PRODUCT MONOGRAPH

PrYONDELIS®*

trabectedin for Injection

1 mg/vial trabectedin

Antineoplastic Agent

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Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION 3
SUMMARY PRODUCT INFORMATION 3
INDICATIONS AND CLINICAL USE 3
CONTRAINDICATIONS 4
WARNINGS AND PRECAUTIONS 4
ADVERSE REACTIONS 9
DRUG INTERACTIONS 17
DOSAGE AND ADMINISTRATION 18
OVERDOSAGE 21
ACTION AND CLINICAL PHARMACOLOGY 21
STORAGE AND STABILITY 23
SPECIAL HANDLING INSTRUCTIONS 24
DOSAGE FORMS, COMPOSITION AND PACKAGING 24

PART II: SCIENTIFIC INFORMATION 25
PHARMACEUTICAL INFORMATION 25
CLINICAL TRIALS 25
DETAILED PHARMACOLOGY 33
TOXICOLOGY 33
REFERENCES 35

PART III: CONSUMER INFORMATION 36

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
intravenous through central line	Sterile lyophilized powder for injection/ 1 mg	None *For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

INDICATIONS AND CLINICAL USE

YONDELIS® (trabectedin) in combination with CAELYX® (pegylated liposomal doxorubicin hydrochloride [PLD]) is indicated for the treatment of patients with platinum-sensitive ovarian cancer for whom one first-line platinum-based chemotherapy regimen, including adjuvant therapy, has failed, and who are not expected to benefit, are ineligible or not willing to receive retreatment with platinum-based chemotherapy.

Approval of YONDELIS® in combination with CAELYX® is based on progression-free survival (PFS) benefit in patients with relapsed ovarian cancer. A prolongation of overall survival or quality of life benefit has not been demonstrated (see **PART II: CLINICAL TRIALS**).

YONDELIS® (trabectedin) is indicated for the treatment of patients with metastatic liposarcoma or leiomyosarcoma after failure of prior anthracycline and ifosfamide chemotherapy.

The clinical effectiveness of YONDELIS® in this indication is based on time to progression (TTP) benefit demonstrated in a randomized study comparing two different dosing regimens of YONDELIS®. Prolongation of overall survival was not demonstrated and quality of life benefits were not assessed (see **PART II: CLINICAL TRIALS**). A clinical study comparing YONDELIS® to either a standard of care or placebo has not been conducted.

Geriatrics (> 65 years of age):
No relevant differences in the safety profile or effectiveness were seen in this patient population **(see DOSAGE AND ADMINISTRATION, Geriatrics).** Dose adjustments based uniquely on age criteria are not routinely recommended.

Pediatrics (< 18 years of age):
The safety and efficacy of YONDELIS® in pediatric patients have not been established. Therefore, this medicinal product should not be used in children and adolescents.

CONTRAINDICATIONS

- Patients who are hypersensitive to YONDELIS® (trabectedin) or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.
- YONDELIS® should not be administered to nursing mothers (see **WARNINGS AND PRECAUTIONS, Special Populations**).
- YONDELIS® should not be administered to patients with an active serious or uncontrolled infection.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

YONDELIS® (trabectedin) should be prescribed by a qualified healthcare professional who is experienced in the use of antineoplastic therapy.

Administration of YONDELIS® through a central venous line is required (see **Injection Site Reactions** below and **DOSAGE AND ADMINSTRATION**).

YONDELIS® must not be used in patients with elevated bilirubin levels (see **Special Populations**, **Hepatic Impairment** section below)

The following are clinically significant adverse events:

- Hepatotoxicity (see **Hepatic** section below)
- Rhabdomyolysis (see **Rhabdomyolysis and severe CPK elevations (>5 x ULN)** section below**)**
- Febrile Neutropenia and Sepsis (see **Hematologic** section below)
- Pulmonary embolism **(**see **Pulmonary embolism** section below**)**
- Injection site reactions (see **Injection Site Reactions** section below)

Please refer to the Product Monograph for CAELYX® for information on its **WARNINGS AND PRECAUTIONS.**

General
Caution should be taken if medicinal products associated with hepatotoxicity are administered concomitantly with YONDELIS®, since the risk of hepatotoxicity may be increased. The concomitant use of YONDELIS® with alcohol must be avoided.

Carcinogenesis and Mutagenesis
Long-term carcinogenicity studies have not been performed. YONDELIS® is genotoxic both in vitro and in vivo (see ***Product Monograph*** **PART II, TOXICOLOGY**).

Cardiovascular
Special attention must be given to the risk of myocardial damage from cumulative doses of doxorubicin HCl. Please refer to the Product Monograph for CAELYX® for additional information on cardiovascular events.

Clinically significant symptomatic cardiac adverse events, defined as cardiac-related adverse events of Grade 2 or higher, were observed in both treatment arms (3% in the YONDELIS® + CAELYX® arm and 2% in the CAELYX® monotherapy arm). Congestive heart failure events (including left ventricular dysfunction, cardiac failure, cardiac failure congestive and ventricular dysfunction) in the YONDELIS® + CAELYX® arm were 2% (n=6) and <1% (n=1) in the CAELYX® monotherapy arm.

A multigated acquisition (MUGA) scan or 2-D echocardiogram should be performed prior to treatment with YONDELIS® in combination with CAELYX®, and patients with a left ventricular ejection fraction below the normal limit for the institution should not be treated.

YONDELIS® has been associated with a transient increase in heart rate (see **ACTION AND CLINICAL PHARMACOLOGY**, **Electrocardiography**). Increases in heart rate may lead to worsening of cardiac conditions in patients with a history of ischemic heart disease or tachyarrhythmia. Cautions should be observed in these patient populations.

Pulmonary embolism
There were 17 (5%) and 8 (2%) cases of pulmonary embolism reported in the YONDELIS® + CAELYX® arm and in the CAELYX® monotherapy arm, respectively.

Gastrointestinal
Grade 3 or 4 vomiting and nausea were reported commonly in patients treated with YONDELIS®. All patients must be premedicated with corticosteroids, such as dexamethasone, to protect the liver and as anti-emetic medication. Additional anti-emetics may be administered as needed (see **DOSAGE AND ADMINISTRATION, Recommended Dose**).

Hematologic
Grade 3 or 4 neutropenia has been very commonly reported and associated with YONDELIS®. In combination therapy with CAELYX®, neutropenia was associated with complications such as febrile neutropenia, sepsis and infections, some of which were fatal. Neutrophil nadirs occurred at a median of 15 days and recovered within a week. Twenty-seven subjects (8%) and 7 subjects (2%) had febrile neutropenia in the YONDELIS® + CAELYX® combination arm and the CAELYX® monotherapy arm, respectively. Three (1.2%) subjects in the combination arm had deaths associated with neutropenia (neutropenic sepsis, sepsis and febrile neutropenia) and one subject in the CAELYX® monotherapy arm died due to sepsis. Colony-stimulating growth factors have been used to manage neutropenia. One hundred and forty (42%) of subjects in the combination arm and 57 subjects (17%) in the CAELYX® monotherapy arm were treated with colony-stimulation growth factors. As monotherapy, febrile neutropenia was reported in 2% of patients treated with YONDELIS®.

Grades 3 or 4 thrombocytopenia associated with YONDELIS® therapy have been very commonly reported. In the pivotal study, Grade 3 or 4 abnormalities in platelet counts were observed for 77 subjects (23%) in the YONDELIS® + CAELYX® combination arm and 14 subjects (4%) in the CAELYX® monotherapy arm. Bleeding-related adverse events were reported in a similar percent of subjects in the YONDELIS® + CAELYX® (9%) and CAELYX® (8%) arms.

A full blood cell count including differential and platelet count must be performed at baseline, weekly for the first two cycles and then once between cycles (see **DOSAGE AND ADMINISTRATION, Recommended Dose**). YONDELIS® should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm^3 and platelets count of less than 100,000 cells/mm^3. If severe neutropenia (ANC< 500 cells/mm^3) lasting more than 5 days or associated with fever or infection occur, dose reduction is recommended (see **DOSAGE AND ADMINISTRATION, Dose Adjustments During Treatment**).

Hepatic

Reversible acute increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been reported in most patients treated with YONDELIS® monotherapy or in combination with CAELYX®. Grade 3/4 transaminase elevations occurred very commonly, grade 4 occurred commonly (see **ADVERSE REACTIONS**). The median time to the occurrence of ALT or AST increase to grade 3/4 was 8 days. Elevated levels decreased to below grade 3/4 in about 8 days. Transaminase elevations were non-cumulative and decreased in magnitude and incidence with each subsequent cycle. In the pivotal study in ovarian cancer 3 (0.9%) patients fulfilled Hy's Law criteria for predicting severe liver toxicity, although none of these 3 subjects developed severe liver toxicity. In 19 YONDELIS® single agent Phase 2 studies, 14 cases (1.2%) met the definition of Hy's Law.

YONDELIS® must not be used in patients with elevated bilirubin at the time of initiation of cycle. Patients with increases in AST, ALT and alkaline phosphatase between cycles may necessitate a dose reduction (see **DOSAGE AND ADMINISTRATION, Dose Adjustments During Treatment**).

Monitoring of alkaline phosphatase, bilirubin, and aminotransferases (AST and ALT) should occur prior to each cycle of therapy, weekly during the first two cycles of therapy, and at least once between treatments in subsequent cycles (see **Monitoring and Laboratory Tests** below).

Injection Site Reactions

Administration through a central venous line is required (see **DOSAGE AND ADMINISTRATION, Dosing Considerations**). Patients may develop a potentially severe injection site reaction when YONDELIS® is administered through a peripheral venous line.

There have been few reported cases of YONDELIS® extravasation, with subsequent tissue necrosis requiring debridement. There is no specific antidote for extravasation of YONDELIS®. Extravasation should be managed by local standard practice (see **PART II, TOXICOLOGY**).

The percentage of catheter related ADRs were 14% vs. 3% in the YONDELIS® in combination with CAELYX® arm vs. CAELYX® arm alone, respectively.

Rhabdomyolysis and severe CPK elevations (>5 x ULN)
YONDELIS® must not be used in patients with CPK >2.5 x ULN (see **DOSAGE AND ADMINISTRATION, Recommended Dose**). Rhabdomyolysis has been uncommonly reported, usually in association with myelotoxicity, severe liver function test abnormalities or renal failure. Severe CPK elevations were observed in 4% and 2% of patients treated with YONDELIS® monotherapy or in combination with CAELYX®, respectively, usually in association with myelotoxicity, severe liver function test abnormalities or renal failure. Therefore, CPK should be closely monitored routinely during therapy and especially whenever a patient may be experiencing any of these toxicities or muscle weakness or muscle pain. CPK should be monitored weekly during the first two cycles of therapy and at least once between treatment and subsequent cycles. If rhabdomyolysis occurs, supportive measures such as parenteral hydration, urine alkalinisation and dialysis should be promptly established, as indicated. Treatment with YONDELIS® should be discontinued until the patient fully recovers.

Caution should be taken if medicinal products associated with rhabdomyolysis (e.g., statins) are administered concomitantly with YONDELIS®, since the risk of rhabdomyolysis may be increased.

Renal
Creatinine clearance must be monitored prior to and during treatment. YONDELIS® as a single agent must not be used in patients with creatinine clearance < 30 mL/min. YONDELIS® in combination with CAELYX® must not be used in patients with creatinine clearance < 60 mL/min (see **DOSAGE AND ADMINISTRATION, Recommended Dose**).

Special Populations

Pregnant Women:
No sufficient clinical data on exposed pregnancies are available. However, based on its known mechanism of action, YONDELIS® may cause serious birth defects when administered during pregnancy. YONDELIS® should not be used during pregnancy unless clearly necessary. If it is used during pregnancy, the patient must be informed of the potential risk to the fetus (see **TOXICOLOGY, Reproductive and Developmental Toxicity**) and be monitored carefully. If YONDELIS® is used at the end of pregnancy, potential adverse reactions should be monitored carefully in the newborns.

Reproduction
Men who are fertile and women of childbearing potential must use effective contraception during treatment and 3 months thereafter for women, and immediately inform the treating physician if a pregnancy occurs and 5 months after treatment for men.

YONDELIS® can have genotoxic effects (see **PART II, TOXICOLOGY**). Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with YONDELIS®.

If pregnancy occurs during treatment genetic counselling should be considered. Genetic counselling is also recommended for patients wishing to have children after therapy.

Nursing Women:
It is not known whether YONDELIS® is excreted in human milk. The excretion of YONDELIS® in milk has not been studied in animals. Breast-feeding is contraindicated during treatment and 3 months thereafter (see **CONTRAINDICATIONS**).

Geriatrics (> 65 years of age):
Of the 1132 patients from single agent clinical trials from an integrated safety analysis in several tumour types, 19% were over 65 years. No relevant differences in the safety profile or effectiveness were seen in this patient population. Of the 672 patients with ovarian cancer who received YONDELIS® in combination with CAELYX®, 24% were 65 years of age or older and 6% were over 75 years. No difference in safety was observed in this patient population. In this study, a multivariate analysis of progression-free survival, age over 65 years did not affect the outcome. Results from population pharmacokinetic analyses indicate that the plasma clearance and distribution volume of YONDELIS® are not influenced by age. Therefore, dose adjustments based uniquely on age criteria are not routinely recommended.

Pediatrics (< 18 years of age):
The safety and efficacy of YONDELIS® in pediatric patients have not yet been established. Therefore, YONDELIS® should not be used in children and adolescents (see **PART II, TOXICOLOGY**).

Renal Impairment
Studies including patients with renal insufficiency (creatinine clearance < 30 mL/min for the monotherapy, and < 60 mL/min for the combination regimen) have not been conducted and therefore YONDELIS® must not be used in this patient population (see **DOSAGE AND ADMINISTRATION**). The pharmacokinetics of YONDELIS® are not expected to be impacted by mild or moderate renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY, Renal Insufficiency**).

Hepatic Impairment
Patients with elevated bilirubin at the time of initiation of cycle must not be treated with YONDELIS®.

Patients must meet specific criteria on hepatic function parameters to start treatment with YONDELIS®:

- Bilirubin ≤ upper limit of normal (ULN)
- Alkaline phosphatase of non-osseous origin ≤ 2.5 x ULN (consider hepatic isoenzymes 5 nucleotidase or GGT, to distinguish if the elevation could be osseous in origin)
- Albumin ≥ 25 g/L
- Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) ≤ 2.5 x ULN

The use of YONDELIS® in patients with impaired hepatic function has not been adequately studied. Since systemic exposure to YONDELIS® may be increased due to hepatic impairment and therefore the risk of hepatotoxicity might be increased, the use of YONDELIS® in patients with clinically relevant liver diseases, such as active chronic hepatitis, is not recommended (see **DOSAGE AND ADMINISTRATION, Recommended Dose**).

Monitoring and Laboratory Tests

Prior to each treatment cycle, patients must fulfill the following baseline criteria:

- Absolute neutrophil count (ANC) ≥ 1,500/mm^3
- Platelets count ≥ 100,000/mm^3
- Hemoglobin ≥9 g/dL
- Bilirubin ≤ ULN
- Alkaline phosphatase of non-osseous origin ≤ 2.5 x ULN
- Aminotransferases (AST and ALT) ≤ 2.5 x ULN
- Albumin ≥ 25 g/L
- Creatinine clearance ≥ 30 ml/min (monotherapy), serum creatinine ≤ 1.5 mg/dL (≤ 132.6 μmol/L) or creatinine clearance ≥ 60 mL/min (combination therapy)
- CPK ≤ 2.5 x ULN

Monitoring of hematological (a full blood count including differential and platelet count) and biochemical parameters (alkaline phosphatase, bilirubin, CPK, and aminotransferases [AST and ALT]) should occur at baseline and weekly during the first two cycles of therapy, and at least once between treatments in subsequent cycles. If any of the following events occur at any time between cycles, the YONDELIS® and CAELYX® dose must be reduced (see **DOSAGE AND ADMINISTRATION**):

- Neutropenia with ANC < 500/mm^3 lasting for more than 5 days or associated with fever or infection
- Thrombocytopenia with platelets count < 25,000/mm^3
- Increase of bilirubin > ULN
- Alkaline phosphatase of non-osseous origin > 2.5 x ULN
- Increase of aminotransferases (AST or ALT) > 2.5 x ULN (monotherapy), or > 5 x ULN (combination therapy), which has not recovered by day 21.
- Any other grade 3 or 4 adverse reactions (such as nausea, vomiting, fatigue)

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse drug reactions (ADRs) are adverse events that are considered to be reasonably associated with the use of YONDELIS® (trabectedin) based on a comprehensive assessment of available adverse event information.

Unless otherwise specified, the following safety profile of YONDELIS® is based on the evaluation in clinical trials of patients treated with the recommended treatment regimens for both indications.

YONDELIS® IN MONOTHERAPY IN METASTATIC LIPOSARCOMA OR LEIOMYOSARCOMA

The following safety profile of YONDELIS® monotherapy is based on the evaluation of a Phase 2 clinical trial (Study ET743-STS-201) in 260 treated patients with metastatic liposarcoma or leiomyosarcoma (L-Sarcoma) who had prior treatment with an anthracycline and ifosfamide. Patients were randomized to trabectedin 1.5 mg/m^2 24-hr infusion given every 3 week (q3wk 24-

h) or a 0.58 mg/m^2 3-h infusion weekly for three weeks in 4-week cycles (qwk 3-h). One hundred and thirty patients were treated in the q3wk 24-h arm. In this treatment arm, the median number of cycles per patient was 5 (range, 1-37) for a median duration of 15.4 weeks.

The most common adverse reactions of any severity grade were nausea, fatigue, vomiting, anorexia, neutropenia, and increases in AST/ALT. Fatal adverse reactions have occurred in 1.9% of patients. They were often the result of a combination of events including pancytopenia, febrile neutropenia, some of them with sepsis, hepatic involvement, renal failure and rhabdomyolysis. Twelve patients (4.6%) discontinued trabectedin treatment due to drug-related AEs: eight patients in the q3wk 24-h group (grade 2 muscle weakness, grade 2 AP increase, grade 3 AP increase, grade 3 thrombocytopenia, grade 4 neutropenia [n=2], grade 3 ALT increase and grade 3 AST increase); and four patients in qwk 3-h group (grade 2 bilirubin increase, grade 2 AP increase, grade 2 neutropenia, and grade 2 asthenia). The most common adverse drug reaction leading to dose reductions were transient AST or ALT increases followed by alkaline phosphatase increases.

Clinical Trial Adverse Drug Reactions

Table 1.1 displays the adverse reactions reported in ≥5% of patients with liposarcoma or leiomyosarcoma treated with YONDELIS® at the recommended regimen (1.5 mg/m^2, 24 hour infusion every 3 weeks) according to the standard MedDRA system organ class. Both adverse reactions and laboratory values have been used to provide frequencies. Within each frequency group, undesirable effects are presented in order of decreasing seriousness.

Table 1.1- Treatment emergent drug related adverse events reported in ≥ 5% of patients in the randomized clinical trial comparing two YONDELIS® regimens [1.5 mg/m^2, 24 hour infusion every 3 weeks (24-h q3wk) to the 0.58 mg/m^2, 3 hour infusion every week for 3 consecutive weeks of a 4 week cycle] for the treatment of metastatic liposarcoma and leiomyosarcoma.

Adverse Drug Reaction System Organ Class Preferred Term	q 3 wk 24-h (N=130) %			q wk 3-h (N=130) %		
	Any (%)	Grade 3	Grade 4	Any (%)	Grade 3	Grade 4
Gastrointestinal Disorders						
Nausea	72	4	0	52	3	0
Vomiting	39	2	0	23	2	0
Constipation	18	0	0	18	0	0
Diarrhoea	15	0	0	14	0	0
Abdominal Pain	5	2	0	2	1	0
Dyspepsia	5	0	0	6	0	0
Investigations						
Alanine Aminotransferase Increased	54	37	2	38	9	0
Aspartate Aminotransferase Increased	47	23	0	27	5	0
Blood Alkaline Phosphatase Increased	28	0	0	25	2	0
Neutrophil Count Decreased	12	6	3	4	2	0
Blood Creatine Phosphokinase Increased	10	2	1	14	5	2
Blood Bilirubin Increased	8	0	0	5	2	0
White Blood Cell Count Decreased	7	3	0	6	1	0
Haemoglobin Decreased	5	0	0	4	1	0
Platelet Count Decreased	5	1	0	3	2	0
Blood Creatinine Increased	5	0	0	2	0	0
Transaminases Increased	5	2	0	2	1	0
General Disorders and Administration Site Conditions						
Fatigue	53	5	1	45	5	0
Asthenia	15	1	0	6	2	0
Pyrexia	5	0	0	5	0	0
Oedema Peripheral	5	0	0	4	0	0
Chest Pain	1	0	0	5	0	0
Blood and Lymphatic System Disorders						
Neutropenia	49	22	13	28	9	2
Anaemia	27	1	0	25	5	0
Thrombocytopenia	20	8	2	8	2	1
Leukopenia	12	3	2	6	2	0
Metabolism and Nutrition Disorders						
Anorexia	19	1	0	12	0	0
Decreased Appetite	6	0	0	2	0	0
Dehydration	5	0	0	4	2	0
Hypokalaemia	5	2	0	2	1	0
Nervous System Disorders						
Headache	15	1	0	9	1	0
Dysgeusia	8	0	0	4	0	0
Dizziness	5	1	0	5	0	0
Musculoskeletal and Connective Tissue Disorders						
Myalgia	10	2	0	7	1	0
Arthralgia	5	1	0	3	0	0
Respiratory, Thoracic and Mediastinal Disorders						

Adverse Drug Reaction System Organ Class Preferred Term	q 3 wk 24-h (N=130) %			q wk 3-h (N=130) %		
Dyspnoea	5	1	0	9	2	0
Psychiatric Disorders						
Insomnia	6	0	0	2	0	0

The following data on treatment-emergent adverse events were from 8 clinical studies (pivotal study + 7 Phase 2) contributing to the integrated safety analysis set treated with YONDELIS® at 1.5 mg/m^2, 24-hour infusion every 3 weeks (24-h q3wk). The integrated safety analysis set included 570 subjects, most with soft tissue sarcomas.

Blood and Lymphatic system disorders

Neutropenia:
Neutropenia is the most common haematological toxicity. Neutrophil nadirs occurred at a median of 15 days and recovered within a week. In the soft tissue population, febrile neutropenia occurred in 2% of patients.

Thrombocytopenia:
Bleeding events associated to thrombocytopenia were reported in < 1% of patients treated with the monotherapy regimen.

Anaemia:
Anaemia occurred in 97% of patients treated with the monotherapy. The percentages of patients anaemic at baseline were 52%.

Hepatobiliary disorders

AST/ALT increases:
The median time to reach the peak values was 5 days for both AST and ALT. Most of the values had decreased to grade 1 or resolved by day 14 - 15. ALT and AST increases did not follow a cumulative pattern but showed a tendency towards less severe elevations over time.

Hyperbilirubinemia:
Liver function tests predicting severe toxicity (meeting Hy´s law) and clinical manifestations of severe hepatic injury were uncommon with a lower than 1% (n=5 patients with liposarcoma or leiomyosarcoma) incidence of individual signs and symptoms including jaundice, hepatomegaly or liver pain. Bilirubin peaks approximately a week after onset and resolves approximately two weeks after onset. Mortality in the presence of hepatic injury occurred in less than 1% of patients.

Other adverse reactions

CPK elevations and rhabdomyolysis:
CPK elevations of any grade were observed in 26% of patients. Grade 3 or 4 increases of CPK were observed in 4% of patients. CPK increases in association with rhabdomyolysis were reported in less than 1% of patients.

Alopecia:
Alopecia was reported in approximately 3% of patients treated with the monotherapy regimen, of which the majority was grade 1 alopecia.

Injection site reactions:
There have been few reported cases of YONDELIS® extravasation, some with subsequent tissue necrosis requiring debridement (see **WARNINGS AND PRECAUTIONS**).

YONDELIS® IN COMBINATION WITH CAELYX® IN ADVANCED OVARIAN CANCER

The most common ADRs, reported in ≥20% of patients treated with YONDELIS® in combination with CAELYX® were neutropenia, leukopenia, anemia, thrombocytopenia, nausea, vomiting, diarrhea, hand-foot syndrome, fatigue, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, constipation, abdominal pain and stomatitis.

In the pivotal study, ADRs leading to dose adjustment and cycle delays occurred in 43% and 65% of patients in the YONDELIS® + CAELYX® combination arm, and in 35% and 37% of patients in the CAELYX® monotherapy arm, respectively. ADRs that led to treatment termination occurred in 17% of subjects in the YONDELIS® + CAELYX® combination arm and 9% of subjects in the CAELYX® monotherapy arm. The most common adverse drug reaction, reported ≥5% leading to drug discontinuation, was neutropenia.

Clinical Trial Adverse Drug Reactions

The following safety profile of YONDELIS® in combination with CAELYX® is based on the evaluation of a phase 3 clinical trial OVA 301 of 663 patients with advanced relapsed ovarian cancer who received either CAELYX® (30 mg/m^2) followed by YONDELIS® (1.1 mg/m^2) every 3 weeks or CAELYX® alone (50 mg/m^2) every 4 weeks. The combination of YONDELIS® with CAELYX® was given to 333 patients in this trial. In the combination arm, the median number of cycles given was 6.0 cycles (range: 1 to 21) for a median of 19 weeks. In the CAELYX® only arm, the median number of cycles given was 5.0 cycles (range: 1 to 22) for a median of 20 weeks. Most ADRs were managed with dose reductions or delays.

Adverse reactions reported among patients treated with YONDELIS® in combination with CAELYX® during clinical studies that occurred at a rate ≥1% are shown in Table 1.2 below.

Table 1.2 Adverse Drug Reactions in ≥1% of Patients with Ovarian Cancer Treated With YONDELIS® in Combination with CAELYX®

Adverse Drug Reaction System Organ Class Preferred Term	YONDELIS®+ CAELYX® (n=333) %			CAELYX® (n=330) %		
	Any (%)	Grade 3	Grade 4	Any (%)	Grade 3	Grade 4
Infections and Infestations						
Neutropenic infection	1	1	0	0	0	0
Neutropenic sepsis	1	<1	<1	0	0	0
Blood and Lymphatic System Disorders						
Neutropenia	77	29	34	38	14	8
Leukopenia	48	25	8	26	7	3
Anemia	48	10	3	25	5	1
Thrombocytopenia	36	10	8	8	2	1
Febrile neutropenia	8	6	2	2	2	<1
Pancytopenia	2	2	1	0	0	0
Bone marrow failure	2	<1	1	<1	<1	0
Granulocytopenia	2	1	<1	0	0	0
Metabolism and Nutrition Disorders						
Dehydration	5	2	1	5	2	0
Hypokalemia	11	4	<1	8	1	0
Anorexia	32	2	0	26	3	<1
Psychiatric Disorders						
Insomnia	10	0	0	5	0	0
Nervous System Disorders						
Headache	16	1	0	8	<1	0
Peripheral sensory neuropathy	5	0	0	3	0	0
Dysgeusia	5	<1	0	3	0	0
Syncope	2	2	0	<1	0	0
Cardiac Disorders						
Palpitations	4	<1	0	0	0	0
Left ventricular dysfunction*	1	<1	0	0	0	0
Respiratory, Thoracic and Mediastinal Disorders						
Dyspnea	15	3	<1	10	2	<1
Cough	12	0	0	12	0	0
Pulmonary embolism	5	1	2	2	1	1
Pulmonary edema	1	0	0	0	0	0
Gastrointestinal Disorders						
Nausea	74	10	0	42	4	0
Vomiting	56	12	<1	30	4	0
Constipation	32	2	0	28	2	0
Diarrhea	26	2	0	19	2	0
Abdominal Pain	20	1	0	33	5	<1
Stomatitis	20	1	0	33	5	<1
Dyspepsia	13	<1	0	11	1	0
Hepatobiliary Disorders						
Hyperbilirubinemia	16	1	0	7	1	0
Hepatoxicity	2	1	0	<1	0	0
Skin and Subcutaneous Tissue Disorders						
Hand-foot syndrome**	24	4	0	54	18	1
Skin hyperpigmentation	6	0	0	3	0	0

Adverse Drug Reaction System Organ Class Preferred Term	YONDELIS®+ CAELYX® (n=333) %			CAELYX® (n=330) %		
Alopecia	12	0	0	14	<1	0
Rash	11	0	0	17	1	0
Musculoskeletal, Connective Tissue, and Bone Disorders						
Musculoskeletal pain	4	<1	0	3	<1	0
Myalgia	5	<1	0	3	0	0
Renal and Urinary Disorders						
Renal failure acute	2	1	<1	1	1	0
General Disorders and Administration Site Conditions						
Pyrexia	20	1	0	13	1	0
Fatigue	46	8	<1	36	5	<1
Asthenia	17	2	0	12	2	0
Mucosal inflammation	12	2	0	19	6	0
Edema peripheral	9	1	0	8	0	<1
Edema	3	<1	0	1	0	0
Catheter site pain	3	0	0	0	0	0
Catheter site erythema	2	0	0	0	0	0
Catheter site inflammation	2	0	0	1	0	0

* All patients reporting left ventricular dysfunction, after discontinuation of study therapy improved.
** For patients who experience hand-foot syndrome, the CAELYX® dose should be modified as described in the CAELYX® Product Monograph.

Hepatotoxicity:
Administration of YONDELIS® + CAELYX® commonly results in reversible liver transaminase elevations. Dexamethasone pre-medication appeared to decrease the frequency and severity of transaminase elevations. In Study OVA-301, 3 (0.9%) subjects fulfilled Hy's Law criteria for predicting severe liver toxicity, but none of these 3 subjects developed severe liver toxicity. This finding was similar to the experience with 19 YONDELIS® single agent Phase 2 studies (14 cases (1.2%) met the definition of Hy's Law but none of these cases developed severe liver toxicity).

Pulmonary Embolism:
There were 17 (5%) and 8 (2%) cases of pulmonary embolism reported in the YONDELIS® + CAELYX® arm and in the CAELYX® monotherapy arm, respectively.

Febrile Neutropenia:
Twenty - seven subjects (8%) had febrile neutropenia in the combination arm and 7 subjects (2%) in CAELYX® monotherapy arm. Three (1.2%) subjects in the combination arm had deaths associated with neutropenia (neutropenic sepsis, sepsis and febrile neutropenia) and one subject in the CAELYX® monotherapy arm died due to sepsis.

Congestive Heart Failure:
Congestive heart failure events (including left ventricular dysfunction, cardiac failure, cardiac failure congestive and ventricular dysfunction) were 2% (n=6) in the YONDELIS® + CAELYX® arm and <1% (n=1) in the CAELYX® monotherapy arm.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Rhabdomyolysis:
Rhabdomyolysis has been uncommonly reported and severe CPK elevations were observed in 2% of patients treated with YONDELIS® in combination with CAELYX®, usually in association with myelotoxicity, severe liver function test abnormalities or renal failure.

Injection site reactions:
There have been few reported cases of YONDELIS® extravasation, some with subsequent tissue necrosis requiring debridement (see **WARNINGS AND PRECAUTIONS**).

Additional data from Clinical Trials

In a phase 2 single agent study with YONDELIS® in 59 subjects with ovarian cancer, reported adverse events with the frequency greater than 10% included arthralgia (12%), phlebitis (15%) and weight increase (20%). In the pivotal study (Study OVA-301), the incidence of arthralgia, phlebitis, and weight increase was 6%, 2%, and 1%, respectively in the combination arm. In a second phase 2 single agent ovarian cancer study in 107 subjects, hypophosphatemia and paresthesia were reported in 34% and 11% of subjects, respectively. In the pivotal phase 3 study, the incidence of hypophosphatemia and paresthesia was 1% and 3%, respectively in the combination arm.

Abnormal Hematologic and Clinical Chemistry Findings

Table 1.3 Abnormal Hematologic and Clinical Chemistry Findings (Laboratory Values)

	------YONDELIS®/CAELYX® ----------			**CAELYX® ----------**		
	(N=333) (%)			**(N=330) (%)**		
Lab Type						
Lab Test Name	**Any**	**Grade 3**	**Grade 4**	**Any**	**Grade 3**	**Grade 4**
Hematology						
Hemoglobin	95	13	6	82	6	2
Neutrophils	92	30	42	74	20	10
Platelets	64	12	11	27	2	2
WBC	95	45	18	82	16	4
Chemistry						
Alkaline Phosphatase	61	2	0	42	1	0
ALT (SGPT)	96	46	5	36	2	0
AST (SGOT)	89	12	2	43	1	<1
Bilirubin	25	<1	0	13	<1	0
Creatine Kinase	22	1	1	14	0	0
Creatinine	28	<1	<1	25	1	0
Potassium (Low)	42	8	1	28	3	1

DRUG INTERACTIONS

Drug-Drug Interactions

Effects of other substances on YONDELIS®

A population analysis based on sparse-sampling data from a Phase 3 study demonstrated that the plasma clearance of trabectedin was decreased by approximately 31% in 86 patients who were co-administered CAELYX® 30 mg/m^2 compared to 745 patients enrolled in 14 studies who received trabectedin alone. Data from a separate Phase I study, in which full pharmacokinetic profiles for trabectedin were obtained for 16 patients who received trabectedin 0.9 to 1.3 mg/m^2 in combination with CAELYX® 30 mg/m^2, indicated a comparable (i.e., a mean difference of 16%) plasma clearance of trabectedin as for the same doses of trabectedin given as a single agent. Results of both analyses are provided to show the degree of change in the clearance values of trabectedin that may be observed upon coadministration of this drug with pegylated liposomal doxorubicin.

Since trabectedin is metabolized mainly by CYP3A4, the concentrations of trabectedin in plasma are likely to be increased in patients who are co-administered drugs that potently inhibit the activity of this isoenzyme (e.g. oral ketoconazole, fluconazole, ritonavir, clarithromycin or aprepitant). Co-administration of YONDELIS® with potent inhibitors of CYP3A4 is not recommended.

Results from the population pharmacokinetic analyses (n = 831 subjects) indicated that the plasma clearance of trabectedin was 19% higher in patients who received any concomitant dexamethasone administration relative to those who did not. The co-administration with potent inducers of CPY3A4 (e.g., rifampicin, phenobarbital, St. John's Wort) may also further increase the metabolic clearance of trabectedin.

Preclinical data have demonstrated that trabectedin is a substrate of P-glycoprotein (P-gp). Concomitant administration of inhibitors of P-gp, e.g. cyclosporine and verapamil, may alter trabectedin distribution or elimination. The clinical relevance of this interaction, e.g. for CNS toxicity, has not been established and caution should be exercised when concomitantly administering YONDELIS® with inhibitors of P-gp.

Trabectedin is highly bound to human plasma protein. In vitro, plasma protein binding of trabectedin was not affected by 14 prototypical drugs (valproic acid, ceftazidime, cloxacillin, erythromycin, warfarin, diazepam, tamoxifen, digitoxin, ondansetron, paracetamol, diclofenac, acetylsalicylic acid, propranolol) that bind to albumin and a1-acid glycoprotein and a slight (28%) increase in the free concentration of trabectedin only occurred with the highest tested concentrations of phenytoin (400 μM).

Impact of YONDELIS® on co-administered drugs

In vitro, trabectedin does not induce or inhibit major cytochrome P450 enzymes.

A population analysis based on sparse-sampling data from a Phase 3 study demonstrated that the plasma pharmacokinetics of PLD 30 mg/m^2 are similar when coadministered with trabectedin 1.1 mg/m^2 (86 patients) and when given alone (80 patients).

Drug-Lifestyle Interactions
No studies on the effects of the ability to drive and to use machines have been performed. However, fatigue or asthenia has been reported in patients receiving YONDELIS®. Patients who experience any of these events during therapy must not drive or operate machines.

The concomitant use of YONDELIS® with alcohol must be avoided due to hepatotoxicity of the medicinal product.

DOSAGE AND ADMINISTRATION

Dosing Considerations
YONDELIS® must be administered under the supervision of a physician experienced in the use of antineoplastic agents. Its use should be confined to personnel specialized in the administration of cytotoxic agents.

Administration through a central venous line is required.

Recommended Dose
For the treatment of liposarcoma or leiomyosarcoma, the recommended starting dose is 1.5 mg/m^2 body surface area, administered as an intravenous infusion over 24 hours with a three-week interval between cycles.

For the treatment of ovarian cancer, YONDELIS® (trabectedin) is used in combination with CAELYX® (PLD) every three weeks. YONDELIS® is administered at a dose of 1.1 mg/m^2 as a 3-hour intravenous infusion after CAELYX® 30 mg/m^2, as a 90-minute intravenous infusion.

For CAELYX® dosage administration instructions, see CAELYX® Product Monograph.

All patients must be premedicated with corticosteroids such as dexamethasone 20 mg IV, 30 minutes before each YONDELIS® infusion; not only as anti-emetic prophylaxis, but also because it appears to provide hepatoprotective effects. Additional anti-emetics may be administered as needed.

The following criteria are required to allow treatment with YONDELIS®:
- Absolute neutrophil count (ANC) $\geq$ 1,500/mm^3
- Platelet count $\geq$ 100,000/mm^3
- Hemoglobin $\geq$ 9 g/dL
- Bilirubin $\leq$ upper limit of normal (ULN)
- Alkaline phosphatase of non-osseous origin $\leq$ 2.5 x ULN (consider hepatic isoenzymes 5 nucleotidase or GGT, to distinguish if the elevation could be osseous in origin)
- Albumin $\geq$ 25 g/L
- Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) $\leq$ 2.5 x ULN
- Creatinine clearance $\geq$ 30 ml/min (monotherapy)
- Serum creatinine $\leq$ 1.5 mg/dL ($\leq$ 132.6 µmol/L) or creatinine clearance $\geq$ 60 mL/min (combination therapy)
- Creatine phosphokinase (CPK) $\leq$ 2.5 x ULN

The same criteria as above (except if CPK > 2.5 x ULN) must be met prior to initiation of next cycles. Otherwise treatment must be delayed for up to 3 weeks until the criteria are met. If these toxicities persist beyond 3 weeks, treatment discontinuation should be considered.

The same dose should be given for all cycles provided that no grade 3-4 toxicities are seen and the patient fulfils the re-treatment criteria.

Dose Adjustments During Treatment

Prior to re-treatment, patients must fulfill the baseline criteria defined above. If any of the following events occur at any time between cycles, the YONDELIS® and CAELYX® dose must be reduced one level, according to Table 1.3 below, for subsequent cycles:

- Neutropenia with ANC < 500/mm^3 lasting for more than 5 days or associated with fever or infection
- Thrombocytopenia with platelets < 25,000/mm^3
- Increase of bilirubin >ULN
- Alkaline phosphatase of non-osseous origin > 2.5 x ULN
- Increase of aminotransferases (AST or ALT) > 2.5 x ULN (monotherapy), or >5 x ULN (combination therapy), which has not recovered by day 21
- Any other grade 3 or 4 adverse reactions (such as nausea, vomiting, fatigue)

Once a dose has been reduced because of toxicity, dose escalation in the subsequent cycles is not recommended. If any of these toxicities reappear in subsequent cycles in a patient exhibiting clinical benefit, the YONDELIS® and CAELYX® dose may be further reduced as per Table 1.4 below. In the event that further dose reductions are necessary, treatment discontinuation should be considered.

Table 1.4 Dose modification table for YONDELIS® (as single agent for liposarcoma or leiomyosarcoma or in combination with CAELYX® for ovarian cancer) and CAELYX®

	Liposarcoma or Leiomyosarcoma	Ovarian Cancer	
	YONDELIS®	YONDELIS®	CAELYX®
Starting dose	1.5 mg/m^2	1.1 mg/m^2	30 mg/m^2
First reduction	1.2 mg/m^2	0.9 mg/m^2	25 mg/m^2
Second reduction	1.0 mg/m^2	0.75 mg/m^2	20 mg/m^2

For additional CAELYX® dosage adjustments, see the CAELYX® Product Monograph.

Duration of Treatment

In clinical trials, there were no pre-defined limits to the number of cycles administered. Treatment continued whilst clinical benefit was noted. YONDELIS® has been administered for 6 or more cycles in 29.5% and 52% of patients treated with monotherapy and combination dose and schedule respectively. The monotherapy and combination regimens have been used for up to 38 and 21 cycles, respectively. No cumulative toxicities have been observed in patients treated with multiple cycles.

Patients With Impaired Hepatic Function
Patients with elevated bilirubin at the time of initiation of cycle must not be treated with YONDELIS®.

Patients with hepatic impairment may be at increased risk for toxicity since systemic exposure may be increased. Recommendations for a starting dose in these patients cannot be made because the use of YONDELIS® in patients with impaired hepatic function has not been adequately studied. Use of YONDELIS® is not recommended in this patient population. Patients must meet specific criteria on hepatic function parameters to start treatment with YONDELIS® (see **WARNINGS AND PRECAUTIONS, Special Populations**).

Patients With Impaired Renal Function
Studies including patients with renal insufficiency (creatinine clearance < 30 mL/min for the monotherapy, and < 60 mL/min in combination regimen) have not been conducted and therefore YONDELIS® must not be used in this patient population (see **WARNINGS AND PRECAUTIONS, Special Populations**).

Pediatrics (< 18 years of age)
The safety and efficacy of YONDELIS® in pediatric patients have not yet been established. Therefore, YONDELIS® should not be used in children and adolescents (see **WARNINGS AND PRECAUTIONS, Special Populations** section).

Geriatrics (> 65 years of age)
Dose adjustments based uniquely on age criteria are not routinely recommended. (See **WARNINGS AND PRECAUTIONS, Special Populations** section).

Administration
YONDELIS® reconstitution and dilution of the reconstituted solution must be conducted under aseptic conditions in a manner consistent with recommended safe procedures for handling cytotoxic compounds. Each vial containing 1 mg of YONDELIS® is reconstituted with 20 mL of sterile water for injections. The solution obtained has a concentration of 0.05 mg/mL and is for single use only.

Reconstitution:
A syringe is used to inject 20 mL of sterile water for injections into the 1 mg vial. Shake the vial until complete dissolution. The reconstituted solution results in a clear, colourless to brownish yellow solution, essentially free of visible particles.

This reconstituted solution contains 0.05 mg/mL of YONDELIS®. It requires further dilution and is for single-use only.

Strength	Vial Size	Volume of Diluent to be Added to Vial	Nominal Concentration per mL
1.0 mg	25 mL	20 mL sterile water for injection	0.05 mg/mL

Instructions for dilution:
The reconstituted solution should be diluted with sodium chloride 9 mg/mL (0.9%) solution for infusion or glucose 50 mg/mL (5%) solution for infusion. The required volume should be calculated as follows:

$$\text{Volume (mL)} = \frac{\text{BSA } (m^2) \times \text{individual dose } (mg/m^2)}{0.05 \text{ mg/mL}}$$

BSA = Body Surface Area

The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 500 mL of normal saline 0.9% solution for infusion or dextrose 5% solution for infusion if administration is to be made through a central venous line.

After administration of the CAELYX® infusion, the intravenous line should be flushed well with 5% dextrose in water (D_5W) before administration of YONDELIS®. CAELYX® must not be mixed with saline.

YONDELIS® must not be mixed or diluted with medicinal products except those mentioned above.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. After reconstitution and dilution, chemical and physical stability has been demonstrated for 30 hours up to 25ºC. The reconstituted solution should be diluted and used immediately. The total elapsed time between initial reconstitution and end of treatment should not be longer than 30 hours.

OVERDOSAGE

There is limited data on the effects of YONDELIS® overdose. The major anticipated toxicities are gastrointestinal, bone marrow suppression and hepatic toxicity. There is no specific antidote for YONDELIS® currently available. In the event of an overdose, patients should be closely monitored and symptomatic supportive care measures instituted as required.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Trabectedin binds to the minor groove of DNA, bending the helix to the major groove. This binding to DNA triggers a cascade of events affecting several transcription factors, DNA binding proteins, and DNA repair pathways, resulting in perturbation of the cell cycle.

Pharmacodynamics

Trabectedin has been shown to exert antiproliferative in vitro and in vivo activity against a range of human tumour cell lines and experimental tumours, including malignancies such as sarcoma, breast, non-small cell lung, ovarian and melanoma.

In vitro and in vivo xenograft models have shown additive or synergistic effects when trabectedin was combined with doxorubicin in several cell lines but the combination study with ovarian cells has not been carried out.

Electrocardiography

A single-blind, multicenter, placebo-controlled, sequential design study was performed to evaluate the effects of single-dose administration of YONDELIS® on the electrocardiogram in 74 subjects with locally advanced or metastatic solid tumours. On day 1 of treatment, a placebo control (intravenous saline over 3 hours) was administered. On day 2 of treatment, YONDELIS® was administered as a 1.3 mg/m^2 intravenous infusion over 3 hours. ECGs were collected predose and 1, 2, 2.75, 4, 6, 8, and 24 h after initiation of the infusions on day 1 and 2. YONDELIS® at this dose was not associated with prolongation of the PR interval, QRS duration, or QTc interval during the 24 h period after initiation of the infusion. YONDELIS® was associated with statistically significant increases in heart rate from 2 to 24 h after initiation of treatment, with a maximum effect of mean 11.0 (90% CI 8.5, 13.5) bpm at the 4 h time point (see **WARNINGS AND PRECAUTIONS**, **Cardiovascular**).

Pharmacokinetics

Systemic exposure after intravenous administration as a constant rate intravenous infusion is dose proportional at doses up to and including 1.8 mg/m^2. The pharmacokinetic profile of trabectedin is consistent with a multiple compartment disposition model, including a terminal half-life in plasma of 175 hours. The concentrations of trabectedin in plasma do not accumulate when administered every 3 weeks.

Distribution:

Trabectedin has a large volume of distribution (greater than 5000 L), consistent with extensive distribution into peripheral tissues.

Trabectedin is highly bound to plasma proteins. The mean free (unbound) fraction in plasma is 2.23% and 2.72% at a total plasma concentration of 10 ng/mL and 100 ng/mL, respectively.

Metabolism:

Trabectedin is extensively metabolized. Cytochrome P450 3A4 is the major cytochrome P450 isozyme responsible for the oxidative metabolism of trabectedin at clinically relevant concentrations. The contribution of other P450 enzymes to the metabolism of trabectedin cannot be ruled-out. No appreciable glucuronidation of trabectedin has been observed.

Excretion:

The mean (SD) recovery of total radioactivity was 58% (17%), and 5.8% (1.73%) in the feces (24 days) and urine (10 days), respectively, after a dose of radio-labelled trabectedin was administered to 8 cancer patients. Negligible quantities (<1% of the dose) of unchanged drug are excreted in the feces and in urine. The clearance of trabectedin in whole blood is approximately 35 L/h. This value is approximately one-half the rate of human hepatic blood flow. Thus the

trabectedin extraction ratio can be considered moderate. The inter-patient variability of the population estimate for plasma clearance of trabectedin was 49% and intra-patient variability was 28%.

Special Populations and Conditions

A population pharmacokinetic analysis indicated that the plasma clearance of trabectedin is not influenced by total body weight (range: 36 to 148 kg), body surface area (range: 0.9 to 2.8 m^2), age (range: 19 to 83 years), or gender.

Race:

The effects of race and ethnicity on trabectedin pharmacokinetics have not been studied.

Hepatic Insufficiency:

The clearance of trabectedin may be decreased in patients with hepatic impairment resulting in higher concentrations of trabectedin in plasma. The effect of hepatic impairment on the pharmacokinetics of trabectedin has not been sufficiently studied and the use of YONDELIS® is not recommended in this patient population. Patients with elevated bilirubin levels must not be treated with YONDELIS®.

Renal Insufficiency:

There is no relevant influence of renal function measured by creatinine clearance on trabectedin pharmacokinetics within the range of values (≥ 30.3 mL/min) present in the patients included in the clinical studies. No data are available in patients with a creatinine clearance of less than 30.3 mL/min. The low recovery (< 9% in all studied patients) of total radioactivity in the urine after a single dose of ^{14}C-labelled trabectedin suggests that renal impairment would have little influence on the elimination of trabectedin or its metabolites.

STORAGE AND STABILITY

Store unopened vials in a refrigerator (2ºC – 8ºC).

After reconstitution, chemical and physical stability has been demonstrated for 30 hours up to 25ºC.

From a microbiological point of view, the reconstituted solution should be diluted and used immediately. If not diluted and used immediately, in-use storage times and conditions prior to use of the reconstituted product are the responsibility of the user and would normally not be longer than 24 hours at 2ºC to 8ºC, unless reconstitution has taken place in controlled and validated aseptic conditions.

After dilution, chemical and physical stability has been demonstrated for 30 hours up to 25ºC. The total hold time between initial reconstitution and end of treatment should not be longer than 30 hours.

SPECIAL HANDLING INSTRUCTIONS

YONDELIS® (trabectedin) is a cytotoxic anticancer medicinal product and, as with other potentially toxic compounds, caution should be exercised during handling. Procedures for proper handling and disposal of cytotoxic medicinal products must be followed. YONDELIS® should be handled and disposed of in a manner consistent with other anticancer drugs. Accidental contact with the skin, eyes or mucous membranes must be treated immediately with copious amounts of water.

Any unused product or waste material should be disposed of in accordance with local requirements for cytotoxic medicinal products.

No incompatibilities have been observed between YONDELIS® and polyvinylchloride (PVC) and polyethylene (PE) bags and tubing, and titanium implantable vascular access systems.

DOSAGE FORMS, COMPOSITION AND PACKAGING

YONDELIS® for injection is supplied as individual 25 mL vials containing 1 mg of trabectedin, as a sterile lyophilized white to off white powder. The nonmedicinal ingredients are phosphoric acid, potassium dihydrogen phosphate, potassium hydroxide and sucrose.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

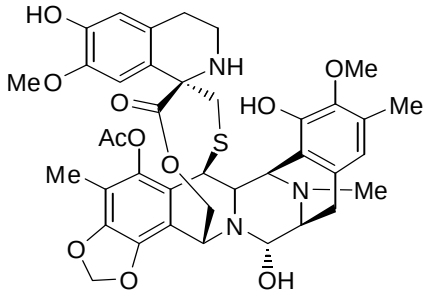
Drug Substance

Proper name: trabectedin

Chemical name: (1'R,6R,6aR,7R,13S,14S,16R)-5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12*H*-1,3-dioxolo[7,8]isoquino[3,2-*b*][3]benzazocine-20,1'(2'*H*)-isoquinolin]-19-one.

Molecular formula and molecular mass: $C_{39}H_{43}N_3O_{11}S$ and 761.84

Structural formula:



Physicochemical properties: Trabectedin is hydrophobic, and has a low solubility in water. Trabectedin solubility is enhanced in acidic media.

CLINICAL TRIALS

<u>Monotherapy in Metastatic Liposarcoma or Leiomyosarcoma</u>

The efficacy and safety of trabectedin in metastatic liposarcoma or leiomyosarcoma was evaluated in a single randomized multi-centre open-label trial in patients whose disease had progressed or relapsed after treatment with at least anthracyclines and ifosfamide. In this trial trabectedin was administered either at 1.5 mg/m^2 as a 24 hour intravenous infusion every 3 weeks (24-h q3wk) or at 0.58 mg/m^2 weekly as a 3 hour intravenous infusion for 3 weeks of a 4 week cycle (3 h qwk). There were no pre-defined limits to the number of cycles administered. Treatment continued while clinical benefit was noted.

The study was originally designed to select the most appropriate dosing regimen for further testing, and the primary endpoint was clinical benefit (complete response, partial response or stable disease lasting at least 24 weeks). Preliminary descriptive data suggested both regimens to be active; consequently the study protocol was amended to allow a formal comparison of the benefit of trabectedin. Sample size was expanded and time to progression (TTP) was designated as the primary efficacy endpoint. In addition, a blinded independent review (IR) panel of tumor assessments was instituted. The final TTP analysis was to take place after 217 events, and an

interim analysis was scheduled with 150 events. TTP was defined as the time between randomization and first documentation of disease progression or death with documented disease progression. The primary endpoint was TTP as assessed by the IR. Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and overall survival (OS). Quality of life was not measured.

A total of 260 patients were randomized into the study, 136 patients to the 24 h q3wk arm and 134 patients to the 3-hour infusion arm. Demographic characteristics were similarly distributed between study arms. The median age was 53 (range 20 to 80) years and 63% of patients were female. All had a confirmed diagnosis of STS, 66% with leiomyosarcoma and 34% with liposarcoma. Primary tumors were most commonly located in the retroperitoneal area (23%), uterus (22%), or lower extremities (21%). Most metastases were located in the lungs (42%), liver (16%), abdomen (11%), pelvis (10%) or thorax (7%). All patients had received prior systemic therapy, with the vast majority (99%) having been treated with both anthracyclines and ifosfamide. A median of 1.3 (range 0.1 to 43) months had elapsed between the documentation of disease progression with previous chemotherapy and randomization.

The final TTP analysis was conducted with 206 independently assessed progression events. The protocol specified final time to progression (TTP) analysis showed a 26.6% reduction in the relative risk of progression for patients treated in the 24 h q3wk group [HR = 0.73 (95% CI 0.55 - 0.97), p=0.0302] (see Figure 2.1). This result is statistically significant given that the level of significance to be reached taking into account the planned interim analysis was 0.0370. Median TTP values were 3.7 months in the 24 h q3wk group and 2.3 months in the 3 h qwk group. The analysis using investigator assessments showed similar results despite discrepancies of approximately 50% in TTP between the independent review and investigator's assessment. Analyses of PFS and OS showed a pattern consistent in trend with the TTP analysis (see Table 2.1). Median OS with the 24 h q3wk regimen was 13.9 months (CI: 12.5 -17.9) and 60.6% of patients were alive at 1 year (CI: 52.3-68.9%). Objective responses were observed in 5.6% of patients in the 24 h q3wk group and 1.6% of patients in the 3 h qwk group.

Figure 2.1- Time to Progression Kaplan Meier-Curve (all randomized - independent review)

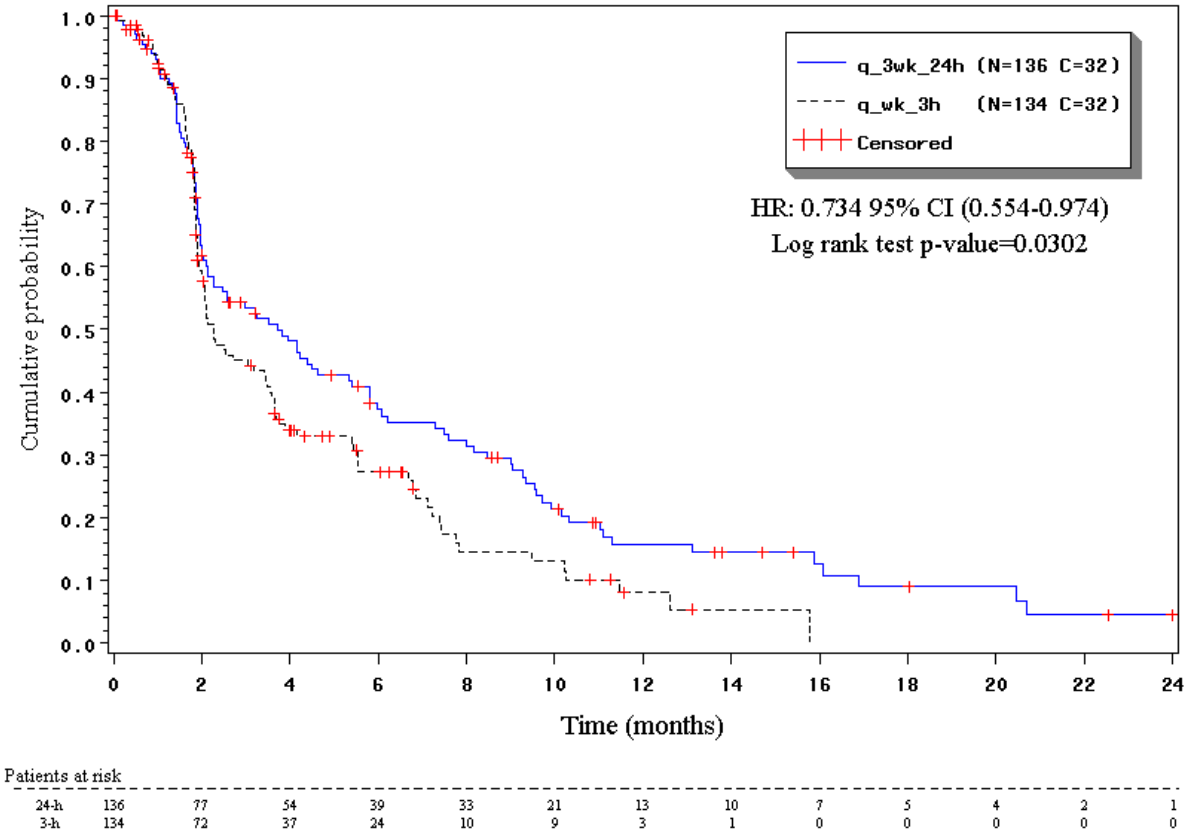


Table 2.1 Summary of Key Efficacy Endpoints

End-point	q3wk 24-h N=136	qwk-3h N=134	HR(95%CI)	p-value
Primary Endpoint				
TTP, Median(95% CI) (months)				
Independent review	3.7 (2.1-5.4)	2.3 (2.0-3.5)	0.73(0.55 - 0.97)	0.0302*
Investigator review	4.2(2.6-6.5)	2.5(2.1-3.5)	0.67(0.51-0.88)	0.0042*
Secondary Endpoints				
PFS, Median, (95% CI) (months)				
Independent review	3.3 (2.1-4.6)	2.3 (2.0-3.4)	0.76(0.57-0.99)	0.0418
Investigator review	4.2 (2.5-6.2)	2.5 (2.1-3.5)	0.69(0.52-0.90)	0.0057
OS, Median, (95% CI) (months)	13.9 (12.5 -17.9)	11.8(9.9-13.9)	0.82	0.1984
ORR (95% CI) %				
Independent review	5.6% (2.3-11.2)	1.6%(0.2-5.8)	_	0.1718**
Investigator review	12.0%(6.9-19.0)	2.4%(0.5-6.8)	_	0.0031**

*Log –rank test; ** Fisher's test

Combination Therapy in Advanced Ovarian Cancer

The safety and efficacy of YONDELIS® in combination with CAELYX® in patients with relapsed ovarian cancer were demonstrated in an open-label, active control, multicentre, randomized phase 3 study. This study included 672 patients randomized to receive either YONDELIS® (1.1 mg/m^2 i.v. for 3 hours) administered after CAELYX® (30 mg/m^2 i.v for 90 min) every 3 weeks or CAELYX® (50 mg/m^2 i.v. for 90 min) every 4 weeks.

At the time of randomization, subjects were stratified on the basis of platinum sensitivity of disease (sensitive or resistant) and baseline Eastern Cooperative Oncology Group (ECOG) performance status score (0 or 1 versus 2). Platinum-sensitive patients were patients who progressed more than 6 months after the end of first-line platinum-based treatment and platinum-resistant patients were patients who progressed earlier than 6 months after the end of treatment. Treatment continued until disease progression occurred or for at least 2 cycles after a confirmed complete response (CR). The analysis of primary efficacy end-point, progression-free survival (PFS) as measured by independent radiologist (which excluded assessment of clinical data) was to be performed after 415 observed events of disease progression or death occurred. PFS was also measured by independent oncologist and investigator: their assessment included clinical evaluation. The study was to end 2 months after the last subject received the last dose of study medication or until 520 deaths were observed, whichever was later. A planned interim analysis on the secondary endpoint overall survival (OS) was conducted in conjunction with PFS at 300 deaths. An ad-hoc OS analysis was also conducted at 419 deaths.

The median age of the patients in the study was 57 years (range 26; 87), 78% were Caucasian, 20% Asian and 2% Black/other. The baseline demographics and disease characteristics are provided in Table 2.2 below:

Table 2.2 Summary of Patients Baseline and Disease Characteristics

	YONDELIS® + CAELYX® N=337	CAELYX® N=335
Median age (range)	56 (26;82)	58 (27;87)
Baseline ECOG performance status (%)		
0	68	57
1	29	39
2	3	3
Platinum sensitivity (%)		
Platinum sensitive	65	63
Platinum resistant	35	37
Prior Taxane therapy (%)	80	81
Platinum free interval (PFI)*	n (%)	n (%)
<6	118 (35)	124 (37)
≥6-12	123 (37)	90 (27)
≥12	95 (28)	121 (36)

*PFI: end of last platinum therapy to time of progression.

The clinical benefit of YONDELIS® + CAELYX® was observed in progression-free survival (PFS) and objective response rate, with a trend in survival in favour of the combination arm. Based on the assessment by independent radiologists, for the overall population, the primary endpoint, progression-free survival (PFS), was significantly longer in patients treated with YONDELIS® in combination with CAELYX® compared with those treated with CAELYX® alone (median PFS: 7.3 vs. 5.8 months respectively). Treatment with YONDELIS® + CAELYX® resulted in a 21% risk reduction for disease progression or death compared to CAELYX® alone [HR=0.79; 95% CI (0.65; 0.96), p=0.0190]. However, this result was not consistent within subgroups. When stratified by platinum sensitivity, for platinum sensitive patients, the PFS was also significantly longer for the YONDELIS® combination with CAELYX® vs. CAELYX® alone (median PFS is 9.2 vs.7.5 months) resulting in a risk reduction of 27% for the combination vs. CAELYX® alone [HR= 0.73; 95% CI (0.56; 0.95), p=0.0170]. For platinum resistant patients, the PFS was not different between the two treatment groups; the median PFS was 4.0 vs. 3.7 months for the YONDELIS® with CAELYX® combination vs. CAELYX® alone, respectively [HR 0.95; 95% CI (0.70;1.30), p=0.754].

The PFS results are considered robust as evidenced by the consistency of these results whether assessed by the independent radiologists, independent oncologists, or investigators.

Objective response rates were higher in YONDELIS® + CAELYX® combination arm than in the CAELYX® monotherapy arm for the overall population and the platinum-sensitive subgroup, but were similar for the platinum-resistant subgroup. The median duration of response for the independent radiologist review in the YONDELIS® + CAELYX® arm was 7.9 months (range; 7.4 to 9.2) compared with the CAELYX® monotherapy arm which was 7.7 months (range; 6.5 to 9.0).

Although survival data were not mature at this time, the interim analysis performed in conjunction with the PFS with 300 deaths showed a trend in favour of the YONDELIS® + CAELYX® arm [HR=0.85; 95% CI (0.67; 1.06), p= 0.15]. The ad hoc analysis at 419 deaths showed the same HR with a narrower confidence interval [HR=0.85 (95% CI, 0.70-1.03);

p=0.09]. The median OS was 22.4 months in the combination arm and 19.5 months in the CAELYX® monotherapy arm. The final OS analysis will be performed after 520 deaths.

In both the interim and ad hoc analysis, the trend in favour of the YONDELIS® +CAELYX® combination on overall survival was more pronounced in platinum sensitive patients than in platinum resistant patients.

No statistically significant differences were found between treatment arms in global measures of Quality of Life.

The results of the analyses for the primary and secondary efficacy end points for the overall population, as well as the analyses stratified for platinum sensitive and platinum resistant populations are shown in Table 2.3. PFS estimates for the overall population as well as the analyses stratified for platinum sensitive and platinum resistant groups are shown in Figures 2.3 and 2.4 respectively.

Table 2.3 Efficacy of YONDELIS® in Combination with CAELYX® in the Treatment of Patients with Ovarian Cancer (Study OVA-301)

	YONDELIS® +CAELYX® N=337	CAELYX® N=335	TREATMENT EFFECT	
PROGRESSION-FREE SURVIVAL (PFS)	**Median (95% CI) (months)**	**Median (95% CI) (months)**	**HR (95%CI)**	**p-value**
†Independent radiologist review (measurable patients)				
Overall population (n=328/317)	7.3 (5.9; 7.9)	5.8 (5.5; 7.1)	0.79 (0.65; 0.96)	0.019[a]
Platinum sensitive (n=215/202)	9.2 (7.4; 11.1)	7.5 (7.0; 9.2)	0.73 (0.56; 0.95)	0.017
Platinum resistant (n=113/115)	4.0 (2.9;5.6)	3.7(3.0; 5.5)	0.95 (0.70; 1.30)	0.754
Independent Oncologist review (ITT population)				
Overall population† (n=336/335)	7.4 (6.4; 9.2)	5.6 (4.2; 6.8)	0.72 (0.60; 0.88)	0.001 [a]
Platinum-sensitive (n=217/212)	9.7 (8.0; 11.1)	7.2 (5.6; 8.4)	0.66 (0.51; 0.85)	<0.001
Platinum-resistant (n=119/123)	3.7 (2.0; 5.6)	3.7(2.7; 4.2)	0.89 (0.67; 1.2)	0.444
OBJECTIVE RESPONSE (CR + PR)	**ORR (95% CI) (%)**	**ORR (95% CI) (%)**	**OR (95% CI)**	**p-value**
††Independent radiologist review (ITT population)				
Overall population	27.6 (22.9; 32.7)	18.8 (14.8; 23.4)	1.65 (1.14;2.37)	0.008 [b]
Platinum-sensitive	35.3 (29.0; 42.1)	22.6 (17.2; 28.9)	1.87 (1.22;2.85)	0.004
Platinum resistant	13.4 (7.9; 20.9)	12.2 (7.0; 19.3)	1.12 (0.53;2.38)	0.848
OVERALL SURVIVAL	**Median (95% CI) (months)**	**Median (95% CI) (months)**	**HR (95%CI)**	**p-value**
Preplanned overall survival: n=300 events* (ITT population)				
Overall population	20.5 (18.7; 24.2)	19.4 (17.3; 21.7)	0.85 (0.67; 1.06)	0.151
Platinum-sensitive (n=430)	25.0 (21.4; 27.0)	24.3 (20.1; 25.8)	0.82 (0.60; 1.13)	0.216
Platinum-resistant (n=242)	14.0 (11.1; 17.1)	12.4 (11.0; 15.2)	0.91 (0.66; 1.26)	0.565
Post-hoc updated overall survival: n=419 events* (ITT population)				
Overall population	22.4 (19.4; 25.1)	19.5 (17.4; 22.1)	0.85 (0.70; 1.03)	0.092 [a]
Platinum-sensitive (n=430)	27.0 (24.2, 31.6)	24.3 (21.3, 26.6)	0.82 (0.63, 1.06)	0.126
Platinum-resistant (n=242)	14.2 (11.1, 16.8)	12.4 (10.6, 15.1)	0.90 (0.68, 1.20)	0.481

† Based on Kaplan Meier estimates; a hazard ratio < 1 indicates an advantage for YONDELIS® + CAELYX®
†† Odds ratio>1 indicates advantage for (YONDELIS® + CAELYX®) calculated with Cochran-Mantel-Haenszel.
[a] Log rank test
[b] Fisher's exact test
*Updated OS May 31, 2009

Figure 2.2- Progression Free Survival Kaplan Meier-Curve

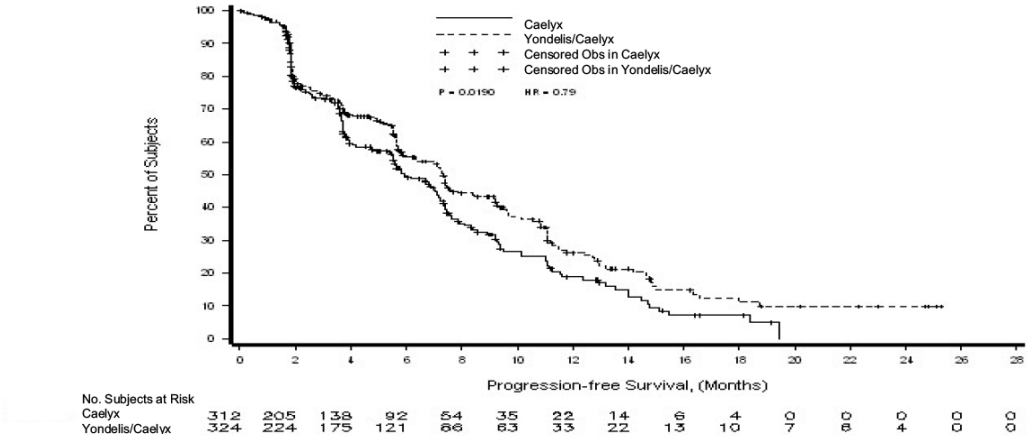
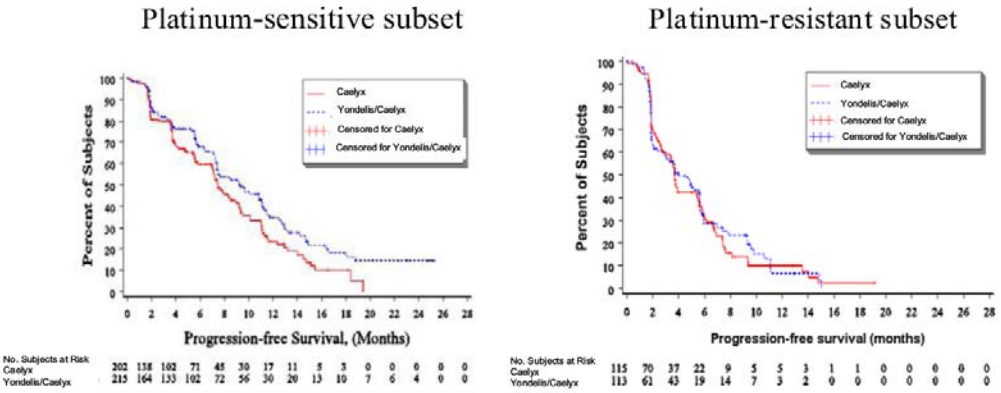


Figure 2.3 –Kaplan-Meier plot of progression-free survival: subset analysis per platinum-free interval (left graph: platinum-sensitive subset; right graph, platinum-resistant disease) (OVA-301 study).



The Objective Response Rate (ORR), as assessed by the investigator, by platinum sensitivity from the integrated three phase 2 ovarian cancer studies using YONDELIS® alone are presented in Table 2.4. These results are consistent with those observed in Study OVA-301 in that the ORR is higher in patients with platinum-sensitive disease than in those with platinum-resistant disease. The ORR as assessed by the investigator, for subjects with platinum-resistant and platinum sensitive disease was 22.7% and 47.2%, respectively, in the YONDELIS® + CAELYX® combination arm.

Table 2.4 Objective Response Rate by Platinum Sensitivity in Integrated Phase 2 Ovarian Studies

	PLATINUM RESISTANT (N=106)		PLATINUM SENSITIVE (N=189)		Total (N=295)
Objective Response Rate	n (%)	95% CI[a]	n (%)	95% CI[a]	n (%)
CR + PR	7 (7)	(2.7; 13.1)	69 (37)	(29.6; 43.8)	76 (26)

CR= complete response; PR= partial response

[a] Exact interval for binomial parameter.

Note: Percentages calculated with the number of subjects in each group as denominator.

DETAILED PHARMACOLOGY

Preclinical data indicate that trabectedin has limited effect on the cardiovascular, respiratory and central nervous system at exposures below the therapeutic clinical range, in terms of AUC. Experiments on exposures within the therapeutic clinical range could not be carried out due to acute toxicities in the animals.

The effects of trabectedin on cardiovascular and respiratory function have been investigated in vivo (anesthetized Cynomolgus monkeys). A 1-hour infusion schedule was selected to attain maximum plasma levels (C_{max} values) in the range of those observed in the clinic. The plasma trabectedin levels attained were 10.6 ± 5.4 (C_{max}), similar to those reached after administration of 1.1 mg/m^2 in 3-hour infusion (C_{max} of 7.9 ± 2.0 ng/mL). Trabectedin-related findings in anesthetized monkeys tended towards decreases in mean, systolic, and diastolic arterial blood pressure. A slight (10%) decrease in hERG mediated current was only seen at the highest concentration (10-5 M) tested in an in vitro hERG assay.

TOXICOLOGY

Injection site lesions, myelosupression and hepatoxicity were identified as the primary toxicity for trabectedin. Findings observed included hematopoietic toxicity (severe leukopenia, decreased red blood cell parameters/anaemia, and lymphoid and bone marrow depletion) as well as increases in alanine aminotransferase, alkaline phosphatase, gamma glutamyltransferase, bilirubin and bile acids tests, hepatocellular and biliary degeneration, intestinal epithelial necrosis, and severe local reactions at the injection site. All effects in all species, including mortality, occurred at dose levels (expressed in terms of body surface area) and systemic exposures (AUC) that were less than those in humans given a 1.1 mg/m^2 infusion dose.

Repeat dose toxicity

In mice, rats, rabbits and monkeys, severe dose-dependent local inflammation was regularly observed at the injection site after i.v. injection particularly after repeated cycles.

In repeated dose toxicity studies in Cynomologus monkeys, severe thrombophlebitis with extensive perivascular inflammation and fibrosis generally with pronounced necrosis, also affecting surrounding tissues was observed after the fourth cycle, and led to premature sacrifice or death in some animals. Mortalities were seen at 0.42 mg/m^2 and above. These adverse effects were observed when trabectedin was administered to animals less than 3 kg. Dogs were less affected likely due to the larger size of the veins injected.

Renal toxicological findings were detected in multi-cycle toxicity studies conducted in monkeys. These findings were secondary to severe local intolerance at the administration site (i.e. catheter tip location), with severe damage of surrounding tissues (e.g. the kidneys) and therefore uncertainly attributable to trabectedin; however, caution must be exercised in the interpretation of these renal findings, and treatment-related toxicity cannot be excluded.

Focal areas of retinal edema were seen during ophthalmic exams in 2 monkeys in only one study, but they were considered a potentially trabectedin-related effect.

Genotoxicity

Trabectedin was genotoxic in both in vitro and in vivo test systems. Long-term carcinogenicity studies have not been performed.

Reproductive and Developmental Toxicity

Trabectedin was not teratogenic in developmental toxicity studies in rats or rabbits. However, because of dose-limiting maternal toxicity the doses used were approximately 46- to 73-fold lower than the clinical dose of 1.1 mg/m^2 based on body surface area. Therefore, the results of these studies are unlikely to have much relevance to human pregnancy.

Fertility studies with trabectedin were not performed but limited histopathological changes were observed in the gonads in the repeat dose toxicity studies. Considering the nature of the compound (cytotoxic and mutagenic), is likely to affect the reproductive capacity.

Local intolerance

Local tolerance studies in rabbits confirmed the high irritation potential of trabectedin.

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PART III: CONSUMER INFORMATION

PrYONDELIS®*
trabectedin for Injection

This leaflet is a summary and will not tell you everything about YONDELIS®. Contact your doctor or pharmacist if you have any questions about the drug. This leaflet is Part III of a three-part "Product Monograph" published when YONDELIS® was approved for sale in Canada and is designed specifically for Consumers.

ABOUT THIS MEDICATION

What the medication is used for:

YONDELIS® (trabectedin) is used for the treatment of patients with metastatic liposarcoma or leiomyosarcoma (forms of soft tissue sarcoma) when previous medicines have been unsuccessful. YONDELIS® has been shown to slow growth of liposarcoma or leiomyosarcoma but it is not known if YONDELIS® prolongs overall survival or improves quality of life of patients with these sarcomas.

YONDELIS® in combination with CAELYX® (pegylated liposomal doxorubicin hydrochloride) (another anti- cancer medicine) is used for the treatment of patients with platinum-sensitive ovarian cancer after one previous therapy. YONDELIS® has been shown to slow growth of ovarian cancer but it is not known if YONDELIS® prolongs overall survival or improves quality of life of patients with ovarian cancer.

What it does:
YONDELIS® is an anticancer medicine that works by preventing the tumour cells from multiplying.

When it should not be used:
- If you are allergic (hypersensitive) to trabectedin or to any ingredient in the formulation or component of the container of YONDELIS®.
- If you are breast-feeding.
- If you have an active serious or uncontrolled infection.

What the medicinal ingredient is:
trabectedin

What the nonmedicinal ingredients are:
phosphoric acid, potassium dihydrogen phosphate, potassium hydroxide, sucrose

What dosage forms it comes in:
YONDELIS® is a powder for injection. The powder is reconstituted in sterile water and further diluted in a sterile salt solution or sugar solution before it is infused. YONDELIS® is available in a vial that contains 1 mg trabectedin.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

YONDELIS® should be prescribed and managed only by a doctor experienced in anticancer drugs.

In order to avoid irritation at the site of injection, YONDELIS® must be given to you through a central venous line.

YONDELIS® or its combination with CAELYX® must not be used if you have increased blood bilirubin levels.

Serious side effects which have been reported with the use of YONDELIS® include:
- Increase in liver enzymes which can be monitored by lab tests
- Severe muscle pain or weakness (rhabdomyolysis)
- Decrease in white blood cells which may lead to infection
- Blood clots in the lung
- Severe reaction at site of injection

BEFORE you use YONDELIS® talk to your doctor or pharmacist if:
- you have a history of myelosuppression (a decrease in the production of blood cells);
- you have any problems with your kidneys;
- you have any problems with your liver;
- you are pregnant, planning to become pregnant or breast-feeding.

YONDELIS® has not been studied in children or adolescents under 18 years of age.

Contraception and Pregnancy:
Both men and women must use effective contraception while receiving YONDELIS®, and for 3 months after treatment for women and 5 months after treatment for men. You must make sure that you do not become pregnant while receiving YONDELIS®, but if you do, inform your doctor immediately and genetic counselling is recommended since YONDELIS® can cause genetic damage. It is advised that you are not given YONDELIS® if you are pregnant.

Genetic counselling is also recommended for patients wishing to have children after therapy. Male patients should seek advice on sperm conservation prior to treatment because of the risk of irreversible infertility due to therapy with YONDELIS®.

Breast-Feeding:
YONDELIS® must not be given to patients who are breast-feeding. Therefore you must stop breast-feeding before you start your treatment and you must not begin breast-feeding again until your doctor has confirmed that it is safe to do so.

Driving and using machines:
Tiredness and weakness have been reported in patients receiving YONDELIS®. Do not drive or operate any dangerous tools or machines if you experience such side effects. Even if you have not felt these effects, you must still be cautious.

INTERACTIONS WITH THIS MEDICATION

Inform your doctor, medical health personnel or pharmacist about all medicines you are taking, whether prescribed for you or bought without a prescription.

The following medications may lower the effect of YONDELIS®:
- Rifampin for bacterial infection
- Phenobarbital for epilepsy
- St. John's Wort, an herbal medicine for depression

The following medicines may increase the effect of YONDELIS®:
- Ketoconazole or fluconazole for fungal infections
- Ritonavir for HIV infection
- Clarithomycin for bacterial infections
- Cyclosporine an immune suppressive medicine
- Verapamil for high blood pressure or heart condition

The following medicines may increase risks of muscle or liver damage (rhabdomyolysis):
- Statins for lowering cholesterol levels

Alcohol must be avoided during treatment with YONDELIS®.

PROPER USE OF THIS MEDICATION

Usual dose:
The dose will be calculated from your height and weight.

For the treatment of metastatic liposarcoma or leiomyosarcoma, the usual dose is 1.5 mg/m^2 body surface area as a 24-hour intravenous infusion.

For the treatment of ovarian cancer, the usual starting dose is 1.1 mg/m^2 body surface area as a 3-hour intravenous infusion after CAELYX® 30 mg/m^2 body surface areas, as a 90-minute intravenous infusion.

The infusion is given every 3 weeks, although occasionally your doctor may recommend dose delays to ensure that you receive the most appropriate dosage of YONDELIS®.

You must be premedicated with corticosteroids such as dexamethasone 20 mg IV, 30 minutes before each YONDELIS® infusion; not only to prevent vomiting, but also because it appears to protect the liver.
Before YONDELIS® is given to you, it is reconstituted and diluted and then put into a drip bag for intravenous use.

In order to avoid irritation at the site of injection, YONDELIS® must be given to you through a central venous line.

During the treatment period, your doctor will carefully monitor you and decide the most appropriate dosage of YONDELIS® to give you. The length of your whole treatment period will depend on your progress and how well you feel. Your doctor will tell you how long your treatment lasts.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed dose:
If you think that you have missed a dose of YONDELIS®, tell your healthcare provider immediately.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, YONDELIS® or its combination with CAELYX® can cause side effects, although not everyone gets them.

Side effects caused by YONDELIS® treatment:
Very common side effects are that you may:
- feel tired
- feel shortness of breath
- bruise more easily
- have nose bleeds
- have a decrease in white blood cells or platelets which may lead to infection or unexpected bruising or bleeding
- have blood infections (neutropenic infection and neutropenic sepsis). Your doctor will order regular blood tests to detect any abnormalities in the blood.
- experience headache and a loss of strength
- lose your appetite, feel sick (nausea) or vomit, and become constipated. If you still feel sick, vomit or are unable to drink fluids and therefore pass less urine, despite being given anti-sickness medication, you should immediately seek medical help.
- have diarrhoea, loss of water from the body, inflammation of the mouth (stomatitis), pain in the abdomen, weight loss, digestive discomfort and a change in your sense of taste

- have the hand and foot syndrome. It may present as red skin of the palms, fingers, and soles of the feet that later may become swollen and violaceous. The lesions may either dry out and desquamate, or blister with ulceration.
- increase in blood bilirubin levels which may lead to yellow eyes or skin, dark urine
- lose hair (alopecia)
- low levels of potassium
- sleep disorder (insomnia)
- pain, redness or swelling of the skin at the site of injection

Your doctor may require blood tests in certain situations in order to avoid developing muscle damage to the muscles (rhabdomyolysis). In very severe cases this could lead to kidney failure. If you experience severe muscle pain or weakness, you should seek medical attention immediately.

Some other common side effects that you may have are:

- a higher skin pigmentation and rash
- coughing
- dizziness, low blood pressure and flushing
- fever. If you have a raised temperature you should seek medical attention immediately
- mucosal inflammation as a swelling redness of the inside of the mouth leading to painful ulcers and mouth sores or as an inflammation of the gastrointestinal tract
- a syncope also called fainting
- a weakness in the ventricles, the heart's major pumping chambers (left ventricular dysfunction), sudden blockage in a lung artery (pulmonary embolism) and an abnormal build up of fluid in the lungs, which leads to swelling (pulmonary oedema)

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Very Common			
Decrease in white blood cells or platelets in blood which may lead to infection or unexpected bruising or bleeding		√	
Nausea, vomiting	√		
Fatigue	√		
Loss of appetite	√		
Increase in blood bilirubin levels which may lead to yellow eyes or skin, dark urine		√	
Reddening painful skin on hands and feet		√	
Increase in blood creatine phosphokinase which may lead to muscle pain, weakness, muscle spasms		√	
Mouth ulceration, mucosal inflammation	√		
Common			
Fever		√	

This is not a complete list of side effects. For any unexpected effects while taking YONDELIS®, contact your doctor or pharmacist.

HOW TO STORE IT

YONDELIS® should be stored in the refrigerator (2ºC – 8ºC).

The reconstituted solution should not be stored longer than 24 hours at 2ºC to 8ºC.

The total hold time between initial reconstitution and end of treatment should not be longer than 30 hours.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at:
http://www.janssen.ca
or by contacting the sponsor, Janssen Inc., at:
1-800-567-3331

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