SAFETY CONSIDERATIONS WITH YONDELIS® (trabectedin)

Please see Important Safety Information on pages 14 and 15
and click here to read the full Prescribing Information.

YONDELIS® (trabectedin)

INDICATION

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

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

WARNINGS AND PRECAUTIONS

- Neutropenic sepsis: Severe, and fatal, neutropenic sepsis may occur. Monitor neutrophil count during treatment. Withhold YONDELIS® for neutrophil count <1,500/mcL
- 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
- Hepatotoxicity: Hepatotoxicity may occur. Monitor and delay and/or reduce dose if needed
- Cardiomyopathy: Severe and fatal cardiomyopathy can occur. Patients with left ventricular ejection fraction (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 developing new or worsening cardiac dysfunction. Discontinue YONDELIS® in patients who develop decreased LVEF or cardiomyopathy
- Capillary leak syndrome: Monitor and discontinue YONDELIS® for capillary leak syndrome
- Embryo-fetal toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use effective contraception

Recommended dose and schedule

The recommended dose is 1.5 mg/m^2 administered as an intravenous infusion over 24 hours through a central venous line every 21 days (3 weeks), until disease progression or unacceptable toxicity

In patients with 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 ULN, and AST and ALT less than 8 times the ULN). Do not administer YONDELIS® to patients with severe hepatic impairment (bilirubin levels above 3 times the ULN, and any AST and ALT)

For complete dosing information, please see pages 12 and 13.

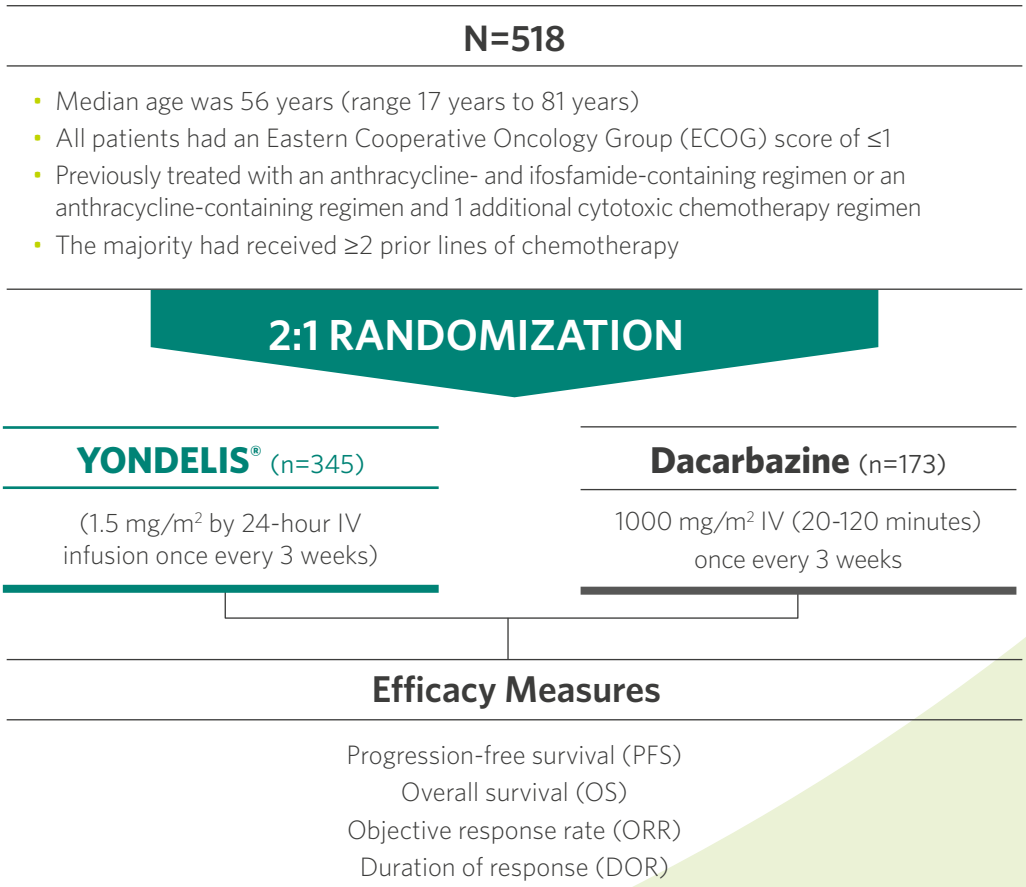
ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

Please see Important Safety Information on pages 14 and 15 and click here to read the full Prescribing Information.

STUDY DESIGN

YONDELIS® phase 3 clinical study design

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



The Safety of YONDELIS®

- The safety of YONDELIS® was evaluated in 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 and 8% (57) of patients were exposed to YONDELIS® for ≥1 year
- The median duration of treatment with YONDELIS® was 13 weeks (range, 1 to 127 weeks), with 30% of patients treated for more than 6 months and 7% for more than 1 year in the pivotal trial

IV = intravenous.

Please see Important Safety Information on pages 14 and 15 and click here to read the full Prescribing Information.

Yondelis® (trabectedin)

NEUTROPENIC SEPSIS

WARNINGS AND PRECAUTIONS

Neutropenic sepsis, including fatal cases, can occur with YONDELIS®. In Trial ET743-SAR-3007, the incidence of Grade 3 or 4 neutropenia, based on laboratory values, was 43% (161/378).

- The median time to the first occurrence of Grade 3 or 4 neutropenia was 16 days (range: 8 days to 9.7 months)
- The 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%)

NEUTROPENIA IN THE PIVOTAL TRIAL

Laboratory Abnormality*	YONDELIS®		Dacarbazine	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Neutropenia	66	43	47	26

*Treatment-emergent laboratory abnormalities including 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 1 on-study laboratory measurement.

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

Please see Important Safety Information on pages 14 and 15 and click here to read the full Prescribing Information.

Modifying the YONDELIS® dosage in response to reduced neutrophil counts

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 neutropenia

RECOMMENDED STARTING DOSES AND DOSE REDUCTIONS

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

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
Absolute neutrophil count	<1,500 neutrophils/microliter	• <1,000 neutrophils/microliter with fever/infection • <500 neutrophils/microliter lasting more than 5 days

For complete dosing information, please see pages 12 and 13.

Please see Important Safety Information on pages 14 and 15 and click here to read the full Prescribing Information.

Yondelis® (trabectedin)

RHABDOMYOLYSIS

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%)
- The median time to first occurrence of Grade 3 or 4 CPK elevations was 2 months (range: 1 to 11.5 months)
- The median time to complete resolution was 14 days (range: 5 days to 1 month)

RHABDOMYOLYSIS AND CPK ELEVATIONS IN THE PIVOTAL TRIAL

Laboratory Abnormality*	YONDELIS®		Dacarbazine	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Increased CPK	33	6.4	9	0.6

*Treatment-emergent laboratory abnormalities including 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 1 on-study laboratory measurement.
YONDELIS® group (range: 373-377 patients) and dacarbazine group (range: 166-168 patients).
CPK = creatine phosphokinase.

Please see Important Safety Information on pages 14 and 15 and click here to read the full Prescribing Information.

Managing CPK levels

Assess CPK levels prior to each administration of YONDELIS®

Withhold, **reduce dose**, or **permanently discontinue** YONDELIS® based on severity of rhabdomyolysis

RECOMMENDED STARTING DOSES AND DOSE REDUCTIONS

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

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
CPK	>2.5 times the ULN	>5 times the ULN

For complete dosing information, please see pages 12 and 13.

Please see Important Safety Information on pages 14 and 15 and click here to read the full Prescribing Information.

Yondelis® (trabectedin)

HEPATOTOXICITY

WARNINGS AND PRECAUTIONS

Hepatotoxicity, including hepatic failure, can occur with YONDELIS®.

- In Trial ET743-SAR-3007, patients with serum bilirubin levels above the ULN or AST or ALT levels >2.5 x ULN were not enrolled
- The incidence of Grade 3-4 elevated LFTs (defined as elevations in ALT, AST, total bilirubin, or ALP) was 35% (134/378) in patients receiving YONDELIS®
  - —The 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 3-4 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)
- The incidence of drug-induced liver injury (defined as concurrent elevation in ALT or AST of more than 3 times the ULN, ALP less than 2 times the ULN, and total bilirubin at least 2 times the ULN) was 1.3% (5/378)
- ALT or AST elevation greater than 8 times the ULN occurred in 18% (67/378) of patients

INCREASES IN LIVER FUNCTION TESTS IN THE PIVOTAL TRIAL

Laboratory Abnormalities*	YONDELIS®		Dacarbazine	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Increased ALT	90	31	33	0.6
Increased AST	84	17	32	1.2
Increased ALP	70	1.6	60	0.6
Hyperbilirubinemia	13	1.9	5	0.6

*Treatment-emergent laboratory abnormalities including those higher in the trabectedin arm compared with the dacarbazine arm by ≥5% (all grades) or by ≥2% (Grade 3-4). Incidence based on number of patients who had both baseline and at least 1 on-study laboratory measurement.

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

ALP = alkaline phosphatase; LFT = liver function test.

Please see Important Safety Information on pages 14 and 15 and click here to read the full Prescribing Information.

Monitor patients' liver enzymes

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

RECOMMENDED STARTING DOSES AND DOSE REDUCTIONS

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

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
Total bilirubin	>ULN	>ULN
AST or ALT	>2.5 times the ULN	>5 times the ULN
ALP	>2.5 times the ULN	>2.5 times the ULN

For complete dosing information, please see pages 12 and 13.

Please see Important Safety Information on pages 14 and 15 and click here to read the full Prescribing Information.

Yondelis® (trabectedin)

CARDIOMYOPATHY

WARNINGS AND PRECAUTIONS

Cardiomyopathy, including cardiac failure, congestive heart failure, ejection fraction decreased, diastolic dysfunction, or right ventricular dysfunction can occur with YONDELIS®. 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
- 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
- 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)
- Cardiomyopathy leading to death occurred in 1 patient (0.3%) receiving YONDELIS® and in none of the patients receiving dacarbazine

CARDIOMYOPATHY IN THE PIVOTAL TRIAL

Adverse Reaction*	**YONDELIS®** (n=378)		**Dacarbazine** (n=172)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Cardiomyopathy	6	4	2.3	1.2

*Toxicity grade is based on National Cancer Institute (NCI) common toxicity criteria, version 4.0.

Assess left ventricular ejection fraction (LVEF) by echocardiogram 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® for 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.

Please see Important Safety Information on pages 14 and 15 and click here to read the full Prescribing Information.

RECOMMENDED STARTING DOSES AND DOSE REDUCTIONS

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.

For complete dosing information, please see pages 12 and 13.

WARNINGS AND PRECAUTIONS

Capillary Leak Syndrome

- 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

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

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®

Please see Important Safety Information on pages 14 and 15 and click here to read the full Prescribing Information.

Yondelis® (trabectedin)

DOSAGE AND ADMINISTRATION

Recommended dose and schedule

- **1.5 mg/m^2 administered as an intravenous infusion** over 24 hours through a central venous line 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

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

Dose Modifications for Adverse Reactions

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 ULN and AST or ALT 3 times the ULN with ALP <2 times the ULN 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.

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%)

Please see Important Safety Information on pages 14 and 15 and click here to read the full Prescribing Information.

RECOMMENDED STARTING DOSES AND DOSE REDUCTIONS

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

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	>ULN	>ULN
AST or ALT	>2.5 times the ULN	>5 times the ULN
ALP	>2.5 times the ULN	>2.5 times the ULN
CPK	>2.5 times the ULN	>5 times the ULN
Other non-hematologic adverse reactions	Grades 3 or 4	Grades 3 or 4

Administration

- 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

Please see Important Safety Information on pages 14 and 15 and click here to read the full Prescribing Information.

Yondelis® (trabectedin)

IMPORTANT SAFETY INFORMATION

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

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.

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.

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.

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

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.

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.

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.

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®.

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Please see Important Safety Information on pages 14 and 15 and click here to read the full Prescribing Information.

Yondelis® (trabectedin)

Yondelis®
(trabectedin)

Janssen Oncology
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