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Medication Policy Manual	**Policy No:** dru440
Topic: Yondelis®, trabectedin	**Date of Origin:** January 8, 2016
Committee Approval Date: January 13, 2017	**Next Review Date:** January 2018
Effective Date: February 1, 2017	

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Trabectedin (Yondelis) is a cytotoxic chemotherapy medication used for the treatment of liposarcomas and leiomyosarcomas, two types of soft tissue sarcomas. It is indicated for disease that cannot be removed with surgery or that has spread to other areas when front-line therapies were not effective. Trabectedin (Yondelis) is given intravenously as a 24-hour infusion through a central line. It is administered by a healthcare provider every 21 days.

Policy/Criteria

I. Most contracts require prior authorization approval of trabectedin (Yondelis) prior to coverage. Trabectedin (Yondelis) may be considered medically necessary when criteria A or B below are met.

A. A diagnosis of liposarcoma (LPS) when criteria 1 and 2 below are met:

1. The LPS is unresectable or metastatic.

AND

2. At least one prior anthracycline-based chemotherapy regimen for LPS has been ineffective.

OR

B. A diagnosis of leiomyosarcoma (LMS) when criteria 1 and 2 below are met:

1. The LMS is unresectable or metastatic.

AND

2. At least one prior anthracycline-based chemotherapy regimen for LMS has been ineffective.

II. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services does not consider trabectedin (Yondelis) to be a self-administered medication.

B. When prior authorization is approved, trabectedin (Yondelis) may be authorized for up to one 24-hour infusion every 21 days.

C. Authorization may be reviewed at least every six months to confirm that current medical necessity criteria are met and that the medication is effective.

III. Trabectedin (Yondelis) is considered not medically necessary when used for the treatment of ovarian cancer.

IV. Trabectedin (Yondelis) is considered investigational when used for all other conditions, including, but not limited to, soft tissue sarcomas other than LPS and LMS.

Position Statement

Summary

- Trabectedin (Yondelis) is a cytotoxic chemotherapy medication used in the treatment of unresectable or metastatic liposarcoma (LPS) or leiomyosarcoma (LMS) after disease progresses on prior cytotoxic chemotherapy regimens.
- Standard front-line therapy for unresectable or metastatic soft tissue sarcoma (STS), including LPS and LMS, is anthracycline-based (e.g. doxorubicin) chemotherapy, given either as a single agent or in combination with other cytotoxic agents, because it has been shown to improve survival relative to non-anthracycline-based regimens.
- All subjects in the trabectedin (Yondelis) clinical study had progression of disease on prior anthracycline-based chemotherapy. There is no evidence for trabectedin (Yondelis) when given after non-anthracycline-based regimens.
- Although trabectedin (Yondelis) demonstrated a progression-free survival (PFS) advantage over standard dose dacarbazine, there was no difference in overall survival between groups. Improvement in PFS, a surrogate endpoint, has not been shown to correlate with improvement in any clinically relevant outcome (e.g. improved symptom control or quality of life).
- Trabectedin (Yondelis) is a palliative therapy, meaning that it is not given with curative intent. National treatment guidelines list trabectedin (Yondelis) among several other single-agent cytotoxic chemotherapy agents for the palliative treatment of metastatic STS. No one chemotherapy agent has been shown to be superior to another in this setting.
- Trabectedin (Yondelis) is administered as a 24-hour continuous infusion via a central line once every 21 days until progression of disease. The median duration of response with trabectedin (Yondelis) was approximately 6 months.
- Trabectedin (Yondelis) was evaluated in metastatic ovarian cancer as an add-on to liposomal doxorubicin; however, no difference in OS was demonstrated in the trial. Additionally, there is greater toxicity when these two agents are used together.
- Trabectedin (Yondelis) has been evaluated in small numbers of patients with other subtypes of STS; however, data is of extremely poor quality so the benefit is unknown.

Clinical Efficacy [1,2]

- The efficacy of trabectedin (Yondelis) is based on a single, published, phase 3 trial in patients with metastatic or recurrent liposarcoma or leiomyosarcoma. These are two of the most common forms of soft tissue sarcoma (STS).
- All patients in the trabectedin (Yondelis) clinical trial had prior cytotoxic chemotherapy, with the majority having received anthracycline-based regimens, the current front-line standard of care.
- The study evaluated trabectedin (Yondelis) as a monotherapy in a dose of 1.5 mg/m^2 intravenously as a 24-hour infusion given every 21 days until disease progression. Subjects in the comparator arm received a standard dose of dacarbazine as monotherapy.

- There was a 2.7-month advantage in progression-free survival (PFS) with trabectedin (Yondelis) versus dacarbazine; however, there was no difference in median overall survival (OS).
- It is not known if improved PFS correlates with improvements in other clinically relevant outcomes such as symptom control or quality of life.
- The median duration of response in the trabectedin (Yondelis) and dacarbazine treatment arms was 6.5 months and 4.2 months, respectively. This difference was not statistically significant.
- There is currently no evidence that trabectedin (Yondelis) is superior to dacarbazine or any other therapy used for the salvage treatment of liposarcoma or leiomyosarcoma with regard to any clinically relevant endpoint.
- The NCCN STS guideline lists trabectedin (Yondelis), as well as many other cytotoxic chemotherapy regimens, as category 2A recommendations for locally advanced or metastatic STS (which includes liposarcomas and leiomyosarcomas). [3]

Not Medically Necessary Uses

- A phase 3 study evaluating trabectedin (Yondelis) plus pegylated liposomal doxorubicin (PLD) versus PLD alone demonstrated improved tumor response rates and progression-free survival (PFS) in the combination arm; however, there was no statistical difference in overall survival based on the mature data set. [4,5]

Investigational Uses

- The safety and effectiveness of trabectedin (Yondelis) in soft tissue sarcomas (STS) other than LPS or LMS have not been adequately assessed. Available studies are in early phases and contain mixed subtypes of STSs with small numbers of any given subtype. [6]
- Trabectedin (Yondelis) had no activity in patients with metastatic pancreatic cancer or triple-negative, HER2-overexpressing metastatic breast cancer based on small, preliminary studies. [7,8]

Regence Pharmacy Services performs independent analyses of oncology medications. The Regence Pharmacy Services analysis and coverage policy may differ from NCCN clinical practice guidelines.

Safety and Administration [1,2]

- Serious adverse events (AEs) reported with trabectedin (Yondelis) include severe neutropenia, rhabdomyolysis, hepatotoxicity, and cardiomyopathy.
- Trabectedin (Yondelis) has only been directly compared with single-agent dacarbazine.
- The incidence of nearly all AEs was numerically higher for trabectedin (Yondelis) than for dacarbazine. Discontinuations due to AEs occurred in 12.6% and 7.7% in the trabectedin (Yondelis) and dacarbazine treatment arms, respectively.
- Trabectedin (Yondelis) is administered via a 24-hour continuous infusion. It must be administered via a central line because extravasation can cause tissue necrosis requiring

tissue debridement.

- Premedication with dexamethasone is required prior to administration of trabectedin (Yondelis) to prevent or minimize infusion reactions.

Appendix 1: Anthracycline medications
daunorubicin (generics, Cerubidine®)
doxorubicin (generics, Adriamycin®)
doxorubicin, liposomal (Doxil, Lipodox®)
epirubicin (generics, Ellence®)

Cross References
Votrient®, pazopanib, Medication Policy Manual, Policy No. dru199
Halaven®, eribulin, Medication Policy Manual, Policy No. dru231

Codes	**Number**	**Description**
HCPCS	J3590	Unclassified biologics
HCPCS	J3490	Unclassified drugs
HCPCS	J9999	Not otherwise classified, antineoplastic drugs
ICD-10	C53.0, C54.0 – C54.3, C54.8, C54.9, C55, C78.00 – C78.02, Z80.49	Soft tissue sarcoma

References

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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*. 2015 Sep 14. PMID: 26371143
3. NCCN Clinical Practice Guidelines in Oncology™. Soft Tissue Sarcoma v.2.2016. [cited 5/20/2016]; Available from: https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf
4. Monk, BJ, Herzog, TJ, Kaye, SB, et al. Trabectedin plus pegylated liposomal doxorubicin (PLD) versus PLD in recurrent ovarian cancer: overall survival analysis. *Eur J Cancer*. 2012 Oct;48(15):2361-8. PMID: 22541893
5. Monk, BJ, Herzog, TJ, Kaye, SB, et al. Trabectedin plus pegylated liposomal Doxorubicin in recurrent ovarian cancer. *J Clin Oncol*. 2010 Jul 1;28(19):3107-14. PMID: 20516432
6. 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. PMID: 24512981
7. Belli, C, Piemonti, L, D'Incalci, M, et al. Phase II trial of salvage therapy with trabectedin in metastatic pancreatic adenocarcinoma. *Cancer Chemother Pharmacol*. 2016 Mar;77(3):477-84. PMID: 26666646
8. Blum, JL, Goncalves, A, Efrat, N, et al. A phase II trial of trabectedin in triple-negative and HER2-overexpressing metastatic breast cancer. *Breast Cancer Res Treat*. 2016 Jan;155(2):295-302. PMID: 26749361

Revision History

Revision Date	Revision Summary
1/13/2017	- No coverage criteria changes. - Updated references for package labeling and NCCN guideline, and added documentation for two additional populations where trabectedin was not found to have activity.
1/8/2016	New policy