Clinical Policy: Eflornithine (Iwilfin)

Reference Number: CP.PHAR.670
Effective Date: 03.01.24
Last Review Date: 02.24
Line of Business: Commercial, HIM, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Eflornithine (Iwilfin™) is an ornithine decarboxylase inhibitor.

FDA Approved Indication(s)

Iwilfin is indicated to reduce the risk of relapse in adult and pediatric patients with high-risk neuroblastoma who have demonstrated at least a partial response to prior multiagent, multimodality therapy including anti-GD2 immunotherapy.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Iwilfin is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Neuroblastoma (must meet all)**:**

1. Diagnosis of high-risk neuroblastoma (*see Appendix D*);
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 1 year;
4. For Iwilfin requests, member must use eflornithine, if available, unless contraindicated or clinically significant adverse effects are experienced;
5. Member previously received multiagent, multimodality therapy including anti-GD2 immunotherapy (e.g., Unituxin®, *see Appendix B for examples*);
6. Provider attestation that neuroblastoma is currently in remission demonstrated by a partial response or better (*see Appendix D*) to prior therapy with no evidence of disease in the bone marrow;
7. Documentation of member's current body surface area (BSA, in m^2);
8. Request meets one of the following (a or b):*
   a. Dose does not exceed the FDA approved maximum recommended dose by BSA listed in *Section V* below;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 6 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Neuroblastoma (must meet all)**:**
1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Iwilfin for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. Member has not received ≥ 2 years of Iwilfin therapy;
4. If request is for a dose increase, request meets one of the following (a or b):*
   a. New dose does not exceed the FDA approved maximum recommended dose by BSA listed in *Section V* below;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 12 months (up to 2 years of total therapy)

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

BSA: body surface area
COG: Children's Oncology Group
FDA: Food and Drug Administration
INRC: International Neuroblastoma Response Criteria
INRGSS: International Neuroblastoma Risk Group Staging System
INSS: International Neuroblastoma Staging System

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
cisplatin, etoposide, vincristine, cyclophosphamide, doxorubicin, topotecan	Used in various combinations in variable dosing regimens	Varies
Unituxin® (dinutuximab), isotretinoin, GM-CSF	Used in various combinations in variable dosing regimens	Varies

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

None reported

Appendix D: General Information

- Defining "high-risk" neuroblastoma: The Children's Oncology Group (COG) risk group system was initially based on the Internationl Neuroblastoma Staging System (INSS) staging system, but is now transitioning to using the International Neuroblastoma Risk Group Staging System (INRGSS), along with the major prognostic factors to place children into 3 different risk groups: low, intermediate, and high. High-risk neuroblastoma patients, per COG, are:
  - Stage 2A or 2B disease and MYCN amplification
  - Stage 3 disease and MYCN amplification

- Stage 3 disease in children age 18 months or older, no MYCN amplification, and unfavorable histopathology
- Stage 4 disease in children younger than 12 months and MYCN amplification
- Stage 4 disease in children between 12 months and 18 months with MYCN amplification, and/or diploidy, and/or unfavorable histology
- Stage 4 disease in children 18 months or older
- Stage 4S disease and MYCN amplification

- International Neuroblastoma Risk Group (INRG) classification is a newer system that is now being used to help researchers in different countries compare results and work together to find the best treatments. This system is based on the newer INRGSS staging system, as well as many of the prognostic factors listed in the staging section, such as: the child's age, tumor histology, presence or absence of MYCN gene amplification, and presence of the 11q aberration, and DNA ploidy. The INRG classification uses these factors to put children into 16 different pre-treatment groups (lettered A through R). Each pre-treatment group falls into 1 of 4 overall risk groups listed below. This system will most likely be used in addition to the COG Risk Classification system in the United States.
  - Very low risk
  - Low risk
  - Intermediate risk
  - High risk
- In Study NMTRC003b (Study 3b), eligible patients were required to be in remission at enrollment. Remission was operationally defined as achieving 1993 International Neuroblastoma Response Criteria (INRC) partial response or better based on imaging disease response evaluation with no evidence of disease in the bone marrow. The 1993 INRC include the following response to treatment definitions:
  - Complete response: no primary tumor; metastatic sites with no tumor; catecholamines normal
  - Very good partial response: primary tumor decreased by 90-99%; metastatic sites with no tumor; catecholamines normal; residual ^{99}Tc bone changes allowed
  - Partial response: primary tumor decreased by > 50%; all measurable metastatic sites decreased by > 50%. Bones and bone marrow: number of positive bone sites decreased by > 50%; no more than 1 positive bone marrow site allowed.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Neuroblastoma	BSA (m^2): Dosage (PO BID) > 1.5: 768 mg (four tablets) 0.75 to 1.5: 576 mg (three tablets) 0.5 to < 0.75: 384 mg (two tablets) 0.25 to < 0.5: 192 mg (one tablet) Recalculate the BSA dosage every 3 months. Administer until disease progression, unacceptable toxicity, or for a maximum of two years.	See dosing regimen

VI. Product Availability

Tablet: 192 mg

VII. References

1. Iwilfin Prescribing Information. US WorldMeds, LLC: Louisville, KY; December 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/215500s000lbl.pdf. Accessed January 2, 2024.
2. American Cancer Society. Treating neuroblastoma. Last revised April 28, 2021. Available at: https://www.cancer.org/content/dam/CRC/PDF/Public/8761.00.pdf. Accessed November 5, 2023.
3. American Cancer Society. Neuroblastoma early detection, diagnosis, and staging. Last revised April 28, 2021. Available at: https://www.cancer.org/content/dam/CRC/PDF/Public/8760.00.pdf. Accessed November 5, 2023.
4. Cancer.net. Neuroblastoma – Childhood: Stages and Groups. Available at: https://www.cancer.net/cancer-types/neuroblastoma-childhood/stages-and-groups. Accessed November 5, 2023.
5. Brodeur GM, Pritchard J, Berthold F, et al: Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. J Clin Oncol 11:1466-1477, 1993.
6. Eflornithine (DFMO) tablets to reduce the risk of relapse in pediatric patients with high-risk neuroblastoma who have completed multiagent, multimodality therapy. Oncologic Drugs Advisory Committee (ODAC) Sponsor Briefing Document. October 4, 2023. Available at: https://www.fda.gov/media/172661/download. Accessed January 2, 2024.
7. ClinicalTrials.gov ID NCT02395666: Preventative Trial of Difluoromethylornithine (DFMO) in High Risk Patients With Neuroblastoma That is in Remission. Available at: https://clinicaltrials.gov/study/NCT02395666. Accessed January 2, 2024.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	01.02.24	02.24

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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