Tafinlar® (dabrafenib)
(Oral)

Document Number: IC-0174

Last Review Date: 10/03/2023
Date of Origin: 06/25/2013
Dates Reviewed: 01/2014, 12/2014, 10/2015, 10/2016, 10/2017, 06/2018, 10/2018, 11/2019, 11/2020, 11/2021, 07/2022, 11/2022, 04/2023, 10/2023

I. Length of Authorization [1]

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

- Adjuvant treatment of melanoma may be renewed for up to 1 year of therapy.

II. Dosing Limits

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

- Tafinlar 50 mg capsules: 4 capsules per day
- Tafinlar 75 mg capsules: 4 capsules per day
- Tafinlar 10 mg tablets for oral suspension: 30 tablets per day

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

- 300 mg daily

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

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

Universal Criteria [1]

- Left ventricular ejection fraction (LVEF) is within normal limits prior to initiating therapy and will be assessed at regular intervals (e.g., every 3 months) during treatment; **AND**
- Patient will avoid coadministration with all of the following, or if therapy is unavoidable, patient will be closely monitored for adverse reactions and/or dose modifications will be implemented:
  - Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, etc.); **AND**
  - Strong CYP2C8 inhibitors (e.g., gemfibrozil, clopidogrel, etc.); **AND**

- Patient does not have colorectal cancer; **AND**

Ampullary Adenocarcinoma ‡ [7]

- Patient has BRAF V600E mutation-positive disease as detected by an FDA approved or CLIA compliant test*; **AND**
- Used in combination with trametinib as subsequent therapy for disease progression

Adult Central Nervous System (CNS) Cancers ‡ [7]

- Patient has BRAF V600E mutation-positive disease as detected by an FDA approved or CLIA compliant test*; **AND**
- Used in combination with trametinib; **AND**
  - Used as adjuvant treatment for incomplete resection, biopsy, or surgically inaccessible location; **AND**
    - Patient has pilocytic astrocytoma OR pleomorphic xanthoastrocytoma (grade 2) OR ganglioglioma; **OR**
  - Patient has recurrent or progressive glioblastoma; **OR**
  - Patient has recurrent or progressive circumscribed glioma; **AND**
    - Patient has received prior fractionated external beam radiation therapy; **OR**
  - Used for brain metastases in patients with BRAF V600E mutation-positive melanoma; **AND**
    - Used as initial treatment in patients with small asymptomatic brain metastases; **OR**
    - Patient has recurrent limited brain metastases; **OR**
    - Used for relapsed disease in patients limited brain metastases and either stable systemic disease or reasonable systemic treatment options; **OR**
    - Used for recurrent disease in patients with extensive brain metastases and stable systemic disease or reasonable systemic treatment options

Esophageal and Esophagogastric Junction Cancer ‡ [7]

- Patient has BRAF V600E mutation-positive disease as detected by an FDA approved or CLIA compliant test*; **AND**
- Patient has adenocarcinoma or squamous cell carcinoma histology; **AND**
- Used in combination with trametinib; **AND**
- Used palliatively as subsequent therapy; **AND**
- Patient is not a surgical candidate or has unresectable locally advanced, recurrent, or metastatic disease

Gastric Cancer ‡ [7]

- Patient has BRAF V600E mutation-positive disease as detected by an FDA approved or CLIA compliant test*; **AND**
- Patient has adenocarcinoma histology; **AND**
- Used in combination with trametinib; **AND**
- Used palliatively as subsequent therapy; **AND**
- Patient is not a surgical candidate or has unresectable locally advanced, recurrent, or metastatic disease

Gastrointestinal Stromal Tumors (GIST) ‡ [7]

- Patient has BRAF V600E mutation-positive disease as detected by an FDA approved or CLIA compliant test*; **AND**
- Used in combination with trametinib; **AND**
    - Used as neoadjuvant therapy; **AND**
        - Used for resectable disease with significant morbidity; **OR**
    - Used as first-line therapy; **AND**
        - Used for gross residual (R2 resection), unresectable primary, recurrent, or metastatic disease OR tumor rupture

Head and Neck Cancer ‡ [7]

- Patient has BRAF V600E mutation-positive disease as detected by an FDA approved or CLIA compliant test*; **AND**
- Patient has salivary gland tumors; **AND**
- Used in combination with trametinib; **AND**
- Used for one of the following:
    - Distant metastases; **OR**
    - Unresectable locoregional recurrence with prior radiation therapy (RT); **OR**
    - Unresectable second primary with prior RT

Histiocytic Neoplasms ‡ [7]

- Used as single agent therapy; **AND**
- Patient has BRAF V600E mutation-positive disease as detected by an FDA approved or CLIA compliant test*; **AND**
- Patient has one of the following:
    - Relapsed/refractory or symptomatic Erdheim-Chester Disease (ECD); **OR**
    - Langerhans Cell Histiocytosis (LCH); **AND**
        - Patient has multisystem disease with symptomatic or impending organ dysfunction or critical organ involvement; **OR**
        - Patient has single-system lung disease; **OR**

- Patient has multifocal single system bone disease not responsive to treatment with a bisphosphonate; **OR**
- Patient has CNS lesions; **OR**
- Patient has relapsed or refractory disease

Cutaneous Melanoma † ‡ Φ [1,7]

- Patient has BRAF V600 mutation-positive disease as detected by an FDA approved or CLIA compliant test*; **AND**
  - Used as first-line therapy in combination with trametinib OR as a single agent for unresectable or metastatic** disease; **OR**
  - Used as initial treatment for limited resectable disease; **AND**
    - Used in combination with trametinib; **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 trametinib; **AND**
    - Patient has lymph node involvement following complete resection †; **OR**
    - Patient has stage III disease; **AND**
      - Patient has resected sentinel node positive disease either during observation without additional nodal surgery and with mandatory radiographic nodal surveillance OR after complete lymph node dissection (CLND); **OR**
      - Patient has clinically positive node(s) following wide excision of the primary tumor and therapeutic lymph node dissection (TLND) OR following neoadjuvant therapy; **OR**
      - Patient has clinical satellite/in-transit metastases and no evidence of disease (NED) after complete excision to clear margins; **OR**
    - Patient has local satellite/in-transit recurrence and NED after complete excision to clear margins; **OR**
    - Patient has resectable disease limited to nodal recurrence following excision and complete TLND OR following neoadjuvant therapy; **OR**
  - Used as subsequent therapy; **AND**
    - Used in combination with trametinib OR as a single agent; **AND**
      - Used for unresectable or metastatic** disease that has progressed; **OR**
      - Used as re-induction therapy in patients with unresectable or metastatic** disease who experience disease control (i.e., complete response, partial response, or stable disease and no residual toxicity) from prior BRAF inhibitor therapy, but subsequently have disease progression/relapse >3 months after treatment discontinuation; **OR**

- Used in combination with pembrolizumab and trametinib; **AND**
  - Used for metastatic or unresectable disease with disease progression or intolerance if BRAF/MEK and/or PD(L)-1 checkpoint inhibition not previously used; **OR**
  - Used as re-induction therapy in patients who experienced disease control (i.e., complete response, partial response, or stable disease with no residual toxicity) from prior combination BRAF/MEK + PD(L)-1 checkpoint inhibitor therapy, but subsequently have disease progression/relapse > 3 months after treatment discontinuation

***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.*

Non-Small Cell Lung Cancer (NSCLC) † ‡ [1,7]

- Patient has BRAF V600E mutation-positive disease as detected by an FDA approved or CLIA compliant test*; **AND**
- Patient has recurrent, advanced, or metastatic disease (excluding locoregional recurrence or symptomatic local disease with no evidence of disseminated disease) or mediastinal lymph node recurrence with prior radiation therapy; **AND**
  - Used in combination with trametinib; **OR**
  - Used as a single agent if use in combination with trametinib is not tolerated

Ovarian Cancer (including Fallopian Tube and Primary Peritoneal Cancer) ‡ [7,14]

- Used in combination with trametinib; **AND**
  - Patient has BRAF V600E mutation-positive disease as detected by an FDA approved or CLIA compliant test*; **AND**
    - Patient has persistent or recurrent Grade 1 Endometrioid Carcinoma, Carcinosarcoma (Malignant Mixed Müllerian Tumors), Mucinous Carcinoma of the Ovary, Epithelial Ovarian/Fallopian Tube/Primary Peritoneal Cancer, or Clear Cell Carcinoma of the Ovary; **AND**
      - Patient is not experiencing an immediate biochemical relapse (i.e., rising CA-125 without radiographic evidence of disease); **OR**
    - Patient has recurrent low-grade serous carcinoma

Pancreatic Adenocarcinoma ‡ [7]

- Patient has BRAF V600E mutation-positive disease as detected by an FDA approved or CLIA compliant test*; **AND**
- Used in combination with trametinib; **AND**
- Patient has good performance status (ECOG PS 0-1 with good biliary drainage and adequate nutritional intake) OR poor PS (ECOG PS 3-4); **AND**

- Used as subsequent therapy for locally advanced, metastatic, progressive, or recurrent disease

Pediatric Central Nervous System (CNS) Cancers † ‡ [1,7,15,27]

- Patient has BRAF V600E mutation-positive disease as detected by an FDA approved or CLIA compliant test*; **AND**
- Used in combination with trametinib; **AND**
  - Patient has low-grade glioma † Φ; **AND**
    - Patient is ≥ 1 year of age < 18 years of age; **AND**
    - Patient requires systemic therapy; **OR**
  - Patient has diffuse high-grade glioma ‡; **AND**
    - Used as adjuvant therapy *(excluding diffuse midline glioma, H3 K27-altered or pontine location)*; **AND**
      - Patient is < 3 years of age; **OR**
      - Patient is ≥ 3 years of age and ≤ 18 years of age; **AND**
        - Used following standard brain radiation therapy (RT) with or without concurrent temozolomide; **OR**
    - Used for recurrent or progressive disease *(excluding oligodendroglioma, IDH-mutant and 1p/19q co-deleted or astrocytoma IDH-mutant)*; **AND**
      - Patient is ≤ 18 years of age

Anaplastic Thyroid Cancer (ATC) † Φ [1,7]

- Patient has BRAF V600E mutation-positive disease as detected by an FDA approved or CLIA compliant test*; **AND**
- Used in combination with trametinib; **AND**
  - Patient has locally advanced disease with no satisfactory locoregional treatment options; **OR**
  - Patient has metastatic disease

Solid Tumors with *BRAF V600E* mutation † ‡ [1,7,12,13]

- Patient is at least 1 year of age; **AND**
- Patient has BRAF V600E mutation-positive solid tumors as detected by an FDA approved or CLIA compliant test*; **AND**
- Patient has unresectable or metastatic disease that has progressed following prior treatment; **AND**
- Patient has no satisfactory alternative treatment options; **AND**
- Used in combination with trametinib; **AND**
- Patient has one of the following solid tumors ¥:

- Thyroid Cancer (Anaplastic Carcinoma, Follicular Carcinoma, Oncocytic Carcinoma, Papillary Carcinoma)
- Biliary Tract Cancers (Gallbladder Cancer, Intra-/Extra-hepatic Cholangiocarcinoma)
- Adenocarcinoma of the Small Intestine
- High or Low Grade Glioma
- Low-Grade Serous Ovarian Carcinoma
- Neuroendocrine and Adrenal Tumors (Extrapulmonary Poorly Differentiated Neuroendocrine Carcinoma/Large or Small Cell Carcinoma/Mixed Neuroendocrine-Non-Neuroendocrine Neoplasm)
- Occult Primary

¥ Note: Solid tumors not listed, that are BRAF V600E mutation-positive, will be reviewed on a case-by-case basis and considered medically necessary when all other relevant medication and indication specific criteria are met.

** 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, cardiomyopathy, uveitis, serious febrile reactions, serious skin toxicities (e.g., Stevens-Johnson syndrome [SJS] and drug reaction with eosinophilia and systemic symptoms [DRESS], etc.), hyperglycemia, new primary malignancies, hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, hemophagocytic lymphohistiocytosis (HLH), etc.; **AND**
- Left ventricular ejection fraction (LVEF) has not had an absolute decrease of > 20% from baseline and is not below the lower limit of normal (LLN) *(LVEF results must be within the previous 3 months)*; **AND**

Adjuvant treatment of Cutaneous Melanoma [1]

- Treatment has not exceeded 1 year of therapy

Cutaneous Melanoma (re-induction therapy) [7]

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

V. Dosage/Administration [1,12,13,15-25,28,29]

<table>
<tr><th>Indication</th><th>Dose</th></tr>
<tr><td>Ampullary Adenocarcinoma, Adult CNS Cancers, Esophageal/ Esophagogastric Junction Cancer, Gastric Cancer, GIST, Head and Neck Cancer, Histiocytic Neoplasms, Cutaneous Melanoma, NSCLC, Ovarian Cancer, Pancreatic Cancer, ATC</td><td>Administer 150 mg orally twice daily, until disease progression/recurrence or unacceptable toxicity
(Note: for adjuvant treatment of melanoma, treat until disease recurrence or unacceptable toxicity for up to 1 year).</td></tr>
<tr><td>Solid Tumors with BRAF V600E mutation</td><td><u>Adult Patients</u>
Administer 150 mg orally twice daily until disease progression or unacceptable toxicity

<u>Pediatric Patients</u>
– Capsules (for use in patients weighing at least 26 kg):
<table><tr><th>Body weight</th><th>Recommended dosage</th></tr><tr><td>26 to 37 kg</td><td>75 mg orally twice daily</td></tr><tr><td>38 to 50 kg</td><td>100 mg orally twice daily</td></tr><tr><td>51 kg or greater</td><td>150 mg orally twice daily</td></tr></table>
– Tablets for Oral Suspension:
NOTE: Prepare suspension with approximately 5 mL of water for 1 to 4 tablets, and approximately 10 mL of water for 5 to 15 tablets in the provided cup. Do not swallow whole, chew or crush TAFINLAR tablets for oral suspension.
<table><tr><th>Body weight</th><th>Recommended dosage</th></tr><tr><td>8 to 9 kg</td><td>20 mg twice daily</td></tr><tr><td>10 to 13 kg</td><td>30 mg twice daily</td></tr><tr><td>14 to 17 kg</td><td>40 mg twice daily</td></tr><tr><td>18 to 21 kg</td><td>50 mg twice daily</td></tr><tr><td>22 to 25 kg</td><td>60 mg twice daily</td></tr><tr><td>26 to 29 kg</td><td>70 mg twice daily</td></tr><tr><td>30 to 33 kg</td><td>80 mg twice daily</td></tr><tr><td>34 to 37 kg</td><td>90 mg twice daily</td></tr><tr><td>38 to 41 kg</td><td>100 mg twice daily</td></tr><tr><td>42 to 45 kg</td><td>110 mg twice daily</td></tr><tr><td>46 to 50 kg</td><td>130 mg twice daily</td></tr><tr><td>≥ 51 kg</td><td>150 mg twice daily</td></tr></table>***Administer until disease progression or unacceptable toxicity.</td></tr>
<tr><td>Pediatric Central Nervous System (CNS) Cancers</td><td><u>Low-Grade Glioma</u>
– Capsules (for use in patients weighing at least 26 kg):
<table><tr><th>Body weight</th><th>Recommended dosage</th></tr><tr><td>26 to 37 kg</td><td>75 mg orally twice daily</td></tr><tr><td>38 to 50 kg</td><td>100 mg orally twice daily</td></tr><tr><td>51 kg or greater</td><td>150 mg orally twice daily</td></tr></table>
– Tablets for Oral Suspension:</td></tr>
</table>

	NOTE: *Prepare suspension with approximately 5 mL of water for 1 to 4 tablets, and approximately 10 mL of water for 5 to 15 tablets in the provided cup. Do not swallow whole, chew or crush TAFINLAR tablets for oral suspension.* **Body weight** / **Recommended dosage** 8 to 9 kg — 20 mg twice daily 10 to 13 kg — 30 mg twice daily 14 to 17 kg — 40 mg twice daily 18 to 21 kg — 50 mg twice daily 22 to 25 kg — 60 mg twice daily 26 to 29 kg — 70 mg twice daily 30 to 33 kg — 80 mg twice daily 34 to 37 kg — 90 mg twice daily 38 to 41 kg — 100 mg twice daily 42 to 45 kg — 110 mg twice daily 46 to 50 kg — 130 mg twice daily ≥ 51 kg — 150 mg twice daily ***Administer until disease progression or unacceptable toxicity. **High-Grade Glioma** Administer a total of 4.5 mg/kg per day orally in 2 divided doses, until disease progression/recurrence or unacceptable toxicity.

VI. Billing Code/Availability Information

HCPCS Code:

- J8999 – Prescription drug oral, chemotherapeutic, Not Otherwise Specified

NDC(s):

- Tafinlar 50 mg capsule: 00078-0682-xx
- Tafinlar 75 mg capsule: 00078-0681-xx
- Tafinlar 10 mg tablet for oral suspension: 00078-1154-xx

VII. References

1. Tafinlar [package insert]. East Hanover, NJ; Novartis Pharmaceuticals Corporation; August 2023. Accessed September 2023.
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. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012 Jul 28; 380(9839):358-65.
4. Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. Lancet Oncol. 2012 Nov; 13(11):1087-95.

5. 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]
6. Robert C, Karaszewska B, Schachter J, et al. COMBI-v: A randomized, open-label, phase III study comparing the combination of dabrafenib (D) and trametinib (T) to vemurafenib (V) as first-line therapy in patients (pts) with unresectable or metastatic BRAF V600E/K mutation positive cutaneous melanoma [abstract]. Ann Oncol 2014;25(Suppl 4):Abstract LBA4
7. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) dabrafenib. National Comprehensive Cancer Network, 2023. 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 2023.
8. Planchard D, Groen HJM, Min Kim T., et al. Interim results of a phase II study of the BRAF inhibitor dabrafenib in combination with the MEK inhibitor trametinib in patients with BRAF V600E mutated metastatic non-small cell lung cancer. Journal of Clinical Oncology, 2015; 33 Abstract 8006.
9. Davies, MA, Salag P, Robert C, et al. Dabrafenib plus trametinib in patients with BRAFV600-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial The Lancet Oncology. 2017:18 (7):863-873.
10. Long GV, Hauschild A, Santinami M, et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. N Engl J Med 2017; 377:1813-1823.
11. Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600-Mutant Anaplastic Thyroid Cancer. J Clin Oncol. 2018 Jan 1;36(1):7-13. doi: 10.1200/JCO.2017.73.6785. Epub 2017 Oct 26. PMID: 29072975; PMCID: PMC5791845.
12. Subbiah V, Bang Y, Lassen U, et al. ROAR: a phase 2, open-label study in patients (pts) with BRAF V600E–mutated rare cancers to investigate the efficacy and safety of dabrafenib (D) and trametinib (T) combination therapy. Journal of Clinical Oncology 2016 34:15_suppl, TPS2604-TPS2604.
13. Salama A, Li S, Macrae E, et al. Dabrafenib and Trametinib in Patients With Tumors With BRAF V600E Mutations: Results of the NCI-MATCH Trial Subprotocol H. J Clin Oncol 2020 Nov 20;38(33):3895-3904. doi: 10.1200/JCO.20.00762. Epub 2020 Aug 6.
14. Flaherty K, Gray R, Chen A, et al. The Molecular Analysis for Therapy Choice (NCI-MATCH) Trial: Lessons for Genomic Trial Design J Natl Cancer Inst. 2020 Oct 1;112(10):1021-1029. doi: 10.1093/jnci/djz245.
15. Toll S, Tran H, Cotter J, et al. Sustained response of three pediatric BRAFV600E mutated high-grade gliomas to combined BRAF and MEK inhibitor therapy. Oncotarget. 2019 Jan 11; 10(4): 551–557. Published online 2019 Jan 11. doi: 10.18632/oncotarget.26560.

16. Falchook GS, Millward M, Hong D, et al. BRAF inhibitor dabrafenib in patients with metastatic BRAF-mutant thyroid cancer. Thyroid. 2015 Jan;25(1):71-7. doi: 10.1089/thy.2014.0123.
17. Rothenberg SM, McFadden DG, Palmer EL, et al. Redifferentiation of iodine-refractory BRAF V600E-mutant metastatic papillary thyroid cancer with dabrafenib. Clin Cancer Res. 2015 Mar 1;21(5):1028-35. doi: 10.1158/1078-0432.CCR-14-2915.
18. Brown NF, Carter T, Kitchen N, Mulholland P. Dabrafenib and trametinib in BRAFV600E mutated glioma. CNS Oncol. 2017 Oct;6(4):291-296. Doi: 10.2217/cns-2017-0006.
19. Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. Lancet Oncol. 2012 Nov;13(11):1087-95. doi: 10.1016/S1470-2045(12)70431-X.
20. Falchook GS, Long GV, Kurzrock R, et al. Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial. Lancet. 2012 May 19;379(9829):1893-901. doi: 10.1016/S0140-6736(12)60398-5.
21. Azer MW, Menzies AM, Haydu LE, et al. Patterns of response and progression in patients with BRAF-mutant melanoma metastatic to the brain who were treated with dabrafenib. Cancer. 2014 Feb 15;120(4):530-6. doi: 10.1002/cncr.28445.
22. Hazim AZ, Ruan GJ, Ravindran A, et al. Efficacy of BRAF-Inhibitor Therapy in BRAFV600E -Mutated Adult Langerhans Cell Histiocytosis. Oncologist. 2020 Dec;25(12):1001-1004. doi: 10.1002/onco.13541.
23. Awada G, Seremet T, Fostier K, et al. Long-term disease control of Langerhans cell histiocytosis using combined BRAF and MEK inhibition. Blood Adv. 2018 Aug 28;2(16):2156-2158. doi: 10.1182/bloodadvances.2018021782.
24. Bhatia A, Ulaner G, Rampal R, et al. Single-agent dabrafenib for BRAFV600E-mutated histiocytosis. Haematologica. 2018 Apr;103(4):e177-e180. doi: 10.3324/haematol.2017.185298.
25. Nordmann TM, Juengling FD, Recher M, et al. Trametinib after disease reactivation under dabrafenib in Erdheim-Chester disease with both BRAF and KRAS mutations. Blood. 2017 Feb 16;129(7):879-882. doi: 10.1182/blood-2016-09-740217.
26. Bouffet E, Hansford J, Garré ML, et al. Primary analysis of a phase II trial of dabrafenib plus trametinib (dab + tram) in BRAF V600–mutant pediatric low-grade glioma (pLGG). Journal of Clinical Oncology 2022 40:17_suppl, LBA2002-LBA2002.
27. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Pediatric Central Nervous System Cancers. Version 2.2023. National Comprehensive Cancer Network, 2023. 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 2023.

28. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Esophageal and Esophagogastric Junction Cancers. Version 3.2023. National Comprehensive Cancer Network, 2023. 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 2023.
29. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Gastric Cancer. Version 2.2023. National Comprehensive Cancer Network, 2023. 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 2023.
30. Lin VTG, Nabell LM, Spencer SA, et al. First-Line Treatment of Widely Metastatic BRAF-Mutated Salivary Duct Carcinoma With Combined BRAF and MEK Inhibition. J Natl Compr Canc Netw. 2018 Oct;16(10):1166-1170. doi: 10.6004/jnccn.2018.7056.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C06.9	Malignant neoplasm of mouth, unspecified
C07	Malignant neoplasm of parotid gland
C08.0	Malignant neoplasm of submandibular gland
C08.1	Malignant neoplasm of sublingual gland
C08.9	Malignant neoplasm of major salivary gland, unspecified
C15.3	Malignant neoplasm of upper third of esophagus
C15.4	Malignant neoplasm of middle third of esophagus
C15.5	Malignant neoplasm of lower third of esophagus
C15.8	Malignant neoplasm of overlapping sites of esophagus
C15.9	Malignant neoplasm of esophagus, unspecified
C16.0	Malignant neoplasm of cardia
C16.1	Malignant neoplasm of fundus of stomach
C16.2	Malignant neoplasm of body of stomach
C16.3	Malignant neoplasm of pyloric antrum
C16.4	Malignant neoplasm of pylorus
C16.5	Malignant neoplasm of lesser curvature of stomach, unspecified
C16.6	Malignant neoplasm of greater curvature of stomach, unspecified

ICD-10	ICD-10 Description
C16.8	Malignant neoplasm of overlapping sites of stomach
C16.9	Malignant neoplasm of stomach, unspecified
C17.0	Malignant neoplasm of duodenum
C17.1	Malignant neoplasm of jejunum
C17.2	Malignant neoplasm of ileum
C17.3	Meckel's diverticulum, malignant
C17.8	Malignant neoplasm of overlapping sites of small intestine
C17.9	Malignant neoplasm of small intestine, unspecified
C22.1	Intrahepatic bile duct carcinoma
C23	Malignant neoplasm of gallbladder
C24.0	Malignant neoplasm of extrahepatic bile duct
C24.1	Malignant neoplasm of ampulla of Vater
C24.8	Malignant neoplasm of overlapping sites of biliary tract
C24.9	Malignant neoplasm of biliary tract, unspecified
C25.0	Malignant neoplasm of head of pancreas
C25.1	Malignant neoplasm of body of pancreas
C25.2	Malignant neoplasm of tail of pancreas
C25.3	Malignant neoplasm of pancreatic duct
C25.7	Malignant neoplasm of other parts of pancreas
C25.8	Malignant neoplasm of overlapping sites of pancreas
C25.9	Malignant neoplasm of pancreas, unspecified
C33	Malignant neoplasm of trachea
C34.00	Malignant neoplasm of unspecified main bronchus
C34.01	Malignant neoplasm of right main bronchus
C34.02	Malignant neoplasm of left main bronchus
C34.10	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.11	Malignant neoplasm of upper lobe, right bronchus or lung
C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
C34.30	Malignant neoplasm of lower lobe, unspecified bronchus or lung
C34.31	Malignant neoplasm of lower lobe, right bronchus or lung
C34.32	Malignant neoplasm of lower lobe, left bronchus or lung
C34.80	Malignant neoplasm of overlapping sites of unspecified bronchus or lung
C34.81	Malignant neoplasm of overlapping sites of right bronchus and lung

ICD-10	ICD-10 Description
C34.82	Malignant neoplasm of overlapping sites of left bronchus and lung
C34.90	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C34.91	Malignant neoplasm of unspecified part of right bronchus or lung
C34.92	Malignant neoplasm of unspecified part of left bronchus or lung
C43.0	Malignant melanoma of lip
C43.111	Malignant melanoma of right upper eyelid, including canthus
C43.112	Malignant melanoma of left 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
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
C48.1	Malignant neoplasm of specified parts of peritoneum
C48.2	Malignant neoplasm of peritoneum, unspecified
C48.8	Malignant neoplasm of overlapping sites of retroperitoneum and peritoneum
C49.A0	Gastrointestinal stromal tumor, unspecified site
C49.A1	Gastrointestinal stromal tumor of esophagus
C49.A2	Gastrointestinal stromal tumor of stomach
C49.A3	Gastrointestinal stromal tumor of small intestine

ICD-10	ICD-10 Description
C49.A4	Gastrointestinal stromal tumor of large intestine
C49.A5	Gastrointestinal stromal tumor of rectum
C49.A9	Gastrointestinal stromal tumor of other sites
C49.4	Malignant neoplasm of connective and soft tissue of abdomen
C49.5	Malignant neoplasm of connective and soft tissue of pelvis
C49.8	Malignant neoplasm of overlapping sites of connective and soft tissue
C49.9	Malignant neoplasm of connective and soft tissue, unspecified
C56.1	Malignant neoplasm of right ovary
C56.2	Malignant neoplasm of left ovary
C56.3	Malignant neoplasm of bilateral ovaries
C56.9	Malignant neoplasm of unspecified ovary
C57.00	Malignant neoplasm of unspecified fallopian tube
C57.01	Malignant neoplasm of right fallopian tube
C57.02	Malignant neoplasm of left fallopian tube
C57.10	Malignant neoplasm of unspecified broad ligament
C57.11	Malignant neoplasm of right broad ligament
C57.12	Malignant neoplasm of left broad ligament
C57.20	Malignant neoplasm of unspecified round ligament
C57.21	Malignant neoplasm of right round ligament
C57.22	Malignant neoplasm of left round ligament
C57.3	Malignant neoplasm of parametrium
C57.4	Malignant neoplasm of uterine adnexa, unspecified
C57.7	Malignant neoplasm of other specified female genital organs
C57.8	Malignant neoplasm of overlapping sites of female genital organs
C57.9	Malignant neoplasm of female genital organ, unspecified
C7A.1	Malignant poorly differentiated neuroendocrine tumors
C7A.8	Other malignant neuroendocrine tumors
C7B.8	Other secondary neuroendocrine tumors
C71.0	Malignant neoplasm of cerebrum, except lobes and ventricles
C71.1	Malignant neoplasm of frontal lobe
C71.2	Malignant neoplasm of temporal lobe
C71.3	Malignant neoplasm of parietal lobe
C71.4	Malignant neoplasm of occipital lobe
C71.5	Malignant neoplasm of cerebral ventricle

ICD-10	ICD-10 Description
C71.6	Malignant neoplasm of cerebellum
C71.7	Malignant neoplasm of brain stem
C71.8	Malignant neoplasm of overlapping sites of brain
C71.9	Malignant neoplasm of brain, unspecified
C72.0	Malignant neoplasm of spinal cord
C72.1	Malignant neoplasm of cauda equina
C72.9	Malignant neoplasm of central nervous system, unspecified
C73	Malignant neoplasm of thyroid gland
C79.31	Secondary malignant neoplasm of brain
C80.0	Disseminated malignant neoplasm, unspecified
C80.1	Malignant (primary) neoplasm, unspecified
C96.0	Multifocal and multisystemic (disseminated) Langerhans-cell histiocytosis
C96.5	Multifocal and unisystemic Langerhans-cell histiocytosis
C96.6	Unifocal Langerhans-cell histiocytosis
C96.9	Malignant neoplasm of lymphoid, hematopoietic and related tissue, unspecified
C96.Z	Other specified malignant neoplasms of lymphoid, hematopoietic and related tissue
D37.1	Neoplasm of uncertain behavior of stomach
D37.8	Neoplasm of uncertain behavior of other specified digestive organs
D37.9	Neoplasm of uncertain behavior of digestive organ, unspecified
D43.0	Neoplasm of uncertain behavior of brain, supratentorial
D43.1	Neoplasm of uncertain behavior of brain, infratentorial
D43.2	Neoplasm of uncertain behavior of brain, unspecified
D43.4	Neoplasm of uncertain behavior of spinal cord
D43.9	Neoplasm of uncertain behavior of central nervous system, unspecified
D76.3	Other histiocytosis syndromes
Z85.00	Personal history of malignant neoplasm of unspecified digestive organ
Z85.01	Personal history of malignant neoplasm of esophagus
Z85.028	Personal history of other malignant neoplasm of stomach
Z85.068	Personal history of other malignant neoplasm of small intestine
Z85.07	Personal history of malignant neoplasm of pancreas
Z85.09	Personal history of malignant neoplasm of other digestive organs
Z85.118	Personal history of other malignant neoplasm of bronchus and lung
Z85.43	Personal history of malignant neoplasm of ovary
Z85.820	Personal history of malignant melanoma of skin

ICD-10	ICD-10 Description
Z85.831	Personal history of malignant neoplasm of soft tissue
Z85.841	Personal history of malignant neoplasm of brain
Z85.848	Personal history of malignant neoplasm of other parts of nervous tissue
Z85.858	Personal history of malignant neoplasm of other endocrine glands

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 Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: https://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
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