Yondelis® (trabectedin)
(Intravenous)

-E-

Document Number: MODA-0402

Last Review Date: 04/06/2021
Date of Origin: 10/30/2018
Dates Reviewed: 10/2018, 01/2019, 04/2019, 07/2019, 10/2019, 01/2020, 04/2020, 07/2020, 10/2020, 01/2021, 04/2021

I. Length of Authorization

Coverage will be provided for six months and may be renewed.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- 1 mg vial for injection: 4 vials every 21 days

B. Max Units (per dose and over time) [HCPCS Unit]:

- **STS/uLMS**
  - 40 billable units every 21 days

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

- Patient is at least 18 years of age; **AND**

Universal Criteria [1]

- Left ventricular ejection fraction (LVEF) is within normal limits prior to initiating therapy and will be assessed at regular intervals (e.g., every 3 months) during treatment; **AND**
- Used as single agent therapy; **AND**

Soft Tissue Sarcoma (STS) ‡ Φ [1-4,1e,3e,6e,8e,9e,21e,23e,24e]

- Patient has unresectable or metastatic liposarcoma or leiomyosarcoma †; **AND**
  - Used as subsequent therapy after an anthracycline-containing regimen (e.g., doxorubicin, etc.); **OR**
- Used as palliative therapy; **AND**

- Patient has a diagnosis of one of the following sub-types of soft tissue sarcoma:
  - Retroperitoneal/Intra-abdominal; **AND**
    - Used as subsequent therapy for recurrent unresectable or stage IV disease; **OR**
  - Extremity/Body Wall, Head/Neck; **AND**
    - Used as subsequent therapy for advanced or metastatic disease with disseminated metastases

Uterine Sarcoma ‡ [2,5]

- Patient has uterine leiomyosarcoma; **AND**
- Used as subsequent therapy after an anthracycline-containing regimen (e.g., doxorubicin, etc.); **AND**
  - Patient has unresectable, metastatic or recurrent disease; **OR**
  - Patient has disease that is not suitable for primary surgery

Preferred therapies and recommendations are determined by review of clinical evidence. NCCN category of recommendation is taken into account as a component of this review. Regimens deemed equally efficacious (i.e., those having the same NCCN categorization) are considered to be therapeutically equivalent.

† FDA approved indication(s); ‡ Compendia recommended indication(s); Φ Orphan Drug

IV. Renewal Criteria [1]

Authorizations can be renewed based on the following criteria:

- Patient continues to meet universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: cardiomyopathy, rhabdomyolysis, hepatotoxicity and/or severe hepatic impairment, capillary leak syndrome (CPS), severe neutropenia/neutropenic sepsis, extravasation resulting in tissue necrosis, etc.; **AND**
- Left ventricular ejection fraction (LVEF) has not had an absolute decrease of ≥ 15% from baseline OR is not below the lower limit of normal (LLN) with an absolute decrease of ≥ 5% (LVEF results must be within the previous 3 months)

V. Dosage/Administration [1]

Indication	Dose
Soft Tissue Sarcoma/Uterine Sarcoma	1.5 mg/m² administered intravenously (IV) every 21 days, until disease progression or unacceptable toxicity

VI. Billing Code/Availability Information

HCPCS Code:

- J9352 - Injection, trabectedin, 0.1 mg: 1 billable unit = 0.1 mg

NDC:

- Yondelis 1 mg vial for injection: 59676-0610-xx

VII. References (STANDARD)

1. Yondelis [package insert]. Horsham, PA; Janssen Products, LP; June 2020. Accessed February 2021.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) trabectedin. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed February 2021.
3. 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(8):786-793.
4. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Soft Tissue Sarcoma Version 1.2021. National Comprehensive Cancer Network, 2021. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. Accessed February 2021.
5. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Uterine Neoplasms Version 1.2021. National Comprehensive Cancer Network, 2021. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. Accessed February 2021.

6. Palmetto GBA. Local Coverage Article (LCA): Billing and Coding: Chemotherapy (A56141). Centers for Medicare & Medicaid Services, Inc. Updated on 11/12/2020 with effective date 11/19/2020. Accessed February 2021.

VIII. References (ENHANCED)

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Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C47.0	Malignant neoplasm of peripheral nerves of head, face and neck
C47.10	Malignant neoplasm of peripheral nerves of unspecified upper limb, including shoulder
C47.11	Malignant neoplasm of peripheral nerves of right upper limb, including shoulder
C47.12	Malignant neoplasm of peripheral nerves of left upper limb, including shoulder
C47.20	Malignant neoplasm of peripheral nerves of unspecified lower limb, including hip
C47.21	Malignant neoplasm of peripheral nerves of right lower limb, including hip
C47.22	Malignant neoplasm of peripheral nerves of left lower limb, including hip
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	Malignant neoplasm of retroperitoneum
C48.1	Malignant neoplasm of specified parts of peritoneum
C48.2	Malignant neoplasm of peritoneum, unspecified
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
C49.10	Malignant neoplasm of connective and soft tissue of unspecified upper limb, including shoulder

ICD-10	ICD-10 Description
C49.11	Malignant neoplasm of connective and soft tissue of right upper limb, including shoulder
C49.12	Malignant neoplasm of connective and soft tissue of left upper limb, including shoulder
C49.20	Malignant neoplasm of connective and soft tissue of unspecified lower limb, including hip
C49.21	Malignant neoplasm of connective and soft tissue of right lower limb, including hip
C49.22	Malignant neoplasm of connective and soft tissue of left 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
C54.0	Malignant neoplasm of isthmus uteri
C54.1	Malignant neoplasm of endometrium
C54.2	Malignant neoplasm of myometrium
C54.3	Malignant neoplasm of fundus uteri
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

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA):

Jurisdiction(s): J&M	**NCD/LCD/LCA Document (s):** A56141
https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A56141&bc=gAAAAAAAAAAA	

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC

Appendix 3 – CLINICAL LITERATURE REVIEW

OS = overall survival; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; DoR = duration of response; TTP = time to progression; FFS = failure-free survival; EFS = event-free survival

Uterine Neoplasms:

Uterine Leiomyosarcoma – Unresectable, metastatic, or recurrent disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Gemcitabine+ docetaxel	2A	No	Phase 3 (GOG-0250), randomized, double-blind, placebo-controlled	Gemcitabine+ docetaxel+ bevacizumab	PFS	First-line	• Gemcitabine plus docetaxel demonstrated to be superior to combination therapy with bevacizumab with an improvement in PFS and OS.
Gemcitabine+ docetaxel	2A	No	Phase 2	N/A	-----	Second-line	• Gemcitabine plus docetaxel demonstrated to be clinically active in second-line therapy based on ORR, PFS, and duration of response.
Doxorubicin	2A preferred	No	Phase 3	Doxorubicin+ dacarbazine	-----	First-line	• Doxorubicin demonstrated an ORR of 16.3% and longer OS in patients with uterine LMS compared to doxorubicin plus dacarbazine.

Doxorubicin	2A preferred	No	Phase 3	Doxorubicin+ cyclophosphamide		First-line	• No significant benefit in PFS or ORR was observed for either doxorubicin or doxorubicin plus cyclophosphamide.
Trabectedin	2A	Yes	Post hoc subgroup analysis of phase 3, randomized	Dacarbazine	OS	Second-line or subsequent therapy	• In patients with uLMS who had received prior anthracycline therapy, trabectedin treatment resulted in significantly longer PFS versus dacarbazine, with an acceptable safety profile. There was no difference in OS.
Eribulin	2B	No	Phase 3, randomized open-label (also see PI clinical studies)	Dacarbazine	OS	Third-line	• Eribulin failed to improve OS and PFS versus dacarbazine in patients with previously treated leiomyosarcoma.

Soft Tissue Sarcoma (STS):

Leiomyosarcoma (LMS) – Unresectable, metastatic, or recurrent disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Gemcitabine+ docetaxel	2A	No	Phase 3 (GeDDiS), randomized, controlled	Doxorubicin	% of patients alive at 24 weeks	First-line therapy	• Gemcitabine plus docetaxel failed to show superiority over doxorubicin in first-line therapy. • No difference in the proportion of patients alive at 24 weeks, PFS,

							and no significant difference in OS was observed. • Also, no differential effect was evident in histological subtypes.
Gemcitabine	2A	No	Phase 2 (TAXOGEM)	Gemcitabine+ docetaxel	ORR	Second-line (after anthracycline-based regimen)	• Both single-agent gemcitabine and gemcitabine plus docetaxel were found to be effective second-line therapies for LMS (both uterine and nonuterine sites of origin).
Trabectedin	1	Yes	Phase 3 (T-SAR), randomized	Best supportive care (BSC)	PFS	Second-line therapy and beyond (including anthracycline)	• PFS benefit was demonstrated for trabectedin over BSC in both L-type and non-L-type pretreated advanced sarcoma. • Benefit seen most with L-type sarcomas.
Trabectedin (every 3 weeks over 24-hours)	1	Yes	Phase 2, randomized	Trabectedin weekly	TTP	Second- or third-line (after anthracycline and ifosfamide combined or sequential)	• Every 3 week dosing of trabectedin is superior to weekly dosing in liposarcoma and leiomyosarcoma.
Trabectedin	1	Yes	Phase 3, randomized open-label, active-controlled, parallel-group	Dacarbazine	OS	Third-line	• Trabectedin demonstrated an improved PFS compared to dacarbazine in patients with advanced liposarcoma and leiomyosarcoma after failure of prior chemotherapy. However, a difference in OS was not observed.

Eribulin	Not recommended	No	Phase 3, randomized open-label (also see PI clinical studies)	Dacarbazine	OS	Third-line	• Eribulin failed to improve OS and PFS versus dacarbazine in patients with previously treated leiomyosarcoma.
Liposarcoma – Unresectable, metastatic, or recurrent disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Trabectedin	1	Yes	Phase 3 (T-SAR), randomized	Best supportive care (BSC)	PFS	Second-line therapy and beyond (including anthracycline)	• PFS benefit was demonstrated for trabectedin over BSC in both L-type and non-L-type pretreated advanced sarcoma. • Benefit seen most with L-type sarcomas.
Trabectedin	1	Yes	Phase 3, randomized open-label, active-controlled, parallel-group	Dacarbazine	OS	Third-line	• Trabectedin demonstrated an improved PFS compared to dacarbazine in patients with advanced liposarcoma and leiomyosarcoma after failure of prior chemotherapy. However, a difference in OS was not observed.
Eribulin	1	Yes	Phase 2, non-randomized	N/A	PFS at 12 weeks	Second- or third-line (after one combination	• Eribulin demonstrated clinical activity based on PFS at 12 weeks in pretreated STS.

						regimen or up to 2 single agents)	
Eribulin	1	Yes	Subgroup analysis of a phase 3, randomized open-label	Dacarbazine	OS	Third-line	• Eribulin was associated with a significantly superior OS and PFS compared with dacarbazine in patients with previously treated liposarcoma.
Neoadjuvant or Adjuvant Therapy of Retroperitoneal/Intra-abdominal and Extremity/Superficial Trunk, Head/Neck							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Histotype-tailored chemotherapy Trabectedin (for high-grade myxoid liposarcoma)	2A	No	Phase 3, open-label, randomized, controlled, multi-center trial	Standard chemotherapy (epirubicin + ifosfamide)	DFS	Neoadjuvant therapy	• In patients with high-risk soft tissue sarcoma, neoadjuvant therapy with histotype-tailored chemotherapy did not show any benefit over the standard chemotherapy regimen.
Retroperitoneal/Intra-abdominal (unresectable or progressive disease) and Extremity/Superficial Trunk, Head/Neck (metastatic or recurrent disease) – Subsequent Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Trabectedin	2A preferred	No	Phase 2b (TRUSTS), randomized	Doxorubicin	PFS	First-line	• Trabectedin failed to show an improvement in PFS versus doxorubicin in first-line therapy of advanced or metastatic soft tissue sarcoma.

Trabectedin	2A preferred	No	Phase 2, randomized, open-label	Best supportive care	PFS	Second-line therapy and beyond	• PFS favored trabectedin in patients with translocation-related sarcomas.
Trabectedin	2A preferred	No	Phase 3 (T-SAR), randomized	Best supportive care (BSC)	PFS	Second-line therapy and beyond (including anthracycline)	• In the overall study population, a PFS benefit was demonstrated for trabectedin over best supportive care in patients with pretreated advanced sarcoma, however there was no statistical difference in OS. • In patients with non L-type sarcomas, trabectedin had similar PFS to those receiving best supportive care.
Trabectedin	2A preferred	No	Phase 2, non-randomized	N/A	-----	Second- or third-line therapy	• Clinical activity of trabectedin was demonstrated based on TTP, PFS, and OS.
Eribulin	2A preferred	No	Phase 2, open-label, multicenter, non-randomized	N/A	-----	Second-line therapy and beyond	• Eribulin showed efficacy based on progression-free rate, PFS and OS.
Pazopanib	2A preferred for non-adipocytic sarcoma	Yes	Phase 3 (PALETTE), randomized, double-blind, placebo-controlled	Placebo	PFS	Previously treated, angiogenesis inhibitor-naïve, non-adipocytic sarcoma	• Pazopanib demonstrated an improved PFS compared to placebo however there was no significant difference in OS.
Rhabdomyosarcoma (RMS)							

Regimen	NCCN Category	FDA Approved	Trial Design	Comparator	Primary End-Point	Line of Therapy	Conclusion
Vincristine, dactinomycin, cyclophosphamide (VAC)	2A	Yes	Phase 3, randomized	VAC/V topotecan/ cyclophosphamide (TC)	FFS	First-line	• VAC/VTC does not significantly improve FFS nor OS versus VAC.
Vincristine, dactinomycin, cyclophosphamide (VAC)	2A	Yes	Phase 3, randomized	VAC alternating with vincristine & irinotecan (VI)	EFS	First-line	• Addition of VI to VAC did not improve EFS or OS for patients with intermediate-risk RMS.
Trabectedin	2A	No	Phase 2, randomized, open-label	Best supportive care	PFS	Second-line therapy and beyond	• PFS favored trabectedin in patients with translocation-related sarcomas.
Trabectedin	2A	No	Phase 3, randomized	Doxorubicin-based regimen	PFS	First-line therapy	• PFS and OS showed non-significant difference between arms in patients with translocation-related sarcomas. • Study was underpowered due to the high rate of censoring. • Study inclusion criteria did not include any rhabdomyosarcoma subtypes.

Trabectedin	2A	No	Phase 2	N/A	-----	Second-line therapy and beyond	• Trabectedin did not demonstrate any significant evidence of activity in children with relapsed recurrent rhabdomyosarcoma, Ewing sarcoma and non-rhabdomyosarcoma soft tissue sarcomas.
Trabectedin	2A	No	Phase 3 (T-SAR), randomized	Best supportive care (BSC)	PFS	Second-line therapy and beyond (including anthracycline)	• PFS benefit was demonstrated for trabectedin over BSC in both L-type and non-L-type pretreated advanced sarcoma, however no statistical difference in OS. • Benefit seen most with L-type sarcomas.
Larotrectinib	2A (for NTRK gene fusion positive non-pleomorphic RMS)	Yes (for patients with solid tumors with a NTRK gene fusion)	Combined analysis of phase 1-2 studies	N/A	ORR	All lines of therapy	• Larotrectinib had an ORR of 7% and durable antitumor activity in patients with NTRK fusion-positive cancer.
Eribulin	2A (pleomor-phic)	No	No clinical literature to support use.				
Angiosarcoma							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

Paclitaxel	2A	No	Phase 2 (ANGIOTAX)	N/A	PFS	All lines of therapy	• Paclitaxel demonstrated a median OS of 8 months in patients with metastatic or unresectable angiosarcoma.
Bevacizumab	2A	No	Phase 2, open-label, single arm	N/A	PFS	All lines of therapy	• Bevacizumab is an effective and well-tolerated treatment for metastatic or locally advanced angiosarcoma and epithelioid hemangio-endothelioma. 17% had a partial response and 50% showed stable disease.
Trabectedin	2A	No	No clinical literature to support use.				
Eribulin	2A	No	No clinical literature to support use.				
Solitary Fibrous Tumors							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Trabectedin	2A other	No	Retrospective review	N/A	-----	All lines of therapy	• In a report with 24 patients, including 3 patients treated with trabectedin in subsequent therapy, there was one partial response, and 20 patients with stable disease.