Clinical Policy: Mitoxantrone (Novantrone)
Reference Number: CP.PHAR.258
Effective Date: 08.01.16
Last Review Date: 08.20
Line of Business: Commercial, HIM, Medicaid

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

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
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 health plans affiliated with Centene Corporation® that Novantrone 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. Aubagio®;
            iii. Gilenya®;
            iv. An interferon-beta agent (Avonex®, Betaseron®, Rebif®, or Plegridy®) or glatiramer (Copaxone®, Glatopa®);
*Prior authorization is required for all disease modifying therapies for MS
Mitoxantrone

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/m² every 3 months (total cumulative lifetime dose of 140 mg/m²).

Approval duration:
Medicaid/HIM – 6 months
Commercial – 6 months or to the member’s renewal date, whichever is longer

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/m² 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/m².

Approval duration:
Medicaid/HIM – 6 months
Commercial – 6 months or to the member’s renewal date, whichever is longer

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/m² 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/m².

Approval duration:
Medicaid/HIM – 6 months
Commercial – 6 months or to the member’s renewal date, whichever is longer

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/m².

Approval duration:
Medicaid/HIM – 6 months
Commercial – 6 months or to the member’s renewal date, whichever is longer

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. 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. Novanthrone is prescribed as a component of an alkylator 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 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/m².

Approval duration:
Medicaid/HIM – 6 months
Commercial – 6 months or to the member’s renewal date, whichever is longer
F. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Multiple Sclerosis (must meet all):

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member meets one of the following (a or b):
   a. If member has received < 1 year of total treatment: Member is responding positively to therapy;
   b. If member has received ≥ 1 year of total treatment: Member meets one of the following (i, ii, iii, or iv):
      i. Member has not had an increase in the number of relapses per year compared to baseline;
      ii. Member has not had ≥ 2 new MRI-detected lesions;
      iii. Member has not had an increase in EDSS score from baseline;
      iv. Medical justification supports that 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/m² every 3 months (total cumulative lifetime dose of 140 mg/m²).

Approval duration:
   Medicaid/HIM – 6 months
   Commercial – 6 months or to the member’s renewal date, whichever is longer

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

1. Currently receiving medication via Centene benefit or documentation supports that member is currently receiving Novantrone 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/m² every 21 days;
   b. ANLL: New dose does not exceed 12 mg/m² 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/m².

Approval duration:
   Medicaid/HIM – 12 months
   Commercial – 6 months or to the member’s renewal date, whichever is longer
C. Other diagnoses/indications (must meet 1 or 2):
   1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
      
      Approval duration: Duration of request or 6 months (whichever is less); or
   2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 – CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid 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  
   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.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/ Maximum Dose</th>
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</thead>
<tbody>
<tr>
<td>Aubagio® (teriflunomide)</td>
<td>7 mg or 14 mg PO QD</td>
<td>14 mg/day</td>
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<tr>
<td>Avonex®, Rebif® (interferon beta-1a)</td>
<td>Avonex: 30 mcg IM Q week</td>
<td>Avonex: 30 mcg/week</td>
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<tr>
<td></td>
<td>Rebif: 22 mcg or 44 mcg SC TIW</td>
<td>Rebif: 44 mcg TIW</td>
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<tr>
<td>Plegridy® (peginterferon beta-1a)</td>
<td>125 mcg SC Q2 weeks</td>
<td>125 mcg/2 weeks</td>
</tr>
<tr>
<td>Betaseron® (interferon beta-1b)</td>
<td>250 mcg SC QOD</td>
<td>250 mg QOD</td>
</tr>
<tr>
<td>glatiramer acetate (Copaxone®, Glatopa®)</td>
<td>20 mg SC QD or 40 mg SC TIW</td>
<td>20 mg/day or 40 mg TIW</td>
</tr>
<tr>
<td>Gilenya® (fingolimod)</td>
<td>0.5 mg PO QD</td>
<td>0.5 mg/day</td>
</tr>
<tr>
<td>Tecfidera® (dimethyl fumarate)</td>
<td>120 mg PO BID for 7 days, followed by 240 mg PO BID</td>
<td>480 mg/day</td>
</tr>
<tr>
<td>Mayzent® (siponimod)</td>
<td>All patients: Day 1 and 2: 0.25 mg PO QD</td>
<td>Day 3: 0.5 mg PO QD</td>
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<td></td>
<td>Day 4: 0.75 mg PO QD</td>
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**V. Dosage and Administration**

<table>
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<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
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<tr>
<td>Relapsing MS</td>
<td>12 mg/m² given as a short (approximately 5 to 15 minutes) intravenous infusion every 3 months</td>
<td>Cumulative lifetime dose of ≥ 140 mg/m²</td>
</tr>
<tr>
<td>Hormone-refractory prostate cancer</td>
<td>12 to 14 mg/m² given as a short intravenous infusion every 21 days</td>
<td>Cumulative lifetime dose of ≥ 140 mg/m²</td>
</tr>
<tr>
<td>ANLL</td>
<td>Induction: 12 mg/m² 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</td>
<td>Cumulative lifetime dose of ≥ 140 mg/m²</td>
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Mitoxantrone

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<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
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<tr>
<td>Consolidaion: 12 mg/m² given by intravenous infusion daily on Days 1 and 2</td>
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VI. Product Availability
Multidose vial: 20 mg/10 mL, 25 mg/12.5 mL, 30 mg/15 mL

VII. References

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.

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
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<tr>
<td>J9293</td>
<td>Injection, mitoxantrone HCl, per 5 mg</td>
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Reviews, Revisions, and Approvals

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<th>Date</th>
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- Policy split from CP.PHAR.18 MS Treatments. Criteria: clarified monotherapy restriction, added criteria for re-authorization. Requirement for the trial and failure of at least 2 preferred regimens from different classes added. Removed specific strength requirement from glatiramer.
- Added age requirement. Removed MRI requirement. Updated preferencing to require at least one of the highly effective DMTs on formulary (Tecfidera or Gilenya). Removed hepatic impairment and hypersensitivity contraindications. Removed reasons to discontinue.
CLINICAL POLICY
Mitoxantrone

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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.

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.

Updated RRMS re-directions per SDC and prior clinical guidance; added COM and HIM lines of business (CP.CPA.334 and HIM.PA.SP53 retired).

2Q 2020 annual review: ALL: added off-label criteria for pediatric ALL per NCCN; references reviewed and updated.

MS: added requirements for documentation of baseline relapses/EDSS and objective measures of positive response upon re-authorization; references reviewed and updated.

MS: Per November and December SDC and prior clinical guidance, removed redirection to Mayzent; for RRMS modified redirection to require generic dimethyl fumarate, Aubagio, Gilenya, and either an interferon-beta agent or glatiramer.

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. The Health Plan 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. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

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This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

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Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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