Clinical Policy: Mitoxantrone

Reference Number: PA.CP.PHAR.258
Effective Date: 01/2018
Last Review Date: 04/2025

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
It is the policy of PA Health & Wellness® that mitoxantrone is **medically necessary** for the following indications:

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 two preferred Multiple Sclerosis Agents (*see list of preferred agents at* https://papdl.com/preferred-drug-list) at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated, unless member is currently stabilized on therapy;
      **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. Mitoxantrone is not prescribed concurrently with other disease modifying therapies for MS (*see Appendix D*);
5. 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. Mitoxantrone 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*);
7. Total cumulative lifetime dose does not exceed 144 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*);
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 or b):
   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*);
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. Member is considered an adult per NCCN guidelines, 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, mesna and mitoxantrone);
      2. FLAM (fludarabine, cytarabine, and mitoxantrone);
      3. For T-ALL only:mitoxantrone, etoposide and cytarabine;

b. Member is considered to be Pediatric or Adolescent and Young Adult (AYA) per NCCN guidelines, and disease is one of the following (i, ii, or iii):
   i. BCR-ABL1-negative B-ALL;
   ii. BCR-ABL1-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/calaspargase, and vincristine);

5. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*);
6. Total cumulative lifetime dose does not exceed 140 mg/m^2.

Approval duration: 6 months

F. Other diagnoses/indications: Refer to PA.CP.PMN.53

II. Continued Approval

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

1. Currently receiving medication via PA Health & Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care policy (PA.PHARM.01) applies;
2. Member is responding positively to therapy;
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 12 mg/m^2 every 3 months (total cumulative lifetime dose of 140 mg/m^2).

Approval duration: 12 months

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

1. Currently receiving medication via PA Health & Wellness benefit or member has previously met initial approval criteria; or the Continuity of Care policy (PA.PHARM.01) applies;
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*);

4. Total cumulative lifetime dose does not exceed one of the following (a or b):
   a. For Acute Nonlymphocytic Leukemia, Lymphoma, and Acute Lymphoblastic Leukemia: 140 mg/m^2.
   b. For Prostate Cancer: 144 mg/m^2.

Approval duration: 12 months

C. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies; or
2. Refer to PA.CP.PMN.53.

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 – PA.CP.PMN.53 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
B-ALL: B-cell acute lymphoblastic leukemia
BCR-ABL1: Philadelphia chromosome
FDA: Food and Drug Administration
MS: multiple sclerosis
NCCN: National Comprehensive Cancer Network
Ph: Philadelphia chromosome
T-ALL: T-cell acute lymphoblastic leukemia

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
Aubagio® (teriflunomide)	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
Gilenya® (fingolimod)	0.5 mg PO QD	0.5 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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™), ocrelizumab/hyaluronidase-ocsq (Ocrevus Zunovo™), 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 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.; April 2021. Available at http://labeling.pfizer.com/ShowLabeling.aspx?id=4536. Accessed January 23, 2025.
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 11, 2025.
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/898.Reaffirmed on October 19, 2024

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
2Q 2018 annual review: approval durations modified from 3 months to 6 months and removed LVEF requirement for MS; oncology: criteria added; references reviewed and updated.	01/2018
2Q 2019 annual review: MS: specified that generic forms of glatiramer are preferred; all blood cancers: added hematologist prescriber option; ANLL: added requirement for combination use; lymphoma: added requirement for combination use and clarified non-Hodgkin lymphomas to specific lymphoma types; added off-label criteria for ALL per NCCN; references reviewed and updated.	04/2019
2Q 2020 annual review: ALL: added off-label criteria for pediatric ALL per NCCN; MS: added requirements for documentation of baseline relapses/EDSS and objective measures of positive response upon re-authorization; added total cumulative life dose criterion to each indication; references reviewed and updated.	04/2020
Added Bafiertam and Zeposia to list of disease-modifying therapies in Appendix D	08/2020

Reviews, Revisions, and Approvals	Date
2Q 2021 annual review: lymphoma: updated use in Hodgkin lymphoma and T-cell prolymphocytic leukemia per NCCN; references reviewed and updated.	04/2021
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.	04/2022
2Q 2023 annual review: no significant changes; clarified lymphoma criteria per NCCN; references reviewed and updated.	04/2023
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.	04/2024
2Q 2025 annual review: for MS, removed requirements for documentation of baseline relapses/expanded disability status score and specific measures of positive response; and increased the continued approval duration from 6 to 12 months for this chronic condition for pediatric ALL, revised "Ph" to "BCR-ABL1" per NCCN; added section III. Diagnoses/Indications for which coverage is NOT authorized; references reviewed and updated.	04/2025