Yondelis® (trabectedin)
(Intravenous)

-E-

Document Number: IC-0402

Last Review Date: 10/03/2022
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, 07/2021, 10/2021, 02/2022, 05/2022, 07/2022, 10/2022

I. Length of Authorization

Coverage will be provided for 6 months and may be renewed.

II. Dosing Limits

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

- Yondelis 1 mg single-dose 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, epirubicin, etc.); **AND**

Liposarcoma ONLY:

- In addition to an anthracycline-containing regimen, patient must also demonstrate an inadequate response to eribulin, unless there is a contraindication or intolerance, prior to approval of trabectedin; **OR**

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

Patients with non-adipocytic soft tissue sarcoma ONLY:

- Patient must demonstrate an inadequate response to pazopanib, unless there is a contraindication or intolerance, prior to approval of trabectedin

Uterine Sarcoma ‡ [2,5]

- Patient has uterine leiomyosarcoma (uLMS); **AND**
- Used as subsequent therapy after an anthracycline-containing regimen (e.g., doxorubicin, epirubicin, etc.); **AND**
  - Patient has metastatic, recurrent, or disseminated 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]

Coverage may be renewed based upon the following criteria:

- Patient continues to meet the 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 (CLS), 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 [1,6,7]

Indication	Dose
Soft Tissue Sarcoma/Uterine Sarcoma	Administer 1.5 mg/m² intravenously 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 single-dose vial for injection: 59676-0610-xx

VII. References (STANDARD)

1. Yondelis [package insert]. Horsham, PA; Janssen Products, LP; June 2020. Accessed August 2022.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) trabectedin. National Comprehensive Cancer Network, 2022. 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 August 2022.
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 2.2022. National Comprehensive Cancer Network, 2022. 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 August 2022.
5. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Uterine Neoplasms Version 1.2022. National Comprehensive Cancer Network, 2022. 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 August 2022.

6. Gronchi A, Ferrari S, Quagliuolo V, et al. Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial. Lancet Oncol. 2017 Jun;18(6):812-822. doi: 10.1016/S1470-2045(17)30334-0. Epub 2017 May 9.
7. 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 Sep;146(3):531-537. doi: 10.1016/j.ygyno.2017.06.018.

VIII. References (ENHANCED)

1e. Schöffski P, Chawla S, Maki RG, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. Lancet. 2016 Apr 16;387(10028):1629-37. doi: 10.1016/S0140-6736(15)01283-0. Epub 2016 Feb 10.

2e. Demetri GD, Schöffski P, Grignani G, et al. Activity of Eribulin in Patients With Advanced Liposarcoma Demonstrated in a Subgroup Analysis From a Randomized Phase III Study of Eribulin Versus Dacarbazine. J Clin Oncol. 2017 Oct 20;35(30):3433-3439. doi: 10.1200/JCO.2016.71.6605. Epub 2017 Aug 30.

3e. Bui-Nguyen B, Butrynski JE, Penel N, et al. A phase IIb multicentre study comparing the efficacy of trabectedin to doxorubicin in patients with advanced or metastatic untreated soft tissue sarcoma: the TRUSTS trial. Eur J Cancer. 2015 Jul;51(10):1312-20.

4e. Seddon B, Strauss SJ, Whelan J, et al. Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDiS): a randomised controlled phase 3 trial. Lancet Oncol. 2017 Oct;18(10):1397-1410.

5e. Le Cesne A, Blay J-Y, Cupissol D, Italiano A, Delcambre C, Penel N, et al. Results of a prospective randomized phase III T-SAR trial comparing trabectedin vs best supportive care (BSC) in patients with pretreated advanced soft tissue sarcoma (ASTS) Ann Oncol. 2016;27(suppl 6):1396O.

6e. Le Cesne A, Blay JY, Judson I, et al. Phase II study of ET-743 in advanced soft tissue sarcomas: a European Organisation for the Research and Treatment of Cancer (EORTC) soft tissue and bone sarcoma group trial. J Clin Oncol. 2005 Jan 20;23(3):576-84.

7e. Kawai A, Araki N, Sugiura H, et al. Trabectedin monotherapy after standard chemotherapy versus best supportive care in patients with advanced, translocation-related sarcoma: a randomised, open-label, phase 2 study. Lancet Oncol. 2015 Apr;16(4):406-16. doi: 10.1016/S1470-2045(15)70098-7. Epub 2015 Mar 18.

8e. Blay JY, Leahy MG, Nguyen BB, et al. Randomised phase III trial of trabectedin versus doxorubicin-based chemotherapy as first-line therapy in translocation-related sarcomas. Eur J Cancer. 2014 Apr;50(6):1137-47. doi: 10.1016/j.ejca.2014.01.012. Epub 2014 Feb 7.

9e. Baruchel S, Pappo A, Krailo M, et al. A phase 2 trial of trabectedin in children with recurrent rhabdomyosarcoma, Ewing sarcoma and non-rhabdomyosarcoma soft tissue sarcomas: a report from the Children's Oncology Group. Eur J Cancer. 2012 Mar;48(4):579-85. doi: 10.1016/j.ejca.2011.09.027. Epub 2011 Nov 14.

10e. Arndt CA, Stoner JA, Hawkins DS, et al. Vincristine, actinomycin, and cyclophosphamide compared with vincristine, actinomycin, and cyclophosphamide alternating with vincristine, topotecan, and cyclophosphamide for intermediate-risk rhabdomyosarcoma: children's oncology group study D9803. J Clin Oncol. 2009 Nov 1;27(31):5182-8. doi: 10.1200/JCO.2009.22.3768. Epub 2009 Sep 21.

11e. Penel N, Bui BN, Bay JO, et al. Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX Study. J Clin Oncol. 2008 Nov 10;26(32):5269-74. doi: 10.1200/JCO.2008.17.3146. Epub 2008 Sep 22.

12e. 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 Sep;146(3):531-537. doi: 10.1016/j.ygyno.2017.06.018. Epub 2017 Jun 24.

13e. Hensley ML, Miller A2, O'Malley DM, et al. Randomized phase III trial of gemcitabine plus docetaxel plus bevacizumab or placebo as first-line treatment for metastatic uterine leiomyosarcoma: an NRG Oncology/Gynecologic Oncology Group study. J Clin Oncol. 2015 Apr 1;33(10):1180-5. doi: 10.1200/JCO.2014.58.3781. Epub 2015 Feb 23.

14e. Hensley ML, Blessing JA, Mannel R, Rose PG. Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II trial. Gynecol Oncol. 2008 Jun;109(3):329-34. doi: 10.1016/j.ygyno.2008.03.010.

15e. Agulnik M, Yarber JL, Okuno SH, et al. An open-label, multicenter, phase II study of bevacizumab for the treatment of angiosarcoma and epithelioid hemangioendotheliomas. Ann Oncol. 2013 Jan;24(1):257-63. doi: 10.1093/annonc/mds237. Epub 2012 Aug 21.

16e. Hawkins DS, Chi YY, Anderson JR, et al. Addition of Vincristine and Irinotecan to Vincristine, Dactinomycin, and Cyclophosphamide Does Not Improve Outcome for Intermediate-Risk Rhabdomyosarcoma: A Report From the Children's Oncology Group. J Clin Oncol. 2018 Sep 20;36(27):2770-2777. doi: 10.1200/JCO.2018.77.9694. Epub 2018 Aug 9.

17e. Muss HB, Bundy B, DiSaia PJ, et al. Treatment of recurrent or advanced uterine sarcoma. A randomized trial of doxorubicin versus doxorubicin and cyclophosphamide (a phase III trial of the Gynecologic Oncology Group). Cancer. 1985 Apr 15;55(8):1648-53.

18e. Omura GA, Major FJ, Blessing JA, Sedlacek TV, Thigpen JT, Creasman WT, Zaino RJ. A randomized study of adriamycin with and without dimethyl triazenoimidazole carboxamide in advanced uterine sarcomas. Cancer. 1983 Aug 15;52(4):626-32.

19e. Kawai A, Araki N, Naito Y, et al. Phase 2 study of eribulin in patients with previously treated advanced or metastatic soft tissue sarcoma. Jpn J Clin Oncol. 2017 Feb 1;47(2):137-144. doi: 10.1093/jjco/hyw175.

20e. Pautier P, Floquet A, Penel N, et al. Randomized multicenter and stratified phase II study of gemcitabine alone versus gemcitabine and docetaxel in patients with metastatic or relapsed leiomyosarcomas: a Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) French Sarcoma Group Study (TAXOGEM study). Oncologist. 2012;17(9):1213-20. Epub 2012 Aug 20.

21e. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. N Engl J Med. 2018;378(8):731–739.

22e. Gronchi A, Ferrari S, Quagliuolo V, et al. Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial. Lancet Oncol. 2017 Jun;18(6):812-822. doi: 10.1016/S1470-2045(17)30334-0. Epub 2017 May 9. Erratum in: Lancet Oncol. 2017 Jun;18(6):e301.

23e. Constantinidou A, Jones RL, Olmos D, et al. Conventional anthracycline-based chemotherapy has limited efficacy in solitary fibrous tumour. Acta Oncol. 2012 Apr;51(4):550-4. doi: 10.3109/0284186X.2011.626450.

24e. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2012 May 19;379(9829):1879-86. doi: 10.1016/S0140-6736(12)60651-5.

25e. Talbot SM, Keohan ML, Hesdorffer M, et al. A phase II trial of temozolomide in patients with unresectable or metastatic soft tissue sarcoma. Cancer. 2003 Nov 1;98(9):1942-6. doi: 10.1002/cncr.11730.

26e. Sutton GP, Blessing JA, Barrett RJ, McGehee R. Phase II trial of ifosfamide and mesna in leiomyosarcoma of the uterus: a Gynecologic Oncology Group study. Am J Obstet Gynecol. 1992 Feb;166(2):556-9. doi: 10.1016/0002-9378(92)91671-v.

27e. Magellan Health, Magellan Rx Management. Yondelis Clinical Literature Review Analysis. Last updated August 2022. Accessed August 2022.

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

ICD-10	ICD-10 Description
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
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: https://www.cms.gov/medicare-coverage-database/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): N/A

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)
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