Clinical Policy Title:	mitoxantrone
Policy Number:	RxA.413
Drug(s) Applied:	mitoxantrone
Original Policy Date:	03/06/2020
Last Review Date:	06/10/2021
Line of Business Policy Applies to:	All lines of business

Background

Mitoxantrone is a synthetic antineoplastic anthracenedione. It 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)
- Brand Novantrone® has been discontinued

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

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
mitoxantrone	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 IV
	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 IV
	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 IV

Dosage Forms

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

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

I. Initial Approval Criteria

A. Multiple Sclerosis (must meet all):

1. Diagnosis of relapsing-remitting or 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
Commercial: 6 months
Medicaid: 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. 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 140 mg/m^2.

Approval Duration
Commercial: 6 months
Medicaid: 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

Commercial: 6 months
Medicaid: 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 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
Commercial: 6 months
Medicaid: 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. 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. Mitoxantrone 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 desatinib 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
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. Multiple Sclerosis (must meet all):

1. Currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
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
Commercial: 6 months
Medicaid: 6 months

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

1. Currently receiving medication that has been authorized by RxAdvance 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);*
4. Total cumulative lifetime dose does not exceed 140 mg/m^2.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
ANLL: acute nonlymphocytic leukemia
B-ALL: B-cell Acute Lymphoblastic Leukemia
FDA: Food and Drug Administration
MS: multiple sclerosis
NCCN: National Comprehensive Cancer Network

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Avonex®, Rebif® (interferon beta-1a)	*Avonex*: 30 mcg IM every week *Rebif*: 22 mcg or 44 mcg SC Three times weekly	*Avonex*: 30 mcg/week *Rebif*: 44 mcg SC Three times weekly
Plegridy® (peginterferon beta-1a)	125 mcg SC every 14 days	125 mcg SC every 14 days
Betaseron®, Extavia® (interferon beta-1b)	250 mcg SC every other day	250 mg SC every other day
Aubagio® (teriflunomide)	7 mg or 14 mg PO once daily	14 mg/day PO

Tysabri® (natalizumab)	300 mg IV every 4 weeks	300 mg/4 weeks

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 include:

- Infusion therapies
  - natalizumab (Tysabri®)
  - mitoxantrone
  - ocrelizumab (Ocrevus™)
  - alemtuzumab (Lemtrada®)
- Injectable therapies
  - glatiramer (Copaxone®, Glatopa®)
  - interferon beta-1a (Avonex®, Rebif®)
  - interferon beta-1b (Betaseron®, Extavia®)
  - peginterferon beta-1a (Plegridy®)
- Oral therapies
  - dimethyl fumarate (Tecfidera®)
  - monomethyl fumarate (Bafiertam™)
  - diroximel fumarate (Vumerity®)
  - teriflunomide (Aubagio®)
  - fingolimod (Gilenya™)
  - siponimod (Mayzent®)
  - ozanimod (Zeposia®)
  - cladribine (Mavenclad®)
  - dalfampridine (Ampyra®)

- 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).

References

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2. Costello K, Halper J, Kalb R, Skutnik L, Rapp R. The use of disease-modifying therapies in multiple sclerosis,

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3. 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. Accessed May 27, 2021.
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6. Clinical Pharmacology [database online] powered by ClinicalKey. Tampa, FL: Elsevier, 2020. Accessed with subscription at: http://www.clinicalkey.com. Updated January 14, 2020. Accessed May 27, 2021.
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Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established	01/2020	03/06/2020
Policy was reviewed: 1. Policy title table was updated: Clinical Policy Title was updated to " mitoxantrone". Drug(s) Applied was updated to “mitoxantrone” Line of Business Policy Applies to was updated to "All". 2. Dosing information was updated: Maximum dose has been updated to "Cumulative lifetime dose of 140 mg/m2 IV". 3. Clinical policy was updated: Initial approval criteria was updated to include “Trial and failure of at least 2 preferred disease modifying therapies, at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced.” 4. Approval duration was updated for both Initial and Continued Approval Criteria; 5. Continued Approval was rephrased to "Currently receiving medication that has been authorized by RxAdvance…".; Added Tysabri and	07/31/2020	09/14/2020

Mayzent to MS criteria. 6. Appendix B was updated: Dosing regimen and maximum dose were updated.; Added off-label criteria for pediatric ALL per NCCN. 7. Added B-ALL to Appendix A. 8. Added Tysabri and Mayzent to Therapeutic Alternatives. 9. Replaced brand Novantrone with generic mitoxantrone throughout policy. 10. Updated Appendix D 11. References were updated.		
Policy was reviewed: 1. Clinical policy title was updated. 2. Continued therapy approval criteria II.A.4 indicating ," Trial and failure of at…….or Zeposia" was removed. 3. References were reviewed and updated.	5/27/21	6/10/21