Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Trabectedin (Yondelis®)	MP-RX-FP-148-24	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drugs

Service Description

This document addresses the use of *Trabectedin (Yondelis®),* an alkylating drug approved by the Food and Drug Administration (FDA) for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen.

Background Information

Trabectedin is a marine-derived tetrahydroisoquinoline alkaloid. It functions by binding to the minor groove of DNA and causing alkylation of guanine at the N2 position, which induces a bend towards the major groove. This interaction is thought to impact various transcription factors crucial for cell proliferation, particularly through its effects on the transcription-coupled nucleotide excision repair system. Trabectedin halts the cell cycle at the G(2) phase, with cells in the G(1) phase being particularly sensitive to its effects. Additionally, it inhibits the over-expression of the multi-drug resistance-1 (MDR-1) gene, which codes for P-glycoprotein—a significant factor in the development of drug resistance in cancer cells.

Uterine Sarcoma

NCCN recommends trabectedin in patients with advanced, metastatic/recurrent or inoperable uterine sarcoma in combination with doxorubicin as first-line therapy, or as single-therapy as second line or subsequent line treatment (NCCN 2A). Recommendation as first-line agent is based on the LMS-04 phase 3 randomized trial that involved 150 patients with uterine and soft-tissue leiomyosarcoma (uLMS and soft-tissue LMS). In the trial the benefits of doxorubicin/trabectedin combination therapy versus doxorubicin alone as first-line treatment were assessed. Results showed that median progression-free survival (PFS) was significantly longer in the combination therapy arm compared to the doxorubicin alone arm (12.2 months vs. 6.2 months, respectively; HR, 0.41; 95% CI, 0.29–0.58; P < .0001). Based on these findings, the panel recommends the use of doxorubicin/trabectedin for patients with leiomyosarcoma.

Trabectedin is recommended as a preferred option for second-line or subsequent therapy in patients with unresectable or metastatic uterine leiomyosarcoma (uLMS) who have previously received an anthracycline-containing regimen. Clinical data suggest that trabectedin may be beneficial for patients who have exhausted standard chemotherapy options. Phase III trial results demonstrated a 2.7-month progression-free survival (PFS) benefit of trabectedin compared to dacarbazine in patients with metastatic liposarcoma or leiomyosarcoma that progressed after anthracycline-based therapy. Subgroup analysis focusing on patients with uLMS revealed a PFS of 4.0 months for trabectedin versus 1.5 months for dacarbazine, with a hazard ratio (HR) of 0.57 and a significant

difference in favor of trabectedin. However, overall survival (OS) did not significantly differ between the treatment arms.

Soft Tissue Sarcoma

Trabectedin has demonstrated objective responses in phase II and III trials among patients with advanced soft tissue sarcomas (STS). Recent phase III data from a randomized trial showed a significant 2.7-month progression-free survival (PFS) benefit compared to dacarbazine in metastatic liposarcoma (LPS) or leiomyosarcoma (LMS) that progressed after anthracycline-based therapy. Trabectedin has also shown efficacy in translocation-related sarcoma. However, a phase III trial comparing trabectedin with doxorubicin-based chemotherapy did not find superiority for either arm in terms of PFS and overall survival (OS), potentially due to underpowering. Preliminary results from the T-SAR trial indicated a PFS benefit for trabectedin over best supportive care in both L-type (LPS and LMS) and non-L-type pretreated advanced sarcoma. Trabectedin is recommended for palliative therapy, with category 1 recommendation for Liposarcoma (LPS) and Leiomyosarcoma (LMS) (L-type) and category 2A for non-L-type sarcomas.

Approved Indications

A. Treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen.

Other Uses

i. None

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Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J9352	Injection, trabectedin, 0.1 mg

ICD-10	Description
C47.0	Malignant neoplasm of peripheral nerves of head, face and neck
C47.10-C47.12	Malignant neoplasm of peripheral nerves of upper limb
C47.20-C47.22	Malignant neoplasm of peripheral nerves of lower limb
C47.3	Malignant neoplasm of peripheral nerves of thorax
C47.4	Malignant neoplasm of peripheral nerves of abdomen
C47.5	Malignant neoplasm of peripheral nerves of pelvis
C47.6	Malignant neoplasm of peripheral nerves of trunk, unspecified
C47.8	Malignant neoplasm of overlapping sites of peripheral nerves and autonomic nervous system
C47.9	Malignant neoplasm of peripheral nerves and autonomic nervous system, unspecified
C48.0-C48.2	Malignant neoplasm of retroperitoneum
C48.8	Malignant neoplasm of overlapping sites of retroperitoneum and peritoneum
C49.0	Malignant neoplasm of connective and soft tissue of head, face and neck
C49.4-C49.6	Malignant neoplasm of connective and soft tissue of abdomen or pelvis
C49.8	Malignant neoplasm of overlapping sites of connective and soft tissue
C49.9	Malignant neoplasm of connective and soft tissue, unspecified
C49.10-C49.12	Malignant neoplasm of connective and soft tissue of upper limb, including shoulder
C49.20-C49.22	Malignant neoplasm of connective and soft tissue of lower limb, including hip
C49.3	Malignant neoplasm of connective and soft tissue of thorax
C49.4	Malignant neoplasm of connective and soft tissue of abdomen
C49.5	Malignant neoplasm of connective and soft tissue of pelvis
C49.6	Malignant neoplasm of connective and soft tissue of trunk, unspecified
C49.8	Malignant neoplasm of overlapping sites of connective and soft tissue
C49.9	Malignant neoplasm of connective and soft tissue, unspecified
D48.1	Neoplasm of uncertain behavior of connective and other soft tissue
C54.0-C54.3	Malignant neoplasm of isthmus uteri, Malignant neoplasm of endometrium, Malignant neoplasm of myometriumMalignant neoplasm of fundus uteri
C54.8	Malignant neoplasm of overlapping sites of corpus uteri
C54.9	Malignant neoplasm of corpus uteri, unspecified

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C55	Malignant neoplasm of uterus, part unspecified
Z85.42	Personal history of malignant neoplasm of other parts of uterus
Z85.831	Personal history of malignant neoplasm of soft tissue

Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Trabectedin (Yondelis®)

A. Criteria For Initial Approval (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

i. Patient has a diagnosis of advanced, recurrent or metastatic Uterine Sarcoma; **AND**
   - A. Patient is using as first-line therapy (NCCN 2A); **AND**
   - B. Yondelis is being used with doxorubicin.

   OR
   - C. Patient is using as second-line or subsequent therapy after an anthracycline-containing regimen (NCCN 2A); **AND**
   - D. Yondelis is being used as single agent.

ii. Patient has a diagnosis of Soft Tissue Sarcoma (STS); **AND**
   - A. Patient has myxoid liposarcoma subtype; **AND**
     1. Patient is using as neoadjuvant (before surgery) and/or adjuvant (after surgery) (NCCN 2A); **AND**
     2. Yondelis is being used as single agent.

   OR
   - B. Patient has advanced or metastatic (STS) disease (including STS subtypes, such as rhabdomyosarcoma, solitary fibrous tumor, leiomyosarcoma, etc); **AND**
     1. Yondelis is being used as second-line or subsequent lines of therapy (NCCN 1 for liposarcoma and leiomyosarcoma; NCCN 2A for all other STS subtypes); **AND**
     2. Yondelis is being used as a single agent;

     OR
     3. Patient has advanced or metastatic leiomyosarcoma (LMS) subtype; **AND**
        - a. Yondelis is being used as first-line agent in combination with doxorubicin (NCCN 2A); **AND**
        - b. Yondelis is being used as second-line therapy either as:

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i. Single agent (NCCN 1); **OR**
ii. In combination with doxorubicin (NCCN 2A)

OR

C. Patient has Solitary Fibrous tumor (NCCN 2A); **AND**
   1. Yondelis is being used as a single agent.

B. Criteria For Continuation of Therapy

i. MMM considers continuation of Trabectedin (Yondelis®) therapy medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval) when there is no evidence of unacceptable toxicity or disease progression while on the current regimen, or the maximum duration of therapy has not been exceeded. The following information should be submitted for reauthorization:
   A. A current oncology note documenting the patient's response to treatment showing no progression of disease.
   B. Current imaging studies and other objective measures, as appropriate, showing no progression of disease when compared with previous results.

C. Authorization Duration

i. Initial Approval Duration: Up to 6 months
ii. Reauthorization Approval Duration: Up to 6 months

D. Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

i. Trabectedin (Yondelis®) may not be approved when the above criteria (Section A: Criteria for Initial Approval) are not met and for all other indications.

Limits or Restrictions

A. Therapeutic Alternatives

The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.

i. N/A

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B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Drug	Recommended Dosing Schedule
Trabectedin (Yondelis®) 1 mg SDV	• 1.5 mg/m^2 BSA IV every 3 weeks (21 days) through a central venous line (24-hours infusion) until disease progression or unacceptable toxicity. - Premedication: dexamethasone 20 mg intravenously, 30 min before each infusion.
Additional Information	
• *Hepatic Impairment*: Administer at 0.9 mg/m2 body surface area as a 24-hour intravenous infusion, every 3 weeks through a central venous line in patients with moderate hepatic impairment. - Do not administer Yondelis to patients with severe hepatic impairment (bilirubin levels above 3 times the upper limit of normal, and any AST and ALT). • *Warnings and precautions:* - Neutropenic sepsis: Severe, and fatal, neutropenic sepsis may occur. Neutrophil count should be monitored during treatment. Withhold YONDELIS for neutrophil count < 1,500/mcL. - Rhabdomyolysis: Rhabdomyolysis may occur. Monitor creatine phosphokinase (CPK) levels prior to each administration. Withhold YONDELIS for CPK more than 2.5 times the upper limit of normal. - Cardiomyopathy: Severe and fatal cardiomyopathy can occur. Discontinue YONDELIS in patients who develop decreased LVEF or cardiomyopathy. - Capillary leak syndrome: Monitor and discontinue YONDELIS for capillary leak syndrome.	

Reference Information

1. Demetri GD, von Mehren M, Jones RL, et al. Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy: Results of a Phase III Randomized Multicenter Clinical Trial. J Clin Oncol 2016;34:786-793
2. Hensley ML, Patel SR, von Mehren M, et al. Efficacy and safety of trabectedin or dacarbazine in patients with advanced uterine leiomyosarcoma after failure of anthracycline-based chemotherapy: Subgroup analysis of a phase 3, randomized clinical trial. Gynecol Oncol 2017;146:531-537
3. NCCN Guidelines Version 1.2024 Uterine Neoplasms- Accessed January 25, 2024.
4. NCCN Guidelines Version 3.2023 Soft Tissue Sarcoma - Accessed January 25, 2024.
5. National Comprehensive Cancer Network (NCCN). Trabectedin. NCCN Drugs and Biologics Compendium. Plymouth Meeting, PA: NCCN; January 2024.

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6. Pautier P, Italiano A, Piperno-Neumann S, et al. Doxorubicin alone versus doxorubicin with trabectedin followed by trabectedin alone as first-line therapy for 2 metastatic or unresectable leiomyosarcoma (LMS 04): a randomized, multicenter, open-label phase 3 trial. Lancet Oncol 2022;23:1044-1054.

Policy History

Revision Type	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Annual Review 12/19/2024	Updated dosage table: added dosage form and strength, added warnings and precautions per FDA label and duration of therapy until disease progression or unacceptable toxicity. Minor wording and formatting changes. Coding Reviewed: no changes.	3/20/2025	4/2/2025
Policy Inception 01/25/2024	New Medical Policy creation	4/18/2024	6/28/2024