HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use YONDELIS® safely and effectively. See full prescribing information for YONDELIS.

YONDELIS (trabectedin) for injection, for intravenous use
Initial U.S. Approval: 2015

Dosage and Administration (2.3) 12/2018
Warnings and Precautions (5.1, 5.2, 5.4) 12/2018

DOSAGE FORMS AND STRENGTHS
For injection: 1 mg sterile lyophilized powder in a single-dose vial (3)

CONTRAINDICATIONS
Known hypersensitivity to trabectedin (4)

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 (2.3, 5.1)
• 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. (2.3, 5.2)

ADVERSE REACTIONS
The most common (≥20%) adverse reactions are nausea, fatigue, vomiting, constipation, decreased appetite, diarrhea, peripheral edema, dyspnea, and headache. The most common (≥5%) grades 3-4 laboratory abnormalities are: neutropenia, increased ALT, thrombocytopenia, anemia, increased AST, and increased creatine phosphokinase. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Products, LP at 1-800-526-7736 (1-800-JANSSEN) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
• CYP3A inhibitors: Avoid concomitant strong CYP3A inhibitors (7.1)
• CYP3A inducers: Avoid concomitant strong CYP3A inducers (7.2)

USE IN SPECIFIC POPULATIONS
• Lactation: Advise not to breastfeed (8.2)
• Hepatic Impairment: Do not administer YONDELIS to patients with severe hepatic impairment (8.6, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 01/2019

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YONDELIS® (trabectedin) for injection

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

YONDELIS® is indicated for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen [see Clinical Studies (14)].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose is 1.5 mg/m² 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/m² 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) [see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)].

2.2 Premedication

Administer dexamethasone 20 mg intravenously 30 minutes prior to each dose of YONDELIS.

2.3 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/m² for patients with normal hepatic function or at 0.3 mg/m² for patients with pre-existing moderate hepatic impairment.
- Severe liver dysfunction: bilirubin two times the upper limit of normal, and AST or ALT three 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 death.
- Grade 3 or 4 rhabdomyolysis.
- Severe liver dysfunction: bilirubin two times the upper limit of normal, and AST or ALT less than 8 times the upper limit of normal.

The recommended dose modifications for adverse reactions are listed in Table 1. Once reduced, the dose of YONDELIS should not be increased in subsequent treatment cycles.

Table 1: Recommended Dose Modification

<table>
<thead>
<tr>
<th>Laboratory Result or Adverse Reaction</th>
<th>DELAY next dose of YONDELIS for up to 3 weeks</th>
<th>REDUCE next dose of YONDELIS by one dose level for adverse reaction(s) during prior cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets</td>
<td>Less than 100,000 platelets/microliter</td>
<td>Less than 25,000 platelets/microliter</td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>Less than 1,500 neutrophils/microliter</td>
<td>More than 1,000 neutrophils/microliter with fever/infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Less than 500 neutrophils/microliter lasting more than 5 days</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>Greater than the upper limit of normal</td>
<td>Greater than the upper limit of normal</td>
</tr>
<tr>
<td>Aspartate aminotransferase (AST)</td>
<td>More than 2.5 times the upper limit of normal</td>
<td>More than 5 times the upper limit of normal</td>
</tr>
<tr>
<td>Alanine aminotransferase (ALT)</td>
<td>More than 2.5 times the upper limit of normal</td>
<td>More than 2.5 times the upper limit of normal</td>
</tr>
<tr>
<td>Alkaline phosphatase (ALP)</td>
<td>More than 2.5 times the upper limit of normal</td>
<td>More than 5 times the upper limit of normal</td>
</tr>
<tr>
<td>Creatine phosphokinase</td>
<td>More than 2.5 times the upper limit of normal</td>
<td>More than 5 times the upper limit of normal</td>
</tr>
<tr>
<td>Other non-hematologic adverse reactions</td>
<td>Grade 3 or 4</td>
<td>Grade 3 or 4</td>
</tr>
</tbody>
</table>

YONDELIS® (trabectedin) for injection

The recommended starting doses and dose reductions for YONDELIS are listed in Table 2:

Table 2: Recommended Starting Doses and Dose Reductions

<table>
<thead>
<tr>
<th>Starting Dose and Dose Reduction</th>
<th>For patients with normal hepatic function or mild hepatic impairment* prior to initiation of YONDELIS treatment</th>
<th>For patients with moderate hepatic impairment** prior to initiation of YONDELIS treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting Dose</td>
<td>1.5 mg/m²</td>
<td>0.9 mg/m²</td>
</tr>
<tr>
<td>Dose Reduction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First dose reduction</td>
<td>1.2 mg/m²</td>
<td>0.6 mg/m²</td>
</tr>
<tr>
<td>Second dose reduction</td>
<td>1.0 mg/m²</td>
<td>0.3 mg/m²</td>
</tr>
</tbody>
</table>

* 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 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.

2.4 Preparation for Administration

- YONDELIS is a cytotoxic drug. Follow applicable special handling and disposal procedures.
- 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.
- Discard any remaining solution within 30 hours of reconstituting the lyophilized powder.
- 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.

2.5 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.

3 DOSAGE FORMS AND STRENGTHS

For injection: 1 mg, lyophilized powder in single-dose vial for reconstitution.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Neutropenic Sepsis

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, in patients receiving YONDELIS was 43% (161/378). The median time to the first occurrence of Grade 2 or 4 neutropenia was 18 days (range: 8 days to 9.7 months); the median time to complete resolution of neutropenia was 13 days (range: 3 days to 23 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 [see Dosage and Administration (2.3)].

5.2 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 (5%) 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
YONDELIS® (trabectedin) for injection

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 86 days). Assess CPK levels prior to each administration of YONDELIS. Withhold reduce dose, or permanently discontinue based on severity of adverse reaction [see Dosage and Administration (2.3)].

5.3 Hepatotoxicity

Hepatotoxicity, including hepatic failure, can occur with YONDELIS. Patients with serum bilirubin levels above the upper limit of normal or ALT or AST levels above 2 times the 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 (LFTs; defined as elevations in ALT, AST, total bilirubin, or alkaline phosphatase) was 35% (134/387) 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).

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. The median time to resolution was 14 days (range: 5 days to 86 days). Manage elevated LFTs with treatment interruption, dose reduction, or permanent discontinuation based on severity and duration of LFT abnormality [see Dosage and Administration (2.3) and Use in Specific Populations (8.6)].

5.4 Cardiomyopathy

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 LVEF was defined as 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 left ventricular ejection fraction (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, 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. The median time to resolution was 14 days (range: 5 days to 86 days). Manage elevated LFTs with treatment interruption, dose reduction, or permanent discontinuation based on severity and duration of LFT abnormality [see Dosage and Administration (2.3)].

5.5 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 [see Adverse Reactions (6.2)].

5.6 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 extravasation. There is no specific antidote for extravasation of YONDELIS. Administer YONDELIS through a central venous line [see Dosage and Administration (2.3)].

5.7 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 [see Use in Specific Populations (8.1, 8.3)].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Anaphylaxis [see Contraindications (4)]
- Neutropenic Sepsis [see Warnings and Precautions (5.1)]
- Rhabdomyolysis [see Warnings and Precautions (5.2)]
- Hepatotoxicity [see Warnings and Precautions (5.3)]
- Cardiomyopathy [see Warnings and Precautions (5.4)]
- Capillary Leak Syndrome [see Warnings and Precautions (5.5)]
- Extravasation Resulting in Tissue Necrosis [see Warnings and Precautions (5.6)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to YONDELIS in 755 patients with soft tissue sarcoma including 197 (26%) patients exposed to YONDELIS for greater than or equal to 1 year. The safety of YONDELIS was evaluated in six open-label, single-arm trials, in which 377 patients received YONDELIS and one open-label, randomized, active-controlled clinical trial in which 378 patients received YONDELIS (Trial ET743-SAR-3007). All patients received YONDELIS at the recommended dosing regimen of 1.5 mg/m² administered as an intravenous infusion over 24 hours once every 3 weeks (q3wk, 24-h). The median age was 54 years (range: 18 to 81 years), 63% were female, and all patients had metastatic soft tissue sarcoma.

Table 3: Selected Adverse Reactionsa Occurring in ≥10% of Patients Receiving YONDELIS and at a Higher Incidence than in the Control Arm - Trial ET743-SAR-3007

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Reaction</th>
<th>YONDELIS (N=378)</th>
<th>Dacarbazine (N=172)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All Grades</td>
<td>Grades 3-4</td>
</tr>
<tr>
<td>Nausea</td>
<td>75</td>
<td>7</td>
<td>50</td>
</tr>
<tr>
<td>Vomiting</td>
<td>46</td>
<td>6</td>
<td>22</td>
</tr>
<tr>
<td>Constipation</td>
<td>37</td>
<td>0.8</td>
<td>31</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>35</td>
<td>1.6</td>
<td>23</td>
</tr>
</tbody>
</table>

Gastrointestinal disorders

| | All Grades | Grades 3-4 |
| 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 |
7.2 Effect of Cytochrome CYP3A Inducers
Coadministration of YONDELIS with rifampin, a strong CYP3A inducer, decreased systemic exposure of trabectedin by 31%. Avoid using strong CYP3A inducers (e.g., rifampin, phenobarbital, St. John’s wort) in patients taking YONDELIS [see Clinical Pharmacology (12.3)].

8. USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Based on its mechanism of action, trabectedin can cause fetal harm when administered during pregnancy [see Clinical Pharmacology (12.1)]. There are no available data with the use of YONDELIS during pregnancy. Animal reproductive and developmental studies at relevant doses have not been conducted with trabectedin; however, placental transfer of trabectedin was demonstrated in pregnant rats. Advise pregnant woman of the potential risk to a fetus. The background risk of major birth defects and miscarriage for the indicated population is unknown; however, the background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies.

8.2 Lactation
Risk Summary
There are no data on the presence of trabectedin in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions from YONDELIS in breastfed infants, advise a nursing woman to discontinue nursing during treatment with YONDELIS.

8.3 Females and Males of Reproductive Potential

8.3.1 Pregnancy Testing
Verify the pregnancy status of females of reproductive potential prior to initiating YONDELIS [see Use in Specific Populations (8.1)].

8.3.2 Contraception
Females
Advise female patients of reproductive potential to use effective contraception during and for 2 months after the last dose of YONDELIS [see Use in Specific Populations (8.1)].

Males
YONDELIS may damage spermatozoa, resulting in possible genetic and fetal abnormalities. Advise males with a female sexual partner of reproductive potential to use effective contraception during and for 5 months after the last dose of YONDELIS [see Nonclinical Toxicology (13.1)].

8.3.3 Infertility
YONDELIS may result in decreased fertility in males and females [see Nonclinical Toxicology (13.1)].

8.4 Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Safety (n=81) and efficacy (n=58) were assessed across five open-label studies (NCT00006463, NCT01453283, NCT00005625, NCT00070109, and CT-B-023-00) in pediatric patients (aged 2 to <17 years) with pediatric histotypes of sarcoma (predominantly rhabdomyosarcoma, osteosarcoma, Ewing sarcoma, and non-rhabdomyosarcoma soft tissue sarcoma). No new safety signals were observed in pediatric patients across these studies. Pharmacokinetic parameters in 17 pediatric patients (aged 3 to 17 years) were within the range of values previously observed in adults given the same dose per body surface area.

8.5 Geriatric Use
Clinical studies of YONDELIS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8.6 Hepatic Impairment
The mean trabectedin exposure was (97%) higher in patients with moderate (bilirubin levels greater than 1.5 to 3 times the upper limit of normal, and AST and ALT less than 8 times the upper limit of normal) hepatic impairment compared to patients with normal (total bilirubin ≤ the upper limit of normal, and AST and ALT ≤ the upper limit of normal) liver function. Reduce YONDELIS dose in patients with moderate hepatic impairment [see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)].

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) [see Warnings and Precautions (5.2)].

8.7 Renal Impairment
No dose adjustment is recommended in patients with mild [creatinine clearance (CrCl) 60-89 mL/min] or moderate (CrCl of 30-59 mL/min) renal impairment.

The pharmacokinetics of trabectedin has not been evaluated in patients with severe renal impairment (CrCl <30 mL/min) or end stage renal disease [see Clinical Pharmacology (12.3)].

Table 3: Selected Treatment-Emergent Laboratory Abnormalitiesa - Trial ET743-SAR-3007

<table>
<thead>
<tr>
<th>Laboratory Abnormalities</th>
<th>YONDELIS (N=378)</th>
<th>Dacarbazine (N=172)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased ALT</td>
<td>90</td>
<td>31</td>
</tr>
<tr>
<td>Increased AST</td>
<td>84</td>
<td>17</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>70</td>
<td>1.6</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>63</td>
<td>3.7</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>46</td>
<td>4.2</td>
</tr>
<tr>
<td>Increased creatine kinase</td>
<td>33</td>
<td>6.4</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>13</td>
<td>1.9</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>96</td>
<td>19</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>66</td>
<td>43</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>59</td>
<td>21</td>
</tr>
</tbody>
</table>

a 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 Grade 3-4 adverse reactions.

b 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.

Other clinically important adverse reactions observed in <10% of patients (N=755) with soft tissue sarcoma receiving YONDELIS were: Nervous system disorders: peripheral neuropathy, paresthesia, hypoesthesia. Respiratory, thoracic, and mediastinal disorders: pulmonary embolism.
YONDELIS® (trabectedin) for injection

10 OVERDOSAGE
There is no specific antidote for YONDELIS. Hemodialysis is not expected to
effectively enhance the elimination of YONDELIS because trabectedin is highly bound to
plasma proteins (97%) and not significantly renally excreted.

11 DESCRIPTION
Trabectedin is an alkylating drug with the chemical name
\[
R,6-R,7-R,13-S,14-S,16-R-5-\text{acetonyl}-3',4',6,6a,7,13,14,16-\text{octahydro-6',8',14-\text{trihydroxy-7',9-dimethoxy-10,23-trimethyl-spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8-i]isoquinolin]-19-one.}
\]
The molecular formula is \(C_{39}H_{42}N_{2}O_{12}\). The molecular weight is 761.84 daltons. The chemical structure is shown below:

Trabectedin is hydrophobic and has a low solubility in water.
YONDELIS (trabectedin) for injection is supplied as a sterile lyophilized
white to off-white powder/cake in a single-dose vial. Each single-dose vial
contains 1 mg of trabectedin, 27.2 mg potassium dihydrogen phosphate,
400 mg sucrose, and phosphoric acid and potassium hydroxide (for pH
adjustment to 3.6 – 4.2).

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Trabectedin is an alkylating drug that binds guanine residues in the minor
groove of DNA, forming adducts and resulting in a bending of the DNA helix
which may affect the subsequent activity of DNA binding proteins, including some
transcription factors, and DNA repair pathways, resulting in perturbation of
the cell cycle and eventual cell death.

12.2 Pharmacodynamics
Cardiac Electrophysiology
The effect of trabectedin on the QT/QTc interval was evaluated in 75 patients
who received placebo on day 1 and trabectedin (1.3 mg/m²) as a 3-hour
intravenous infusion on day 2. No patients in the study showed a QTc interval
exceeding 500 msec or more than 60 msec increase from baseline, and no
large changes in the mean QTc interval (i.e., >20 msec) were observed.

12.3 Pharmacokinetics
The pharmacokinetics of trabectedin is characterized by a rapid decline
phase at the end of the infusion and slower exponential phases. Population
pharmacokinetic analyses suggest that the pharmacokinetics of trabectedin
are dose-proportional (over the dose range of 0.024 to 1.8 mg/m²) and exposure
is time-independent. No accumulation of trabectedin in plasma is observed
upon repeated administrations every 3 weeks.

Distribution
Binding of trabectedin to human plasma proteins was approximately
97%, independent of trabectedin concentrations ranging from 10 ng/mL to
100 ng/mL. Steady state volume of distribution of trabectedin exceeds 5000 L.

Elimination
The estimated mean (% coefficient of variation) clearance of trabectedin
is 315 L/hr (50%) and the terminal elimination half-life is approximately
175 hours.

Metabolism
CYP3A is the predominant CYP enzyme responsible for the hepatic
metabolism of trabectedin.

Trabectedin was extensively metabolized with negligible unchanged drug in
urine and feces following administration of trabectedin to humans.

Excretion
In patients with solid tumors, following a 3-hour or a 24-hour intravenous
infusion of \(^{14}C\)-labeled trabectedin, 64% of the total administered radioactive
dose was recovered in 24 days, with 58% in feces and 8% in urine.

YONDELIS® (trabectedin) for injection

Specific Populations
The following population characteristics are not associated with a significant
change on the pharmacokinetics of trabectedin: sex, age (19 to
82 years), body weight (36 to 148 kg), body surface area (0.8 to 2.3 m²), mild
hepatic impairment, or mild to moderate renal impairment. The effects of
severe hepatic impairment, severe renal impairment or end stage renal
disease on trabectedin exposure are unknown.

Hepatic Impairment
The geometric mean dose normalized trabectedin exposure (AUC) increased
by 97% (90% CI: 20%, 222%) in patients with moderate hepatic impairment
(alkaline 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) following administration of a single YONDELIS dose of 0.58 mg/m² or 0.9 mg/m²
compared to patients with normal liver function following administration of a single YONDELIS dose of 1.3 mg/m² [see Dosage and Administration (2.1) and
Use in Specific Populations (8.6)].

Drug Interactions
Effect of Strong CYP3A Inhibitors on Trabectedin
Co-administration of multiple doses of ketoconazole (200 mg twice daily for
7.5 days) with a single dose of YONDELIS (0.58 mg/m²) on day 1 increased
trabectedin dose-normalized AUC by 66% and Cmax by 22% compared to a single YONDELIS dose (1.3 mg/m²) given alone.

Effect of Strong CYP3A Inducers on Trabectedin
Co-administration of multiple doses of rifampin (600 mg daily for 6 days) with a single YONDELIS dose (1.3 mg/m²) on day 6 decreased trabectedin
AUC by 31% and Cmax by 21% compared to a single YONDELIS dose (1.3 mg/m²)
given alone.

Effect of Trabectedin on CYP Enzymes
In vitro, trabectedin has limited inhibition or induction potential of major CYP
enzymes (CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4).

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Trabectedin is genotoxic in both in vitro and in vivo studies. Long-term
carcinogenicity studies have not been performed.

Fertility studies with trabectedin were not performed. In male rats there were
limited histopathological signs of hemorrhage and degeneration in the testes
following repeated administration of trabectedin at doses approximately
0.2 times the 1.5 mg/m² human dose based on body surface area.

14 CLINICAL STUDIES
The clinical efficacy and safety of YONDELIS in patients with metastatic
or recurrent leiomyosarcoma or liposarcoma were demonstrated in Trial ET743-SAR-3007 (NCT01343277), a randomized (2:1), open-label,
active-controlled trial comparing treatment with YONDELIS 1.5 mg/m² as a
24-hour continuous intravenous infusion once every 3 weeks to dacarbazine
1000 mg/m² intravenous infusion (20 to 120 minutes) once every 3 weeks.
Treatment continued in both arms until disease progression or unacceptable
toxicity, all patients in the YONDELIS arm were required to receive dacarbazine 20 mg intravenous injection per 24 hours for 4 days following the YONDELIS infusion.

Patients were required to have unresectable, locally advanced or metastatic
leiomyosarcoma or liposarcoma (dedifferentiated, myxoid round cell, or
pleomorphic) and previous treatment with an anthracycline- and ifosfamide-
containing regimen or an anthracycline-containing regimen and one
additional cytotoxic chemotherapy regimen. Randomization was stratified
by subtype of soft tissue sarcoma (leiomyosarcoma vs. liposarcoma), ECOG
performance status (0 vs. 1), and number of prior chemotherapy regimens
(1 vs. ≥2). The efficacy outcome measures were investigator-assessed
progression-free survival (PFS) according to the Response Evaluation Criteria
in Solid Tumors (RECIST v1.1), overall survival (OS), objective response rate
(ORR), and duration of response (DOR). Patients in the dacarbazine arm were
not offered YONDELIS at the time of disease progression.

A total of 518 patients were randomized, 345 to the YONDELIS arm and
173 patients to the dacarbazine arm. The median patient age was 56 years
(range: 17 to 81); 30% were male; 76% White, 12% Black, and 4% Asian; 76%
were male and 76% were ≥65 years old. The most common (≥20%) pre-study chemotherapeutic agents administered were doxorubicin (90%),
gemcitabine (81%), docetaxel (74%), and ifosfamide (99%). Approximately
10% of patients had received pazopanib.

Trial ET743-SAR-3007 demonstrated a statistically significant improvement in
PFS. 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. Efficacy results
from Trial ET743-SAR-3007 are presented in the table below.
Table 5: Efficacy Results for Trial ET743-SAR-3007

<table>
<thead>
<tr>
<th>Efficacy Endpoint</th>
<th>YONDELIS N=345</th>
<th>Dacarbazine N=173</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-free survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS Events, n (%)</td>
<td>217 (63%)</td>
<td>112 (65%)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>204</td>
<td>109</td>
</tr>
<tr>
<td>Death</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Median (95% CI) (months)</td>
<td>4.2 (3.0, 4.8)</td>
<td>1.5 (1.5, 2.6)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.55 (0.44, 0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events, n (%)</td>
<td>258 (67%)</td>
<td>123 (64%)</td>
</tr>
<tr>
<td>Median (95% CI) (months)</td>
<td>13.7 (12.2, 16.0)</td>
<td>13.1 (9.1, 16.2)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.93 (0.75, 1.15)</td>
<td>0.49</td>
</tr>
<tr>
<td>Objective Response Rate (ORR: CR+PR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients (%)</td>
<td>23 (7%)</td>
<td>10 (6%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>(4.3, 9.8)</td>
<td>(2.8, 10.4)</td>
</tr>
<tr>
<td>Duration of Response (CR+PR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (95% CI) (months)</td>
<td>6.9 (4.5, 7.6)</td>
<td>4.2 (2.9, NE)</td>
</tr>
</tbody>
</table>

- Cox proportional hazards model with treatment group as the only covariate.
- Unstratified log rank test.
- Based on 384 patients randomized to YONDELIS arm and 193 patients randomized to dacarbazine.
- Fisher’s exact CI.
- CR=Complete Response; PR=Partial Response; CI=Confidence Interval, HR=hazard ratio, NE=not estimable.

Figure 1: Kaplan-Meier Curves of Progression-Free Survival in Trial ET743-SAR-3007

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING
YONDELIS is supplied in a glass vial containing 1 mg trabectedin. Each carton contains one vial (NDC: 59676-610-01).

Storage and Handling
Store YONDELIS vials in a refrigerator at 2°C to 8°C (36°F to 46°F).
YONDELIS is a cytotoxic drug. Follow applicable special handling and disposal procedures.¹

17 PATIENT COUNSELING INFORMATION
Advertise the patient to read the FDA-approved patient labeling (Patient Information).

Myelosuppression: Inform patients of the risks of myelosuppression. Instruct patients to immediately contact their healthcare provider for fever or unusual bruising, bleeding, tiredness, or paleness.

Rhabdomyolysis: Advise patients to contact their healthcare provider if they experience severe muscle pain or weakness.

Hepatotoxicity: Advise patients to contact their healthcare provider immediately for yellowing of skin and eyes (jaundice), pain in the upper right quadrant, severe nausea or vomiting, difficulty in concentrating, disorientation, or confusion.
### PATIENT INFORMATION
**YONDELIS®** (yon-DEL-ess) (trabectedin) for injection

#### What is YONDELIS?
YONDELIS is a prescription medicine used to treat people with liposarcoma or leiomyosarcoma that:
- cannot be treated with surgery or has spread to other areas of the body, and
- who have received treatment with certain other medicines.

It is not known if YONDELIS is safe and effective in children.

#### Who should not receive YONDELIS?
- You will not be given YONDELIS if you have had a severe allergic reaction to trabectedin, the active ingredient in YONDELIS. See the end of this leaflet for a complete list of ingredients in YONDELIS.

#### What should I tell my healthcare provider before receiving YONDELIS?
Before receiving YONDELIS, tell your healthcare provider about all of your medical conditions, including if you:
- have liver or kidney problems
- are pregnant or plan to become pregnant. YONDELIS can harm your unborn baby. You should not become pregnant during treatment with YONDELIS.
  - **Females** who are able to become pregnant should use an effective form of birth control during treatment with YONDELIS and for 2 months after your last dose of YONDELIS.
  - **Males** should use an effective form of birth control when having sex with female partners who are able to become pregnant, during your treatment with YONDELIS and for 5 months after your last dose of YONDELIS.
- are breastfeeding or plan to breastfeed. It is not known if YONDELIS passes into your breast milk. You should not breastfeed during treatment with YONDELIS.
- tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

#### How will I receive YONDELIS?
- YONDELIS is given by an intravenous (IV) infusion into a vein over 24 hours. To help avoid irritation at the site where it is infused, YONDELIS is given to you into a large vein through a type of IV line called a central venous line.
- YONDELIS is usually given every 3 weeks.
- Your healthcare provider may decrease your dose or delay doses if you have certain side effects. If you have any side effects that are severe, your healthcare provider may stop your treatment with YONDELIS.
- Before each treatment with YONDELIS, you will receive a steroid medicine to help reduce your risk of getting certain side effects.
- Your healthcare provider will decide how long you will continue treatment with YONDELIS.
- Your healthcare provider may do certain tests while you are receiving YONDELIS to check you for side effects, and to see how well you respond to the treatment.

#### What are the possible side effects of YONDELIS?
YONDELIS may cause serious side effects, including:
- **Severe infections due to decreased white blood cells.** Decreased low white blood cell count is common with YONDELIS, but it can also lead to severe infections and death. Your healthcare provider may need to decrease your dose of YONDELIS, delay or stop your treatment, if your white blood cell count is too low or you get a serious infection. Call your healthcare provider right away if you develop fever or other signs of infection.
- **Severe muscle problems (rhabdomyolysis).** YONDELIS can cause muscle problems that can be severe and lead to death. Tell your healthcare provider right away if you have severe muscle pain or weakness.
What are the possible side effects of YONDELIS? (continued)

**YONDELIS may cause serious side effects, including:**

- **Liver problems, including liver failure.** Tell your healthcare provider right away if you get:
  - yellowing of your skin and whites of your eyes
  - pain in your upper right stomach-area (abdomen)
  - nausea
  - vomiting

- **Heart muscle problems, including heart failure.** Your healthcare provider will do a test to check your heart function before you start YONDELIS, and during treatment. If you develop heart muscle problems or heart failure during treatment with YONDELIS, your healthcare provider may stop your treatment. Tell your healthcare provider right away if you develop new chest pain, shortness of breath, tiredness, swelling of your legs, ankles, or feet, or heart palpitations.

- **Leakage of YONDELIS out of your vein during the infusion.** If YONDELIS leaks into the tissues around your infusion site, it can cause damage and death of tissue cells around the infusion site. You may need to have surgery to remove any dead tissue. Tell your healthcare provider right away if you see any YONDELIS leaking out of your vein or around the catheter during your infusion, or if you notice any redness, swelling, itching or discomfort at the infusion site at any time.

- **Some people have had allergic reactions to YONDELIS. Some of these reactions were severe. Your healthcare provider may need to stop your treatment with YONDELIS, and may give you medicines to treat the allergic reaction. Signs of an allergic reaction can include: difficulty breathing, chest tightness, wheezing, swelling of the lips, or skin rash.**

- **Capillary leak syndrome.** YONDELIS can cause fluid to leak from the blood vessels into the body’s tissues. This condition is called “Capillary Leak Syndrome” (CLS). CLS can cause you to have symptoms that may lead to death. Tell your healthcare provider right away if you develop swelling, dizziness or lightheadedness with or without a sudden drop in blood pressure.

**The most common side effects of YONDELIS include:**

- nausea
- tiredness
- vomiting
- constipation
- decreased appetite
- diarrhea
- swelling of your hands, ankles, or feet
- shortness of breath
- headache
- decreased red cell count (cells which carry oxygen in the blood). Tell your healthcare provider if you feel more tired than usual or look pale.
- decreased platelet cell counts (cells which help blood to clot). Tell your healthcare provider if you bruise easily or have bleeding.
- changes in liver and kidney function blood tests

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of YONDELIS. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**General information about the safe and effective use of YONDELIS**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your healthcare provider or pharmacist for information about YONDELIS that is written for health professionals.

**What are the ingredients in YONDELIS?**

**Active ingredient:** trabectedin

**Inactive ingredients:** potassium dihydrogen phosphate, sucrose, phosphoric acid and potassium hydroxide.

Product of Spain
Manufactured by: Baxter Oncology GmbH, Halle/Westfalen Germany
Manufactured for: Janssen Products, LP, Horsham, PA
For more information, call 1-800-526-7736 or go to www.YONDELIS.com.