Prior Authorization Review Panel

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CHC-MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review. Policies submitted without this form will not be considered for review.

Plan: PA Health & Wellness	**Submission Date: 05/01/2021**
Policy Number: PA.CP.PHAR.258	**Effective Date: 01/2018** **Revision Date: 04/2021**
Policy Name: Mitoxantrone (Novantrone)	

Type of Submission – Check all that apply:

- ☐ **New Policy**
- ✓ **Revised Policy***
- ☐ **Annual Review - No Revisions**
- ☐ **Statewide PDL -** *Select this box when submitting policies for Statewide PDL implementation and when submitting policies for drug classes included on the Statewide PDL.*

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any changes or clarifying information for the policy below:

2Q 2021 annual review: lymphoma: updated use in Hodgkin lymphoma and T-cell prolymphocytic leukemia per NCCN; references reviewed and updated.

Name of Authorized Individual (Please type or print): **Auren Weinberg, MD**	**Signature of Authorized Individual:** 

Clinical Policy: Mitoxantrone (Novantrone)

Reference Number: PA.CP.PHAR.258
Effective Date: 01/18
Last Review Date: 07/2021

Coding Implications
Revision Log

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 (ANLL) (including myelogenous, promyelocytic, monocytic, and erythroid acute leukemias) in adults in combination with other approved drug(s)

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

Policy/Criteria
It is the policy of Pennsylvania Health and 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. 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*);
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. 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*);
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*);
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. Member is considered an adult per NCCN guidelines, 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 alkylator combination regimen (e.g., etoposide, ifosfamide, and mitoxantrone) or FLAM (fludarabine, cytarabine, and mitoxantrone);
    b. Member is considered to be Pediatric or Adolescent and Young Adult (AYA) per NCCN guidelines, 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*);
5. 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 Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
2. 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 PA Health and Wellness benefit or member has previously met initial approval criteria; or the Continuity of Care policy (PA.LTSS.PHAR.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 Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies; or
2. Refer to PA.CP.PMN.53.

III. 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
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® (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
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 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).

IV. 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

V. Product Availability

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

VI. 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 February 8, 2021.

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.

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	Approval 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.	01.05.18	
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.	04.17.19	
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	
2Q 2021 annual review: lymphoma: updated use in Hodgkin lymphoma and T-cell prolymphocytic leukemia per NCCN; references reviewed and updated.	04/2021	