PRODUCT MONOGRAPH

PrYONDELIS®

trabectedin for Injection

1 mg/vial trabectedin

Antineoplastic Agent

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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 **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**). Dose adjustments based on age are not recommended.

Pediatrics (< 18 years of age):

The safety of YONDELIS® in pediatric patients has not been established. A Phase 2 study indicated that YONDELIS® had no efficacy in pediatric patients with sarcomas (see **WARNINGS AND PRECAUTIONS, Special Populations**). YONDELIS® 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 ADMINISTRATION**).

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.

Co-administration of YONDELIS® with potent inhibitors of the enzyme CYP3A4 should be

avoided (see **DRUG INTERACTION, Drug-Drug Interactions**). If this is not possible, close monitoring of toxicities are required and dose reductions of trabectedin should be considered.

Allergic Reactions
During post-marketing experience, serious cases of hypersensitivity reactions, including cases with fatal outcome, have been reported in association with YONDELIS® administration (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS**).

Capillary Leak Syndrome (CLS)
Cases of CLS (including cases with fatal outcomes) have been reported with YONDELIS®. If symptoms of possible CLS develop, such as unexplained edema with or without hypotension, reassess albumin level and withhold YONDELIS®. A rapid decline in albumin level may be indicative of CLS. If a diagnosis of CLS is confirmed after exclusion of other causes, permanently discontinue YONDELIS® and promptly initiate CLS treatment according to institutional guidelines.

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
Cardiac dysfunction has occurred in patients receiving YONDELIS®. In the phase 3 study of YONDELIS® combination therapy in ovarian cancer, 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.

In a post-market comparative study in patients treated for liposarcoma or leiomyosarcoma who received prior anthracyclines, cardiac dysfunction occurred in 20 (5.3%) of 378 patients receiving YONDELIS®, compared to 5 (2.9%) of 172 patients receiving dacarbazine. Grade 3 or 4 cardiac dysfunction was observed in 15 (4%) of the 378 patients on YONDELIS®, while only 2 (1.2%) patients experienced Grade 3 cardiac dysfunction on dacarbazine. One patient taking YONDELIS® suffered fatal cardiac failure. In the dacarbazine group no cardiac dysfunction events were reported with a Grade 4 event or an event that led to death.

Patients with LVEF < LLN, prior cumulative anthracycline dose of ≥300 mg/m^2, or a history of cardiovascular disease may be at increased risk of cardiac dysfunction, based on multivariate analyses conducted on integrated datasets from clinical trials. Conduct a thorough cardiac assessment including determination of LVEF by echocardiogram or multigated acquisition (MUGA) scan before initiation of YONDELIS® and at 2 to 3-month intervals thereafter until YONDELIS® is discontinued. Patients with a left ventricular ejection fraction below the normal limit for the institution should not be treated with YONDELIS®.

Patients should be monitored for cardiac-related adverse events or myocardial dysfunction, particularly patients who have a higher risk of cardiomyopathy due to prior anthracycline exposure, the presence of symptoms of decreasing cardiac function, history of cardiovascular

disease or advanced age (≥65 years). In patients who experience Grade 3 or 4 cardiac AEs or serious cardiac events indicative of cardiomyopathy or in patients with an LVEF that decreases below the LLN, YONDELIS® should be discontinued.

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
The grade 3 or 4 hematologic laboratory abnormalities (neutropenia, leukopenia, thrombocytopenia and anemia) were very commonly reported in Phase 2 and Phase 3 clinical studies of patient with soft tissue sarcoma and ovarian cancer treated with YONDELIS®.

In combination therapy with CAELYX® among patients with ovarian cancer, neutropenia was associated with complications such as febrile neutropenia, sepsis and infections, some of which were fatal. Among patients with Grade 3 or 4 decreased neutrophil counts, neutrophil count nadir 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 w
ere treated with colony-stimulation growth factors.

As monotherapy, among patients with soft tissue sarcoma with Grade 3-4 decreased neutrophil counts, the first median value of Grade 3 severity was observed at Day 12, followed by recovery to Grade 2 by Day 24. Abnormalities in neutrophil counts were non-cumulative, including in patients who received prolonged treatment with trabectedin (≥6 cycles). Febrile neutropenia was reported in 2% of patients treated with YONDELIS®.

Cases of drug-related septic shock, some of which were fatal, have been uncommonly reported with patients receiving YONDELIS® either as a single agent or in combination with other chemotherapeutic agents (see **ADVERSE DRUG REACTIONS, Post-Market Adverse Drug Reactions**).

Grade 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 /mm^3, platelets count of less than 100,000 /mm^3 or hemoglobin < 9 g/dL. If neutropenia (ANC< 500 /mm^3) lasting more than 5 days or neutropenia associated with fever or infection, or thrombocytopenia (platelet counts < 25,000/mm^3) occur, dose reduction is recommended (see **DOSAGE AND ADMINISTRATION, Dose Adjustments During Treatment**).

Supportive care/colony stimulating factors should be considered if needed according to institutional guidelines.

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.

Patients with increases in AST, ALT or alkaline phosphatase between cycles may necessitate a dose reduction (see **DOSAGE AND ADMINISTRATION, Dose Adjustments During Treatment**). YONDELIS® must not be used in patients with elevated bilirubin at the time of initiation of cycle. Bilirubin elevations that occurred since the previous dose should be reviewed for cause prior to next dosing, and dose reduction considered (see **DOSAGE AND ADMINISTRATION**).

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).

Cases of hepatic failure (including cases with fatal outcomes) have been reported in post-market experience and uncommonly in clinical trials, in patients with serious underlying medical conditions treated with YONDELIS®. Some potential risk factors that may have contributed to increased YONDELIS® toxicity observed in these cases were dose management inconsistent with recommended dosing guidelines, lack of dexamethasone prophylaxis (see **DOSAGE AND ADMINISTRATION**), or potential CYP3A4 interaction due to multiple competing CYP3A4 substrates or CYP3A4 inhibitors (see **DRUG INTERACTIONS, Drug-Drug Interactions**).

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 (see **PART II, TOXICOLOGY**).

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**.**

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)
In clinical studies of patients treated for soft tissue sarcoma, CPK elevations (Grade 3-4) in association with renal failure, rhabdomyolysis, and other muscle-related toxicities such as myostitis, muscle weakness or muscle pain were observed in 4% of patients (n=31). Of these, four patients had fatal outcomes; two due to rhabdomyolysis and two due to renal failure. In total rhabdomyolysis was reported in four patients (0.5%).

Rhabdomyolysis has been uncommonly reported, usually in association with myelotoxicity, severe liver function test abnormalities or renal failure. Post-market cases of rhabdomyolysis leading to multi-organ failure, some resulting in fatal outcomes, have been reported. 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.

CPK should be closely monitored with strict adherence to treatment guidelines during the treatment phase and prior to re-treatment. YONDELIS® must not be used in patients with CPK >2.5 x ULN (see **DOSAGE AND ADMINISTRATION, Recommended Dose**). 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.

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. If pregnancy occurs during treatment, the patient must be informed of the potential risk to the fetus (see **TOXICOLOGY, Reproductive and Developmental Toxicity**).

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 on age are not recommended.

Pediatrics (< 18 years of age)
The safety of YONDELIS® in pediatric patients has not been established. In a Phase 2 study investigating the activity of YONDELIS® in 42 pediatric patients with recurrent or refractory sarcomas (non-rhabdomyosarcoma soft tissue sarcoma, Ewing sarcoma, and rhabdomyosarcoma), no efficacy was observed. Preclinical studies in Cynomologous monkeys less than 3 kg have shown an increased risk of local infusion-related tissue damage even when administered through a central venous line (see **PART II, TOXICOLOGY**). YONDELIS® should not be used in children and adolescents.

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 new treatment 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

Since systemic exposure to YONDELIS® is 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 is not recommended (see **WARNINGS AND PRECAUTIONS, Hepatic** and **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
- Platelet 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 **WARNINGS AND PRECAUTIONS, Hepatic** and **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)

Patients should be monitored for cardiac-related adverse events or myocardial dysfunction, particularly patients who have a higher risk of cardiomyopathy (see **WARNINGS AND PRECAUTIONS, Cardiovascular)**.

ADVERSE REACTIONS

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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

In Phase 2 and 3 studies in patients with soft tissue sarcoma receiving YONDELIS® at the recommended dose (N=755), adverse reactions of Grade 3 or 4 severity were reported in 57% of patients, with 14% being classified as serious. The most common adverse reactions (≥20%) of any severity grade were nausea, fatigue, vomiting, diarrhea, constipation, decreased appetite, dyspnea, headache, increases in AST/ALT, neutropenia, anemia, leukopenia, thrombocytopenia, blood creatine phosphokinase increased, blood creatinine increased, blood alkaline phosphatase increased and blood albumin decreased, pyrexia. Fatal adverse reactions have occurred in 2.3% of patients. They were often the result of a combination of events including myelosuppression, febrile neutropenia (some with sepsis), hepatic dysfunction, renal or multiorgan failure, and rhabdomyolysis.

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-hour infusion given every 3 weeks (q3wk 24-h) or a 0.58 mg/m^2 3-hour infusion weekly for three weeks in 4-week cycles (qwk 3-h). One hundred and thirty patients were treated in the q3wk 24-hour 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.

Twelve patients (4.6%) discontinued trabectedin treatment due to drug-related AEs: 8 patients in the q3wk 24-hour 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 4 patients in qwk 3-hour 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/m2, 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
Hemoglobin 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
Edema 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
Anemia	27	1	0	25	5	0

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
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
Hypokalemia	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						
Dyspnea	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.

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

Hepatobiliary disorders

AST/ALT increases:
Transient Grade 3 and Grade 4 increases of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were observed in 37% and 44% (Grade 3) and 3% and 7% (Grade 4) of the patients, respectively. 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 and less than 2% of cycles had recovery times longer than 25 days. ALT and AST increases did not follow a cumulative pattern but showed a tendency towards less severe elevations over time (see **WARNINGS AND PRECAUTIONS, Hepatic**).

Hyperbilirubinemia:
Grades 1 to 2 bilirubin increases were observed in 23% of the patients. Grade 3 hyperbilirubinemia occurred in 1% of patients. Bilirubin peaks approximately a week after onset and resolves approximately two weeks after onset (see **WARNINGS AND PRECAUTIONS, Hepatic**).

Severe liver injury:
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. 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**).

Allergic reactions:
Based on the pooled analysis of 19 clinical trials, hypersensitivity was reported in 2% of patients receiving YONDELIS® as monotherapy. Most of these cases were Grade 1 or 2 in severity.

Additional Data from Clinical Trials

Treatment emergent drug related adverse events reported in ≥1% of patients in clinical trials assigned to the recommended regimen [1.5 mg/m^2, 24 hr infusion every 3 weeks (24-h q3wk)]

Blood and lymphatic system disorders: febrile neutropenia, lymphopenia
Gastrointestinal disorders: stomatitis, upper abdominal pain
General disorders and administration site conditions: edema, injection site reaction
Infections and infestations: infection, pneumonia, catheter site infection, sepsis
Investigations: blood albumin decreased, weight decreased, gamma-glutamyltransferase increased
Musculoskeletal and connective tissue disorders: back pain, rhabdomyolysis

Nervous system disorders: paresthesia, peripheral sensory neuropathy
Skin and subcutaneous tissue disorders: alopecia
Vascular disorders: flushing, hypotension

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, palmar-plantar erythrodysaesthesia syndrome, fatigue, pyrexia, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, constipation, abdominal pain, stomatitis and anorexia. Fatal adverse drug reactions have occurred in 0.9% of patients.
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/m2) followed by YONDELIS® (1.1 mg/m2) every 3 weeks or CAELYX® alone (50 mg/m2) 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.

In study OVA-301 in the YONDELIS® + CAELYX® arm, non-white (mainly Asian) patients had a higher incidence than white patients in grade 3 or 4 adverse reactions (96% versus 87%), and serious adverse reactions (44% versus 23% all grades). The differences were mainly observed in relation with neutropenia (93% versus 66%), anemia (37% versus 14%) and thrombocytopenia (41% versus 19%). The incidence of adverse events within the Infection and Infestation system organ class are similar in both subpopulations with 38% in the non-white and 42% in the white subpopulation. Twenty percent of non-white and 16% of white patients discontinued treatment due to drug related adverse events. The number of deaths due to treatment-emergent adverse events were 2 (3%) in the non-white and 3 (1%) in the white subpopulation.

Adverse reactions reported among patients treated with YONDELIS® in combination with CAELYX® during OVA-301 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® from Study OVA-301

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
Alopecia	12	0	0	14	<1	0

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
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.
Allergic reactions:

During the clinical trial, hypersensitivity was reported in 2% of patients receiving YONDELIS® in combination with CAELYX®. Most of these cases were Grade 1 or 2 in severity.

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.

Other clinically important adverse reactions observed in ≥1% of patients with relapsed ovarian cancer, treated with YONDELIS in combination with CAELYX in clinical trials (N =619):

Blood and lymphatic system disorders: lymphopenia

Infections and infestations disorders: device-related infections, pneumonia (including lower respiratory tract infection), sepsis, septic shock, upper respiratory tract infection (including respiratory infection viral)
Investigations: blood urea increased, weight decreased,
Metabolism and nutrition disorders: hypoalbuminemia
Musculoskeletal and connective tissue disorders: arthralgia, back pain
Nervous system disorders: dizziness, dizziness postural, lethargy, paresthesia
Vascular disorders: flushing, hypotension

Abnormal Hematologic and Clinical Chemistry Findings

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

	YONDELIS®/CAELYX® (N=333) (%)			CAELYX® (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

Post-Market Adverse Drug Reactions

The following serious adverse reactions have been derived from spontaneous case reports, literature cases, expanded access programs, and clinical studies other than the global registration trials. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

General disorders and administration site conditions: multi-organ failure
Hepatobiliary disorders: hepatic failure
Immune system disorders: allergic reaction
Infections and infestations disorders: septic shock
Vascular disorders: capillary leak syndrome

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 metabolic clearance of trabectedin may be decreased in patients who are co-administered inhibitors of this isoenzyme. Similarly, the co-administration of trabectedin with inducers of CYP3A4 may increase the metabolic clearance of trabectedin. Two drug-drug interaction Phase 1 studies have demonstrated increased and decreased trabectedin exposures when administered with ketoconazole and rifampin, respectively. In addition, results from the population pharmacokinetic analyses indicated that the plasma clearance of trabectedin was higher in patients who received concomitant dexamethasone (a CYP3A4 inducer) administration relative to those who did not.

In a drug-drug interaction study (n=8) with ketoconazole, a potent CYP3A4 inhibitor, systemic exposure of trabectedin was increased by approximately 21% (C_{max}) and 66% (AUC_{last}), when trabectedin was given concomitantly with ketoconazole (total daily dose of 400 mg). Co-administration of YONDELIS® with potent inhibitors of the enzyme CYP3A4 (e.g. oral ketoconazole, ritonavir, clarithromycin, itraconazole, posaconazole, voriconazole, telithromycin, indinavir, lopinavir, boceprevir, nelfinavir or saquinavir) should be avoided. If this is not possible, close monitoring of toxicities are required and dose reductions of trabectedin should be considered (see **DOSAGE AND ADMINISTRATION**).

In a drug-drug interaction study (n=8) with rifampin, a potent CYP3A4 inducer, systemic exposure of trabectedin was decreased by approximately 22% (C_{max}) and 31% (AUC_{last}), when trabectedin was given concomitantly with rifampin (total daily dose of 600 mg). Therefore, the concomitant use of trabectedin with strong CYP3A4 inducers (e.g., rifampin, phenorbarbital, Saint John's Wort) should be avoided if possible.

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 (a CYP3A4 inducer) administration relative to those who did not. 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.

In vitro preclinical studies have shown trabectedin is a substrate of multiple efflux transporters including P-gp, MRP2 and potentially MRP3 and MRP4, but not BCRP. 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).

The potential for other compounds to displace trabectedin from its plasma protein binding is considered to be very limited on the basis of *in vitro* data.

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).

Maximal total and unbound trabectedin plasma levels reached in STS patients are about 1.8 and 0.05 nM, respectively, and in relapsed ovarian cancer patients are about 10.3 and 0.26 nM, respectively, and are only present during infusion, i.e., during day 1 of a 3-week treatment cycle; a clinically relevant inhibition of transporters by trabectedin at this low concentration level is not expected.

In view of the extremely low trabectedin plasma levels relative to the physiological levels of plasma proteins, the potential for trabectedin to displace other compounds from their plasma protein binding is considered to be very unlikely.

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.

Co-administration of YONDELIS® with potent inhibitors of the enzyme CYP3A4 (e.g. oral ketoconazole, fluconazole, ritonavir, clarithromycin or aprepitant) should be avoided. If this is not possible, close monitoring of toxicities are required and dose reductions of trabectedin should be considered (see **DRUG INTERACTIONS, Drug-Drug Interactions**).

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 and 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 (see **WARNINGS AND PRECAUTIONS, Hepatic).**

The following criteria are required to allow treatment with YONDELIS®:

- Absolute neutrophil count (ANC) ≥ 1,500/mm^3
- Platelet count ≥ 100,000/mm^3
- Hemoglobin ≥ 9 g/dL
- 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
- Creatinine clearance ≥ 30 mL/min (monotherapy)
- Serum creatinine ≤ 1.5 mg/dL (≤ 132.6 μmol/L) or creatinine clearance ≥ 60 mL/min (combination therapy)
- Creatine phosphokinase (CPK) ≤ 2.5 x ULN

The same criteria as above 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 fulfills 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 1.4 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

Trabectedin exposure is increased in patients with hepatic impairment. YONDELIS® is not recommended in this patient population.

Patients with elevated serum bilirubin levels at baseline must not be dosed with YONDELIS®.

Patients must meet specific criteria on hepatic function parameters to start treatment with YONDELIS® (see **WARNINGS AND PRECAUTIONS, Special Populations**).

Hepatic function should always be monitored during treatment with YONDELIS® as dose adjustments may be indicated.

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)

YONDELIS® should not be used in children and adolescents (see **WARNINGS AND PRECAUTIONS, Special Populations**).

Geriatrics (> 65 years of age)
Dose adjustments based on age are not recommended. (see **WARNINGS AND PRECAUTIONS, Special Populations**).

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:

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

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, multicentre, 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 hours 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-hour period after initiation of the infusion. YONDELIS® was associated with statistically significant increases in heart rate from 2 to 24 hours after initiation of treatment, with a maximum effect of mean 11.0 (90% CI 8.5, 13.5) bpm at the 4-hour 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:
Administration of YONDELIS® as a single 3 hour infusion to patients with hepatic dysfunction (total bilirubin >1.5 to ≤3 times the ULN and AST and ALT <8 times the ULN) indicated that hepatic impairment is associated with increased trabectedin exposure. The geometric mean ratio for dose normalized C_{max} was 1.40 in subjects with hepatic dysfunction (administered 0.58 [n=3] or 0.9 mg/m^2 [n=3]), compared with subjects with normal hepatic function (administered 1.3 mg/m^2 [n=9]) and 1.97 for dose normalized AUC_{last}.

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

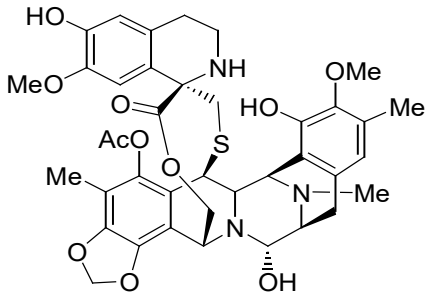
Drug Substance

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 tumour 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 tumours 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)

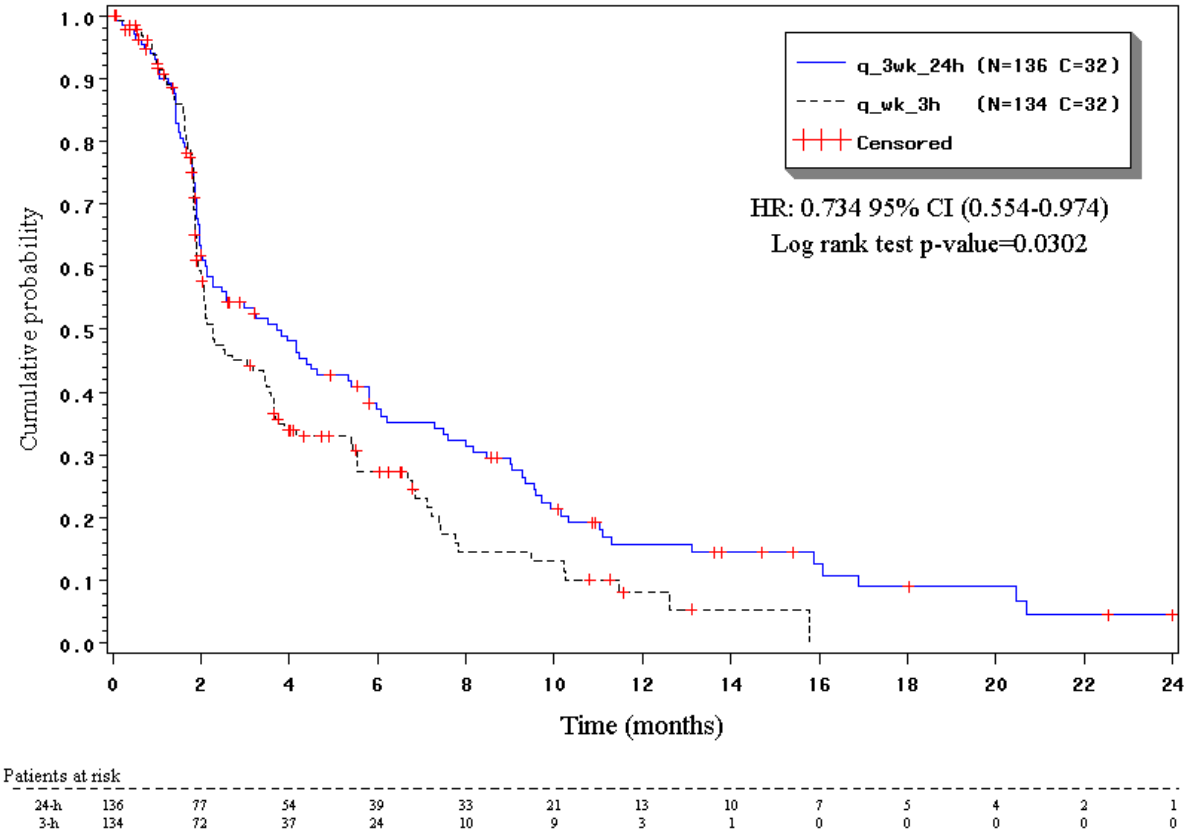


Table 2.1 Summary of Key Efficacy Endpoints

End-point	q3wk 24-h N=136	qwk 3-h 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 analyses, 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 2.2 and 2.3 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

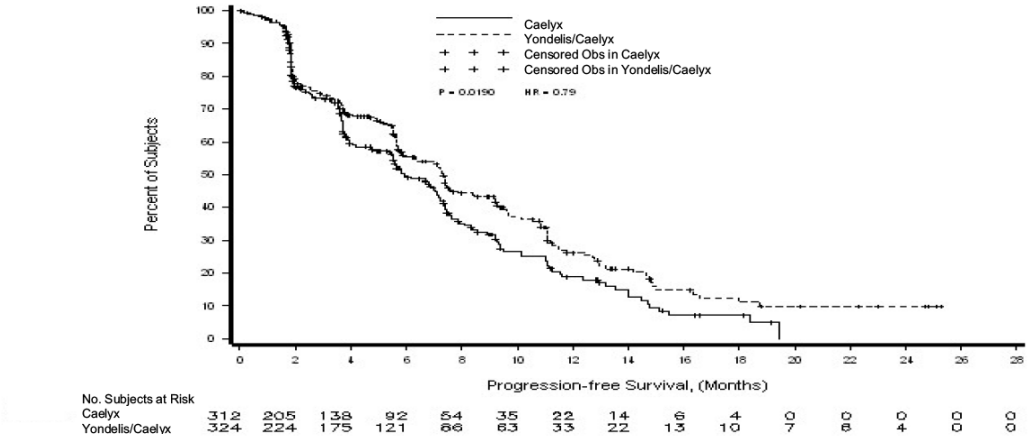
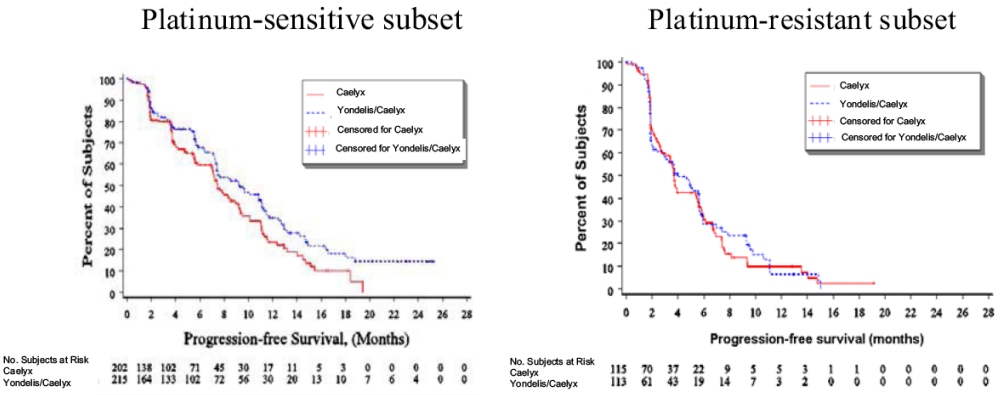


Figure 2.3 - Kaplan-Meier Plot of Progression-Free Survival: subset analysis per platinum-free interval (left graph: platinum-sensitive subset; right graph, platinum-resistant disease) (OVA-301 study).



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

In vitro preclinical studies have shown trabectedin is a substrate of multiple efflux transporters including P-gp, MRP2 and potentially MRP3 and MRP4, but not BCRP. Preclinical models suggest P-gp, MRP2, and MRP3 are involved in the hepatic efflux of trabectedin metabolites and have an important and partially redundant function in protecting from trabectedin-mediated (liver) toxicity.

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.

REFERENCES

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6. Demetri, G, Chawla S, Von Mehren M, et al. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior antracyclines and ifosfamide: results of a randomized phase II study of two different schedules. J Clin Oncol. 2009;17:4188-96.

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® is not recommended 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. YONDELIS® may harm your fetus. You should not take YONDELIS® if you are pregnant.

Genetic counselling is 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 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 (may affect more than 1 in 10 people) 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 diarrhea, 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 (may affect up to 1 in 10 people) 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)
- pain in your back, muscles and joints
- damage to your nerves which may result in tingling, numbness, and burning sensation in the extremities
- general swelling or swelling of the limbs

In uncommon (may affect up to 1 in 100 people) cases you may experience yellowing of your skin and eyeballs (jaundice), pain in the upper right area of your abdomen, nausea, vomiting, a general sense of not feeling well, difficulty in concentrating, disorientation or confusion, and sleepiness. These signs could mean that your liver is not working properly. If you experience any of these symptoms you should seek medical attention immediately.

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 *(may affect more than 1 in 10 people)*			
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 *(may affect up to 1 in 10 people)*			
Fever		√	
Heart muscle problems, including heart failure that may be present as new chest pain, shortness of breath, tiredness, swelling in your legs, ankles or feet, or heart palpitations		√	
Rare *(may affect up to 1 in 1000 people)*			
Allergic reaction (hypersensitivity) that may present as fever, difficulty breathing, redness or flushing of the skin or a rash, feeling sick (nausea) or being sick (vomiting)		√	
Unknown			
Capillary leak syndrome, the symptoms of which may include sudden swelling (edema) of the arms, legs and other parts of the body, occurring with or without sudden drop in blood pressure		√	

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 1908C
    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

For questions, concerns, or the full Product Monograph go to: www.valeopharma.com or contact the manufacturer, Valeo Pharma Inc., at:
1-514-694-0150 or 1-855-694-0151 (toll-free).

This leaflet was prepared by
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