Medical Policy

Utilization Management and Clinical Medical Policy

Policy Name:	Policy Number:	Scope:	Origination Date:	Effective Date:
trabectedin (Yondelis®, Evdi®)	**MP-RX-FP-148-24**	☒ **MMM MA** ☒ **MMM MultiHealth**	**6/28/2024** **Last Review Date:** **10/21/2026**	**10/21/2026** **Frequently Revision:** **Annual**

Service Category:

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

Service Description:

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

Background Information:

Trabectedin is a marine-derived tetrahydroisoquinoline alkaloid classified as an alkylating drug. It binds guanine residues in the minor groove of DNA, forming adducts that bend the DNA helix toward the major groove. This adduct formation affects DNA-binding proteins, including certain transcription factors, and DNA-repair pathways, resulting in perturbation of the cell cycle and eventual cell death.

Trabectedin is marketed as Yondelis® and EVDI®. Both products are FDA-approved for the treatment of adults with unresectable or metastatic liposarcoma or leiomyosarcoma who previously received an anthracycline-containing regimen. Yondelis is supplied as a 1-mg lyophilized powder in a single-dose vial, whereas EVDI is supplied as a 1-mg/20-mL (0.05-mg/mL) solution in a single-dose vial.

Bone Cancer

The NCCN recommends trabectedin (EVDI or Yondelis) in combination with irinotecan as second-line therapy for Ewing sarcoma or mesenchymal chondrosarcoma, with trabectedin identified as a preferred option for mesenchymal chondrosarcoma. The regimen may be used, with or without radiation therapy, for relapsed disease, progressive disease following primary treatment, or metastatic disease. Other primary round cell tumors of bone, such as CIC::DUX4- or BCOR::CCNB3-rearranged tumors, may be treated according to recommendations for Ewing sarcoma. These uses carry an NCCN Category 2A recommendation for Ewing sarcoma and other primary round cell tumors and a Category 2B recommendation for mesenchymal chondrosarcoma.

Uterine Sarcoma

The NCCN Drugs and Biologics Compendium specifically recommends Yondelis in combination with doxorubicin as a preferred Category 2A regimen for first-line treatment of advanced, recurrent/metastatic, or inoperable uterine leiomyosarcoma (uLMS). The combination may also be used as second-line or subsequent therapy when not previously administered. Yondelis as a single agent is a preferred Category 2A option for second-line or subsequent treatment of uLMS when not previously used.

Recommendation as a preferred first-line combination regimen 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,

Policy Name: trabectedin (Yondelis®, Evdi®)	Policy Number: MP-RX-FP-148-24	Scope: ☒ MMM MA ☒ MMM MultiHealth	Origination Date: 6/28/2024	Effective Date: 10/21/2026
			Last Review Date: 10/21/2026	Frequently Revision: Annual

0.29–0.58; P < .0001). Based on these findings, the panel recommends the use of doxorubicin/trabectedin for patients with leiomyosarcoma.

Evidence supporting later-line single-agent trabectedin includes a phase III trial in patients with metastatic liposarcoma or leiomyosarcoma that progressed after anthracycline-based therapy. The trial demonstrated a 2.7-month PFS benefit with trabectedin compared with dacarbazine. A subgroup analysis of patients with uLMS showed a median PFS of 4.0 months with trabectedin versus 1.5 months with dacarbazine (HR, 0.57), with a significant difference favoring trabectedin. However, overall survival did not differ significantly between treatment arms.

Soft Tissue Sarcoma

Trabectedin has demonstrated objective responses in phase II and III trials among patients with advanced soft tissue sarcomas (STS). Phase III data demonstrated a 2.7-month PFS benefit compared with dacarbazine in patients with metastatic liposarcoma or leiomyosarcoma whose disease progressed after anthracycline-based therapy. Trabectedin has also shown efficacy in translocation-related sarcomas. A phase III trial comparing trabectedin with doxorubicin-based chemotherapy did not demonstrate superiority for either treatment in PFS or overall survival, potentially because the trial was underpowered.

The current NCCN compendial recommendations provided specifically identify Yondelis for additional soft tissue sarcoma uses. These include single-agent therapy, useful in certain circumstances, for myxoid liposarcoma in selected neoadjuvant, adjuvant, primary-treatment, or recurrent-disease settings; preferred first-line or subsequent-line therapy in combination with doxorubicin for leiomyosarcoma, depending on the clinical setting; and preferred single-agent palliative therapy in subsequent lines for advanced or metastatic disease. Additional Category 2A uses include selected treatment settings for pleomorphic rhabdomyosarcoma, solitary fibrous tumor, dedifferentiated liposarcoma, and epithelioid hemangioendothelioma. NCCN assigns a Category 1 recommendation to preferred single-agent palliative subsequent-line therapy for liposarcoma and leiomyosarcoma and Category 2A recommendations to the other listed soft tissue sarcoma uses.

Approved Indications

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

Other Uses

A. See Background Information section above.

Policy Name:	Policy Number:	Scope:	Origination Date:	Effective Date:
trabectedin (Yondelis®, Evdi®)	**MP-RX-FP-148-24**	☒ **MMM MA** ☒ **MMM MultiHealth**	**6/28/2024** **Last Review Date:** **10/21/2026**	**10/21/2026** **Frequently Revision:** **Annual**

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®, Evdi®)

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.)*

Requests for trabectedin **(Yondelis, Evdi)** may be approved if *one* the following criteria is met:

i. Patient has unresectable or metastatic liposarcoma or leiomyosarcoma (Label); **AND**
ii. Patient is 18 years of age or older; **AND**
iii. Patient has received a prior anthracycline-containing regimen; **AND**
iv. The requested product, Yondelis or Evdi, is being used as a single agent;

OR

v. Patient has a diagnosis of bone cancer (NCCN 2A); **AND**
vi. Patient has Ewing sarcoma, mesenchymal chondrosarcoma or other primary round cell tumor of bone, such as a CIC::DUX4- or BCOR::CCNB3-rearranged tumor; **AND**
vii. The requested product is being used as second-line therapy in combination with irinotecan for one of the following:
    A. Relapsed disease, with or without radiation therapy; **OR**
    B. Progressive disease following primary treatment; **OR**
    C. Metastatic disease.

Requests for trabectedin **(Yondelis)** may be approved if *one* the following criteria is met:

i. Patient has a diagnosis of advanced, recurrent, metastatic, or inoperable uterine leiomyosarcoma (uLMS) (NCCN 2A); **AND**
    A. Patient is using Yondelis as first-line therapy; **AND**
    B. Yondelis is being used in combination with doxorubicin;
    OR
    C. Patient is using Yondelis as second-line or subsequent therapy if trabectedin was not previously used.

OR

ii. Patient has a diagnosis of Soft Tissue Sarcoma (STS) (NCCN 2A); **AND**

Policy Name: trabectedin (Yondelis®, Evdi®)	Policy Number: MP-RX-FP-148-24	Scope: ☒ MMM MA ☒ MMM MultiHealth	Origination Date: 6/28/2024	Effective Date: 10/21/2026
			Last Review Date: 10/21/2026	Frequently Revision: Annual

A. Patient has myxoid liposarcoma subtype; **AND**
B. Patient is using Yondelis as one of the following:
    1. Neoadjuvant systemic therapy, with or without radiation therapy; **OR**
    2. Adjuvant systemic therapy, with or without radiation therapy; **OR**
    3. Primary systemic therapy for disease that is unresectable or for which resection would result in unacceptable functional outcomes; **OR**
    4. Part of primary tumor management for synchronous stage IV oligometastatic disease with limited tumor burden amenable to local therapy; **AND**
C. Yondelis is being used as a single agent;

OR

D. Patient has unresectable or progressive STS following initial therapy for unresectable localized disease or advanced/metastatic STS with disseminated metastases; **AND**
E. Yondelis is being used as single-agent palliative therapy in the second-line or subsequent-line setting (NCCN 1 for liposarcoma and leiomyosarcoma; NCCN 2A for other STS subtypes);

OR

F. Patient has unresectable, progressive, advanced, or metastatic leiomyosarcoma (LMS) subtype; **AND**
G. Yondelis is being used in combination with doxorubicin in one of the following settings (NCCN 2A):
    1. As preferred first-line therapy for advanced or metastatic disease; **OR**
    2. As alternative systemic therapy for unresectable or progressive disease following initial treatment for unresectable localized disease; **OR**
    3. As subsequent-line palliative therapy for advanced or metastatic disease with disseminated metastases.

Note: When Yondelis is administered with doxorubicin in a subsequent line of therapy, the patient's lifetime cumulative exposure to doxorubicin should be considered.

OR

H. Patient has one of the following STS subtypes or clinical presentations (NCCN 2A):
    1. Advanced or metastatic pleomorphic rhabdomyosarcoma requiring subsequent-line palliative therapy; **OR**
    2. Solitary fibrous tumor requiring palliative therapy; **OR**
    3. Dedifferentiated liposarcoma, with or without concurrent well-differentiated liposarcoma; **OR**
    4. Epithelioid hemangioendothelioma; **AND**

Policy Name: trabectedin (Yondelis®, Evdi®)	Policy Number: MP-RX-FP-148-24	Scope: ☒ MMM MA ☒ MMM MultiHealth	Origination Date: 6/28/2024	Effective Date: 10/21/2026
			Last Review Date: 10/21/2026	Frequently Revision: Annual

I. Yondelis is being used as a single agent.

B. Criteria For Continuation of Therapy

i. MMM considers continuation of Trabectedin (Yondelis®, Evdi®) 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. Trabectedin may be continued until disease progression or unacceptable toxicity. 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. Current clinical and laboratory documentation confirms appropriate safety monitoring, including blood cell counts, liver function, CPK, and LVEF assessments, with no evidence of unacceptable toxicity requiring permanent discontinuation; any abnormal findings are being managed with treatment interruption or dose modification according to the Prescribing Information.

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

Policy Name: trabectedin (Yondelis®, Evdi®)	Policy Number: MP-RX-FP-148-24	Scope: ☒ MMM MA ☒ MMM MultiHealth	Origination Date: 6/28/2024	Effective Date: 10/21/2026
			Last Review Date: 10/21/2026	Frequently Revision: Annual

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

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 **trabectedin (Evdi®)** 1 mg/20 mL 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. o Premedication: dexamethasone 20 mg intravenously, 30 min before each infusion.
Exceptions	
• 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 (bilirubin levels greater than 1.5 times to 3 times the upper limit of normal, and AST and ALT less than 8 times the upper limit of normal). o 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: o Neutropenic sepsis: Severe, and fatal, neutropenic sepsis may occur. Neutrophil count should be monitored during treatment. Withhold YONDELIS for neutrophil count < 1,500/mcL. o 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. o Cardiomyopathy: Severe and fatal cardiomyopathy can occur. Discontinue YONDELIS in patients who develop decreased LVEF or cardiomyopathy. o Capillary leak syndrome: Monitor and discontinue YONDELIS for capillary leak syndrome.	

Policy Name: trabectedin (Yondelis®, Evdi®)	Policy Number: MP-RX-FP-148-24	Scope: ☒ MMM MA ☒ MMM MultiHealth	Origination Date: 6/28/2024	Effective Date: 10/21/2026
			Last Review Date: 10/21/2026	Frequently Revision: Annual

Codes Information:

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.

ICD-10 Diagnostic Codes:

ICD-10	Description
C40.00-40.02	Malignant neoplasm of scapula and long bones of upper limb (unspecified, right, or left)
C40.10-C40.12	Malignant neoplasm of short bones of upper limb (unspecified, right, or left)
C40.20-C40.22	Malignant neoplasm of long bones of lower limb (unspecified, right, or left)
C40.30-C40.32	Malignant neoplasm of short bones of lower limb (unspecified, right, or left)
C40.80-C40.82	Malignant neoplasm of overlapping sites of bone and articular cartilage of limb (unspecified, right, or left)
C40.90-C40.92	Malignant neoplasm of unspecified bones and articular cartilage of limb (unspecified, right, or left)
C41.0-C41.4	Malignant neoplasm of bones of skull and face, mandible, vertebral column, ribs, sternum, clavicle, pelvic bones, sacrum, or coccyx
C41.9	Malignant neoplasm of bone and articular cartilage, unspecified
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 myometrium, Malignant neoplasm of fundus uteri

Policy Name:	Policy Number:	Scope:	Origination Date:	Effective Date:
trabectedin (Yondelis®, Evdi®)	MP-RX-FP-148-24	☒ MMM MA ☒ MMM MultiHealth	6/28/2024	10/21/2026
			Last Review Date: 10/21/2026	Frequently Revision: Annual

C54.8	Malignant neoplasm of overlapping sites of corpus uteri
C54.9	Malignant neoplasm of corpus uteri, unspecified
C55	Malignant neoplasm of uterus, part unspecified
Z85.42	Personal history of malignant neoplasm of other parts of uterus
Z85.830	Personal history of malignant neoplasm of bone
Z85.831	Personal history of malignant neoplasm of soft tissue

HCPCS Codes:

Codes	Description
J9352	Injection, trabectedin, 0.1 mg

Policy Name: trabectedin (Yondelis®, Evdi®)	Policy Number: MP-RX-FP-148-24	Scope: ☒ MMM MA ☒ MMM MultiHealth	Origination Date: 6/28/2024	Effective Date: 10/21/2026
			Last Review Date: 10/21/2026	Frequently Revision: Annual

Reference Information:

1. Apotex Corp. EVDI (trabectedin) injection, for intravenous use: Prescribing information. Revised May 2026. Accessed September 2, 2026.
2. 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
3. Drugs.com. EVDI injection: Package insert/prescribing information. https://www.drugs.com/pro/evdi-injection.html. Updated July 6, 2026. Accessed September 2, 2026.
4. 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
5. Janssen Products, LP. Yondelis® (trabectedin) for injection, for intravenous use: Prescribing information. Revised January 2026. Accessed September 2, 2026.
6. NCCN Clinical Practice Guidelines in Oncology™. © 2026 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed September 2, 2026.
    a. Bone Cancer – Version 1.2027. Revised: July 21, 2026
    b. Soft Tissue Sarcoma - Version 3.2026
    c. Uterine Neoplasms - Version 5.2026. Revised July 23, 2026
7. 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.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

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Policy Name:	Policy Number:	Scope:	Origination Date:	Effective Date:
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			Last Review Date: 10/21/2026	Frequently Revision: Annual

Policy History:

Type of Review	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Annual Review	Updated the Background Information and clinical criteria to add EVDI and align with current Prescribing Information and NCCN Category 1 and 2A recommendations. Separated shared and Yondelis-only criteria, updated continuation requirements and quantity limits table. Coding reviewed: Added ICD-10-CM codes C40.00–C40.02, C40.10–C40.12, C40.20–C40.22, C40.30–C40.32, C40.80–C40.82, C40.90–C40.92, C41.0–C41.4, C41.9, and Z85.830. Updated reference information and incorporated new policy template.	10/15/2026	10/21/2026
Annual Review	Clarified Uterine sarcoma criteria: Patient is using as second-line or subsequent therapy for advanced, recurrent/metastatic, or inoperable disease (NCCN 2A). Minimal changes; Coding reviewed: No changes.	12/3/2025	12/11/2025
Annual Review	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	New Medical Policy creation	4/18/2024	6/28/2024