results From the Phase III BEACON Colorectal Cancer Study. J Clin Oncol. 2019 Jun 10;37(17):1460-1469.
7. Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, Binimetinib, and Cetuximab in BRAF V600E-Mutated Colorectal Cancer. N Engl J Med. 2019;381(17):1632–1643. doi:10.1056/NEJMoa1908075.
8. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Melanoma: Cutaneous. Version 3.2022. National Comprehensive Cancer Network, 2022. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed September 2022.

9. Mekinist [package insert]. East Hanover, NJ; Novartis Pharmaceuticals Corporation; June 2022. Accessed September 2022.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of large intestines
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C43.0	Malignant melanoma of lip
C43.10	Malignant melanoma of unspecified eyelid, including canthus
C43.11	Malignant melanoma of right eyelid, including canthus
C43.12	Malignant melanoma of left eyelid, including canthus
C43.111	Malignant melanoma of right upper eyelid, including canthus
C43.112	Malignant melanoma of right lower eyelid, including canthus
C43.121	Malignant melanoma of left upper eyelid, including canthus
C43.122	Malignant melanoma of left lower eyelid, including canthus
C43.20	Malignant melanoma of unspecified ear and external auricular canal
C43.21	Malignant melanoma of right ear and external auricular canal
C43.22	Malignant melanoma of left ear and external auricular canal
C43.30	Malignant melanoma of unspecified part of face
C43.31	Malignant melanoma of nose
C43.39	Malignant melanoma of other parts of face
C43.4	Malignant melanoma of scalp and neck
C43.51	Malignant melanoma of anal skin
C43.52	Malignant melanoma of skin of breast

ICD-10	ICD-10 Description
C43.59	Malignant melanoma of other part of trunk
C43.60	Malignant melanoma of unspecified upper limb, including shoulder
C43.61	Malignant melanoma of right upper limb, including shoulder
C43.62	Malignant melanoma of left upper limb, including shoulder
C43.70	Malignant melanoma of unspecified lower limb, including hip
C43.71	Malignant melanoma of right lower limb, including hip
C43.72	Malignant melanoma of left lower limb, including hip
C43.8	Malignant melanoma of overlapping sites of skin
C43.9	Malignant melanoma of skin, unspecified
C78.00	Secondary malignant neoplasm of unspecified lung
C78.01	Secondary malignant neoplasm of right lung
C78.02	Secondary malignant neoplasm of left lung
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
Z85.038	Personal history of other malignant neoplasm of large intestine

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Article (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC