For unresectable or metastatic liposarcoma or leiomyosarcoma after an anthracycline

PROPEL TREATMENT FORWARD WITH YONDELIS®

INDICATION

YONDELIS® (trabectedin) is indicated for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS—YONDELIS® is contraindicated in patients with known severe hypersensitivity, including anaphylaxis, to trabectedin.

Please see Important Safety Information on pages 12 and 13 and click here to see full Prescribing Information.

Yondelis® (trabectedin)

PROPEL TREATMENT FORWARD WITH YONDELIS® (trabectedin)

Study Design and Patient Characteristics[1]

YONDELIS® was studied in a phase 3 randomized, open-label, active-controlled, multicenter trial of patients with unresectable, locally advanced or metastatic leiomyosarcomas (73%) or liposarcomas (27%).[1]

N=518

- Median age was 56 years (range 17 years to 81 years)
- All patients had an Eastern Cooperative Oncology Group (ECOG) score of ≤1
- Previously treated with an anthracycline- and ifosfamide-containing regimen or an anthracycline-containing regimen and 1 additional cytotoxic chemotherapy regimen
- The majority had received ≥2 prior lines of chemotherapy

2:1 RANDOMIZATION

YONDELIS® (n=345)	**Dacarbazine** (n=173)
(1.5 mg/m^2 by 24-hour IV infusion once every 3 weeks)	(1 g/m^2 IV infused for 20 to 120 minutes once every 3 weeks)

Efficacy Measures

Progression-free survival (PFS)
Overall survival (OS)
Objective response rate (ORR)
Duration of response (DOR)

IV = intravenous.

Liposarcoma and leiomyosarcoma are 2 of the most common subtypes of soft tissue sarcoma.[2]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Neutropenic sepsis, including fatal cases, can occur. In Trial ET743-SAR-3007, the incidence of Grade 3 or 4 neutropenia, based on laboratory values, was 43% (161/378). Median time to the first occurrence of Grade 3 or 4 neutropenia was 16 days (range: 8 days to 9.7 months). Median time to complete resolution of neutropenia was 13 days (range: 3 days to 2.3 months). Febrile neutropenia (fever ≥38.5°C with Grade 3 or 4 neutropenia) occurred in 18 patients (5%) treated with YONDELIS®. Ten patients (2.6%) experienced neutropenic sepsis, 5 of whom had febrile neutropenia, which was fatal in 4 patients (1.1%). Assess neutrophil count prior to administration of each dose of YONDELIS® and periodically throughout the treatment cycle. Withhold or reduce dose of YONDELIS® based on severity of adverse reaction.

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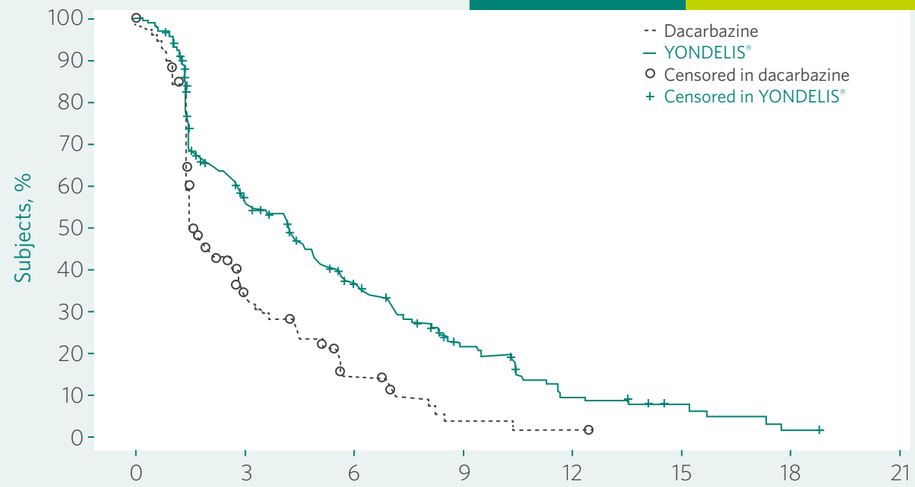
The first FDA-approved treatment for liposarcoma and leiomyosarcoma studied against an active comparator in a phase 3 trial.[1]

KAPLAN-MEIER CURVE OF PFS

45% REDUCTION OF RISK vs dacarbazine



NUMBER OF SUBJECTS AT RISK:

Dacarbazine	173	35	10	2	1	0		
YONDELIS®	345	133	71	29	10	5	1	0

YONDELIS® resulted in a 45% reduction in the risk of disease progression or death compared with dacarbazine in a phase 3 open-label study[1]

- YONDELIS® improved median PFS* vs dacarbazine: 4.2 months with YONDELIS® vs 1.5 months for dacarbazine (hazard ratio [HR]†=0.55; 95% CI: 0.44, 0.70; *P*<0.001‡)[1]

PFS = the time from randomization to the occurrence of disease progression or death, whichever comes first.[3]

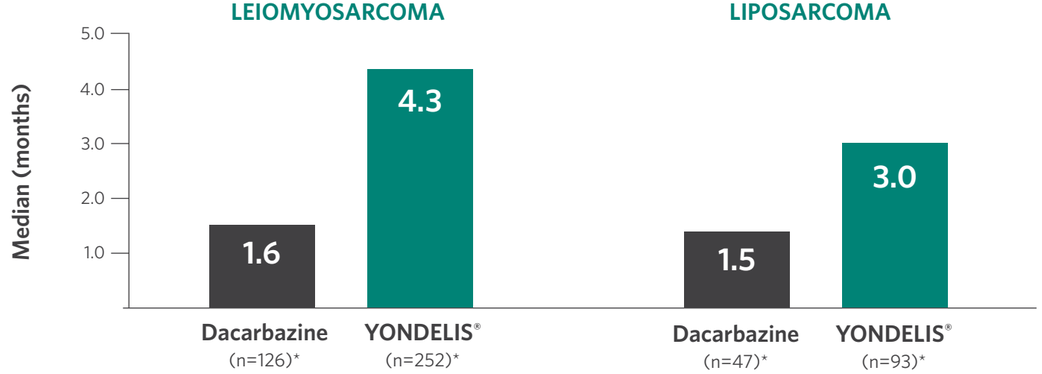
*An exploratory analysis of independent radiology committee-determined PFS, in a subgroup consisting of approximately 60% of the total population, provided similar results to the investigator-determined PFS.

†HR is estimated using Cox proportional hazards model with treatment group as the only covariate.

‡*P* value is based on unstratified log-rank test.

YONDELIS® (trabectedin) DEMONSTRATED ACTIVITY IN BOTH LEIOMYOSARCOMA AND LIPOSARCOMA

PFS OUTCOMES BY SUBTYPE[4]



(HR=0.55; 95% CI: 0.42, 0.73)

(Clinical trial included uterine and nonuterine subtypes)

(HR=0.55; 95% CI: 0.34, 0.87)

(Clinical trial included dedifferentiated, myxoid ± round cell, and pleomorphic subtypes)

* n values represent the number of patients in each subgroup.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Rhabdomyolysis—YONDELIS® can cause rhabdomyolysis and musculoskeletal toxicity. In Trial ET743-SAR-3007, rhabdomyolysis leading to death occurred in 3 (0.8%) of the 378 patients receiving YONDELIS®. Elevations in creatine phosphokinase (CPK) occurred in 122 (32%) of the 378 patients receiving YONDELIS®, including Grade 3 or 4 CPK elevation in 24 patients (6%), compared to 15 (9%) of the 172 patients receiving dacarbazine with any CPK elevation, including 1 patient (0.6%) with Grade 3 CPK elevation. Among the 24 patients receiving YONDELIS® with Grade 3 or 4 CPK elevation, renal failure occurred in 11 patients (2.9%); rhabdomyolysis with the complication of renal failure occurred in 4 of these 11 patients (1.1%). Median time to first occurrence of Grade 3 or 4 CPK elevations was 2 months (range: 1 to 11.5 months). Median time to complete resolution was 14 days (range: 5 days to 1 month). Assess CPK levels prior to each administration of YONDELIS®. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

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ADDITIONAL EFFICACY DATA

Yondelis® (trabectedin)

Overall Survival[†1] (median):

13.7 months for YONDELIS® **VS** **13.1 months** for dacarbazine

(HR[‡]=0.93; 95% CI: 0.75, 1.15; *P*=0.49[§])

Objective Response Rate (CR+PR)[1]:

7% (23/345) for YONDELIS® (95% CI[¶]: 4.3, 9.8) **VS** **6%** (10/173) for dacarbazine (95% CI[¶]: 2.8, 10.4)

Duration of Response (CR+PR) (median)[1]:

6.9 months for YONDELIS® (95% CI: 4.5, 7.6) **VS** **4.2 months** for dacarbazine (95% CI: 2.9, NE)

CR=complete response;
NE=not estimable;
PR=partial response.

Duration of response = duration of response for patients with complete response or partial response; objective response rate = percentage of patients achieving complete response or partial response[3]; overall survival = the time between randomization and death from any cause.[3]

[†]Based on 384 patients randomized to the YONDELIS® arm and 193 patients randomized to dacarbazine.
[‡]HR is estimated using Cox proportional hazards model with treatment group as the only covariate.
[§]*P* value is based on unstratified log-rank test.
[¶]Fisher's exact CI.

YONDELIS® (trabectedin) HAS AN ESTABLISHED SAFETY PROFILE

The safety profile of YONDELIS® was established in 755 patients[1]

- 6 open-label, single-arm trials, in which 377 patients received YONDELIS®, and 1 open-label, randomized, active-controlled pivotal trial, in which 378 patients received YONDELIS®

  —26% (197) of patients were exposed to YONDELIS® for 6 months or longer

  —8% (57) of patients were exposed to YONDELIS® for 1 year or longer

Safety in the pivotal trial[1]

INCIDENCE OF SELECTED TREATMENT-EMERGENT LABORATORY ABNORMALITIES IN THE PIVOTAL TRIAL*[1]

Laboratory Abnormalities	YONDELIS®		Dacarbazine	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Chemistry				
Increased ALT	90	31	33	0.6
Increased AST	84	17	32	1.2
Increased ALP	70	1.6	60	0.6
Hypoalbuminemia	63	3.7	51	3.0
Increased creatinine	46	4.2	29	1.2
Increased CPK	33	6.4	9	0.6
Hyperbilirubinemia	13	1.9	5	0.6
Hematology				
Anemia	96	19	79	12
Neutropenia	66	43	47	26
Thrombocytopenia	59	21	57	20

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase.

*Treatment-emergent laboratory abnormalities included those higher in the trabectedin arm compared with the dacarbazine arm by ≥5% (all grades) or by ≥2% (Grades 3-4). Incidence based on number of patients who had both baseline and at least one on-study laboratory measurement.

YONDELIS® group (range: 373 to 377 patients) and dacarbazine group (range: 166 to 168 patients).

SELECTED ADVERSE REACTIONS† OCCURRING IN ≥10% OF PATIENTS RECEIVING YONDELIS® AND AT A HIGHER INCIDENCE THAN IN THE CONTROL ARM IN THE PIVOTAL TRIAL‡[1]

System Organ Class Adverse Reaction	YONDELIS® (n=378)		Dacarbazine (n=172)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal disorders				
Nausea	75	7	50	1.7
Vomiting	46	6	22	1.2
Constipation	37	0.8	31	0.6
Diarrhea	35	1.6	23	0
General disorders and administration-site conditions				
Fatigue§	69	8	52	1.7
Peripheral edema	28	0.8	13	0.6
Metabolism and nutrition disorders				
Decreased appetite	37	1.9	21	0.6
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	25	4.2	20	1.2
Nervous system disorders				
Headache	25	0.3	19	0
Musculoskeletal and connective tissue disorders				
Arthralgia	15	0	8	1.2
Myalgia	12	0	6	0
Psychiatric disorders				
Insomnia	15	0.3	9	0

†Limited to adverse reactions at a rate of ≥10% in the trabectedin arm and at a rate higher in the trabectedin arm compared with dacarbazine arm by ≥5% in overall incidence or by ≥2% for Grades 3-4 adverse reactions.

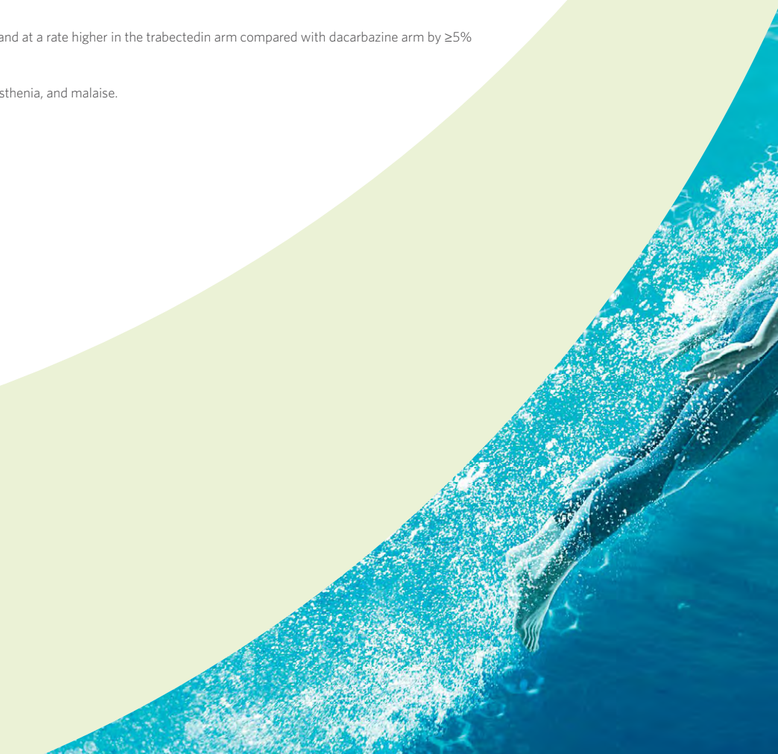
‡Toxicity grade is based on NCI common toxicity criteria, version 4.0.

§Fatigue is a composite of the following adverse event terms: fatigue, asthenia, and malaise.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hepatotoxicity, including hepatic failure, can occur. Patients with serum bilirubin levels above the upper limit of normal or AST or ALT levels >2.5 x upper limit of normal were not enrolled in Trial ET743-SAR-3007. In Trial ET743-SAR-3007, the incidence of Grade 3-4 elevated liver function tests (defined as elevations in ALT, AST, total bilirubin, or alkaline phosphatase) was 35% (134/378) in patients receiving YONDELIS®. Median time to development of Grade 3-4 elevation in ALT or AST was 29 days (range: 3 days to 11.5 months). Of the 134 patients with Grade 3 to 4 elevations in LFTs, 114 (85%) experienced complete resolution with the median time to complete resolution of 13 days (range: 4 days to 4.4 months). In Trial ET743-SAR-3007, the incidence of drug-induced liver injury (defined as concurrent elevation in ALT or AST of more than three times the upper limit of normal, alkaline phosphatase less than two times the upper limit of normal, and total bilirubin at least two times the upper limit of normal) was 1.3% (5/378) in patients receiving YONDELIS®. ALT or AST elevation greater than eight times the upper limit of normal occurred in 18% (67/378) of patients receiving YONDELIS®. Assess LFTs prior to each administration of YONDELIS® and as clinically indicated based on underlying severity of pre-existing hepatic impairment. Manage elevated LFTs with treatment interruption, dose reduction, or permanent discontinuation based on severity and duration of LFT abnormality.



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YONDELIS® (trabectedin) TREATMENT EXPOSURE

Approximately one third of patients were able to stay on YONDELIS® 6 cycles or longer

1 IN 3 PATIENTS (34%)

continued on YONDELIS® treatment for

6 CYCLES OR MORE[4]

1 IN 10 PATIENTS (10%)

continued on YONDELIS® treatment for

12 CYCLES OR MORE[4]

YONDELIS® TREATMENT CYCLES

CUMULATIVE TREATMENT CYCLES RECEIVED (ALL TREATED PATIENTS)[5]

Treatment cycles received	YONDELIS® (n=340) % (n)	Dacarbazine (n=155) % (n)
≥3	57.1 (194)	43.2 (67)
≥6	34.4 (117)	17.4 (27)
≥9	17.4 (59)	5.2 (8)
≥12	10.3 (35)	1.9 (3)

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Cardiomyopathy, including cardiac failure, congestive heart failure, ejection fraction decreased, diastolic dysfunction, or right ventricular dysfunction can occur. In Trial ET743-SAR-3007, a significant decrease in left ventricular ejection fraction (LVEF) was defined as an absolute decrease of ≥15% or below the lower limit of normal with an absolute decrease of ≥5%. Patients with a history of New York Heart Association Class II to IV heart failure or abnormal LVEF at baseline were ineligible. In Trial ET743-SAR-3007, cardiomyopathy occurred in 23 patients (6%) receiving YONDELIS® and in four patients (2.3%) receiving dacarbazine. Grade 3 or 4 cardiomyopathy occurred in 15 patients (4%) receiving YONDELIS® and 2 patients (1.2%) receiving dacarbazine; cardiomyopathy leading to death occurred in 1 patient (0.3%) receiving YONDELIS® and in none of the patients receiving dacarbazine. The median time to development of Grade 3 or 4 cardiomyopathy in patients receiving YONDELIS® was 5.3 months (range: 26 days to 15.3 months). Patients with LVEF < lower limit of normal, prior cumulative anthracycline dose of ≥300 mg/m^2, age ≥65 years, or a history of cardiovascular disease may be at increased risk of cardiac dysfunction. Assess LVEF by echocardiogram (ECHO) or multigated acquisition (MUGA) scan before initiation of YONDELIS® and at 2- to 3-month intervals thereafter until YONDELIS® is discontinued. Discontinue treatment with YONDELIS® based on severity of adverse reaction.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Capillary leak syndrome (CLS) characterized by hypotension, edema, and hypoalbuminemia has been reported with YONDELIS®, including serious CLS resulting in death. Monitor for signs and symptoms of CLS. Discontinue YONDELIS® and promptly initiate standard management for patients with CLS, which may include a need for intensive care.

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YONDELIS® (trabectedin) DOSING AND ADMINISTRATION

Recommended dose and schedule[1]

- **The recommended dose** for YONDELIS® is 1.5 mg/m^2 administered as an intravenous infusion over 24 hours through a central venous line once every 21 days (3 weeks), until disease progression or unacceptable toxicity
- **Hepatic impairment:** The recommended dose is 0.9 mg/m^2 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). 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)

Premedication[1]

- **Administer dexamethasone** 20 mg intravenously 30 minutes prior to each dose of YONDELIS®

Dose modifications[1]

Permanently discontinue YONDELIS® for:

- Persistent adverse reactions requiring a delay in dosing of more than 3 weeks
- Adverse reactions requiring dose reduction following YONDELIS® administered at 1.0 mg/m^2 for patients with normal hepatic function or at 0.3 mg/m^2 for patients with pre-existing moderate hepatic impairment
- Severe liver dysfunction: bilirubin 2 times the upper limit of normal, and AST or ALT 3 times the upper limit of normal, and alkaline phosphatase less than 2 times the upper limit of normal in the prior treatment cycle for patients with normal liver function at baseline
- Exacerbation of liver dysfunction in patients with pre-existing moderate hepatic impairment
- Capillary leak syndrome
- Rhabdomyolysis
- Grade 3 or 4 cardiac adverse events (AEs) indicative of cardiomyopathy or for subjects with an LVEF that decreases below the lower limit of normal

The recommended dose modifications for adverse reactions are listed in the table on the following page. Once reduced, the dose of YONDELIS® should not be increased in subsequent treatment cycles.

RECOMMENDED STARTING DOSES AND DOSE REDUCTIONS[1]

Starting Dose and Dose Reduction	For patients with normal hepatic function or mild hepatic impairment* prior to initiation of YONDELIS® treatment	For patients with moderate hepatic impairment** prior to initiation of YONDELIS® treatment
Starting dose	1.5 mg/m^2	0.9 mg/m^2
Dose reduction		
First dose reduction	1.2 mg/m^2	0.6 mg/m^2
Second dose reduction	1.0 mg/m^2	0.3 mg/m^2

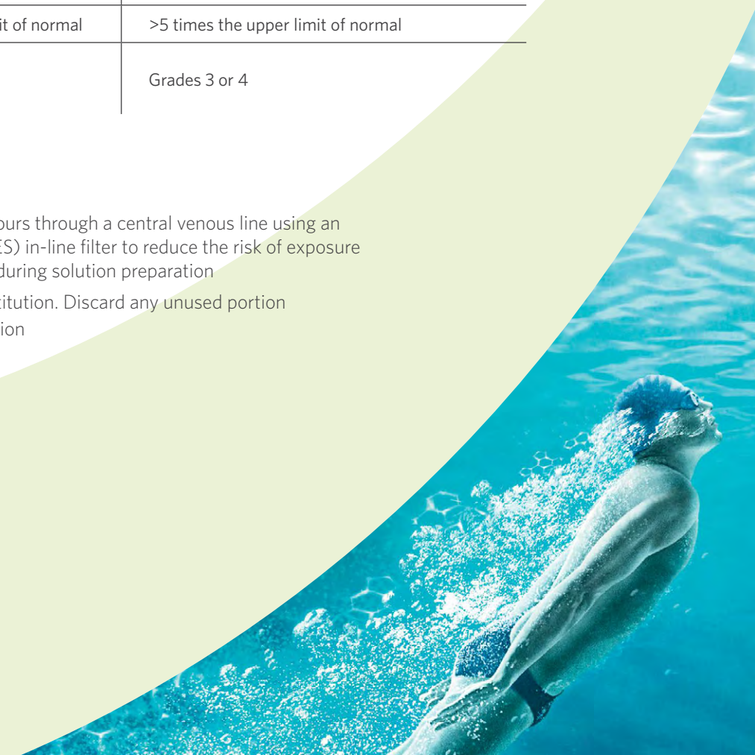
*Including patients with bilirubin greater than 1 to 1.5 times the upper limit of normal, and any AST or ALT.
**Including patients with bilirubin levels greater than 1.5 times to 3 times the upper limit of normal, and AST and ALT less than 8 times the upper limit of normal.

RECOMMENDED DOSE MODIFICATIONS[1]

Laboratory Result or Adverse Reaction	DELAY Next Dose for up to 3 Weeks	REDUCE Next Dose by 1 Dose Level for Adverse Reaction(s) During Prior Cycle
Platelets	<100,000 platelets/microliter	<25,000 platelets/microliter
Absolute neutrophil count	<1,500 neutrophils/microliter	• <1,000 neutrophils/microliter with fever/infection • <500 neutrophils/microliter lasting more than 5 days
Total bilirubin	>upper limit of normal	>upper limit of normal
AST or ALT	>2.5 times the upper limit of normal	>5 times the upper limit of normal
ALP	>2.5 times the upper limit of normal	>2.5 times the upper limit of normal
CPK	>2.5 times the upper limit of normal	>5 times the upper limit of normal
Other nonhematologic adverse reactions	Grades 3 or 4	Grades 3 or 4

Administration[1]

- Infuse the reconstituted, diluted solution over 24 hours through a central venous line using an infusion set with a 0.2-micron polyethersulfone (PES) in-line filter to reduce the risk of exposure to adventitious pathogens that may be introduced during solution preparation
- Complete infusion within 30 hours of initial reconstitution. Discard any unused portion of the reconstituted product or of the infusion solution



IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Extravasation Resulting in Tissue Necrosis—Extravasation of YONDELIS®, resulting in tissue necrosis requiring debridement, can occur. Evidence of tissue necrosis can occur more than 1 week after the extravasation. There is no specific antidote for extravasation of YONDELIS®. Administer YONDELIS® through a central venous line.

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Embryo-Fetal Toxicity—Based on its mechanism of action, YONDELIS® can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during therapy and for at least 2 months after the last dose of YONDELIS®. Advise males with female partners of reproductive potential to use effective contraception during therapy and for at least 5 months after the last dose of YONDELIS®.

Adverse Reactions—The most common (≥20%) adverse reactions are nausea (75%), fatigue (69%), vomiting (46%), constipation (37%), decreased appetite (37%), diarrhea (35%), peripheral edema (28%), dyspnea (25%), and headache (25%).

The most common (≥5%) grades 3-4 laboratory abnormalities are: neutropenia (43%), increased ALT (31%), thrombocytopenia (21%), anemia (19%), increased AST (17%), and increased creatine phosphokinase (6.4%).

DRUG INTERACTIONS

Effect of Cytochrome CYP3A Inhibitors—Avoid using strong CYP3A inhibitors (e.g., oral ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, telithromycin, indinavir, lopinavir, ritonavir, boceprevir, nelfinavir, saquinavir, telaprevir, nefazodone, conivaptan) in patients taking YONDELIS®. If a strong CYP3A inhibitor for short-term use (i.e., less than 14 days) must be used, administer the strong CYP3A inhibitor 1 week after the YONDELIS® infusion, and discontinue it the day prior to the next YONDELIS® infusion.

Effect of Cytochrome CYP3A Inducers—Avoid using strong CYP3A inducers (e.g., rifampin, phenobarbital, St. John's wort) in patients taking YONDELIS®.

Click here to read the full Prescribing Information for YONDELIS®.

References: 1. YONDELIS® (trabectedin) [Prescribing Information]. Horsham, PA: Janssen Products, LP. **2.** Toro JR, Travis LB, Wu HJ, Zhu K, Fletcher CDM, Devesa SS. Incidence patterns of soft tissue sarcomas, regardless of primary site, in the Surveillance, Epidemiology and End Results program, 1978–2001: an analysis of 26,758 cases. *Int J Cancer.* 2006;119(12):2922–2930. **3.** Chmielowski B, Federman N, Tap WD. Clinical trial end points for assessing efficacy of novel therapies for soft-tissue sarcomas. *Expert Rev Anticancer Ther.* 2012;12(9):1217-1228. **4.** 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. **5.** Demetri GD, von Mehren M, Jones RL, et al. Patient-reported outcomes from randomized, phase 3 study of trabectedin vs dacarbazine in advanced leiomyosarcoma or liposarcoma. Poster presented at: American Society of Clinical Oncology (ASCO) Annual Meeting: June 3-7, 2016; Chicago, IL. **6.** HALAVEN® (eribulin) [Prescribing Information]. Woodcliff Lake, NJ: Eisai Inc. **7.** VOTRIENT® (pazopanib) [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation.

cp-63569v2

Liposarcoma and leiomyosarcoma are 2 of the most common subtypes of soft tissue sarcoma[2]

YONDELIS® is the only treatment approved specifically for unresectable or metastatic liposarcoma or leiomyosarcoma after an anthracycline-containing regimen[1,6,7]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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Please see Important Safety Information on pages 12 and 13 and click here to see full Prescribing Information.

Yondelis® (trabectedin)

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