Clinical Policy: Mitoxantrone (Novantrone)

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Line of Business: Illinois Medicaid

Revision Log

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

Description

Mitoxantrone (Novantrone®) is a synthetic antineoplastic anthracenedione.

FDA Approved Indication(s)

Novantrone 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 (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 multiple sclerosis.

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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Novantrone 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, and failure of the following at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced: dimethyl fumarate (*Tecfidera® brand is preferred*) and any of the following: an interferon-beta agent *(Betaseron® and Rebif® are preferred agents)* or glatiramer *(Copaxone® 20 mg is preferred*);
      **Prior authorization is required for all disease modifying therapies for MS*
   b. Secondary-progressive MS;
2. Prescribed by or in consultation with a neurologist;
3. Age ≥ 18 years;
4. Novantrone is not prescribed concurrently with other disease modifying therapies for MS (*see Appendix D*);
5. Documentation of baseline number of relapses per year and expanded disability status scale (EDSS) score;
6. Dose does not exceed 12 mg/m^2 every 3 months (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. Novantrone is prescribed concurrently with a corticosteroid;
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. Novantrone 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. Relapsed/refractory classical Hodgkin lymphoma as a third-line or subsequent therapy as a component of MINE (mesna, ifosfamide, mitoxantrone, and etoposide);
   b. One of the following B-cell lymphomas as subsequent therapy as a component of MINE (mesna, ifosfamide, mitoxantrone, and etoposide): follicular lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma, high grade B-cell lymphoma, AIDS-related B-cell lymphoma, or post-transplant lymphoproliferative disorder;
   c. 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. Member meets one of the following (a or b):
   a. Age ≥ 18 years, and both of the following (i and ii):
      i. One of the following (1 or 2):
         1. Disease is Philadelphia chromosome (Ph)-negative, and relapsed or refractory;
         2. Disease is Ph-positive, and refractory to tyrosine kinase inhibitor therapy (e.g., dasatinib, imatinib, ponatinib, nilotinib, bosutinib);

ii. Novantrone is prescribed as a component of an akylator combination regimen (e.g., etoposide, ifosfamide, and mitoxantrone) or FLAM (fludarabine, cytarabine, and mitoxantrone);

b. Age < 18 years, and one of the following (i, ii, or iii):
   i. Relapsed/refractory Ph-negative B-ALL;
   ii. Relapsed/refractory Ph-positive B-ALL in combination with dasatinib or imatinib;
   iii. Relapsed/refractory T-ALL as a component of UKALL R3 Block 1 (dexamethasone, mitoxantrone, pegaspargase, and vincristine)

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

F. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Multiple Sclerosis (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member meets one of the following (a or b):
   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;
3. Novantrone 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 12 mg/m^2 every 3 months (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 a health plan affiliated with Envolve Pharmacy Solutions or documentation supports that member is currently receiving Novantrone 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. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or

2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 – ERX.PA.01 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 and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Rebif® (interferon beta-1a)	22 mcg or 44 mcg SC TIW	44 mcg TIW
Betaseron® (interferon beta-1b)	250 mcg SC QOD	250 mg QOD
glatiramer acetate (Copaxone®)	20 mg SC QD or 40 mg SC TIW	20 mg/day or 40 mg TIW
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®), teriflunomide (Aubagio®), alemtuzumab (Lemtrada®), mitoxantrone (Novantrone®), natalizumab (Tysabri®), ocrelizumab (Ocrevus®), cladribine (Mavenclad®), siponimod (Mayzent®), ozanimod (Zeposia®), 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 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

Indication	Dosing Regimen	Maximum Dose
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 vial: 20 mg/10 mL, 25 mg/12.5 mL, 30 mg/15 mL

VII. References
1. Mitoxantrone Prescribing Information. Lake Forest, IL: Hospira Inc.; May 2018. Available at http://labeling.pfizer.com/ShowLabeling.aspx?id=4536. Accessed February 8, 2021.
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 January 27, 2020.
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.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	04.19.21	05.21

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.

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