YONDELIS® (trabectedin)
DOSING & ADMINISTRATION GUIDE

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 8 to 11 and accompanying full Prescribing Information.

Yondelis® (trabectedin)

RECOMMENDED DOSING FOR YONDELIS® (trabectedin)

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 normal bilirubin and AST or ALT less than or equal to 2.5 times the upper limit of normal
- **Hepatic impairment:** The recommended dose is 0.9 mg/m^2 in patients with moderate hepatic impairment (bilirubin levels 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 to 10 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

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 (all of the following: bilirubin 2 times the upper limit of normal and AST or ALT 3 times the upper limit of normal with ALP 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

The recommended dose modifications for specific 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

Starting Doses and Dose Reductions	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 1 to 1.5 times the upper limit of normal, and any AST or ALT.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Neutropenic sepsis, including fatal cases, can occur. In Trial 1, 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%). 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 YONDELIS® for neutrophil counts of less than 1500 cells/microliter on the day of dosing. Permanently reduce the dose of YONDELIS® for life-threatening or prolonged, severe neutropenia in the preceding cycle.

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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*	>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
Decreased left ventricular ejection fraction	• <lower limit of normal; or • Clinical evidence of cardiomyopathy	• Absolute decrease of 10% or more from baseline and <lower limit of normal; or • Clinical evidence of cardiomyopathy
Other nonhematologic adverse reactions	Grades 3 or 4	Grades 3 or 4

*Permanently discontinue YONDELIS® when liver dysfunction is exacerbated for patients with pre-existing moderate hepatic impairment.

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

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

Rhabdomyolysis—YONDELIS® can cause rhabdomyolysis and musculoskeletal toxicity. In Trial 1, rhabdomyolysis leading to death occurred in 3 (0.8%) of the 378 patients. 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 YONDELIS® for serum CPK levels more than 2.5 times the upper limit of normal. Permanently discontinue YONDELIS® for rhabdomyolysis.

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PREPARING YONDELIS® (trabectedin) FOR ADMINISTRATION

YONDELIS® is a cytotoxic drug. Follow applicable special handling and disposal procedures.

Reconstitute

- Using aseptic technique, inject 20 mL of Sterile Water for Injection, USP into the vial. Shake the vial until complete dissolution. The reconstituted solution is clear, colorless to pale brownish-yellow, and contains 0.05 mg/mL of trabectedin
- Inspect for particulate matter and discoloration prior to further dilution. Discard vial if particles or discoloration are observed

Dilute

- Immediately following reconstitution, withdraw the calculated volume of trabectedin and further dilute in 500 mL of 0.9% Sodium Chloride, USP or 5% Dextrose Injection, USP
- Do not mix YONDELIS® with other drugs

Infuse

- Infuse the reconstituted, diluted solution over 24 hours 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

Discard

- Discard any remaining solution within 30 hours of reconstituting the lyophilized powder

Compatibility

- YONDELIS® diluted solution is compatible with Type I colorless glass vials, polyvinylchloride (PVC) and polyethylene (PE) bags and tubing, PE and polypropylene (PP) mixture bags, polyethersulfone (PES) in-line filters, titanium, platinum or plastic ports, silicone and polyurethane catheters, and pumps having contact surfaces made of PVC, PE, or PE/PP

For additional information, please see the full Prescribing Information.

Yondelis® (trabectedin)

ADMINISTERING YONDELIS® (trabectedin)

Administration

- Infuse the reconstituted, diluted solution over 24 hours
- Infuse through a central venous line using an infusion set with a 0.2-micron PES in-line filter
- Complete infusion within 30 hours of initial reconstitution
- Discard any unused portion of the reconstituted product or of the infusion solution

Other considerations

An ambulatory pump may be used for administration at the discretion of the physician

HANDLING YONDELIS®

How supplied

- YONDELIS® is supplied in a glass vial containing 1 mg trabectedin
- Each outer carton of YONDELIS® contains 1 vial
- NDC code: 59676-610-01

Bottle shown is not actual size.

Storage and handling

Store in a refrigerator at 2°C to 8°C (36°F to 46°F).

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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 ULN were not enrolled in Trial 1. In Trial 1, 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). 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 1, 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). ALT or AST elevation greater than eight times the ULN occurred in 18% (67/378) of patients. 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)

IMPORTANT SAFETY INFORMATION

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

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Rhabdomyolysis—YONDELIS® can cause rhabdomyolysis and musculoskeletal toxicity. In Trial 1, rhabdomyolysis leading to death occurred in 3 (0.8%) of the 378 patients. 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 YONDELIS® for serum CPK levels more than 2.5 times the upper limit of normal. Permanently discontinue YONDELIS® for rhabdomyolysis.

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 ULN were not enrolled in Trial 1. In Trial 1, 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). 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 1, 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). ALT or AST elevation greater than eight times the ULN occurred in 18% (67/378) of patients. 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.

Cardiomyopathy, including cardiac failure, congestive heart failure, ejection fraction decreased, diastolic dysfunction, or right ventricular dysfunction can occur. In Trial 1, patients with a history of New York Heart Association Class II to IV heart failure or abnormal left ventricular ejection fraction (LVEF) at baseline were ineligible. In Trial 1, 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). 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. Withhold YONDELIS® for LVEF below lower limit of normal. Permanently discontinue YONDELIS® for symptomatic cardiomyopathy or persistent left ventricular dysfunction that does not recover to lower limit of normal within 3 weeks.

Please see accompanying full Prescribing Information.

Yondelis® (trabectedin)

IMPORTANT SAFETY INFORMATION (cont)

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.

Embryofetal 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®.

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Please see accompanying full Prescribing Information.

Yondelis® (trabectedin)

HAVE ANY QUESTIONS ABOUT YONDELIS®?

Call Janssen Medical Information Center at
1-800-JANSSEN (1-800-526-7736)

or visit **www.janssenmd.com**

To learn more, please visit
www.yondelis.com.

Please see Important Safety Information on pages 8 to 11 and accompanying full Prescribing Information.

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