Iowa Medicaid
IOWA HHS

PDL DRUG REVIEW

Proprietary Name: Iwilfin®
Common Name: eflornithine
PDL Category: Antineoplastics

Comparable Products	Preferred Drug List Status
Unituxin	Medical

Pharmacology/Usage: Eflornithine, the active ingredient of Iwilfin®, is an ornithine decarboxylase inhibitor. It is an irreversible inhibitor of the enzyme ornithine decarboxylase (ODC), the first and rate-limiting enzyme in the biosynthesis of polyamines and a transcriptional target of *MYCN*. Polyamines are involved in differentiation and proliferation of mammalian cells and are important for neoplastic transformation. Inhibition of polyamine synthesis by eflornithine restored the balance of the LIN28/Let-7 metabolic pathway, which is involved in regulation of cancer stem cells and glycolytic metabolism, by decreasing expression of the oncogenic drivers MYCN and LIN28B in *MYCN*-amplified neuroblastoma. Treatment with eflornithine prevented or delayed tumor formation in mice injected with limiting dilutions of *MYCN*-amplified neuroblastoma cells.

Indication: 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.

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings from animal studies and its mechanism of action, Iwilfin® can cause fetal harm when administered to a pregnant woman. There are no available data on use in pregnant women. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Verify pregnancy status in females of reproductive potential prior to starting therapy. Advise females of reproductive potential, as well as males with female partners of reproductive potential, to use effective contraception during treatment and for 1 week after the last dose. The safety and efficacy of use have been established in the pediatric population for the approved indication of Iwilfin®.

Dosage Form: Tablets: 192mg.

Recommended Dosage: Prior to starting treatment, perform complete blood count, liver function tests, and baseline audiogram.

The recommended Iwilfin® dosage, based on body surface area (BSA), is presented in the table below, which was adapted from the prescribing information. Recalculate the BSA dosage every 3 months during Iwilfin® treatment.

BSA (m^2)	Dosage
>1.5	768mg (4 tabs) PO BID
0.75 to 1.5	576mg (3 tabs) PO BID
0.5 to <0.75	384mg (2 tabs) PO BID
0.25 to <0.5	192mg (1 tab) PO BID

Take Iwilfin® PO BID, with or without food, for two years or until recurrence of disease or unacceptable toxicity. Tablets can be swallowed whole, chewed, or crushed. For patients having difficulty swallowing tablets, Iwilfin® can be chewed, or crushed then mixed with two tablespoons of soft food or liquid. Discard crushed tablet preparation after one hour.

A missed Iwilfin® dose should be administered as soon as possible. If the next dose is due within 7 hours, the missed dose should be skipped. If vomiting occurs after taking Iwilfin®, an additional dose should not be administered. Continue with the next scheduled dose.

Refer to the prescribing information for additional information regarding dosage modification for adverse reactions, such as neutrophil count decreased, platelet count decreased, anemia, hepatotoxicity, hearing loss, or other adverse reactions such as nausea, vomiting, or diarrhea.

Drug Interactions: There are no drug interactions listed with this product.

Box Warning: This product does not have a box warning.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Iwilfin®) for all grades. There was no placebo data to compare with in the prescribing information.* The most frequently reported adverse events included otitis media (32%), sinusitis (13%), pneumonia (12%), upper respiratory tract infection (11%), conjunctivitis (11%), skin infection (7%), urinary tract infection (6%), diarrhea (15%), vomiting (11%), cough (15%), allergic rhinitis (11%), pyrexia (11%), and hearing loss (7%).

Laboratory abnormalities for all grades included increased ALT (9%), increased AST (8%), increased alkaline phosphatase (4.7%), decreased potassium (2.4%), decreased glucose (2.4%), decreased sodium (2.4%), increased potassium (1.2%), increased glucose (1.2%), decreased neutrophils (9%), decreased hemoglobin (4.7%), decreased white blood cells (2.4%), and decreased platelets (1.2%).

Iwilfin® can cause myelosuppression. Perform blood counts including neutrophil count, platelet count, and hemoglobin level prior to starting Iwilfin® and periodically during treatment. Withhold, reduce the dose, or permanently discontinue Iwilfin® based on severity.

Iwilfin® can cause hepatotoxicity. Perform liver function tests (ALT, AST, and bilirubin) prior to the start of Iwilfin®, every month for the first six months of treatment, then once every 3 months or as clinically indicated, with more frequent testing in patients who develop transaminase or bilirubin elevations. Withhold and reduce the dose or permanently discontinue Iwilfin® based on severity.

Iwilfin® can cause hearing loss. In the pooled safety population, 81% of patients had an abnormal audiogram at baseline. New or worsening hearing loss occurred in 13% of patients who received Iwilfin®; hearing loss worsened from baseline to Grade 3 or 4 in 12% of patients. Tinnitus occurred in 1 patient. Hearing loss leading to dose interruption or reduction occurred in 4% of patients. Perform audiogram prior to the start of therapy and at 6 month intervals, or as clinically indicated, to monitor for potential hearing loss. Withhold and reduce the dose or permanently discontinue Iwilfin® based on severity.

Contraindications: There are no contraindications listed with this product.

Manufacturer: US World Meds.

Analysis: The efficacy of Iwilfin® is based on an externally controlled trial comparison of Study 3b (investigational arm) and Study ANBL0032 (clinical trial-derived external control arm).

Study 3b was a multicenter, open-label, non-randomized trial with two cohorts. Eligible patients in one cohort (Stratum 1) were pediatric patients with HRNB who demonstrated at least a partial response to prior multiagent, multimodality therapy, including induction, consolidation, and anti-GD2 immunotherapy. Eligible patients (N=105) received Iwilfin® BID, with dosage based on BSA, until disease progression, unacceptable toxicity, or for a maximum of 2 years. Tumor assessments were performed at 3, 6, 9, 12, and 18 months, completion of treatment, and as clinically indicated. After completing Iwilfin® therapy, patients were followed for a total duration of 7 years. The major efficacy outcome measure was event free survival (EFS), defined as disease progression, relapse, secondary cancer, or death due to any cause. An additional efficacy outcome was overall survival (OS), defined as death due to

any cause. Study 3b was prospectively designed to compare outcomes to the historical EFS rate from Study ANBL0032 reported in published literature.

The external control arm was derived from 1,241 patients on the experimental arm of *Study ANBL0032*, a multicenter, open-label, randomized trial of dinutuximab, granulocyte-macrophage colony-stimulating factor, interleukin-2, and cis-retinoic acid compared to cis-retinoic acid alone in pediatric patients with HRNB previously treated with induction and consolidation therapy who demonstrated at least a partial response. Tumor assessments were performed post-immunotherapy at 3, 6, 9, 12, 18, 24, 30, and 36 months, and then per standard of care for a total of 10 years.

The efficacy population for the comparative analysis of Study 3b and ANBL0032 included patients from both studies who were less than 21 years of age with histologic verification of HRNB and who demonstrated at least a partial response based on imaging, with no evidence of disease in the bone marrow, at the end of immunotherapy, and did not experience an EFS event prior to starting Iwilfin® maintenance therapy (for Study 3b), or for at least 30 days from the end of immunotherapy (for ANBL0032). Eligible patients on Study 3b received immunotherapy on ANBL0032 or were treated off study per the ANBL0032 protocol. Patients who met the criteria for the comparison and had complete data for specified clinical covariates were matched using propensity scores; the matched efficacy populations for the primary analysis included 90 patients treated with Iwilfin® and 270 control patients from ANBL0032. The demographics of the primary analysis population (N=360) included mostly males (59%), while the median age at diagnosis was 3 years and 88% were white. The majority of patients had Stage 4 disease (86%) and MYCN amplification was observed in 44% of tumors. End of immunotherapy responses were complete response (CR; 87%), very good partial response (VGPR; 8%), or partial response (PR; 5%).

In the protocol-specific primary analysis, the EFS hazard ratio (HR) was 0.48 and OS HR was 0.32. Given the uncertainty in treatment effect estimation associated with the externally controlled study design, supplementary analyses in subpopulations or using alternative statistical methods were performed. In these analyses, the EFS HR ranged from 0.43 to 0.59, and the OS HR ranged from 0.29 to 0.45.

Place in Therapy: Iwilfin® is an oral ornithine decarboxylase inhibitor indicated 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. Prior to initiation of Iwilfin®, perform baseline audiogram, complete blood count, and liver function tests. Dosage is based on BSA, and it is recommended to recalculate the BSA dosage every 3 months during treatment with Iwilfin®. The efficacy of Iwilfin® is based on an externally controlled trial comparison of Study 3b (investigational arm) and Study ANBL0032 (clinical trial-derived external control arm). In the protocol-specified primary analysis, the event free survival (EFS) hazard ratio (HR) was 0.48 and overall survival (OS) HR was 0.32. Iwilfin® provides a treatment option for children and adults with HRNB. Due to the uncertainty in treatment effect estimation associated with the externally controlled study design, supplementary analyses in subpopulations or using alternative statistical methods were performed. In these analyses, the EFS HR ranged from 0.43 to 0.59, and the OS HR ranged from 0.29 to 0.45.

It is recommended that Iwilfin® should be non-recommended in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended with Conditions**

References

[1] Iwilfin [package insert]. Louisville, KY: US World Meds; 2023.