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YONDELIS®
Janssen

NAME OF THE MEDICINAL PRODUCT
YONDELIS® Trabectedin for Injection (1 mg)

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 1 mg of trabectedin.
1 mL of reconstituted solution contains 0.05 mg of trabectedin (see Instructions for Use, Handling and Disposal).
For excipients, see List of Excipients.

PHARMACEUTICAL FORM
Powder for concentrate for solution for infusion.
YONDELIS® drug product is provided as a sterile lyophilized white to off-white powder.

CLINICAL PARTICULARS
Therapeutic Indications
YONDELIS® in combination with pegylated liposomal doxorubicin hydrochloride (PLD) is indicated for the treatment of patients with relapsed ovarian cancer.

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

Posology and Method of Administration
YONDELIS® must be administered under the supervision of a physician experienced in the use of chemotherapy. Its use should be confined to personnel specialized in the administration of cytotoxic agents.

For the treatment of soft tissue sarcoma, 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® is used in combination with DOXIL® every three weeks. YONDELIS® is administered at a dose of 1.1 mg/m^2 as a 3-hour intravenous infusion after DOXIL® 30 mg/m^2, as a 90-minute intravenous infusion. For PLD dosage administration instructions, see local manufacturers' prescribing information. Administration through a central venous line is strongly recommended (see Special Warnings and Special Precautions for Use and Instructions for Use, Handling and Disposal). All patients must be premedicated with corticosteroids such as dexamethasone 20 mg IV, 30 minutes before each YONDELIS® infusion; not only as anti-emetic prophylaxis, but also because it appears to provide hepatoprotective effects.

Additional anti-emetics may be administered as needed.

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

- Absolute neutrophil count (ANC) ≥1500/mm^3 • Platelet count ≥100000/mm^3
- Haemoglobin ≥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; 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 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.

Additional monitoring of haematological and biochemical parameters [alkaline phosphatase, bilirubin, CPK, and aminotransferases (AST and ALT)] should occur weekly during the first two cycles of

therapy, and at least once between treatments in subsequent cycles.

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

Dose adjustments during treatment

Prior to re-treatment, patients must fulfill the baseline criteria defined above. If any of the following events occur at any time between cycles, the YONDELIS® dose must be reduced to 1.2 mg/m^2 in subsequent cycles in monotherapy, and reduced to 0.9 mg/m^2 in combination therapy.

- Neutropenia <500/mm^3 lasting for more than 5 days or associated with fever or infection
- Thrombocytopenia <25000/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 which has not recovered by day 21; combination therapy for ovarian cancer AST or ALT >5 x ULN which has not recovered by day 21. The PLD dose should also be reduced to 25 mg/m^2.
- 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® dose may be further reduced to 1 mg/m^2 for YONDELIS® monotherapy or 0.75 mg/m^2 when YONDELIS® is used in combination therapy with PLD. In the event that further dose reductions are necessary, treatment discontinuation should be considered. Colony stimulating factors can be administered for hematologic toxicity in subsequent cycles according to local standard practice.

For additional PLD dosage adjustments, see local manufacturers' prescribing information. For instructions on reconstitution and dilution of the medicinal product before administration, see Instructions for Use, Handling and Disposal.

Special patient populations

Pediatric patients

The safety and efficacy of trabectedin in pediatric patients have not yet been established. Therefore, this medicinal product should not be used in children and adolescents until further data become available.

Preclinical studies in Cynomologus 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 Preclinical Safety Data).

Elderly patients

Of the 1132 patients from single agent clinical trials from an integrated safety analysis in several tumor 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 PLD, 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 effect the outcome. Results from population pharmacokinetic analyses indicate that the plasma clearance and distribution volume of trabectedin are not influenced by age. Therefore, dose adjustments based uniquely on age criteria are not routinely recommended.

Patients with impaired hepatic function

Patients with hepatic impairment may be at increased risk for toxicity. Recommendations for a starting dose in these patients cannot be made because the use of trabectedin in patients with impaired hepatic function has not been adequately studied. However, special caution is advised and dose adjustments may be necessary in these patients since systemic exposure may be increased and the risk of hepatotoxicity might be increased. Patients with elevated bilirubin at the time of initiation of cycle must not be treated with YONDELIS® (see Special Warnings and Special Precautions for Use).

Patients with impaired renal function
Studies including patients with renal insufficiency (creatinine clearance <30 mL/min); combination therapy for ovarian cancer <60 mL/min) have not been conducted and therefore YONDELIS® must not be used in these patient populations (see Special Warnings and Special Precautions for Use). The pharmacokinetics of trabectedin are not expected to be impacted by mild or moderate renal impairment (see Pharmacokinetic Properties).

Contraindications
YONDELIS® should not be administered to nursing mothers (see Pregnancy and Lactation).
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.

Special Warnings and Special Precautions for Use

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

Neutropenia, thrombocytopenia and leucopenia
Grades 3 or 4 neutropenia and thrombocytopenia associated with trabectedin therapy have been very commonly reported. In addition, Grade 3 or 4 leucopenia has been very commonly reported and associated with trabectedin combination therapy with PLD. Neutrophil nadirs 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 Posology and Method of Administration). YONDELIS® should not be administered to patients with baseline neutrophil counts of less than 1500 cells/mm^3 and platelets count of less than 100000 cells/mm^3. If severe neutropenia (ANC<500 cells/mm^3) lasting more than 5 days or associated with fever or infection occur, dose reduction is recommended (see Posology and Method of Administration).

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 Posology and Method of Administration).

Rhabdomyolysis and severe CPK *elevations (>5 x ULN)* Trabectedin must not be used in patients with CPK >2.5 ULN (see Posology and Method of Administration). Rhabdomyolysis has been uncommonly reported and severe CPK elevations were observed in 4% and 2% of patients treated with YONDELIS® monotherapy or in combination with PLD respectively, usually in association with myelotoxicity, severe liver function test abnormalities or renal failure. Therefore, CPK should be closely monitored whenever a patient may be experiencing any of these toxicities or muscle weakness or muscle pain. 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 trabectedin, since the risk of rhabdomyolysis may be increased.

Liver Function Test (LFT) abnormalities

Reversible acute increases in aspartate aminotransferase (AST) and alanine aminotransferase (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 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. YONDELIS® must not be used in patients with elevated bilirubin at the time of initiation of cycle. Patients with increases in AST, ALT and alkaline phosphatase between cycles may necessitate dose reduction (see Posology and Method of Administration).

Injection site reactions

The use of central venous access is strongly recommended (see Posology and Method of 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 (see Preclinical Safety Data).

Others

Caution should be taken if medicinal products associated with hepatotoxicity are administered concomitantly with trabectedin, since the risk of hepatotoxicity may be increased. The concomitant use of trabectedin with alcohol must be avoided. 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 (see Pregnancy and Lactation).

PLD special warnings and special precautions for use

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

Interactions with Other Medicinal Products and Other Forms of Interaction

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^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 PLD 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.

Since trabectedin is metabolized mainly by CYP3A4, the concentrations of trabectedin in plasma are likely to be increased in patients who are co-administered drugs that potently inhibit the activity of this isoenzyme (e.g. oral ketoconazole, fluconazole, ritonavir, clarithromycin or aprepitant). If such combinations are needed, close monitoring of toxicities is required.

Results from the population pharmacokinetic analyses (n = 831 subjects) indicated that the plasma clearance of trabectedin was 19% higher in patients who received any concomitant dexamethasone administration relative to those who did not. The co-administration with potent inducers of CPY3A4 (e.g., rifampicin, phenorbarbital, Saint John's Wort) may also further increase the metabolic clearance of trabectedin. Preclinical data have demonstrated that trabectedin is a substrate of P-glycoprotein (P-gp). Concomitant administration of inhibitors of P-gp, e.g. cyclosporine and verapamil, may alter trabectedin distribution or elimination. The clinical relevance of this interaction, e.g. for CNS toxicity, has not been established and caution should be exercised when concomitantly administering trabectedin with inhibitors of P-gp.

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^2 are similar when coadministered with trabectedin 1.1 mg/m^2 (86 patients) and when given alone (80 patients).

Pregnancy and Lactation

Use during 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 should not be used during pregnancy unless clearly necessary. If it is used during pregnancy, the patient must be informed of the potential risk to the foetus (see Preclinical Safety Data) and be monitored carefully. If trabectedin is used at the end of pregnancy, potential adverse reactions should be monitored carefully in the newborns.

Fertility

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 (see Preclinical Safety Data) and 5 months after treatment for men (see Special Warnings and Special Precautions for Use).

Trabectedin can have genotoxic effects. 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 counseling should be considered. Genetic counseling is also recommended for patients wishing to have children after therapy.

Use during lactation

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).

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.

Undesirable Effects

Monotherapy

YONDELIS® in monotherapy in advanced STS The following safety profile of YONDELIS® is based on the evaluation in phase II clinical trials of 570 patients assigned to the recommended treatment regime in several cancer types including soft tissue sarcoma, breast cancer, osteosarcoma, ovarian cancer, GIST, melanoma and renal carcinoma. The most common adverse reactions of any severity grade were nausea, fatigue, vomiting, anorexia, neutropenia, and increases in AST/ALT. Fatal adverse reactions have occurred in 1.9% of patients. They were often the result of a combination of events including pancytopenia, febrile neutropenia, some of them with sepsis, hepatic involvement, renal failure and rhabdomyolysis.

Adverse reactions

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. Undesirable effects are presented in order of decreasing frequency.

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

YONDELIS® n=570	
System Organ Class/Preferred term	**All grades %**
Investigations	
Blood creatinine increased*	31
Blood creatine phosphokinase increased*	26
Blood albumin decreased*	55
Weight decreased	6

Table 1- Treatment emergent drug related adverse events reported in ≥1% of patients in clinical trials assigned to the recommended regime [1.5 mg/m², 24 hour infusion every 3 weeks (24-h q3wk)]	
YONDELIS® n=570	
System Organ Class/Preferred term	**All grades %**
Blood and Lymphatic System Disorders	
Anaemia*	97
Leucopenia*	93
Neutropenia*	79
Thrombocytopenia*	49
Febrile neutropenia	2
Nervous System Disorders	
Headache	11
Dysgeusia	4
Peripheral sensory neuropathy	2
Dizziness	2
Paraesthesia	2
Respiratory, Thoracic and Mediastinal Disorders	
Dyspnoea	5
Cough	1
Gastrointestinal disorders	
Nausea	63
Vomiting	39
Constipation	16
Diarrhea	10
Stomatitis	6
Abdominal pain	5
Dyspepsia	3
Upper abdominal pain	2
Skin and Subcutaneous Tissue Disorders	
Alopecia	3
Musculoskeletal and Connective Tissue Disorders	
Myalgia	5
Arthralgia	2
Back pain	1
Metabolism and Nutrition Disorders	
Anorexia	20
Dehydration	2
Decreased appetite	1
Hypokalemia	1
Infections and Infestations	
Infection	3
Vascular Disorders	
Flushing	2
Hypotension	2

Table 1- Treatment emergent drug related adverse events reported in ≥1% of patients in clinical trials assigned to the recommended regime [1.5 mg/m², 24 hour infusion every 3 weeks (24-h q3wk)]	
YONDELIS® n=570	
System Organ Class/Preferred term	**All grades %**
General Disorders and Administration Site Conditions	
Fatigue	55
Asthenia	11
Pyrexia	6
Edema	2
Edema peripheral	2
Injection site reaction	2
Hepatobiliary Disorders*	
Alanine aminotransferase increased	95
Aspartate aminotransferase increased	94
Gamma-glutamyltransferase increased	84
Blood alkaline phosphatase increased	60
Hyperbilirubinemia	24
Psychiatric Disorders	
Insomnia	2
*Based on laboratory measurements	

Most frequent adverse reactions

Blood and Lymphatic system disorders

Neutropenia: Neutropenia occurred in 79% of patients. Grade 3 and 4 neutropenia occurred in 27% and 24% of patients respectively). Neutropenia followed a predictable pattern of rapid onset and reversibility, and was rarely associated with fever or infection.

Thrombocytopenia: Grade 3 and 4 thrombocytopenia occurred in 18% and 3% of patients respectively. Bleeding events associated to thrombocytopenia occurred in <1% of patients. *Anaemia*: Anaemia occurred in 97% of patients although 52% of patients were anaemic at baseline. Grade 3 and 4 anaemia occurred in 13% and 4% of patients respectively.

Hepatobiliary disorders

AST/ALT increases: Transient grade 3 increases of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were observed in 38% and 44% of the patients and grade 4 elevations in 3% and 7% 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.

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. Clinical manifestations of severe hepatic injury were uncommon with a lower than 1% 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

Nausea, vomiting, diarrhoea and constipation: Nausea and vomiting were reported in 63% and 39% of patients respectively. Grade 3-4 nausea and vomiting were reported in 6% and 7% of patients, respectively. Grade 3-4 diarrhoea and constipation were reported in less than 1% of patients.

Stomatitis: Grade 3-4 mucositis was reported in less than 1% of the patients.

Fatigue/Asthenia: Grade 3-4 fatigue/asthenia occurred in 9% and less than 1% of patients respectively.

Anorexia: Grade 3-4 anorexia occurred in 1% of the patients. 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.

Dyspnoea: Grade 3-4 dyspnoea reported as trabectedin related occurred in 2% of the patients.

Alopecia: Alopecia was reported in approximately 3% of all patients, of which the majority was grade 1 alopecia.

Combination therapy

YONDELIS® in combination with PLD in advanced ovarian cancer

The following safety profile of YONDELIS® is based on the evaluation of a phase III clinical trial OVA 301 of 663 patients with advanced relapsed ovarian cancer who receive either PLD (30 mg/m^2) followed by YONDELIS® (1.1 mg/m^2) every 3 weeks or PLD alone (50 mg/m^2) every 4 weeks. The combination of YONDELIS® with PLD 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 PLD 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 (see Posology and Method of Administration). The most common ADRs, reported in ≥20% of patients treated with YONDELIS® in combination with PLD were neutropenia, leucopenia, anemia, thrombocytopenia, nausea, vomiting, diarrhoea, stomatitis, hand-foot syndrome, fatigue, alanine aminotransferase increased, aspartate aminotransferase increased and blood alkaline phosphatase increased.

The most common adverse drug reaction, reported ≥5% leading to drug discontinuation was neutropenia.

Adverse reactions reported among patients treated with YONDELIS® in combination with PLD during clinical studies that occurred at a rate ≥1% are shown in **Table 2** below.

Table 2-Adverse Drug Reactions in ≥1% of Patients with Ovarian Cancer Treated With YONDELIS® in Combination with PLD

Adverse Drug Reaction System Organ Class Preferred Term	YONDELIS®+ PLD (n=333) %			PLD (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
Leucopenia	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	
Metabolism and Nutrition Disorders						
Dehydration	5	2	1	5	2	0
Hypokalaemia	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
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	
Investigations						
Alanine aminotransferase increased	55	29	2	9	1	0
Aspartate aminotransferase increased	40	6	1	10	1	<1
Blood alkaline phosphatase increased	23	1	0	8	1	0
Blood creatine phosphokinase increased	7	1	1	3	0	0
Blood creatinine increased	6	<1	<1	6	<1	0
Gammaglutamyltransferase increased	4	2	0	2	0	0
Bilirubin conjugated increased	1	0	0	0	0	0

* All patients reporting Left ventricular dysfunction, after discontinuation of study therapy improved.

The following clinically significant adverse reaction was observed in less than 1% of patients treated with YONDELIS® in combination with PLD: rhabdomyolysis (YONDELIS® + PLD ≤1% (Grade 3; 0%, Grade 4; ≤1%), and PLD alone 0%).

Overdose

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

toxicity. 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

Pharmacotherapeutic 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 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 YONDELIS® was combined with doxorubicin.

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^2) 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.

Clinical efficacy

Monotherapy

The efficacy and safety of trabectedin is based in a randomized trial 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^2 as a 24-hour intravenous infusion every 3 weeks or at 0.58 mg/m^2 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 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 (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 13.8 months (CI: 12.5-17.9) and 60.6% of patients were alive at 1 year (CI: 52.3-68.9%).

Additional efficacy data are available from 3 single-arm Phase II 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.

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^2 i.v. for 3 hours) administered after PLD® (30 mg/m^2 i.v for 90 min) every 3 weeks or PLD (50 mg/m^2 i.v. for 90 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 3 below:

Table 3- 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 1 2	68 29 3	57 39 3
Platinum sensitivity (%)		
Platinum sensitive Platinum resistant Prior Taxane therapy (%)	65 35 80	63 37 81
Platinum free interval (PFI)*	**n (%)**	**n (%)**
<6 ≥6-12 ≥12	118 (35) 123 (37) 95 (28)	124 (37) 90 (27) 121 (36)

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

The clinical benefit of YONDELIS® + PLD was observed in progression free survival (PFS) and objective response rate, with a trend in survival in favor of the combination arm.

The primary endpoint, progression free survival (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].

Although survival data were not mature at this time, the interim analysis showed a trend in favor of the YONDELIS® + PLD arm [HR=0.85 (0.67; 1.06), p= 0.1506]. Efficacy results are summarized in Table 4.

Table 4- Efficacy of YONDELIS® in Combination with PLD in the Treatment of Patients with Ovarian Cancer (Study OVA-301)

	YONDELIS® + PLD	PLD	p-value
Independent radiologist review	n=328	n=317	
Median PFS (95% CI) months*	7.3 (5.9; 7.9)	5.8 (5.5; 7.1)	0.0190[a]
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[b]
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 [a]
Hazard ratio (95% CI)	0.95 (0.62;1.46)		
Independent Oncologist review	n=336	n=335	
Median PFS (95% CI) months*	7.4 (6.4; 9.2)	5.6 (4.2; 6.8)	0.0008 [a]
Hazard ratio (95% CI)	0.72 (0.60; 0.88)		
Objective response rate (%)	30.4	19.1	30.4
Odds Ratio**	1.846 (1.290-2.641)		0.0009 [b]

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

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

[a] Log rank test

[b] 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)]. Objective response rate 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]. Objective response rate was 39.2% in the YONDELIS®+PLD arm vs. 23.6% in the PLD monotherapy arm.

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^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.

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 intra-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^2), age (range 19 to 83 years), or gender. The effects of race and ethnicity on trabectedin pharmacokinetics have not been studied.

Impaired renal function

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.

Impaired hepatic function

The clearance of trabectedin, may be decreased in patients with hepatic impairment; resulting in higher concentrations of trabectedin in plasma. Close monitoring of toxicity is warranted when administering trabectedin to patients with impaired hepatic function.

Preclinical Safety Data

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_{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).

Myelosupression and hepatoxicity were identified as the primary toxicity for trabectedin. Findings observed included haematopoietic toxicity (severe leucopenia, anaemia, 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 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. These adverse effects were observed when trabectedin was administered to animals less than 3 kg. Mortalities were seen at 0.42 mg/m^2 and above (see Posology and Method of Administration, Special patient populations-pediatric patients).

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.

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

List of Excipients

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

Incompatibilities

YONDELIS® must not be mixed or diluted with medicinal products except those mentioned in Instructions for Use, Handling and Disposal.

Shelf Life

Observe expiry date on the outer pack.

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 Precautions for Storage

Store in a refrigerator (2ºC - 8ºC).

For storage conditions of the reconstituted and diluted medicinal product, see Shelf Life.

Keep out of reach of children.

Nature and Contents of Container

YONDELIS® is supplied in a Type I colourless glass vial with a bromobutyl stopper covered with an aluminum flip-off seal.

Each vial contains 1 mg of trabectedin.

Each outer carton contains one vial.

Instructions for Use, Handling and Disposal

Preparation for intravenous infusion

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 trabectedin 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.

Instructions for reconstitution

A syringe is used to inject 20 ml of sterile water for injections into the 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 trabectedin. It requires further dilution and is for single-use only.

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:

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

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.

If central venous access is not feasible and a peripheral venous line has to be used, the reconstituted solution may be further diluted in an infusion bag containing ≥1000 mL of normal saline 0.9% solution for infusion or dextrose 5% solution for infusion.

After administration of the PLD infusion, the intravenous line should be flushed well with 5% dextrose in water (D5W) before administration of YONDELIS®. PLD must not be mixed with saline.

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.

Instructions for handling and disposal

YONDELIS® 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.

MANUFACTURED BY

See outer carton.

DATE OF REVISION OF THE TEXT

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