Clinical Policy: Mitoxantrone (Novantrone)

Reference Number: PA.CP.PHAR.258
Effective Date: 01/18
Last Review Date: 04/19

Coding Implications
Revision Log

Description
Mitoxantrone (Novantrone®) is a synthetic antineoplastic anthracenedione.

Policy/Criteria
It is the policy of Pennsylvania Health and Wellness® that mitoxantrone is **medically necessary** for the following indications:

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.

I. Initial Approval Criteria

A. Multiple Sclerosis (must meet all):

1. Diagnosis of relapsing-remitting or secondary-progressive multiple sclerosis (MS);
2. Prescribed by or in consultation with a neurologist;
3. Age ≥ 18 years;
4. If member has relapsing-remitting MS, failure of one of the following (a or b) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced, unless member is currently stabilized on therapy:
   a. Tecfidera® or Gilenya® and any of the following: an interferon-beta agent *(Avonex® and Plegridy® are preferred agents)*, or glatiramer *((generic [including Glatopa®] is preferred)*;
   b. Tecfidera and Gilenya;
5. Member will not use other disease modifying therapies for MS concurrently (*see Appendix D*);
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-recurrent);
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*);

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*);

Approval duration: 6 months

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

1. Diagnosis of one of the following (a b, or c):
   a. Classical Hodgkin lymphoma in combination with other therapies for the diagnosis;
   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. T-cell prolymphocytic leukemia as a componenet 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*);

Approval duration: 6 months

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

1. Diagnosis of acute lymphoblastic leukemia;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. One of the following (a or b):

a. Disease is Philadelphia chromosome-negative, and relapsed or refractory;
b. Disease is Philadelphia chromosome-positive, and refractory to tyrosine kinase inhibitor therapy (e.g., dasatinib, imatinib, ponatinib, nilotinib, bosutinib);

5. Novantrone is prescribed as a component of an akylator combination regimen (e.g., etoposide, ifosfamide, and mitoxantrone) or FLAM (fludarabine, cytarabine, and mitoxantrone);
6. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*);

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. Member is not using other disease modifying therapies for MS concurrently (*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*);

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

ANLL: acute nonlymphocytic leukemia
FDA: Food and Drug Administration
MS: multiple sclerosis
NCCN: National Comprehensive Cancer Network

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
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
Tecfidera® (dimethyl fumarate)	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®), fingolimod (Gilenya®), teriflunomide (Aubagio®), alemtuzumab (Lemtrada®), mitoxantrone (Novantrone®), natalizumab (Tysabri®), and ocrelizumab (Ocrevus™).
- 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

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	

References

1. Mitoxantrone Prescribing Information. Lake Forest, IL: Hospira Inc.; May 2018. Available at http://labeling.pfizer.com/ShowLabeling.aspx?id=4536. Accessed February 4, 2019.
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. Costello K, Halper J, Kalb R, Skutnik L, Rapp R. The use of disease-modifying therapies in multiple sclerosis, principles and current evidence – a consensus paper by the Multiple Sclerosis Coalition. March 2017. Accessed February 4, 2019.
4. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed February 4, 2019.
5. 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.