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יוני 2013

רופא/ה נכבד/ה
רוקח/ת נכבד/ת

ברצוננו להביא לידיעתכם את הנוסח החדש של העלון לרופא של התכשיר: Yondelis

השינוים מסומנים בעלון המצורף כאשר הטקסט המודגש באדום הוסף לעלון ואילו הטקסט המחוק בכחול נגרע ממנו.

העלון לרופא מפורסם במאגר התרופות שבאתר משרד הבריאות.

כמו כן ניתן לקבלו מודפס על ידי פניה אלינו לטלפון 09-9591111 .

להלן העדכונים.

בברכה,

ליליאנה בלטר
רוקחת ממונה

YONDELIS

1. NAME OF THE MEDICINAL PRODUCT

Yondelis 1 mg powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1 mg of trabectedin.
1 ml of reconstituted solution contains 0.05 mg of trabectedin.

Excipients:
Each vial contains 8 mg of potassium and 0.4 g of sucrose.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.
Yondelis drug product is provided as a sterile lyophilized White to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 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.

Administration through a central venous line is strongly recommended (see section 6.6).

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

The following criteria are required to allow treatment with Yondelis:

- Absolute neutrophil count (ANC) $\geq$ 1,500/mm^3

- Platelet count ≥ 100,000/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
- Creatine phosphokinase (CPK) ≤ 2.5 x ULN

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

Additional monitoring of haematological and biochemical parameters [bilirubin, alkaline phosphatase, aminotransferases (AST and ALT) and CPK] 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

Dose adjustments during treatment

Prior to re-treatment, patients must fulfil the baseline criteria defined above. If any of the following events occur at any time between cycles, the Yondelis dose must be reduced to 1.2mg/m^2 in subsequent cycles.÷

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

Once a dose has been reduced because of toxicity, dose escalation in the subsequent cycles is not recommended. If any of these toxicities reappear in subsequent cycles in a patient exhibiting clinical benefit, the Yondelis dose may be further reduced to 1 mg/m^2 ÷

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 instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

Special patient populations

Paediatric patients

The safety and efficacy of trabectedin in paediatric patients have not yet been established. Therefore, this medicinal product must 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 section 5.3).

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.
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 section 4.4).

Patients with impaired renal function

Studies including patients with renal insufficiency (creatinine clearance < 30 ml/min) have not been conducted and therefore Yondelis must not be used in this patient population (see section 4.4). The pharmacokinetics of trabectedin are not expected to be impacted by mild or moderate renal impairment. (Section 5.2)

4.3 Contraindications

YONDELIS should not be administered to nursing mothers (see section 4.6)

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

Combination with yellow fever vaccine (see section 4.4)

4.4 Special warnings and 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 section 4.2).

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 (see section 4.2).

Neutropenia and thrombocytopenia
Grades 3 or 4 neutropenia and thrombocytopenia associated with Yondelis therapy have been very commonly reported. 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 section 4.2).
Yondelis should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm^3 and platelets count of less than 100,000 cells/mm^3. If severe neutropenia (ANC < 500 cells/mm^3) lasting more than 5 days or associated with fever or infection occurs, dose reduction is recommended (see section 4.2).

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 section 4.2).

Rhabdomyolysis and severe CPK elevations (> 5 x ULN)
Trabectedin must not be used in patients with CPK > 2.5 x ULN (see section 4.2).
Rhabdomyolysis has been uncommonly reported and severe CPK elevations were observed in 4% of patients, usually in association with myelotoxicity, severe liver function test abnormalities and/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 most patients treated with Yondelis. 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 section 4.2).

Injection site reactions

The use of central venous access is strongly recommended (see section 4.2). 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 section 5.3).

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 sections 4.3 and 4.8).

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 .

Concomitant use of trabectedin with phenytoin may reduce phenytoin absorption leading to an exacerbation of convulsions. Combination of trabectedin with phenytoin or live attenuated vaccines is not recommended and with yellow fever vaccine is specifically contraindicated (see section 4.3).[2]

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 section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other substances on trabectedin

Since trabectedin is metabolised 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 .

Alcohol consumption must be avoided during treatment with trabectedin due to the hepatotoxicity of the medicinal product (see section 4.4).

Preclinical data have demonstrated that trabectedin is a substrate to P-glycoprotein (P-gp). Concomitant administration of inhibitors of P-gp, e.g. cyclosporine and verapamil, may alter trabectedin distribution and/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.

4.6 Pregnancy and lactation
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 section 5.3) 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 section 5.3) and 5 months after treatment for men (see section 4.4).

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.

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 section 4.3)

4.7 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 and/or asthenia have been reported in patients receiving trabectedin. Patients who experience any of these events during therapy must not drive or operate machines.

4.8 Undesirable effects

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.

Most patients treated with YONDELIS can be expected to have adverse reactions of any grade (91%) with 10% reporting adverse reactions of grade 3 or 4 severity. The most common adverse reactions of any severity grade were nausea, fatigue, vomiting, anorexia, neutropenia, ~~and~~ increases in AST/ALT, anemia and thrombocytopenia. 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~~ dysfunction, renal or multiorgan 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
Blood and Lymphatic System Disorders	
Anaemia*	97
Leukopenia*	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
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 anemic at baseline.- Grade 3 and 4 anemia 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 patients, of which the majority was grade 1 alopecia.

Hepatic failure
Rare cases of hepatic failure (including cases with fatal outcomes) have been reported in patients with serious underlying medical conditions treated with trabectedin. Some potential risk factors that may have contributed to increased trabectedin toxicity observed in these cases were dose management inconsistent with recommended guidelines, potential CYP3A4 interaction due to multiple competing CYP3A4 substrates or CYP3A4 inhibitors, or lack of dexamethasone prophylaxis.

Allergic reactions
During clinical trials, hypersensitivity was reported in 2% of patients receiving trabectedin, and most of these cases were Grade 1 or 2 in severity.
During postmarketing experience, rare cases of hypersensitivity reactions, with very rare occurrence of fatal outcome, have been reported in association with trabectedin administration (see sections 4.3 and 4.4).

Extravasation and Tissue necrosis
During post marketing surveillance, a few cases of trabectedin extravasation with subsequent tissue necrosis requiring debridement have been reported (see section 4.4).

Septic shock

Cases of ~~S~~septic shock, some of which were fatal, have been ~~was~~ uncommonly reported in clinical studies and postmarketing experience, in patients.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 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.

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
The efficacy and safety of trabectedin is based in a randomised 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 (HR)=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 regimen 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 regimen. These trials evaluated a total of 100 patients with lipo and leiomyosarcoma and 83 patients with other types of sarcoma.

5.2 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.

Trabacedin 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 radioactibvity -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 age (range 19-83 years), gender, total body weight (range: 36 to 148 kg), or body surface area (range: 0.9 to 2.8 m^2). 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 indicates that renal impairment has 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.

5.3 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* (anesthetised 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 1.1mg/m^2 in 3 hour-infusion (C_{max} of 7.9± 2.0ng/ml).

Myelosupression and hepatoxicity were identified as the primary toxicity for trabectedin. Findings observed included haematopoietic toxicity (severe leukopenia, 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 section 4.2, 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Yondelis must not be mixed or diluted with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life
Unopened vials: ~~24~~ 36 months.

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.

6.4 Special precautions for storage

Store in a refrigerator (2ºC - 8ºC).
For storage conditions of the reconstituted and diluted medicinal product, see section 6.3.

6.5 Nature and contents of container
Yondelis is supplied in a Type I colourless glass vial with a bromobutyl rubber stopper covered with an aluminium flip-off seal.
Each vial contains 1 mg of trabectedin.
Each outer carton contains one vial.

6.6 Special precautions for disposal and other handling

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:

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

BSA = Body Surface Area

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

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 ≥ 1,000 ml of normal saline 0.9% solution for infusion or dextrose 5% solution for infusion.

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 type I glass bottles, polyvinylchloride (PVC) and polyethylene (PE) bags and tubing, polyisoprene reservoirs and titanium implantable vascular access systems.

7. MANUFACTURER

Janssen Pharmaceutica NV, Beerse, Belgium

8. LICENSE HOLDER

J-C Health Care Ltd. Kibbutz Shefayim 60990, Israel