Clinical Policy: Mitoxantrone

Reference Number: OR.CP.PHAR.258
Effective Date: 10.01.21
Last Review Date: 05.24
Line of Business: Medicaid – Oregon Health Plan

Coding Implications
Revision Log

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

Description
Mitoxantrone is a synthetic antineoplastic anthracenedione.

FDA Approved Indication(s)
Mitoxantrone is indicated for:

- Reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis (MS) (i.e., patients whose neurologic status is significantly abnormal between relapses)
- Treatment of patients with pain related to advanced hormone-refractory prostate cancer as initial chemotherapy in combination with corticosteroids
- Initial therapy of acute nonlymphocytic leukemia (ANLL) (including myelogenous, promyelocytic, monocytic, and erythroid acute leukemias) in adults in combination with other approved drug(s)

Limitation(s) of use: Mitoxantrone is not indicated in the treatment of patients with primary progressive MS.

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 Trillium Community Health Plan that mitoxantrone is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Multiple Sclerosis (must meet all)**:**

1. Diagnosis of one of the following (a or b):
   a. Relapsing-remitting MS, and failure of all of the following at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated (i, ii, iii, and iv):*
      i. **Dimethyl fumarate** (generic Tecfidera®);
      ii. **Teriflunomide** (generic Aubagio®);
      iii. **Fingolimod** (Gilenya®);
      iv. An **interferon-beta agent** (Avonex®, Betaseron®/Extavia®†, Rebif®, or Plegridy®) or **glatiramer** (Copaxone®, Glatopa®);

**Prior authorization may be required for all disease modifying therapies for MS*
† Extavia is preferred

b. Secondary progressive MS;

2. Prescribed by or in consultation with a neurologist;
3. Age ≥ 18 years;
4. Mitoxantrone is not prescribed concurrently with other disease modifying therapies for MS (*see Appendix D*);
5. Documentation of baseline number of relapses per year or expanded disability status scale (EDSS) score;
6. Dose does not exceed the following (a and b):
   a. 12 mg/m^2 every 3 months;
   b. Total cumulative lifetime dose of 140 mg/m^2.

Approval duration: 6 months

B. Prostate Cancer (must meet all)**:**

1. Diagnosis of advanced or metastatic prostate cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is hormone-refractory (i.e., castration-resistant);
5. Mitoxantrone is prescribed concurrently with a corticosteroid (e.g., prednisone);
6. Request meets one of the following (a or b):*
   a. Dose does not exceed 14 mg/m^2 every 21 days;
   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.*
7. Total cumulative lifetime dose does not exceed 140 mg/m^2.

Approval duration: 6 months

C. Acute Nonlymphocytic Leukemia (must meet all)**:**

1. Diagnosis of ANLL (including myelogenous [i.e., acute myelogenous leukemia], promyelocytic, monocytic, and erythroid acute leukemias);
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Mitoxantrone is prescribed in combination with other therapies for the diagnosis;
5. Request meets one of the following (a or b):*
   a. Dose does not exceed 12 mg/m^2 per infusion;
   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.*
6. Total cumulative lifetime dose does not exceed 140 mg/m^2.

Approval duration: 6 months

D. Lymphoma (off-label) (must meet all)**:**

1. Diagnosis of one of the following (a, b, or c):
   a. One of the following B-cell lymphomas: diffuse large B-cell lymphoma, high grade B-cell lymphoma, HIV-related B-cell lymphoma, or post-transplant lymphoproliferative disorder; and both (i and ii):

i. Prescribed as second line or subsequent therapy;
ii. Prescribed as a component of MINE (mesna, ifosfamide, mitoxantrone, and etoposide);

b. Symptomatic T-cell prolymphocytic leukemia as a component of FMC (fludarabine, mitoxantrone, and cyclophosphamide);

2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. 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.*
5. Total cumulative lifetime dose does not exceed 140 mg/m^2.

Approval duration: 6 months

E. Acute Lymphoblastic Leukemia (off-label) (must meet all)**:**

1. Diagnosis of acute lymphoblastic leukemia (ALL);
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Disease is relapsed/refractory;
4. Member meets one of the following (a or b):
   a. Age ≥ 18 years, and both of the following (i and ii):
      i. Disease is one of the following (1, 2, or 3):
         1) Philadelphia chromosome (Ph)-negative B-ALL;
         2) Ph-positive B-ALL, and refractory to tyrosine kinase inhibitor therapy (e.g., dasatinib, imatinib, ponatinib, nilotinib, bosutinib);
         3) T-ALL;
      ii. Mitoxantrone is prescribed as a component of one of the following (1, 2, or 3):
         1) An alkylator combination regimen (e.g., etoposide, ifosfamide, and mitoxantrone);
         2) FLAM (fludarabine, cytarabine, and mitoxantrone);
         3) For T-ALL only: mitoxantrone, etoposide, and cytarabine;
   b. Age < 18 years, and disease is one of the following (i, ii, or iii):
      i. Ph-negative B-ALL;
      ii. Ph-positive B-ALL in combination with dasatinib or imatinib as a component of UKALL R3 or COG AALL 1331;
      iii. T-ALL as a component of UKALL R3 Block 1 (dexamethasone, mitoxantrone, pegaspargase, and vincristine);
5. 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.*
6. Total cumulative lifetime dose does not exceed 140 mg/m^2.

Approval duration: 6 months

F. 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 PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or

b. For drugs NOT on the PDL (Medicaid), the non-formulary policy for the relevant line of business: OR.CP.PMN.1001 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.PMN.53 for Medicaid.

II. Continued Therapy

A. Multiple Sclerosis (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member meets one of the following (a, b or c):
   a. If member has received < 1 year of total treatment: Member is responding positively to therapy;
   b. If member has received ≥ 1 year of total treatment: Member meets one of the following (i, ii, iii, or iv):
      i. Member has not had an increase in the number of relapses per year compared to baseline;
      ii. Member has not had ≥ 2 new MRI-detected lesions;
      iii. Member has not had an increase in EDSS score from baseline;
      iv. Medical justification supports that member is responding positively to therapy;
   c. Member is actively relapsing and all of the following are met (i, ii, iii):
      i. Prescribed by or in consultation with a neurologist;
      ii. Member is adherent to therapy as evidenced by claims for at least 144 days of therapy in the last 180 days;
      iii. Provider has completed evaluation of alternative treatment options or plans to do so at next scheduled office visit;
3. Mitoxantrone is not prescribed concurrently with other disease modifying therapies for MS (*see Appendix D*);

4. If request is for a dose increase, new dose does not exceed the following (a and b):
   a. 12 mg/m^2 every 3 months;
   b. Total cumulative lifetime dose of 140 mg/m^2.

Approval duration: 6 months

B. All Other Indications in Section I (must meet all)**:**

1. Currently receiving medication via Centene benefit or documentation supports that member is currently receiving mitoxantrone for an oncology indication listed in Section I;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a, b, or c):*
   a. Prostate cancer: New dose does not exceed 14 mg/m^2 every 21 days;
   b. ANLL: New dose does not exceed 12 mg/m^2 per infusion;
   c. Any indication: 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.*
4. Total cumulative lifetime dose does not exceed 140 mg/m^2.

Approval duration: 12 months

C. 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 PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the PDL (Medicaid), the non-formulary policy for the relevant line of business: OR.CP.PMN.1001 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.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 policy – CP.PMN.53 for Medicaid or evidence of coverage documents;

B. Primary progressive MS.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ALL: acute lymphoblastic leukemia
ANLL: acute nonlymphocytic leukemia
EDSS: expanded disability status scale
FDA: Food and Drug Administration
MS: multiple sclerosis
NCCN: National Comprehensive Cancer Network
Ph: Philadelphia chromosome

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
teriflunomide (Aubagio®)	7 mg or 14 mg PO QD	14 mg/day
Avonex®, Rebif® (interferon beta-1a)	*Avonex*: 30 mcg IM Q week *Rebif*: 22 mcg or 44 mcg SC TIW	*Avonex*: 30 mcg/week *Rebif*: 44 mcg TIW
Plegridy® (peginterferon beta-1a)	125 mcg SC Q2 weeks	125 mcg/2 weeks
Betaseron®, Extavia® (interferon beta-1b)	250 mcg SC QOD	250 mg QOD
glatiramer acetate (Copaxone®, Glatopa®)	20 mg SC QD or 40 mg SC TIW	20 mg/day or 40 mg TIW
fingolimod (Gilenya®)	0.5 mg PO QD	0.5 mg/day
dimethyl fumarate (Tecfidera®)	120 mg PO BID for 7 days, followed by 240 mg PO BID	480 mg/day

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
- Contraindication(s): prior hypersensitivity to mitoxantrone
- Boxed warning(s): cardiotoxicity, secondary leukemia

Appendix D: General Information
- Disease-modifying therapies for MS are: glatiramer acetate (Copaxone®, Glatopa®), interferon beta-1a (Avonex®, Rebif®), interferon beta-1b (Betaseron®, Extavia®), peginterferon beta-1a (Plegridy®), dimethyl fumarate (Tecfidera®), diroximel fumarate (Vumerity®), monomethyl fumarate (Bafiertam™), fingolimod (Gilenya®, Tascenso ODT™), teriflunomide (Aubagio®), alemtuzumab (Lemtrada®), mitoxantrone (Novantrone®), natalizumab (Tysabri®, and biosimilar Tyruko®), ocrelizumab (Ocrevus®), cladribine (Mavenclad®), siponimod (Mayzent®), ozanimod (Zeposia®), ponesimod (Ponvory™), ublituximab-xiiy (Briumvi™), and ofatumumab (Kesimpta®).
- Mitoxantrone has Drugdex IIa recommendations for use in anthracycline-resistant breast cancer, liver cancer, and ovarian cancer; however, these indications are not supported by the National Comprehensive Cancer Network (NCCN). Of note, use of mitoxantrone in invasive breast cancer is actually listed as a use no longer recommended by the NCCN.
- Per the NCCN, prostate cancer that stops responding to traditional androgen deprivation therapy (i.e., hormone therapy) is categorized as castration-recurrent (also known as castration-resistant).

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Relapsing MS	12 mg/m^2 given as a short (approximately 5 to 15 minutes) intravenous infusion every 3 months	Cumulative lifetime dose of ≥ 140 mg/m^2
Hormone-refractory prostate cancer	12 to 14 mg/m^2 given as a short intravenous infusion every 21 days	Cumulative lifetime dose of ≥ 140 mg/m^2
ANLL	Induction: 12 mg/m^2 of mitoxantrone injection (concentrate) daily on Days 1 to 3 given as an intravenous infusion. A second induction course (2 days) may be given if there is an incomplete antileukemic response Consolidation: 12 mg/m^2 given by intravenous infusion daily on Days 1 and 2	Cumulative lifetime dose of ≥ 140 mg/m^2

VI. Product Availability

Multidose vials: 20 mg/10 mL, 25 mg/12.5 mL, 30 mg/15 mL

VII. References

1. Mitoxantrone Prescribing Information. Lake Forest, IL: Hospira Inc.; April 2021. Available at http://labeling.pfizer.com/ShowLabeling.aspx?id=4536. Accessed January 10, 2024.
2. Goodin DS, Frohman EM, Garmany GP, et al. Disease modifying therapies in multiple sclerosis: Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. Neurology. 2002; 58(2): 169-178.
3. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed February 1, 2024.
4. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2018; 90(17): 777-788. Full guideline available at: https://www.aan.com/Guidelines/home/GetGuidelineContent/904. Reaffirmed on September 18, 2021.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J9293	Injection, mitoxantrone HCl, per 5 mg

Reviews, Revisions, and Approvals	Date	Plan Approval Date
Policy created: adapted from previously approved policy CP.PHAR.258 Mitoxantrone (Novantrone); changed requirement to		07.15.21

Reviews, Revisions, and Approvals	Date	Plan Approval Date
report EDSS score in I.A.5 to either baseline number of relapses per year; expanded II.A.2 to allow approval for actively relapsing		
2Q 2022 annual review: removed references to the brand product Novantrone as it is no longer on market; removed mantle cell lymphoma as a coverable B-cell lymphoma and clarified coverable ALL types per NCCN; clarified interferon-beta product redirections for each line of business per SDC; references reviewed and updated.	03.17.22	04.07.22
2Q 2023 annual review: no significant changes; clarified lymphoma criteria per NCCN; template changes applied to other diagnoses/indications and continued therapy section; references reviewed and updated.	03.10.23	04.06.23
Per August SDC, added generic references to Aubagio and Gilenya redirections.	09.22.23	11.21.23
2Q 2024 annual review: for ALL, rearranged existing criteria to clarify that disease must be relapsed/refractory, added additional allowable regimen for adult T-ALL, and specified the allowable regimens for pediatric Ph-positive B-ALL per NCCN; removed Hodgkin lymphoma/follicular lymphoma as coverable diagnoses as NCCN no longer recommends these uses; references reviewed and updated.	03.29.24	05.21.24

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.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

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.