

**PRODUCT NAME**

YONDELIS® 1 mg for injection

**DOUSAGE FORMS AND STRENGTHS**

Powder for concentrate for solution for infusion.

YONDELIS® drug product is provided as a sterile lyophilized white to off-white powder.

Each vial contains 1 mg of trabectedin.

1 mL of reconstituted solution contains 0.05 mg of trabectedin (see *Instructions for Use and Handling and Disposal*).

INN: Trabectedin; CAS Registry No.: 114899-77-3

Chemical Name: (CAS): (1*R*,6*R*,6a*R*,7*R*,13*S*,14*S*,16*R*)-5-(acetyloxy)-3',4',6,6a',7,13,14,16-octahydro-6',8,14-trihydroxy-7,9-dimethoxy-4,10,23-trimethoxy-spiro[6,16] (epithioropyranoxymethano)-7,13-imino-12*H*-1,3-dioxolo[7,8]-isooquinolo[3,2-*b*]benzazocine-20,1'(2*H*)-isooquinolin-19-one.

Molecular Formula: The molecular formula is C<sub>28</sub>H<sub>43</sub>N<sub>3</sub>O<sub>11</sub>S.

Molecular Weight: The molecular weight of trabectedin is 761.84 g/mol.

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

For excipients, see *List of Excipients*.

**CLINICAL INFORMATION**

**Indications**

YONDELIS® is indicated for the treatment of adult patients with advanced soft tissue sarcoma (STS), after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients.

YONDELIS® in combination with pegylated liposomal doxorubicin hydrochloride (PLD) is indicated for the treatment of patients with relapsed platinum-sensitive ovarian cancer.

**Dosage and Administration**

YONDELIS® must be administered under the supervision of a physician experienced in the use of chemotherapy. Its use should be confined to qualified oncologists or other health professionals specialized in the administration of cytotoxic agents.

**Posology**

For the treatment of soft tissue sarcoma (STS), the recommended starting dose is 1.5 mg/m<sup>2</sup> 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® is administered every three weeks as a 3-hour infusion at a dose of 1.1 mg/m<sup>2</sup> immediately after PLD 30 mg/m<sup>2</sup>. To minimize the risk of PLD infusion reactions, the initial dose is administered at a rate no greater than 1 mg/minute. If no infusion reaction is observed, subsequent PLD infusions may be administered over a 1-hour period. (See also PLD package insert for specific administration advice).

All patients must receive corticosteroids e.g. 20mg of dexamethasone intravenously 30 minutes prior to PLD (in combination therapy) or YONDELIS® (in monotherapy); not only as anti-emetic prophylaxis, but also because it appears to provide hepatoprotective effects. Additional anti-emetics may be administered as needed. The following criteria are required to allow treatment with YONDELIS®:

- Absolute neutrophil count (ANC) ≥ 1,500/mm<sup>3</sup>
- Platelet count ≥ 100000/mm<sup>3</sup>
- 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 gamma glutamyl trans-peptidase (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;
- Combination therapy for ovarian cancer: serum creatinine ≤ 1.5 mg/dL (≤ 132.6 μmol/L) or creatinine clearance ≥ 60 mL/min
- Creatine phosphokinase (CPK) ≤ 2.5 x ULN

The same criteria as above must be met prior to re-treatment. Otherwise treatment must be delayed for up to 3 weeks until the criteria are met.

Additional monitoring of hematological parameters bilirubin, alkaline phosphatase, aminotransferases and CPK should occur weekly during the first two cycles of therapy, and at least once between treatments in subsequent cycles.

The same doses should be given for all cycles provided that no grade 3 – 4 toxicities are seen and that 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 dose must be reduced one level, according to table 1 below, for subsequent cycles:

- Neutropenia < 500/mm<sup>3</sup> lasting for more than 5 days or associated with fever or infection
- Thrombocytopenia < 25 000/mm<sup>3</sup>
- Increase of bilirubin > ULN and/or alkaline phosphatase > 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 dose may be further reduced (see below). Colony stimulating factors can be administered for hematologic toxicity in subsequent cycles according to local standard practice.

**Table 1: Dose modification table for YONDELIS® (as single agent for soft tissue sarcoma (STS) or in combination for ovarian cancer) and PLD**

	Soft tissue sarcoma	Ovarian cancer	
	YONDELIS®	YONDELIS®	PLD
Starting dose	1.5 mg/m <sup>2</sup>	1.1 mg/m <sup>2</sup>	30 mg/m <sup>2</sup>
First reduction	1.2 mg/m <sup>2</sup>	0.9 mg/m <sup>2</sup>	25 mg/m <sup>2</sup>
Second reduction	1 mg/m <sup>2</sup>	0.75 mg/m <sup>2</sup>	20 mg/m <sup>2</sup>

See the PLD package insert for more detailed information on PLD dose adjustments.

In the event that further dose reductions are necessary, treatment discontinuation should be considered.

**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 the 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.

**Paediatric population**

As no efficacy was observed, YONDELIS® should not be used in children below 18 years with paediatric sarcomas (see *Pharmacodynamic Properties*).

**Elderly**

No specific studies in older people have been performed. Overall 20% of the 1,164 patients in the integrated safety analysis of monotherapy clinical trials were over 65 years. Of the 333 patients with ovarian cancer who received trabectedin in combination with PLD, 24% were 65 years of age or older and 6% were over 75 years. No relevant differences in the safety profile were seen in this patient population. It seems that plasma clearance and distribution volume of trabectedin are not influenced by age. Therefore, dose adjustments based uniquely on age criteria are not routinely recommended.

**Hepatic impairment**

No studies with the proposed regimen have been conducted in patients with liver dysfunction. Thus, data are not available to recommend a lower starting dose in patients with hepatic impairment. However, special caution is advised and dose adjustments may be necessary in these patients since systemic exposure is probably increased and the risk of hepatotoxicity might be increased. Patients with elevated bilirubin must not be treated with YONDELIS® (see *Warnings and Precautions*).

**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 *Warnings and Precautions*). Considering the pharmacokinetic characteristics of trabectedin (see *Pharmacokinetic Properties*), no dose adjustments are warranted in patients with mild or moderate renal impairment.

**Method of administration**

Intravenous administration through a central venous line is strongly recommended (see *Warnings and Precautions and Instructions for Use and Handling and Disposal*).

For instructions on reconstitution and dilution of the medicinal product before administration, see *Instructions for Use and Handling and Disposal*.

**Soft tissue sarcoma**

Intravenous infusion over 24 hours with a three-week interval between cycles.

**Ovarian cancer**

Intravenous infusion over 3 hours after PLD 30 mg/m<sup>2</sup> as a 90-minute intravenous infusion. For PLD dosage administration instructions, see local manufacturers' prescribing information.

**Contraindications**

YONDELIS® should not be administered to nursing mothers (see *Pregnancy, Breast-feeding and Fertility*). YONDELIS® should not be administered to patients with known hypersensitivity to any of its components. YONDELIS® should not be administered to patients with an active serious or uncontrolled infection.

**Warnings and Precautions**

**Hepatic impairment**

Patients must meet specific criteria on hepatic function parameters to start treatment with YONDELIS®. Since systemic exposure to trabectedin is increased due to hepatic impairment and therefore the risk of hepatotoxicity might be increased, patients with clinically relevant liver diseases should be closely monitored and the dose adjusted if needed. Patients with elevated bilirubin at the time of initiation of a new treatment cycle must not be treated with trabectedin (see *Dosage and Administration*).

**Renal impairment**

Creatinine clearance must be monitored prior to and during treatment. Trabectedin as a single agent must not be used in patients with creatinine clearance < 30 mL/min or in patients treated in combination with PLD with creatinine clearance < 60 mL/min (see *Dosage and Administration*).

**Myelosuppression**

Grade 3-4 hematologic laboratory abnormalities (neutropenia, leukopenia, thrombocytopenia and anemia) were very commonly (>10%) reported in Phase 2 and 3 clinical studies of patients with STS and ovarian cancer treated with YONDELIS®. Among patients with STS 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).

Among patients with ovarian cancer with Grade 3-4 decreased neutrophil counts, neutrophil count nadir occurred at a median of 15 days and recovered within a week.

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*). YONDELIS® should not be administered to patients with baseline neutrophil counts of less than 1500/mm<sup>3</sup>, platelets count of less than 100000/mm<sup>3</sup> or hemoglobin < 9 g/dL. If neutropenia (ANC < 500/mm<sup>3</sup> lasting more than 5 days or neutropenia associated with fever or infection, or thrombocytopenia (platelet counts < 250000/mm<sup>3</sup>) occur, dose reduction is recommended (see *Dosage and Administration*).

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

**Nausea and vomiting**

Grade 3 or 4 vomiting and nausea were reported commonly. All patients must be premedicated with corticosteroids such as dexamethasone. Additional anti-emetics may be administered as needed (see *Dosage and Administration and Interactions*).

**Rhabdomyolysis and severe CPK elevations (> 5 x ULN)**

In Phase 2 and 3 clinical studies of patients treated for STS, CPK elevations (Grade 3-4) in association with renal failure, rhabdomyolysis, and other muscle-related toxicities such as myositis, muscle weakness or muscle pain were observed in 41% 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 non-occurantly reported and severe CPK elevations were observed in 2% of patients treated with YONDELIS® in combination with PLD usually in association with myelotoxicity, severe liver function test abnormalities or renal failure.

Therefore, CPK should be closely monitored with strict adherence to treatment guidelines during the treatment phase and prior to re-treatment. Trabectedin must not be used in patients with CPK > 2.5 xULN (see *Dosage and Administration*). If rhabdomyolysis occurs, supportive measures such as parental 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 trabectedin, since the risk of rhabdomyolysis may be increased.

**Liver function test (LFT) abnormalities**

Reversible acute increases in AST and ALT have been reported in patients treated with YONDELIS® monotherapy or in combination with PLD. Grade 3 or 4 transaminase elevations occurred very commonly; Grade 4 transaminase elevations occurred commonly. The median time to the occurrence of ALT or AST increase to Grade 3 or 4 levels was 8 days. Elevated levels decreased to below Grade 3 or 4 in about 8 days. Transaminase elevations were non-cumulative and decreased in magnitude and incidence with each subsequent cycle. Increases with increases in AST, ALT or alkaline phosphatase between cycles may necessitate dose reduction (see *Dosage and Administration*). 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*).

**Cardiac dysfunction**

In a Phase 3 clinical study of patients treated for liposarcoma or leiomyosarcoma who received prior anthracyclines, cardiac dysfunction (including cardiac failure, cardiac failure acute, congestive heart failure, cardiomyopathy, ejection fraction decreased, diastolic dysfunction, left ventricular dysfunction or right ventricular dysfunction) occurred in 20 (5.2%) of 378 patients receiving YONDELIS®, 15 (4%) of whom developed Grade 3 or 4 cardiac dysfunction. One patient suffered fatal cardiac failure. In the dacarbazine group (n=172), cardiac dysfunction occurred in 4 (2.3%) patients, 2 (1.2%) of whom reported Grade 3 events. No cardiac dysfunction events in this treatment group were reported with a Grade 4 event or an event that led to death.

Protocol specified assessments of left ventricular ejection fraction (LVEF) [echocardiogram or multigated acquisition (MUGA)] at baseline and at the time of treatment discontinuation were obtained in 251 patients (66%) receiving YONDELIS® and in 100 patients (58%) receiving dacarbazine. Absolute decreases of LVEF ≥15% at the end of treatment or an absolute decrease of ≥5% if the ejection fraction was lower than the normal range were similar for the YONDELIS® group (13.5%) and dacarbazine group (11%) despite the greater increase in overall exposure for the YONDELIS® group (median 4 cycles within YONDELIS® group versus 2 cycles within the dacarbazine group).

Multivariate analyses (MVA) revealed cardiac risk factors associated with YONDELIS®.

In the treatment of L-type sarcomas using monotherapy, a MVA of data from a single Phase 3 study demonstrated that prior cumulative anthracycline dose of ≥300 mg/m<sup>2</sup> and baseline LVEF less than the lower limit of normal (<LNL) were risk factors for the development of cardiac-related treatment-emergent adverse events (TEAEs). A MVA from an integrated data set of 11 studies conducted using monotherapy for various solid tumors, demonstrated that age ≥65 years and history of cardiovascular disease were also associated with an increased risk of cardiac-related TEAEs. A MVA evaluating data from 2 ovarian cancer studies in which combination therapy was used (trabectedin+DOXIL [pegylated liposomal doxorubicin hydrochloride]) showed an increased risk of cardiac-related TEAEs for patients with a history of prior cardiac medication use.

Patients with LVEF < LNL, prior cumulative anthracycline dose of ≥300 mg/m<sup>2</sup>, or a history of cardiovascular disease may be at increased risk of cardiac dysfunction. Conduct a thorough cardiac assessment including determination of LVEF by echocardiogram or MUGA scan before initiation of YONDELIS® and at 2 to 3-month intervals thereafter until YONDELIS® is discontinued.

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).

**Injection site reactions**

The use of central venous access is strongly recommended (see *Dosage and Administration*). Patients may develop a potentially severe injection site reaction when trabectedin is administered through a peripheral venous line.

There have been few reported cases of trabectedin extravasation, with subsequent tissue necrosis requiring debridement. There is no specific antidote for extravasation of trabectedin. Extravasation should be managed by local standard practice.

**Drug interactions**

Close monitoring of toxicities is required in patients receiving trabectedin in combination with potent CYP3A4 inhibitors (e.g. oral ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, telithromycin, indinavir, lopinavir, ritonavir, saquinavir, nelfinavir, saquinavir, telaprevir, nefazodone, conivaptan) and such combinations should be avoided if possible. In addition, aprepitant and systemic fluconazole should be used with caution during YONDELIS® treatment. If such combinations are needed, appropriate dose adjustments should be applied in the event of toxicities (see *Dosage and Administration*).

**Capillary leak syndrome (CLS)**

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

**Allergic reactions**

During postmarketing experience, rare cases of hypersensitivity reactions, with very rare occurrence of fatal outcome, have been reported in association with trabectedin administration either alone or in combination with PLD (see *Contraindications and Adverse Reactions*).

**Men and women of childbearing potential**

Women of childbearing potential must use effective contraception during treatment and 3 months thereafter. Men who are fertile must use effective contraception during treatment and 5 months after treatment (see *Pregnancy, Breast-feeding and Fertility*).

**Immediately inform the treating physician if a pregnancy occurs.**

**PLD special warnings and special precautions for use**

See PLD manufacturer's prescribing information for special warnings and precautions regarding PLD.

**Interactions**

**Effects of other substances on trabectedin**

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 PLD 30 mg/m<sup>2</sup> compared to 745 patients enrolled in 14 studies who received trabectedin alone. Data from a separate Phase 1 study, in which full pharmacokinetic profiles for trabectedin were obtained for 16 patients who received trabectedin 0.9 to 1.3 mg/m<sup>2</sup> in combination with PLD 30 mg/m<sup>2</sup>, 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 from the population pharmacokinetic analyses (n=831 subjects) indicated that the plasma clearance of trabectedin was 19% higher in patients who received any concomitant dexamethasone administration relative to those who did not.

Since trabectedin is metabolized mainly by CYP3A4, the metabolic clearance of trabectedin is likely to be decreased in patients who are co-administered drugs that potently inhibit the activity of this isoenzyme. Similarly, the co-administration of trabectedin with potent inducers of CYP3A4 may increase the metabolic clearance of trabectedin.

In a drug-drug interaction Phase 1 studies have confirmed trends toward increased and decreased trabectedin exposures when administered with ketoconazole and rifampin, respectively.

In a drug-drug interaction study (n=8) with ketoconazole, a potent CYP3A4 inhibitor, systemic exposure of trabectedin was increased by approximately 21% (C<sub>max</sub>) and 66% (AUC<sub>0-24</sub>), when trabectedin was given concomitantly with ketoconazole (total daily dose of 400 mg). Close monitoring of toxicities is required in patients receiving trabectedin in combination with potent CYP3A4 inhibitors (e.g. oral ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, telithromycin, indinavir, lopinavir, ritonavir, boceprevir, nelfinavir, saquinavir, telaprevir, nefazodone, conivaptan) and such combinations should be avoided if possible. In addition, aprepitant and systemic fluconazole should be used with caution during YONDELIS® treatment. If such combinations are needed, appropriate dose adjustments should be applied in the event of toxicities (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<sub>max</sub>) and 31% (AUC<sub>0-24</sub>), 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, phenobarbital, Saint John's Wort) should be avoided if possible.

In *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. The clinical relevance of this interaction e.g., for CNS toxicity, has not been established and caution should be exercised when concomitantly administering trabectedin with inhibitors of P-gp.

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 trabectedin 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<sup>2</sup> are similar when co-administered with trabectedin 1.1 mg/m<sup>2</sup> (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.

**Pregnancy, Breast-feeding and Fertility**

**Pregnancy**

No sufficient clinical data on exposed pregnancies are available. However, based on its known mechanism of action, trabectedin may cause serious birth defects when administered during pregnancy. Trabectedin crossed the placenta when administered to pregnant rats. The use of trabectedin during pregnancy is not recommended. If pregnancy occurs during treatment, the patient must be informed of the potential risk to the fetus (see *Non-Clinical Information*).

Women of childbearing potential must use effective contraception during treatment and 3 months thereafter. Men who are fertile must use effective contraception during treatment and 5 months after treatment (see *Warnings and Precautions and Non-Clinical Information*).

Immediately inform the treating physician if a pregnancy occurs.

If pregnancy occurs during treatment genetic counseling should be considered.

**Breast-feeding**

It is not known whether trabectedin is excreted in human milk. The excretion of trabectedin in milk has not been studied in animals. Breast-feeding is contraindicated during treatment and 3 months thereafter (see *Contraindications*).

**Fertility**

Trabectedin can have genotoxic effects. Advice on conservation of oocytes or sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with YONDELIS®.

Genetic counselling is also recommended for patients wishing to have children after therapy.

**Effects on Ability to Drive and Use Machines**

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 trabectedin. Patients who experience any of these events during therapy must not drive or operate machines.

**Adverse Reactions**

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of trabectedin based on the comprehensive assessment of the available adverse event information. A causal relationship with trabectedin cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

**Monotherapy**

YONDELIS® in monotherapy in advanced STS.

In Phase 2 and 3 studies in patients with STS 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 anemia, increases in AST/ALT, leukopenia, neutropenia, nausea, fatigue, blood alkaline phosphatase increased, blood albumin decreased, thrombocytopenia, vomiting, blood creatinine increased, constipation, decreased appetite, blood creatine phosphokinase increased, diarrhea, dyspnea, headache, and 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 table below displays the adverse reactions reported in ≥ 1% of patients according to the standard MedDRA system organ class. Both adverse reactions and laboratory values have been used to provide frequencies. Adverse reactions are presented in order of decreasing frequency.

**Table 2: Adverse reactions reported in ≥1% of patients with soft tissue sarcoma in clinical trials (Phase 2 and 3) assigned to the recommended regimen [1.5 mg/m<sup>2</sup>, 24 hour infusion every 3 weeks (24-h q3wk)]**

System/Organ Class Adverse Reaction	---- Toxicity Grade ----			
	All Grades N=755 %	Grade 3 %	Grade 4 %	Grade 3-4 %
<b>Blood and lymphatic system disorders</b>				
Anemia (N=754)	96.3	16.3	0	16.3
Leukopenia (N=648)	77.9	27.6	11.0	38.6
Neutropenia (N=709)	73.8	26.4	22.4	48.8
Thrombocytopenia (N=753)	50.5	7.2	10.0</	

#### Septic shock

Cases of septic shock, some of which were fatal, have been uncommonly reported in clinical studies and postmarketing experience, in patients treated either with monotherapy or combination therapy.

#### Postmarketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during postmarketing experience (Table 4). In the table, frequencies are provided according to the following convention:

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/1000 and < 1/100
Rare	≥ 1/10000 and < 1/1000
Very rare	< 1/10000, including isolated reports
Not known	Cannot be estimated from the available data.

In Table 4, adverse reactions are presented by frequency category based on spontaneous reporting rates and by frequency category based on incidence in clinical trials or epidemiologic studies, when known.

Table 4: Adverse reactions identified during postmarketing experience with YONDELIS®		
System Organ Class Adverse Reaction	Frequency Category Estimated from Spontaneous Reporting Rates	Frequency Category Estimated from Clinical Trials with YONDELIS®
Vascular disorders		
Capillary leak syndrome	Not known	Uncommon

#### Overdose

##### Symptoms and signs

There is limited data on the effects of trabectedin overdose. The major anticipated toxicities are gastrointestinal, bone marrow suppression and hepatic toxicity.

##### Treatment

There is no specific antidote for trabectedin currently available. In the event of an overdose, patients should be closely monitored and symptomatic supportive care measures instituted as required.

#### PHARMACOLOGICAL PROPERTIES

##### Pharmacodynamic Properties

Pharmacotheapeutic group: Antineoplastic agent, ATC code: L01CX01

##### 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.

Trabectedin has been shown to exert antiproliferative *in vitro* and *in vivo* activity against a range of human tumor cell lines and experimental tumors, 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 YONDELIS® was combined with doxorubicin.

##### Pharmacodynamic effects

###### Electrocardiogram

The effects of trabectedin on the QT/QTc interval were evaluated in a single-blind placebo controlled, sequential design study in patients with locally advanced or metastatic solid tumors who received ≤ 3 prior lines of chemotherapy. In this study, 75 patients received placebo (saline solution) and trabectedin (1.3 mg/m<sup>2</sup>) as 3-h IV infusions on days 1 and 2, respectively. This study showed no patients with a QTc exceeding 500 ms or a time-matched increase from baseline in QTc that exceeded 60 ms at any time point. A therapeutic dose of trabectedin did not prolong the QTc interval.

###### Absolute Neutrophil Count (ANC)

An association was observed between the time course of ANC during treatment and trabectedin plasma concentrations, suggesting higher trabectedin exposure may increase the incidence and severity of neutropenia (see *Warnings and Precautions*).

###### Alanine Amino Transferase (ALT)

Serum ALT elevation during trabectedin administration is transient and non-cumulative following subsequent cycles of trabectedin treatment. The magnitude of the transient serum ALT elevation after trabectedin administration is dependent on the dose, but not on the duration of the infusion. The elevation of serum ALT does not appear to be associated with trabectedin exposure at the recommended dose. A liver protection effect of dexamethasone has been demonstrated when treating cancer subjects with trabectedin.

###### Total bilirubin

An association between the incidence of total bilirubin toxicity Grade ≥ 2 and trabectedin plasma AUC and C<sub>max</sub> has been observed (see *Warnings and Precautions*).

#### Clinical studies

##### Monotherapy

The clinical efficacy and safety of trabectedin for the treatment of patients with leiomyosarcoma or liposarcoma (L-sarcoma) was demonstrated in Study ET743-SAR-3007, a Phase 3, randomized controlled study of trabectedin versus dacarbazine in patients with advanced L-type sarcoma. Patients in the study had been previously treated in any order with at least an anthracycline and ifosfamide containing regimen, or an anthracycline containing regimen and one additional cytotoxic chemotherapy regimen. Three hundred eighty four (384) patients were randomized to the trabectedin group [1.5 mg/m<sup>2</sup> once every 3 weeks (q3wk 24h)] and 193 patients to the dacarbazine group (1 gm/m<sup>2</sup> once every 3 weeks). The median patient age was 56 years (range 17 to 81), 30% were male, 77% Caucasian, 12% African American and 4% Asian.

Major prognostic factors were well balanced among patients; 73% had leiomyosarcomas, 27% liposarcomas and all patients had an ECOG score of ≤1. The majority of patients in both treatment groups received 2 prior lines of chemotherapy and the median time since last disease progression was less than 1 month (0.85 month).

Patients in the trabectedin and dacarbazine arms received a median of 4 and 2 cycles respectively.

The primary efficacy endpoint of the study was overall survival (OS) with final analysis to occur at the time of 376 observed death events. The major secondary endpoints based upon investigator assessment of disease response were Progression Free Survival (PFS), Objective Response Rate (ORR), Duration of Response (DOR), and Time to Progression (TTP). The disease response criteria were assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.

With a median survival follow-up of 21.2 months, 381 patients died (258 [67%] in the trabectedin treatment group and 123 [64%] in the dacarbazine treatment group). The median OS was 13.7 months (95% CI: 12.2, 16.0) for the trabectedin treatment group and 13.1 months (95% CI: 9.1, 16.2) for the dacarbazine treatment group. The HR was 0.927 (95% CI: 0.743, 1.159; p=0.4920), which represents a 7.3% reduction in the risk of death for patients in the trabectedin treatment group. Other efficacy results from study ET743-SAR-3007 at the time of the interim analysis are presented in the table below. The PFS results were audited through a retrospective review by independent radiologists.

**Table 5: Efficacy results from study ET743-SAR-3007**

Efficacy endpoint	Trabectedin	Dacarbazine
N: ITT patients	345	173
<b>Progression free survival<sup>a</sup></b>		
Events n (%)	217 (63%)	112 (65%)
Median (95% CI) (months)	4.21 (2.99, 4.83)	1.54 (1.48, 2.60)
HR (95% CI) <sup>b</sup>	0.550 (0.436, 0.696)	
p-value <sup>c</sup>	< 0.0001	
<b>Time to Progression</b>		
Events n (%)	205 (59%)	112 (65%)
Median (95% CI) (months)	4.24 (3.22, 4.93)	1.54 (1.48, 2.60)
HR (95% CI) <sup>b</sup>	0.522 (0.412, 0.661)	
p-value <sup>c</sup>	< 0.0001	
<b>Objective Response Rate (ORR; CR+PR)</b>		
Objective response rate n (%)	34 (10%)	12 (7%)
ORR (95% CI) <sup>a</sup>	(6.9, 13.5)	(3.6, 11.8)
OR (95% CI) <sup>d</sup>	1.467 (0.717 - 3.197)	
p-value <sup>d</sup>	0.3269	
<b>Duration of Response (CR+ PR)</b>		
n: response-evaluable patients	34	12
Median <sup>e</sup> (95% CI) (months)	6.47 (3.58, 7.62)	4.17 (2.14, NE)
HR (95% CI) <sup>b</sup>	0.471 (0.168, 1.318)	
p-value	0.1415	
<b>Clinical Benefit Rate (CBR)</b>		
CBR, n (%)	118 (34%)	32 (19%)
CBR 95% CI <sup>a</sup>	(29.2, 39.5)	(13.0, 25.1)

OR (95% CI) <sup>d</sup>	2.291 (1.446 - 3.692)	
p-value <sup>d</sup>	0.0002	
<b>Duration of stable disease</b>		
n (%): patients with best response of stable disease	177 (51%)	60 (35%)
Events, n (%)	90 (51%)	35 (58%)
Median (95% CI), months	6.01 (4.86, 6.97)	4.17 (2.89, 5.49)
HR (95% CI) <sup>b</sup>	0.449 (0.300, 0.673)	
p-value <sup>c</sup>	0.0001	

<sup>a</sup> Based on investigator assessment.

<sup>b</sup> Hazard ratio is estimated using Cox proportional hazards model with treatment group as the only covariate

<sup>c</sup> A hazard ratio <1 indicates an advantage for trabectedin

<sup>d</sup> P-value is based on unstratified log rank test.

<sup>e</sup> Based on Fisher's exact test.

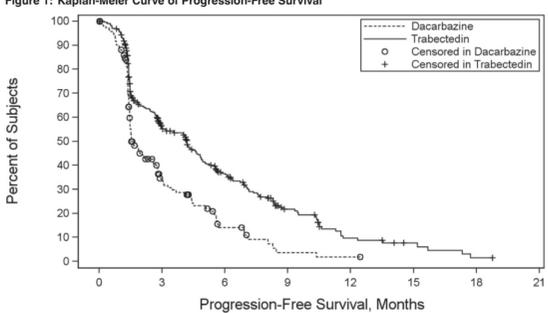
<sup>f</sup> ORR 95% CI is based on Fisher's exact CI;

CR=Complete Response; CRU=Complete response unconfirmed; PR=Partial Response; CI=Confidence Interval.

HR=hazard ratio; ITT=intent to treat; OR=odds ratio; CBR=Clinical Benefit Rate

Note: Objective response rate (ORR) is defined as the proportion of subjects who achieved a CR or PR as best response. Clinical benefit is defined as subject whose best overall response is CR, PR, or SD ≥18wks.

**Figure 1: Kaplan-Meier Curve of Progression-Free Survival**



#### No. Subjects at Risk

Dacarbazine	173	35	10	2	1	0
Trabectedin	345	133	71	29	10	5

In Study ET743-SAR-3007, M.D. Anderson Symptom Inventory (MDASI) scores were used to assess patient's perceived symptom burden (symptom severity, and symptom interference relating to physical and mental function) and to determine the impact of treatment on symptom change or stability. The MDASI scores demonstrated low levels of symptoms at baseline in both trabectedin and dacarbazine groups; which were maintained for the duration of therapy without any meaningful difference between treatment groups.

Randomized study ET743-ST5-201 evaluated the efficacy and safety of trabectedin in patients with locally advanced or metastatic liposarcoma or leiomyosarcoma, 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<sup>2</sup> as a 24-hour intravenous infusion every 3 weeks or at 0.58 mg/m<sup>2</sup> weekly as a 3-hour intravenous infusion for 3-weeks of a 4-week cycle. There were no pre-defined limits to the number of cycles administered. Treatment continued while clinical benefit was noted. No cumulative toxicities were observed in patients treated with multiple cycles. The protocol specified final TTP analysis showed a 26.6% reduction in the relative risk of progression for patients treated in the 24-h q3wk group (Hazard Ratio = 0.734 CI 0.554 - 0.974). Median TTP values were 3.7 months (CI: 2.1 - 5.4 m) in the 24-h q3wk group and 2.3 months (CI: 2.0 - 3.5 m) in the 3-h qwk group (p = 0.0302). No significant differences were detected in overall survival (OS). Median OS with the 24-h q3wk regime was 13.9 months (CI: 12.5 - 18.6) and 60.3% of patients were alive at 1 year (CI: 52.0 - 68.5%). Additional efficacy data are available from 3 single-arm Phase 2 trials with similar populations treated with the same regime. These trials evaluated a total of 100 patients with lipo and leiomyosarcoma and 83 patients with other types of sarcoma.

Results from an expanded access program for patients with STS show that among the 903 patients assessed for OS, the median survival time was 11.9 months [95% CI: 11.2, 13.8]. The median survival by histology tumor type was 16.2 months [95% CI: 14.1, 19.5] for patients with leiomyosarcomas and liposarcomas, and 8.4 months [95% CI: 7.1, 10.7] for patients with other types of sarcomas. The median survival for patients with liposarcoma was 18.1 months [95% CI: 15.0, 26.4] and for patients with leiomyosarcoma 16.2 months [95% CI: 11.7, 24.3].

##### Combination therapy

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

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 6 below:

**Table 6: Summary of patients baseline and disease characteristics**

	YONDELIS® + PLD N = 337	PLD 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® + PLD was observed in PFS and objective response rate, with a trend in survival in favor of the combination arm at the time of the final analysis.

The primary endpoint, PFS, was significantly longer in patients treated with YONDELIS® in combination with PLD® compared with those treated with PLD alone (median PFS: 7.3 vs. 5.8 months respectively). Treatment with YONDELIS® + PLD resulted in a 21% risk reduction for disease progression compared to PLD alone [HR = 0.79; 95% CI (0.65,0.96), p = 0.0190].

The final survival analysis was performed based on 522 events with a median follow up of 47.4 months. Efficacy results are summarized in Table 7.

**Table 7: Efficacy of YONDELIS® in combination with PLD in the treatment of patients with ovarian cancer (Study OVA-301)**

	YONDELIS®+PLD	PLD	p-value
<b>Independent radiologist</b>	n = 328	n = 317	
Median PFS (95% CI) months*	7.3 (5.9; 7.9)	5.8 (5.5; 7.1)	0.0190 <sup>a</sup>
Hazard ratio (95% CI)	0.79 (0.65; 0.96)		
ITT population	n = 337	n = 335	
Objective response rate (%)	27.6	18.8	0.0080 <sup>b</sup>
Odds ratio**	1.646 (1.144-2.367)		
Median duration of response (months)*	7.9 (7.4; 9.2)	7.7 (6.5; 9.0)	0.8203 <sup>a</sup>
Hazard ratio (95% CI)	0.95 (0.62; 1.46)		
<b>Independent oncologist review</b>	n = 336	n = 335	
Median PFS (95% CI) months*	7.4 (6.4; 9.2)	5.6 (4.2; 6.8)	0.0008 <sup>a</sup>
Hazard ratio (95% CI)	0.72 (0.60; 0.88)		

Objective response rate (%) 30.4 19.1 0.0009<sup>b</sup>

Odds ratio\*\* 1.846(1.290-2.641)

#### Overall survival (OS) (Final analysis n = 522 events)

All randomized n = 337 n = 335

Median OS (95% CI) (months) 22.2 (19.3-25.0) 18.9 (17.1-21.5) 0.0835

Hazard ratio<sup>a</sup> 0.86 (0.72-1.02)

#### Overall survival in platinum sensitive population (Final analysis n = 316 events)

Median OS (95% CI) (months) n = 218 n = 212 24.1 (24.1-31.4) 24.1 (20.9-26.9) 0.1056

Hazard ratio<sup>a</sup> 0.83 (0.67-1.04)

#### Overall survival in platinum resistant population (Final analysis n = 205 events)

Median OS (95% CI) (months) n = 119 n = 123 14.2 (11.1-16.8) 12.4 (10.6-14.8) 0.5452

Hazard ratio<sup>a</sup> 0.92 (0.70-1.21)

<sup>a</sup> Based on Kaplan Meier estimates; a hazard ratio < 1 indicates an advantage for YONDELIS®+PLD

<sup>b</sup> Odds ratio > 1 indicates advantage for (YONDELIS® +PLD) calculated with Cochran-Mantel-Haenszel.

<sup>c</sup> Log rank test

<sup>d</sup> Fisher's exact test

Based on independent oncologist review, patients who had platinum free intervals (PFI) less than 6 months had similar PFS between the two arms with both showing median PFS of 3.7 months [HR = 0.89 (95% CI: 0.67-1.20)]. ORR was 14.3% in the YONDELIS® +PLD arm vs. 11.4% in the PLD monotherapy arm. For patients who had PFI ≥ 6 months, median PFS was 9.7 months in the YONDELIS®+PLD arm compared with 7.2 months in the PLD monotherapy arm [HR = 0.66 (95%CI 0.51-0.85), p-value = 0.0010]. ORR rate was 39.2% in the YONDELIS®+PLD arm vs. 23.6% in the PLD monotherapy arm.

In the final analysis, the treatment effect on overall survival was more pronounced in the YONDELIS®+PLD combination vs. PLD alone in patients with PFI ≥ 6 months (platinum-sensitive population: 27.0 vs. 24.1 months, HR = 0.83, CI : 0.67-1.04) than in those with PFI < 6 months (platinum-resistant population: 14.2 vs. 12.4 months, HR = 0.92, CI : 0. 70-1.21).

In the multivariate analyses including PFI, the treatment effect was statistically significant favoring the YONDELIS®+PLD combination over PLD alone (PFS, p = 0.0157; OS, p = 0.0285).

##### Pharmacokinetic Properties

Systemic exposure after intravenous administration as a constant rate intravenous infusion is dose proportional at doses up to and including 1.8 mg/m<sup>2</sup>. 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 extensively bound to plasma alpha-1 acid glycoprotein and albumin. 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.

*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.

##### 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.

##### Elimination

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 radiolabeled 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 in-patient variability was 28%.

##### Special populations

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<sup>2</sup>), age (range: 19 to 83 years), or gender.

##### Pediatrics (18 years of age and younger)

The pharmacokinetics of trabectedin have been investigated in pediatric patients (age range: 2 years to 18 years, N=30) with refractory solid tumors, including sarcomas. Pharmacokinetic parameters in the pediatric population were similar to those previously observed in adults given the same dose per body surface area (see *Dosage and Administration*).

##### Elderly (65 years of age and older)

Results from population pharmacokinetic analyses indicate that the plasma clearance and distribution volume of trabectedin are not influenced by age. Thus, adjustment of the starting dose of trabectedin due to potential age-related changes in its pharmacokinetic properties is not recommended (see *Dosage and Administration*).

##### Renal impairment

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 <sup>14</sup>C-labeled trabectedin suggests that renal impairment would have little influence on the elimination of trabectedin or its metabolites.

##### Hepatic impairment

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<sub>max</sub> was 1.40 in subjects with hepatic dysfunction (administered 0.58 mg/m<sup>2</sup> [n=3] or 0.9 mg/m<sup>2</sup> [n=3]), compared with subjects with normal hepatic function (administered 1.3 mg/m<sup>2</sup> [n=9]) and 1.97 for dose normalized AUC<sub>0-∞</sub>.

##### Other populations

###### Race/ethnicity

A population pharmacokinetic analysis of a limited number of subjects showed that race and ethnicity are not expected to have clinically relevant effects on trabectedin pharmacokinetics. A Phase 1 study in a limited number of subjects showed that trabectedin plasma concentrations observed in the Japanese population at a dose of 1.2 mg/m<sup>2</sup> were similar to those obtained in the Western population at 1.5 mg/m<sup>2</sup>.

##### Non-Clinical Information

###### Pharmacology/Toxicology

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.

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<sub>max</sub> values) in the range of those observed in the clinic. The plasma trabectedin levels attained were 10.6 ± 5.4 ng/mL (C<sub>max</sub>), similar to those reached after administration of 1.1 mg/m<sup>2</sup> in 3-hour-infusion (C<sub>max</sub> of 7.9 ± 2.0 ng/mL).

Myelosuppression and hepatotoxicity were identified as the primary toxicity for trabectedin. Findings observed included hematopoietic toxicity (severe leukopenia, anemia, and lymphoid and bone marrow depletion) as well as increases in liver function tests, hepatocellular degeneration, intestinal epithelial necrosis, and severe local reactions at the injection site.

In mice, rats, rabbits and monkeys, 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 Cynomolgus 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. These adverse effects were observed when trabectedin was administered to animals less than 3 kg. Mortalities were seen at 0.42 mg/m<sup>2</sup> and above (see *Dosage and Administration Pediatrics*).

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.

###### Carcinogenicity and mutagenicity

Trabectedin is genotoxic both *in vitro* and *in vivo*. Long-term carcinogenicity studies have not been performed.

###### Fertility

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), it is likely to affect the reproductive capacity.

#### PHARMACEUTICAL INFORMATION

##### List of Excipients

Sucrose  
Potassium dihydrogen phosphate  
Phosphoric acid (for pH-adjustment)  
Potassium hydroxide (for pH adjustment)