

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207953Orig1s000

LABELING

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

INDICATIONS AND USAGE

YONDELIS is an alkylating drug indicated for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen (1)

DOSAGE AND ADMINISTRATION

- Administer at 1.5 mg/m² body surface area as a 24-hour intravenous infusion, every 3 weeks through a central venous line (2.1, 2.5)
- Premedication: dexamethasone 20 mg IV, 30 min before each infusion (2.2)

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 Grade 2 or greater neutropenia (5.1)
- Rhabdomyolysis: Rhabdomyolysis may occur; withhold YONDELIS for severe or life-threatening increases in creatine phosphokinase level (5.2)

- Hepatotoxicity: Hepatotoxicity may occur. Monitor and delay and/or reduce dose if needed (5.3)
- Cardiomyopathy: Severe and fatal cardiomyopathy can occur. Withhold YONDELIS in patients with left ventricular dysfunction (5.4)
- Embryofetal toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use effective contraception (5.6, 8.1, 8.3)

ADVERSE REACTIONS

The most common (≥20%) adverse reactions are nausea, fatigue, vomiting, constipation, decreased appetite, diarrhea, peripheral edema, dyspnea, 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 Biotech, Inc. 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: Breastfeeding not recommended (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling

Revised: 10/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dose and Schedule
- 2.2 Premedication
- 2.3 Dose Modifications
- 2.4 Preparation for Administration
- 2.5 Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Neutropenic Sepsis
- 5.2 Rhabdomyolysis
- 5.3 Hepatotoxicity
- 5.4 Cardiomyopathy
- 5.5 Extravasation Resulting in Tissue Necrosis
- 5.6 Embryofetal Toxicity

6 ADVERSE REACTIONS

- 6.1 Adverse Reactions in Clinical Trials

7 DRUG INTERACTIONS

- 7.1 Effect of Cytochrome CYP3A Inhibitors
- 7.2 Effect of Cytochrome CYP3A Inducers

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.3 Females and Males of Reproductive Potential

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Hepatic Impairment

8.7 Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

- 16.1 How Supplied
- 16.2 Storage and Handling

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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 Dose and Schedule

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, in patients with normal bilirubin and AST or ALT less than or equal to 2.5 times the upper limit of normal.

There is no recommended dose of YONDELIS in patients with serum bilirubin levels above the institutional upper limit of normal [*see Warnings and Precautions (5.3)* and *Clinical Pharmacology (12.3)*].

2.2 Premedication

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

2.3 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/m²
- Severe liver dysfunction (all of the following: bilirubin two times the upper limit of normal and AST or ALT three times the upper limit of normal with alkaline phosphatase less than two times the upper limit of normal) in the prior treatment cycle

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. The dose reductions for YONDELIS are:

- First dose reduction: YONDELIS 1.2 mg/m² every 3 weeks
- Second dose reduction: YONDELIS 1.0 mg/m² every 3 weeks

Table 1: Recommended Dose Modification

Laboratory Result or Adverse Reaction	DELAY next dose of YONDELIS for up to 3 weeks	REDUCE next dose of YONDELIS by one dose level for adverse reaction(s) during prior cycle
Platelets	Less than 100,000 platelets/microliter	Less than 25,000 platelets/microliter
Absolute neutrophil count	Less than 1,500 neutrophils/microliter	- Less than 1,000 neutrophils/microliter with fever/infection - Less than 500 neutrophils/microliter lasting more than 5 days
Total bilirubin	Greater than the upper limit of normal	Greater than the upper limit of normal
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT)	More than 2.5 times the upper limit of normal	More than 5 times the upper limit of normal
Alkaline phosphatase (ALP)	More than 2.5 times the upper limit of normal	More than 2.5 times the upper limit of normal
Creatine phosphokinase	More than 2.5 times the upper limit of normal	More than 5 times the upper limit of normal
Decreased left ventricular ejection fraction	- Less than lower limit of normal; or - Clinical evidence of cardiomyopathy	- Absolute decrease of 10% or more from baseline and less than lower limit of normal; or - Clinical evidence of cardiomyopathy
Other non-hematologic adverse reactions	Grade 3 or 4	Grade 3 or 4

2.4 Preparation for Administration

- YONDELIS is a cytotoxic drug. Follow applicable special handling and disposal procedures.¹
- 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 1, 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 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 $\geq 38.5^{\circ}\text{C}$ 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 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 [see *Dosage and Administration* (2.3)].

5.2 Rhabdomyolysis

YONDELIS can cause rhabdomyolysis and musculoskeletal toxicity. In Trial 1, 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).

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 [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 AST or ALT levels $>2.5 \times \text{ULN}$ 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) 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 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) in patients receiving YONDELIS. ALT or AST elevation greater than eight times the ULN occurred in 18% (67/378) of patients receiving YONDELIS.

Assess LFTs prior to each administration of YONDELIS. 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)*].

5.4 Cardiomyopathy

Cardiomyopathy including cardiac failure, congestive heart failure, ejection fraction decreased, diastolic dysfunction, or right ventricular dysfunction can occur with YONDELIS. 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 [see *Dosage and Administration (2.3)*].

5.5 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 [see *Dosage and Administration (2.5)*].

5.6 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 [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)*]
- Extravasation Resulting in Tissue Necrosis [see *Warnings and Precautions (5.5)*]

6.1 Adverse Reactions in Clinical Trials

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 6 months and 57 (8%) 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 1). 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.

Tables 2 and 3 present selected adverse reactions and laboratory abnormalities, respectively, observed in Trial 1, an open-label, randomized (2:1), active-controlled trial in which 550 patients with previously treated leiomyosarcoma or liposarcoma (dedifferentiated, myxoid round cell, or pleomorphic) received YONDELIS 1.5 mg/m² intravenous infusion over 24 hours once every 3 weeks (n=378) or dacarbazine 1000 mg/m² intravenous infusion over 20 to 120 minutes once every 3 weeks (n=172) [see *Clinical Studies (14)*]. All patients treated with YONDELIS were required to receive dexamethasone 20 mg intravenous injection 30 minutes prior to start of the YONDELIS infusion.

In Trial 1, patients had been previously treated with an anthracycline- and ifosfamide-containing regimen or with an anthracycline-containing regimen and one additional cytotoxic chemotherapy regimen. The trial excluded patients with known central nervous system metastasis, elevated serum bilirubin or significant chronic liver disease, such as cirrhosis or active hepatitis, and history of myocardial infarction within 6 months, history of New York Heart Association Class II to IV heart failure, or abnormal left ventricular ejection fraction at baseline. The median age of patients in Trial 1 was 57 years (range: 17 to 81 years), with 69% female, 77% White, 12% Black or African American, 4% Asian, and <1% American Indian or Alaska Native. The median duration of exposure to trabectedin was 13 weeks (range: 1 to 127 weeks) with 30% of patients exposed to YONDELIS for greater than 6 months and 7% of patients exposed to YONDELIS for greater than 1 year.

In Trial 1, adverse reactions resulting in permanent discontinuation of YONDELIS occurred in 26% (98/378) of patients; the most common were increased liver tests (defined as ALT, AST, alkaline phosphatase, bilirubin) (5.6%), thrombocytopenia (3.4%), fatigue (1.6%), increased creatine phosphokinase (1.1%), and decreased ejection fraction (1.1%). Adverse reactions that led to dose reductions occurred in 42% (158/378) of patients treated with YONDELIS; the most common were increased liver tests (24%), neutropenia (including febrile neutropenia) (8%), thrombocytopenia (4.2%), fatigue (3.7%), increased creatine phosphokinase (2.4%), nausea (1.1%), and vomiting (1.1%). Adverse reactions led to dose interruptions in 52% (198/378) of patients treated with YONDELIS; the most common were neutropenia (31%), thrombocytopenia (15%), increased liver tests (6%), fatigue (2.9%), anemia (2.6%), increased creatinine (1.1%), and nausea (1.1%).

The most common adverse reactions (≥20%) were nausea, fatigue, vomiting, constipation, decreased appetite, diarrhea, peripheral edema, dyspnea, and headache. The most common laboratory abnormalities (≥20%) were increases in AST or ALT, increased alkaline phosphatase, hypoalbuminemia, increased creatinine, increased creatine phosphokinase, anemia, neutropenia, and thrombocytopenia.

Table 2: Selected Adverse Reactions^a occurring in ≥10% of Patients receiving YONDELIS and at a higher incidence than in the Control Arm - Trial 1

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

^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.

^c 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.

Table 3: Incidence of Selected Treatment-Emergent Laboratory Abnormalities^a - Trial 1

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

^a Treatment-emergent laboratory abnormalities including those higher in the trabectedin arm compared with the dacarbazine arm by $\geq 5\%$ (all Grades) or by $\geq 2\%$ (Grade 3-4). Incidence based on number of patients who had both baseline and at least one on-study laboratory measurement

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

7 DRUG INTERACTIONS

7.1 Effect of Cytochrome CYP3A Inhibitors

Coadministration of YONDELIS with ketoconazole, a strong CYP3A inhibitor, increases systemic exposure of trabectedin by 66%. Avoid use of 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. Avoid taking grapefruit or grapefruit juice during YONDELIS treatment. 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 [*see Clinical Pharmacology (12.3)*].

7.2 Effect of Cytochrome CYP3A Inducers

Coadministration of YONDELIS with rifampin, a strong CYP3A inducer, decreased systemic exposure of trabectedin by 31%. Avoid administering strong CYP3A inducers (e.g., rifampin, phenobarbital, St. John's wort) to patients who are 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 are 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

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)*].

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.

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 pharmacokinetics of trabectedin has not been evaluated in patients with a total bilirubin greater than the upper limit of normal [*see Clinical Pharmacology (12.3)*].

8.7 Renal Impairment

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

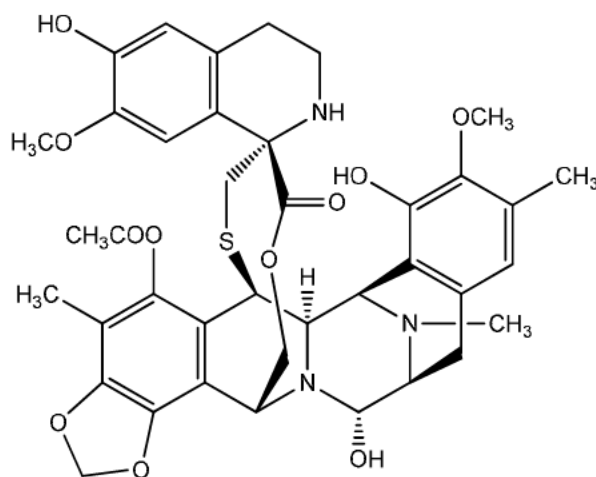
The pharmacokinetics of trabectedin has not been evaluated in patients with severe renal impairment (CLcr <30 mL/min) or end stage renal disease [see *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

There is no specific antidote for YONDELIS. Hemodialysis is not expected to 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 agent with the chemical name (1'*R*,6*R*,6*aR*,7*R*,13*S*,14*S*,16*R*)-5-(acetyloxy)-3',4',6,6*a*,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethylspiro[6,16-(epithiopropoxymethano)-7,13-imino-12*H*-1,3-dioxolo[7,8]isoquino[3,2-*b*][3]benzazocine-20,1'(2'*H*)-isoquinolin]-19-one. The molecular formula is C₃₉H₄₃N₃O₁₁S. 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 towards the major groove. Adduct

formation triggers a cascade of events that can 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 is 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 31.5 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 ¹⁴C-labeled trabectedin, 64% of the total administered radioactive dose was recovered in 24 days, with 58% in feces and 6% in urine.

Specific Populations

The following population characteristics are not associated with a clinically significant effect on the pharmacokinetics of trabectedin: sex, age (19 to 83 years), body weight (36 to 148 kg), body surface area (0.9 to 2.8 m²), or mild to moderate renal impairment. The effect of any degree of

hepatic impairment, severe renal impairment, or end stage renal disease on trabectedin exposure is unknown.

Drug Interactions

Effect of Strong CYP3A Inhibitors on Trabectedin

Coadministration 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 C_{max} by 22% compared to a single YONDELIS dose (1.3 mg/m²) given alone.

Effect of Strong CYP3A Inducers on Trabectedin

Coadministration 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 C_{max} 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 1, 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 dexamethasone 20 mg intravenous injection prior to each 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; 73% had leiomyosarcomas and 27% liposarcomas; 49% had an ECOG PS of 0; and 89% received ≥ 2 prior chemotherapy regimens. The most common ($\geq 20\%$) pre-study chemotherapeutic agents administered were doxorubicin (90%), gemcitabine (81%), docetaxel (74%), and ifosfamide (59%). Approximately 10% of patients had received pazopanib.

Trial 1 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 1 are presented in the table below.

Table 4: Efficacy Results for Trial 1

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

^a Cox proportional hazards model with treatment group as the only covariate.

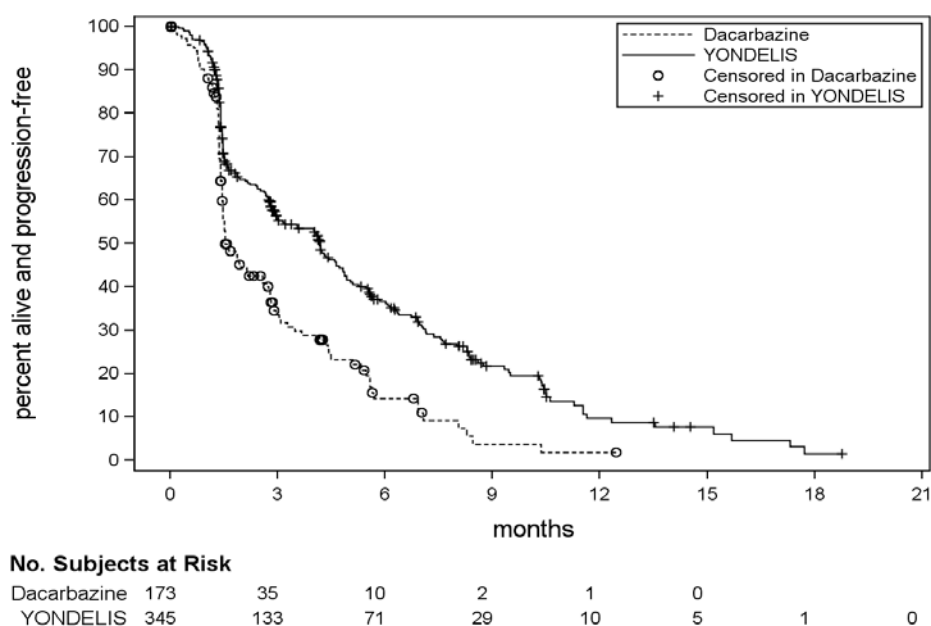
^b Unstratified log rank test.

^c Based on 384 patients randomized to YONDELIS arm and 193 patients randomized to dacarbazine.

^d 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 1



15 REFERENCES

1. "Hazardous Drugs", *OSHA*, <http://www.osha.gov/SLTC/hazardousdrugs/index.html>

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

YONDELIS is supplied in a glass vial containing 1 mg trabectedin. Each carton contains one vial (NDC: 59676-610-01).

16.2 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

Advise 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.

Cardiomyopathy: Advise patients to contact their healthcare provider for new onset chest pain, shortness of breath, fatigue, lower extremity edema, or heart palpitations.

Hypersensitivity: Advise patients to seek immediate medical attention for symptoms of allergic reactions including difficulty breathing, chest tightness, wheezing, severe dizziness or light-headedness, swelling of the lips or skin rash.

Extravasation: Inform patients of the risks of extravasation and to notify their healthcare provider for redness, swelling, itchiness and discomfort or leakage at the injection site.

Embryofetal toxicity: Advise pregnant women of the potential risk to a fetus. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with YONDELIS [see *Warnings and Precautions* (5.6) and *Use in Specific Populations* (8.1)].

Females and males of reproductive potential: Advise females of reproductive potential to use effective contraception during treatment with YONDELIS and for at least 2 months after last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with YONDELIS and for at least 5 months after the last dose [see *Warnings and Precautions* (5.6) and *Use in Specific Populations* (8.3)].

Lactation: Advise females not to breastfeed during treatment with YONDELIS [see *Use in Specific Populations* (8.2)].

Manufactured by:
Baxter Oncology GmbH
Halle/Westfalen Germany

Manufactured for:
Janssen Products, LP
Horsham, PA

© Janssen Products, LP. 2015

Under license from Pharma Mar, S.A.

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 should I avoid while receiving YONDELIS?

- Avoid grapefruit and grapefruit juice during treatment with YONDELIS.

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.
- **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
 - generally do not feel well
 - problem with concentration
 - confusion
 - sleepiness
- **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 doctor 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.

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.

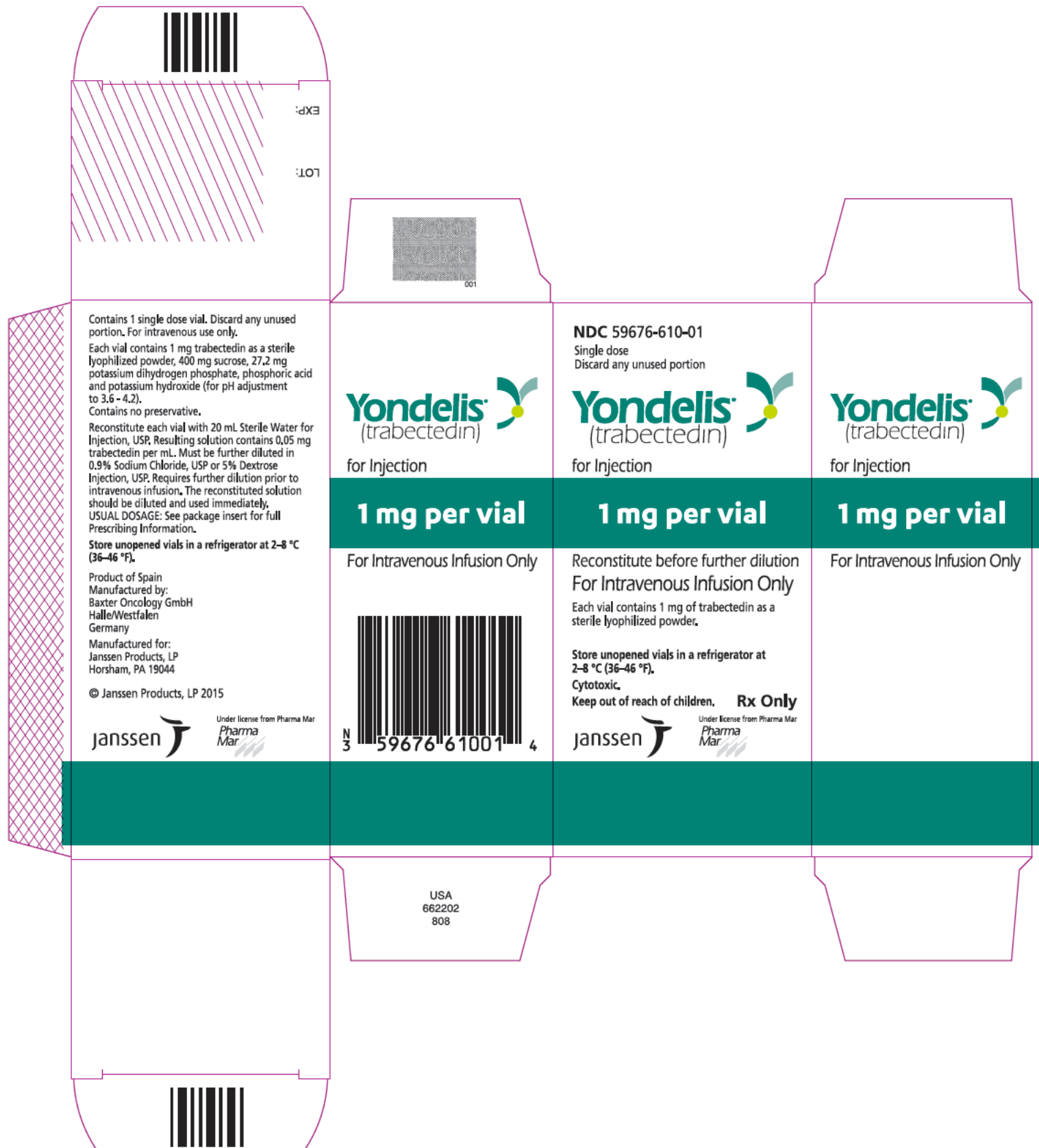
Manufactured by: Baxter Oncology GmbH, Halle/Westfalen Germany

Manufactured for: Janssen Products, LP, Horsham, PA

For more information, call 1-800-526-7736 or go to www.YONDELIS.com.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Issued: October/2015



(b) (4)

NDC 59676-610-01

Yondelis
(trabectedin)

for Injection

1 mg per vial

For Intravenous Infusion Only

Single dose
Discard any unused portion
Rx Only

Cytotoxic.
Store unopened vials in a refrigerator at
2-8 °C (36-46 °F).
Reconstitute each vial with 20 mL Sterile
Water for Injection, USP.
Resulting solution contains 0.05 mg
trabectedin per mL.



Janssen Products, LP, Horsham, PA 19044
Under License from Pharmacia Inc.


Pharmacia
Janssen

USA -- 662200

LOT: 
662200

EXP: 

(b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD PAZDUR
10/23/2015