Yondelis® (trabectedin)

PREPARATION AND ADMINISTRATION CHECKLIST

INDICATION

YONDELIS® 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 full Important Safety Information on pages 3 and 4, and click here to read the full Prescribing Information.

PREPARATION AND ADMINISTRATION CHECKLIST

The purpose of this checklist is to give an overview of the preparation and infusion process for YONDELIS® (trabectedin). It is not intended to be a comprehensive checklist to cover all clinical scenarios, or a substitute for the healthcare professional's expertise and clinical judgment. Please click here to read the full Prescribing Information for complete preparation and administration instructions.

✓ INDICATION

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

✓ ASSESS CLINICAL STATUS (See Prescribing Information section 2 [Dosage and Administration])

- ☐ In addition to a clinical assessment, it is recommended that laboratory values are monitored before and during administration (CBC with platelets and absolute neutrophil count; liver function tests; creatine phosphokinase)
- ☐ Assess left ventricular ejection fraction by echocardiogram or multigated acquisition scan before initiation of YONDELIS® and at 2- to 3-month intervals until YONDELIS® is discontinued

✓ PREMEDICATE (See Prescribing Information section 2.2 [Premedication])

- ☐ Premedicate with dexamethasone 20 mg intravenously 30 minutes prior to each dose of YONDELIS®

✓ DETERMINE DOSAGE (See Prescribing Information section 2 [Dosage and Administration])

- ☐ 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
  - ☐ The recommended dose is 0.9 mg/m^2 in patients with moderate hepatic impairment.*
  - ☐ Do not administer YONDELIS® to patients with severe hepatic impairment†
- ☐ Avoid the use of concomitant strong CYP3A inducers and inhibitors
- ☐ For additional dose modifications based on abnormal laboratory results and/or adverse events, refer to Table 1 and Table 2 in the full Prescribing Information
- ☐ Conditions that warrant permanent discontinuation of YONDELIS® can be found in section 2.3 of the full Prescribing Information (See Prescribing Information section 2.3 [Dose Modifications])

IMPORTANT SAFETY INFORMATION

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®.

Learn more at **www.yondelis.com**.

For questions about YONDELIS®, please contact Janssen Medical Information by calling **1-800-JANSSEN (1-800-526-7736)**, e-mailing questions to **www.askjanssenmedinfo.com**, or visiting **www.janssenmd.com**.

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✓ PREPARE YONDELIS® (See Prescribing Information section 2.4 [Preparation for Administration])

- ☐ 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
- ☐ 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
- ☐ 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

✓ ADMINISTER (See Prescribing Information section 2.5 [Administration])

- ☐ Infuse YONDELIS® solution over 24 hours 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 remaining solution)
- ☐ Discard any unused portion of the reconstituted product or of the infusion solution

*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.
†Bilirubin levels above 3 times the upper limit of normal, and any AST and ALT.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS — YONDELIS® 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.

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

Yondelis® (trabectedin)

IMPORTANT SAFETY INFORMATION (CONT)

WARNINGS AND PRECAUTIONS (CONT)

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.

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/m2, 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 theextravasation. 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

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