tovorafenib (Ojemda™)

EOCCO POLICY

Policy Type:PA/SP Pharmacy Coverage Policy: EOCCO308

Description

Tovorafenib (Ojemda) is a type II RAF kinase inhibitor of mutant BRAF V600E, wild-type BRAF, and wild-type CRAF kinases.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
tovorafenib (Ojemda)	Relapsed or refractory pediatric low-grade glioma (LGG) harboring a BRAF fusion or rearrangement, or BRAF V600 mutation	25 mg/mL suspension	See Appendix*
		100 mg tablet	24 tablets/28 days

**Please note that the dose is based on body surface area (BSA). Please see appendix for dosing limits.*

Initial Evaluation

I. **Tovorafenib (Ojemda)** may be considered medically necessary when the following criteria are met:
   A. Member is 6 months of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. Medication will not be used in combination with any other oncology therapy; **AND**
   D. Documentation of member's weight and height; **OR**
      1. Documentation of the member's body surface area (BSA); **AND**
   E. A diagnosis of **relapsed or refractory pediatric low-grade glioma (pLGG)** when the following are met:
      1. Documentation of BRAF fusion or rearrangement, or BRAF v600 mutation; **AND**
      2. Member has progressive disease after trial of a prior systemic therapy [e.g., carboplatin/vincristine, vinblastine, carboplatin/vincristine/etoposide, dabrafenib (Tafinlar)/trametinib (Mekinist), etc.]; **AND**
      3. Treatment with a second-line of chemotherapy (e.g., carboplatin/vincristine, vinblastine, carboplatin/vincristine/etoposide) has been ineffective, contraindicated, or not tolerated; **AND**
      4. Provider attestation that member is <u>not</u> eligible for any ongoing clinical trials for the treatment of BRAF-mutated relapsed or refractory low-grade glioma (pLGG)

II. Tovorafenib (Ojemda) is considered investigational when used for all other conditions, including but not limited to:
   A. Tovorafenib (Ojemda) used in combination with another oncology therapy
   B. Pediatric low-grade glioma (LGG) 1st line systemic therapy
   C. High grade glioma (HGG)
   D. Melanoma
   E. Langerhans cell histiocytosis
   F. Craniopharyngioma

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**
IV. Documentation of member's weight and height; **OR**
   1. Documentation of the member's body surface area (BSA); **AND**
V. Medication will not be used in combination with any other oncology therapy

Supporting Evidence

I. Tovorafenib (Ojemda) is being evaluated in several clinical trials; however, efficacy, pharmacokinetic, and pharmacodynamic parameters have been studied in pediatric patients six months of age and older. Safety and efficacy in adults has not been established at this time.
II. Given the specialized, high-touch care, nuances of treatment, monitoring, and consideration for patient specific goals required for the treatment of BRAF mutated cancers, therapy choices should be directed by an oncologist.
III. Tovorafenib (Ojemda) has not been adequately studied in combination with any other oncology therapy, therefore, use of tovorafenib (Ojemda) in combination with other oncology treatments is considered experimental and investigational at this time.
IV. The dosing regimen of tovorafenib (Ojemda) is dependent on the patient's body surface area (BSA) for once weekly administration. Documentation of the member's BSA is required to establish the correct dosing parameters.
V. Tovorafenib (Ojemda) is a type II RAF kinase inhibitor FDA-approved for the treatment of patients six months of age and older with relapsed or refractory pediatric low-grade glioma

(LGG) harboring a BRAF fusion or rearrangement, or BRAF v600 mutation. It is administered as a once weekly suspension or tablet.

VI. Pediatric low-grade gliomas (pLGG) are the most frequent solid malignant tumors diagnosed in children and young adults with an estimated 2,600 patients diagnosed in 2020. Although overall survival averages from 80-90%, prognosis is influenced by many factors including the degree of tumor resection achieved, histological and molecular tumor classification, or presence of disseminated disease. Children will typically present with seizures or focal neurological deficits: weakness, difficulty swallowing, sensory loss, visual impairment, or changes in academic/athletic performance.

VII. Surgery is the first treatment modality for almost 80% of all LGG patients. Following surgery, observation may be the only treatment indicated. When there is residual disease, or for those where surgery isn't an option, drug therapy is indicated. Chemotherapy combinations of vincristine and carboplatin are standard per United Kingdom (UK) guidelines and are typical practice in the United States (U.S.). There are currently no standardized guidelines for pLGG in the U.S. Results of chemotherapy trials are consistent, showing overall survival rates between 70-95%, but a low progression free survival at around 45% at 5 years. Other approved therapies for first line systemic treatment include dabrafenib (Tafinlar)/trametinib (Mekinist) in patients aged ≥1 year with LGG with a BRAF V600E mutation. For those with residual tumor present, 35% to 55% will relapse or be refractory and may require second line treatment. Tovorafenib (Ojemda) was studied in a Phase 2 open-label trial in 77 pediatric patients with an activating BRAF alteration who had previously been treated with at least one line of prior systemic therapy with evidence of radiographic progression. The primary efficacy outcome was the objective response rate (ORR) as assessed by Response Assessment in Neuro-Oncology for high-grade gliomas (RANO-HGG) criteria, though overall response rate (ORR) assessed by Response Assessment in Pediatric Neuro-Oncology for low-grade gliomas (RAPNO-LGG) is included in the FDA label. Baseline characteristics of the trial participants: median age was nine years (range, 1–24), white (58%), astrocytic tumors (93%), KIAA1549:BRAF fusion (74%), BRAF V600E mutation (16%), median of three lines of prior therapy (range, 1–10), with 61% having received a prior MEK and/or BRAF inhibitor. The ORR as assessed by RAPNO-LGG criteria was 51% with partial response (37%) and minimal response (14%) driving the efficacy. Thirty percent of participants were able to establish stable disease. The median duration of response was 13.8 months (11.3, NR) with a median time to response of 5.3 months (1.6, 11.2).

VIII. The most common adverse reactions (AEs) were rash (77%), hair color changes (76%), fatigue (55%), viral infection (55%), and vomiting (50%). Serious adverse reactions occurred in 45% of patients who received tovorafenib (Ojemda). Serious adverse reactions in >2% of patients included viral infection (9%), pneumonia (4%), and sepsis (4%). Tovorafenib (Ojemda) showed a 57% dose interruption rate in clinical trials and a 24% dose reduction rate due to intolerable AEs. Permanent discontinuation only occurred in 7% of patients. Tumor hemorrhage (one patient; which was a fatal AE) and reduction in growth velocity (two patients).

IX. As pLGG tumors undergo senescence in adults, the goal of therapy is to stabilize the tumor in pediatric and adolescent patients while retaining quality of life and physical functioning. A partial response, minor response, and/or stable disease may be considered clinically meaningful if there is some degree of tumor shrinkage/stabilization paired with a lack of progression of symptoms (e.g., neurological deficits, vision changes). The single-arm, open-label trial design makes the data observational; however, this concern may be mitigated as pLGG tumors are not expected to regress without treatment. The impact of tovorafenib (Ojemda) on long term efficacy, morbidity, and mortality remains unknown. Coupled with potential bias due to a small sample size, the overall confidence in a substantial benefit is considered low but the data may be sufficient to make healthcare decisions.

X. Current second-line systemic treatment options include additional chemotherapy, retreatment with prior chemotherapy agents if there is good response and a prolonged period between treatment and subsequent relapse or progression, or combination BRAF/MEK inhibitors (e.g., dabrafenib (Tafinlar)/trametinib (Mekinist).

XI. Second-line chemotherapy regimens have been evaluated in multiple clinical trials with known side effect profiles. While treatment with second-line chemotherapy may be more cost effective than newer targeted therapies and is required prior to allowing coverage to tovorafenib (Ojemda) in eligible patients, individual patient specific factors should be taken into account when considering further treatment with chemotherapy in the relapsed/refractory setting. Examples of patient specific factors that may make additional lines of chemotherapy inappropriate include previous therapy intolerance, a caregiver's inability to take member to appointments, logistical considerations, etc.

Investigational or Not Medically Necessary Uses

I. Tovorafenib (Ojemda) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Tovorafenib (Ojemda) used in combination with another oncology therapy
   B. Pediatric low-grade glioma (LGG) 1st line systemic therapy
      i. Tovorafenib (Ojemda) is currently under investigation for the treatment of pLGG harboring an activating RAF alteration who require first-line systemic therapy. LOGGIC/FIREFLY-2 is a two-arm, randomized, open-label, multicenter, global, Phase 3 trial to evaluate the efficacy, safety, and tolerability of tovorafenib (Ojemda) monotherapy vs. current standard of care (SoC) chemotherapy in patients < 25 years of age. Primary completion is expected in June 2026. Requests for this indication are considered experimental and investigational at this time.
   C. High grade glioma (HGG)
      i. There is currently no active trial evaluating the use of tovorafenib (Ojemda) in patients with high grade glioma (HGG). There is insufficient evidence to support to the safety and efficacy of tovorafenib (Ojemda) in this disease space.

D. Melanoma
    i. Tovorafenib (Ojemda) is currently under investigation in a Phase 1b/2, multi-center, open label umbrella study of patients ≥12 years of age with recurrent, progressive, or refractory melanoma or other solid tumors with alterations in the key proteins of the RAS/RAF/MEK/ERK pathway, referred to as the MAPK pathway. Primary completion is expected in December 2025. Requests for this indication are considered experimental and investigational at this time.

E. Langerhans cell histiocytosis
    i. Tovorafenib (Ojemda) is currently under investigation in a Phase 2 trial of patients with R/R Langerhans cell histiocytosis. Primary completion is expected in May 2025. Requests for this indication are considered experimental and investigational at this time.

F. Craniopharyngioma
    i. Tovorafenib (Ojemda) is currently under investigation in combination with PD-1 (nivolumab) for the treatment of young adults with craniopharyngioma (NCT05465174). Results are not expected until March 2027. Requests for this indication are considered experimental and investigational at this time.

Appendix

Table 1: Recommended Dosage for tovorafenib (Ojemda) Oral Tablets Based on Body Surface Area

Body Surface Area (m^2)	Recommended Dosage
0.30-0.89	Administer tovorafenib (Ojemda) oral suspension once weekly
0.90-1.12	400 mg once weekly
1.13-1.39	500 mg once weekly
≥ 1.40	600 mg once weekly

I. Table 2: Recommended Dosage for tovorafenib (Ojemda) Oral Suspension Based on Body Surface Area

Body Surface Area (m^2)	Dose Volume (mL)	Recommended Dosage	Quantity Level Limit
0.30-0.35	5	125 mg once weekly	48 mL/28 days
0.36-0.42	6	150mg once weekly	48 mL/28 days
0.43-0.48	7	175 mg once weekly	48 mL/28 days
0.49-0.54	8	200 mg once weekly	48 mL/28 days
0.55-0.63	9	225 mg once weekly	48 mL/28 days
0.64-0.77	11	275 mg once weekly	48 mL/28 days
0.78-0.83	12	300 mg once weekly	48 mL/28 days
0.84-0.89	14	350 mg once weekly	96 mL/28 days
0.90-1.05	15	375 mg once weekly	96 mL/28 days
1.06-1.25	18	450 mg once weekly	96 mL/28 days
1.26-1.39	21	525 mg once weekly	96 mL/28 days

≥ 1.40	24	600 mg once weekly	96 mL/28 days

References

1. Ojemda. Package Insert. Day One Biopharmaceuticals, Inc; April 2024.
2. Kilburn LB, Khuong-Quang DA, Hansford JR, et al. The type II RAF inhibitor tovorafenib in relapsed/refractory pediatric low-grade glioma: the phase 2 FIREFLY-1 trial [published correction appears in Nat Med. 2024 Mar 11;:]. Nat Med. 2024;30(1):207-217.
3. Children's Cancer and Leukaemia Group. Guidelines for the diagnosis and management of paediatric and adolescent Low-Grade Glioma. July 2020. Accessed May 8, 2024. LGG_Guidelines_July_2020.pdf (cclg.org.uk)
4. Food and Drug Administration. FDA grants accelerated approval to tovorafenib for patients with relapsed or refractory BRAF-altered pediatric low-grade glioma. FDA.gov. April 23, 2024. Accessed May 6, 2024. FDA grants accelerated approval to tovorafenib for patients with relapsed or refractory BRAF-altered pediatric low-grade glioma | FDA
5. Ojemda product dossier. Day One Biopharmaceuticals, Inc. May 2024.
6. van Tilburg CM, Kilburn LB, Perreault S, et al. LOGGIC/FIREFLY-2: a phase 3, randomized trial of tovorafenib vs. chemotherapy in pediatric and young adult patients with newly diagnosed low-grade glioma harboring an activating RAF alteration. *BMC Cancer*. 2024;24(1):147. Published 2024 Jan 30.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
encorafenib (Braftovi®), binimetinib (Mektovi®)	Malignant melanoma, unresectable or metastatic, with BRAF V600E or V600K mutation, combination therapy; Metastatic colorectal cancer, with BRAF V600E mutation, combination therapy (Braftovi only)
Dabrafenib (Tafinlar), Trametinib (Mekinist)	Anaplastic thyroid carcinoma, advanced or metastatic, BRAF V600E mutated, combination therapy; Melanoma, adjuvant therapy for malignant disease, BRAF V600E or K mutated, combination therapy; Melanoma, malignant unresectable or metastatic disease, BRAF V600E or K mutated, combination therapy; Melanoma, malignant unresectable or metastatic disease, BRAF V600E or K mutated, monotherapy in BRAF treatment naïve patients; Non-small cell lung cancer, metastatic, BRAF V600E mutated, combination therapy; Unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options; Pediatric low-grade glioma (LGG) with a BRAF V600E mutation, combination therapy
cobimetinib (Cotellic®), vemurafenib (Zelboraf®)	Unresectable or metastatic melanoma with a BRAF V600E or V600K mutation; Histiocytic neoplasms in adults (Cotellic only); Erdheim-Chester disease with a BRAF v600 mutation (Zelboraf only)
Selumetinib (Koselugo)	Neurofibromatosis type 1 (NF1)

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	08/2024