Clinical Policy: Mitoxantrone

Reference Number: LA.PHAR.258
Effective Date: 11.04.23
Last Review Date: 05.14.26~~05.13.25~~ Coding Implications
Line of Business: Medicaid Revision Log

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

****Please note: This policy is for medical benefit****

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

It is the policy of Louisiana Healthcare Connections that mitoxantrone 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 MS, and failure of all of the following at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated (i, ii, iii, and iv~~):*~~):*
      i. **Dimethyl fumarate** (generic Tecfidera®);
      ii. **Teriflunomide** (generic Aubagio®);
      iii. **Fingolimod** (Gilenya®);

iv. An **interferon-beta agent** (Avonex®, Betaseron®/Extavia®†, Rebif®, or Plegridy®) or **glatiramer** (Copaxone®, Glatopa®);
**Prior authorization may be 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 the following (a and b):
   a. 12 mg/m^2 every 3 months;
   b. Total cumulative lifetime dose of 140 mg/m^2.

Approval duration: ~~6~~ 12 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 (e.g., prednisone);
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~~ 12 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*);
   **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~~ 12 months

D. ~~Lymphoma~~T-Cell Prolymphocytic Leukemia (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.~~1. ~~Symptomatic~~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. Prescribed as a component of FMC (fludarabine, mitoxantrone, and cyclophosphamide);
5. 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~~ 12 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. Age ≥ 18 years, 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, and mitoxantrone);
         2) FLAM (fludarabine, cytarabine, and mitoxantrone);
         3) For T-ALL only: mitoxantrone, etoposide, and cytarabine;
   b. Age < 18 years, and disease is one of the following (i, ii, or iii):
      i. BCR::ABL1-negative B-ALL~~;~~ as a component of UKALL R3 or COG AALL 1331;
      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, and vincristine);
5. 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~~ 12 months

~~**F.A. Other diagnoses/indications** (must meet 1 or 2)~~**:**

~~1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to LA.PMN.255~~

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F. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to LA.PMN.255
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy LA.PMN.53.

II. Continued Therapy

A. Multiple Sclerosis (must meet all)**:**
1. Currently receiving medication via Louisiana Healthcare Connections benefit or member has previously met initial approval criteria;
~~2. Member meets one of the following (a or b):~~
~~a. If member has previously met initial approval criteria;~~
~~b. Member is responding positively to therapy;~~
~~3.~~2. Member is responding positively to therapy;
~~4.~~3. Mitoxantrone is not prescribed concurrently with other disease modifying therapies for MS (*see Appendix D*);
~~5.~~4. If request is for a dose increase, new dose does not exceed the following (a and b):
   a. 12 mg/m^2 every 3 months;
   b. Total cumulative lifetime dose of 140 mg/m^2.

Approval duration: ~~6~~ 12 months

B. All Other Indications in Section I (must meet all)**:**
1. Currently receiving medication via Louisiana Healthcare Connections benefit 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*);

   **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.~~ If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to LA.PMN.255
~~**C.A. Other diagnoses/indications** (must meet 1 or 2)**:**~~

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~~1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to LA.PMN.255~~

~~2.~~1. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy LA.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 – LA.PMN.53;

B. Primary progressive MS.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ALL: acute lymphoblastic leukemia
ANLL: acute nonlymphocytic leukemia
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
teriflunomide (Aubagio®)	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
fingolimod (Gilenya®)	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®, 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 vials: 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~~July 2025. Available at http://labeling.pfizer.com/ShowLabeling.aspx?id=4536. Accessed January 23, ~~2025~~2026.
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~~3, 2026.
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	LDH Approval Date
Converted corporate to local policy.	06.15.23	10.05.23
Added generic references to Aubagio and Gilenya redirections.	04.22.24	07.10.24
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.	08.14.24	11.14.24
Annual review: for MS, removed requirements for documentation of baseline relapses/expanded disability status score and specific measures of positive response per competitor analysis, removed notation that Extavia is the preferred interferon beta-1b product for the Medicaid line; increased the continued approval duration from 6 to 12 months for this chronic condition; for pediatric ALL, revised "Ph" to "BCR::ABL1" per NCCN; references reviewed and updated.	05.13.25	08.14.25
Annual review: for pediatric BCR::ABL1-negative B-ALL, added requirement for use as a component of UKALL R3 or COG AALL 1331 per NCCN; removed B-cell lymphomas as coverable diagnoses as NCCN no longer recommends these uses; extended initial approval duration from 6 to 12 months ~~f~~; references reviewed and updated.	05.14.26	

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. LHCC makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable LHCC-level administrative policies and procedures.

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