eflornithine (Iwilfin™)

EOCCO POLICY

Policy Type:PA/SP Pharmacy Coverage Policy: EOCCO302

Description

Eflornithine (Iwilfin) is an ornithine decarboxylase inhibitor.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months*; maximum total (lifetime) fills should not exceed #24 30-day fills

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
eflornithine (Iwilfin)	High-risk neuroblastoma (HRNB) who have demonstrated at least a partial response to prior multiagent, multimodality therapy including anti-GD2 immunotherapy	192 mg tablets	See appendix*

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

Initial Evaluation

I. **Eflornithine (Iwilfin)** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   B. Medication will not be used in combination with any other oncology therapy; **AND**
   C. A diagnosis of **high-risk neuroblastoma (HRNB)** when the following are met:
      1. Provider attestation that the member has high-risk disease as defined by International Neuroblastoma Risk Group Classification criteria; **AND**
      2. Documentation of member's weight and height within the last three months; **OR**
         i. Documentation of the member's body surface area (BSA) within the last three months; **AND**
      3. The member has undergone prior therapy with induction therapy (e.g. cisplatin, etoposide, vincristine, cyclophosphamide, doxorubicin, topotecan, surgical resection); **AND**
      4. The member has been previously treated with consolidation therapy [e.g., myeloablative chemotherapy (carboplatin, etoposide, melphalan or busulfan, melphalan) and HSCT]; **AND**
      5. The member has been previously treated with post consolidation therapy consisting of all of the following unless contraindicated, or not tolerated:
         i. Isotretinoin
         ii. Granulocyte-macrophage colony-stimulating factor (e.g., sargramostim)
         iii. Anti-GD2 immunotherapy (e.g., dinutuximab)

II. Eflornithine (Iwilfin) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Reduction of unwanted facial hair

III. Eflornithine (Iwilfin) is considered investigational when used for all other conditions, including but not limited to:
   A. Eflornithine (Iwilfin) used in combination with another oncology therapy
   B. Low-risk neuroblastoma
   C. Intermediate risk neuroblastoma
   D. West African trypanosomiasis

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. Disease 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 within the last three months; **OR**
   A. Documentation of the member's body surface area (BSA) within the last three months; **AND**
V. The member has not received treatment with eflornithine (Iwilfin) for more than 24 months

Supporting Evidence

I. Eflornithine (Iwilfin) is an ornithine decarboxylase inhibitor FDA approved to reduce the risk of relapse in adult and pediatric patients with high-risk neuroblastoma (HRNB) who have demonstrated at least a partial response to prior multiagent, multimodality therapy including anti-GD2 immunotherapy.
II. Neuroblastomas are the most common extracranial solid tumor in childhood. They can arise anywhere throughout the sympathetic nervous system though the adrenal gland is the most common primary site (40%). Symptoms at presentation vary based on the site of primary disease, the most common symptoms include abdominal masses, bone pain and pancytopenia from bone marrow metastasis, and proptosis and periorbital ecchymosis due to retrobulbar metastases.
III. Outcomes for patients with HRNB remain poor despite treatment with multiple treatment modalities. Treatment for patients is generally divided into three steps including induction (chemotherapy and surgery), consolidation (tandem cycles of myeloablative therapy and HSCT and radiation therapy to the site of the primary tumor and residual metastatic sites), and post

consolidation [immunotherapy with granulocyte-macrophage colony-stimulating factor (GM-CSF), dinutuximab, and isotretinoin therapy). However, after post consolidation treatment options are limited. Eflornithine (Iwilfin) is the first FDA approved maintenance therapy for those with HRNB after multimodal therapy (i.e., induction, consolidation, post consolidation including anti-GD2s).

IV. The diagnosis of neuroblastoma requires the involvement of pathologists who are familiar with childhood tumors. Some neuroblastomas cannot be differentiated morphologically, via conventional light microscopy. Given the complexities related to diagnosis, treatment, and management of HRNB, treatment in this disease space must be initiated by, or in consultation with, an oncologist.

V. Eflornithine (Iwilfin) is an orally administered tablet given twice per day based on body surface area. Per the FDA label it is recommended to recalculate the BSA every three months. Therefore, this policy asks for the member's height and weight within the past three months in order to calculate an appropriate dose.

VI. Eflornithine (Iwilfin) was studied in a Phase 2, multi-center, open label, non-randomized trial (Study 3b). Study 3b was prospectively designed to compare outcomes to the historical benchmark event free survival (EFS) rate from Study ANBL0032 (clinical trial-derived external control arm). The external control arm was derived from 1,241 patients on the experimental arm of Study ANBL0032, a Phase 3, multi-center, open-label, randomized trial of dinutuximab, GM-CSF, interleukin-2, and cis-retinoic acid compared to cis-retinoic acid alone in pediatric patients with HRNB.

VII. Patients eligible for Study 3b had a histologically confirmed diagnosis of neuroblastoma with high-risk disease according to the International Neuroblastoma Risk Group Classification. Patients are stratified by several factors that define the risk of relapse, including age, disease stage, and other tumor attributes. Based on these factors, patients are diagnosed with low-, intermediate- or high-risk disease. Current neuroblastoma high-risk stratification criteria include:

- Stage 2A or 2B disease and MYCN amplification
- Stage 3 disease and MYCN amplification
- Stage 3 disease in children aged ≥ 18 months, no MYCN amplification and unfavorable histopathology
- Stage 4 disease in children younger than 12 months and with MYCN amplification
- Stage 4 disease in children aged 12–18 months with MYCN amplification and/or diploidy and/or unfavorable histology
- Stage 4 disease in children aged ≥ 18 months
- Stage 4S disease and MYCN amplification

VIII. Trial participants had received upfront therapy defined as chemotherapy (5-7 cycles), surgery as indicated, consolidation therapy as indicated, radiation therapy as indicated, anti-GD2 antibody therapy with retinoic acid up to 6 cycles.

- While induction chemotherapies are not standardized across institutions, the most common backbone of therapy includes dose-intensive cycles of cisplatin and

etoposide alternating with vincristine, cyclophosphamide, and doxorubicin. Topotecan and cyclophosphamide were added to this regimen on the basis of the anti-neuroblastoma activity seen in patients with relapsed disease. After a response to induction chemotherapy, resection of the primary tumor is usually attempted. The consolidation phase of high-risk regimens involves myeloablative chemotherapy and HSCT, which attempts to eradicate minimal residual disease (MRD) using otherwise lethal doses of ablative chemotherapy rescued by autologous stem cells (collected during induction chemotherapy) to repopulate the bone marrow. Most current protocols use tandem chemotherapy and HSCT with carboplatin/etoposide/melphalan or busulfan/melphalan as conditioning for HSCT. Post consolidation therapy is designed to treat potential MRD after HSCT. For high-risk patients in remission after HSCT, dinutuximab combined with GM-CSF given together with isotretinoin demonstrated improved EFS as demonstrated in study ANBL0032. The end of study ANBL0032 represented the end of immunotherapy and served as the baseline for Study 3b.

IX. Patients who met the criteria for the comparative analysis of Study 3b and ANBL0032, with complete data for specified clinical covariates (age at high-risk diagnosis, sex, race, stage at HRNB, pre-ASCT response, transplant type, time from ASCT to start of immunotherapy, duration of immunotherapy, overall response at immunotherapy end, time from diagnosis to immunotherapy end, and MYCN category), were matched (1:3) using propensity scores. The efficacy populations for the primary analysis included 90 patients treated with eflornithine (Iwilfin) and 270 control patients from Study ANBL0032.

X. Four-year EFS and OS outcomes were reported in two populations, the propensity score matched (PSM) the group and the overall population. In the PSM population a four-year EFS of 84% was reported in the (Iwilfin) compared to 73% in the external control arm for a treatment difference of 0.48 (95% CI, 0.27 to 0.85; P=.01). The four-year OS was found to be 96% in the eflornithine (Iwilfin) treated group compared to 84% in the external control arm for a treatment difference of 0.32 (95% CI, 0.15 to 0.70; P=.005). Similar results were reported in the overall population with a four-year EFS of 84% vs 72% respectively [HR 0.50 (95% CI, 0.29 to 0.84; P= .008)] and a four-year OS of 96% vs 84% [HR 0.38 (95% CI, 0.19 to 0.76; P=.007)].

XI. Most adverse effects (AE) were mild to moderate in severity. In a pooled safety population, the most common adverse reactions were hearing loss (11%), otitis media (10%), pyrexia (7%), pneumonia (5%), and diarrhea (5%). There are no specific contraindications to the use of eflornithine (Iwilfin).

XII. The use of eflornithine (Iwilfin) has not been studied in combination with other oncolytic therapies. Due to a lack of safety and efficacy data with a combination regimen eflornithine (Iwilfin) is to be used as monotherapy.

Investigational or Not Medically Necessary Uses

I. Reduction of unwanted facial
   A. Treatment with eflornithine (Iwilfin) for the reduction of unwanted hair falls in the category of medications that are not covered under the prescription benefit. Drugs used for cosmetic purposes are excluded from coverage.

II. Eflornithine (Iwilfin) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Eflornithine (Iwilfin) used in combination with another oncology therapy
   B. Low-risk neuroblastoma
   C. Intermediate risk neuroblastoma
   D. West African trypanosomiasis
      i. Injectable eflornithine is donated to the World Health Organization (WHO) by the manufacturer. In the United States, eflornithine injection is available through the CDC for treatment of second-stage African trypanosomiasis (caused by Trypanosoma brucei gambiense) with CNS involvement.

Appendix

I. Table 1: Recommended Dose

Body Surface Area (m^2)	Dosage
>1.5	768 mg (four tablets) orally twice a day
0.75 to 1.5	576 mg (three tablets) orally twice a day
0.5 to < 0.75	384 mg (two tablets) orally twice a day
0.25 to <0.5	192 mg (one tablet) orally twice a day

References

1. Iwilfin. Package Insert. USWorldMeds; December 2023.
2. Oesterheld J, Ferguson W, Kraveka JM, et al. Eflornithine as Postimmunotherapy Maintenance in High-Risk Neuroblastoma: Externally Controlled, Propensity Score-Matched Survival Outcome Comparisons. *J Clin Oncol*. 2024;42(1):90-102.
3. Sholler GLS, Ferguson W, Bergendahl G, et al. Maintenance DFMO Increases Survival in High Risk Neuroblastoma. *Sci Rep*. 2018;8(1):14445. Published 2018 Sep 27.
4. PDQ® Pediatric Treatment Editorial Board. PDQ Neuroblastoma Treatment. Bethesda, MD: National Cancer Institute. Updated 12/22/2023. Available at: https://www.cancer.gov/types/neuroblastoma/hp/neuroblastoma-treatment-pdq. Accessed 01/18/2024. [PMID: 26389190]
5. National Comprehensive Cancer Network. Neuroblastoma (Version 1.2024). NCCN. February 7, 2024. Accessed March 19, 2024. https://www.nccn.org/professionals/physician_gls/pdf/neuroblastoma.pdf

Related Policies

The 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
ALK+ Inhibitors Policy	ALK+ metastatic NSCLC
	ROS1+ metastatic NSCLC
	ALK+ R/R inflammatory myofibroblastic tumors

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2024