YONDELIS 1mg

1. NAME OF THE MEDICINAL PRODUCT

Yondelis 1 mg powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder contains 1 mg of trabectedin.
1 ml of reconstituted solution contains 0.05 mg of trabectedin *(see Instructions for Use and Handling and Disposal)*.

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.

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 *(see Interactions)*.

The following criteria are required to allow treatment with Yondelis:

- Absolute neutrophil count (ANC) ≥ 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 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.

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% of patients. The monotherapy regimen has been used for up to 38 cycles. No cumulative toxicities have been observed in patients treated with multiple cycles.

Special patient populations

Paediatric patients (18 years of age and younger)

The safety and efficacy of trabectedin in paediatric patients have not been established. Therefore, this medicinal product must not be used in children and adolescents

Elderly patients (65 years of age and older)

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. 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
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 *Warnings and Precautions*).

Renal impairment
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 *Warnings and Precautions*). The pharmacokinetics of trabectedin are not expected to be impacted by mild or moderate renal impairment. (*see Pharmacokinetic Properties*)

Administration
Intravenous infusion.
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*.

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

4.3 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

Combination with yellow fever vaccine (see section 4.4)

4.4 warnings and precautions

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 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 (see *Dosage and Administration*).

Neutropenia, and thrombocytopenia
Grades 3 or 4 neutropenia and thrombocytopenia associated with Yondelis therapy have been very commonly reported. 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*). Patients who develop fever should promptly seek medical attention. If this occurs, active supportive therapy should be started immediately.

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 *Dosage and Administration*).

Nausea and vomiting
Anti-emetic prophylaxis with corticosteroids such as dexamethasone must be administered to all patients (see *Dosage and Administration and Interactions*).

Rhabdomyolysis and severe CPK elevations (> 5 x ULN)
Trabectedin must not be used in patients with CPK > 2.5 x ULN (see section *Dosage and Administration*). Rhabdomyolysis has been uncommonly reported usually in association with myelotoxicity, severe liver function test abnormalities and/or renal or multiorgan 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 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. 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 *Dosage and Administration*).

Injection site reactions

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

Trabectedin extravasation may cause tissue necrosis requiring debridement. There is no specific antidote for extravasation of trabectedin. Extravasation should be managed by local standard practice.

Allergic Reactions

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

Others

Co administration of Yondelis with potent inhibitors of the enzyme CYP3A4 should be avoided (see Interactions). If this is not possible, close monitoring of toxicities are required and dose reductions of trabectedin should be considered.

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).

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.

This medicine contains potassium, less than 1 mmol (39 mg) per vial, i.e. essentially "potassium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other substances on trabectedin

Interaction studies have only been performed in adults.

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. Similarly, the co-administration of trabectedin with potent inducers of CPY3A4 may increase the metabolic clearance of trabectedin. Two in vivo drug-drug interaction phase 1 studies have confirmed trends toward increased and decreased trabectedin exposures when administered with ketoconazole and rifampicin, respectively.

When ketoconazole was co-administered with trabectedin, the plasma exposure of trabectedin was increased by approximately 21% for C_{max} and 66% for AUC, but no new safety concerns were identified. Close monitoring of toxicities is required in patients receiving trabectedin in combination with potent CYP3A4 inhibitors (e.g. oral ketoconazole, fluconazole, ritonavir, clarithromycin or aprepitant) and such combinations should be avoided if possible. If such combinations are needed, appropriate dose adjustments should be applied in the event of toxicities (see sections 4.2 and 4.4).

When rifampicin was co-administered with trabectedin, it resulted in reduced plasma exposure of trabectedin by approximately 22% for C_{max} and 31% for AUC. Therefore, the concomitant use of trabectedin with strong CYP3A4 inducers (e.g., rifampicin, phenobarbital, Saint John's Wort) should be avoided if possible (see section 4.4).
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-gp. Concomitant administration of inhibitors of P-gp, e.g. cyclosporine and verapamil, may alter trabectedin distribution and/or elimination. The relevance of this interaction e.g. central nervous system (CNS) toxicity has not been established. Caution should be taken in such situations.

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 fetus (see *Non-Clinical Information*) and be monitored carefully. If trabectedin is used at the end of pregnancy, potential adverse reactions should be monitored carefully in the newborns.

Women of childbearing potential

Women of childbearing potential must use effective contraception during treatment and 3 months thereafter, and immediately inform the treating physician if a pregnancy occurs (see section 5.3).
If pregnancy occurs during treatment the possibility of genetic counselling should be considered.

Fertility

Men in fertile age must use effective contraception during treatment and 5 months after treatment (see section 4.4).
Trabectedin can have genotoxic effects. Advice on conservation of ovules or sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with Yondelis.

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 *Contraindications*)

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
Most patients treated with Yondelis can be expected to have adverse reactions of any grade (91%) and less than one third serious adverse reactions of grade 3 or 4 severity (10%). The most common adverse reactions of any severity grade were neutropenia, nausea, vomiting, increases in AST/ALT, anemia, fatigue, thrombocytopenia, anorexia and diarrhoea.

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 or multiorgan failure and rhabdomyolysis.

Tabulated summary of adverse reactions
The frequencies of the adverse reactions reported below are classified as very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100).

The table below displays the adverse reactions reported in ≥ 1% of patients treated with the soft tissue sarcoma recommended regimen (1.5 mg/m2, 24 hour infusion every 3 weeks) according to the standard MedDRA (Medical Dictionary for Regulatory Activities) system organ class. Both adverse reactions and laboratory values have been used to provide frequencies. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Adverse reactions reported in ≥ 1% of patients with soft tissue sarcoma in clinical trials.
Infections and Infestations	**Common** Infection
Blood and Lymphatic System Disorders	**Very Common** Neutropenia* (Grade 3 = 26%, Grade 4 = 24%), Thrombocytopenia* (Grade 3 = 11%, Grade 4 = 2%), Anaemia* (Grade 3 = 10%, Grade 4 = 3%), Leukopenia* **Common** Febrile neutropenia
Metabolism and Nutrition Disorders	**Very Common** Anorexia (Grade 3-4 < 1%) **Common** Dehydration, Decreased appetite, Hypokalaemia
Psychiatric Disorders	**Common** Insomnia
Nervous System Disorders	**Very Common** Headache **Common**

	Peripheral sensory neuropathy, Dysgeusia, Dizziness, Paraesthesia
Vascular Disorders	**Common** Hypotension, Flushing
Respiratory, Thoracic and Mediastinal Disorders	**Common** Dyspnoea (Grade 3-4 = 2%), Cough
Gastrointestinal disorders	**Very Common** Vomiting (Grade 3-4 = 6.5%), Nausea (Grade 3-4 = 6%), Constipation (Grade 3-4 < 1%) **Common** Diarrhoea (Grade 3-4 < 1%), Stomatitis (Grade 3-4 < 1%), Abdominal pain, Dyspepsia, Upper abdominal pain
Hepatobiliary Disorders	**Very Common** Hyperbilirubinemia* (Grade 3 = 1%), Alanine aminotransferase increased* (Grade 3 = 38%, Grade 4 = 3%), Aspartate aminotransferase increased* (Grade 3 = 44%, Grade 4 = 7%), Blood alkaline phosphatase increased*, Gamma-glutamyltransferase increased*
Skin and Subcutaneous Tissue Disorders	**Common** Alopecia
Musculoskeletal and Connective Tissue Disorders	**Common** Myalgia, Arthralgia, Back pain
General Disorders and Administration Site Conditions	**Very Common** Fatigue (Grade 3-4 = 9%), Asthenia (Grade 3-4 = 1%) **Common** Pyrexia, Oedema, Oedema peripheral, Injection site reaction
Investigations	**Very Common** Blood creatine phosphokinase increased* (Grade 3-4 = 4%), Blood creatinine increased*, Blood albumin decreased* **Common** Weight decreased

* Derived from laboratory data

Description of selected adverse reactions
Most frequent adverse reactions

Blood and lymphatic system disorders

Neutropenia:
Neutropenia is the most common haematological toxicity. It followed a predictable pattern of rapid onset and reversibility, and was rarely associated with fever or infection. Neutrophil nadirs occurred at a median of 15 days and recovered within a week. The analysis per cycle performed in patients treated with the monotherapy regimen showed neutropenia of grade 3 and 4 in approximately 19% and 8% of cycles respectively. In this population febrile neutropenia occurred in 2% of patients and in < 1% of cycles.

Thrombocytopenia:
Bleeding events associated to thrombocytopenia occurred in < 1% of patients treated with the monotherapy regimen. The analysis per cycle performed in these patients showed thrombocytopenia of grade 3 and 4 in approximately 3% and < 1% of cycles respectively.

Anaemia:
Anaemia occurred in 93% of patients treated with the monotherapy .The percentages of patients anaemic at baseline were 46%. The analysis per cycle performed in patients treated with the monotherapy regimen showed anaemia of grade 3 and 4 in approximately 3% and 1% of cycles respectively.

Hepatobiliary disorders

AST/ALT increases:
The median time to reach the peak values was 5 days for both AST and ALT. Most of the values had decreased to grade 1 or resolved by day 14-15 (see section 4.4). The analysis per cycle performed in patients treated with the monotherapy regimen showed grade 3 elevations of AST and ALT in 12% and 20% of cycles respectively. Grade 4 elevations of AST and ALT occurred in 1% and 2% of cycles respectively. Most transaminase elevations improved to grade 1 or to pre-retreatment levels within 15 days, and less than 2% of cycles had recovering 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:
Bilirubin peaks approximately a week after onset and resolves approximately two weeks after onset.

Liver function tests predicting severe toxicity (meeting Hy´s law) and 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

CPK elevations and rhabdomyolysis: CPK elevations of any grade were observed in 23-26% of patients. CPK increases in association with rhabdomyolysis were reported in less than 1% of patients.

Alopecia: Alopecia was reported in approximately 3% of patients, 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, both in clinical trials and in post marketing setting. 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 post marketing experience, 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 septic shock, some of which were fatal, have been uncommonly reported in clinical studies and postmarketing experience.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9 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.

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.

Pharmacodynamic effects

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 (ECG) investigations

In a placebo-controlled QT/QTc study, trabectedin did not prolong the QTc interval in patients with advanced solid malignancies.

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. 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 13.9 months (CI: 12.5-18.6) and 60.2 % of patients were alive at 1 year (CI: 52.0-68.5%).

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.

Results from an expanded access program for patients with STS (study ET743-SAR-3002) 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].

Paediatric population

In SAR-2005 phase I-II study, a total of 50 paediatric patients with rhabdomyosarcoma, Ewing sarcoma or non rhabdomyosarcoma soft tissue sarcoma were enrolled. Eight patients were treated with a dose of 1.3 mg/m2 and 42 with 1.5 mg/m2. Trabectedin was administered as a 24-hour intravenous infusion every 21 days. Forty patients were fully evaluable for response. One partial response (PR) centrally confirmed was observed: overall RR: 2.5% CI95% (0.1%-13.2%). The PR corresponded to a patient with an alveolar rhabdomyosarcoma. Duration of the response was 6.5 months No responses were observed for Ewing sarcoma and NRSTS, [RR: 0% CI95% (0%-30.9%)]. Three patients achieved stable disease (one with rhabdomyosarcoma after 15 cycles, one with spindle cell sarcoma after 2 cycles, and one with Ewing sarcoma after 4 cycles.

Adverse reactions, included reversible elevation of liver enzymes and haematological events; in addition, fever, infection, dehydration and thrombosis/embolism were also reported.

5.2 Pharmacokinetic properties

Distribution

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.

Following intravenous administration, trabectedin demonstrates a high apparent volume of distribution, consistent with extensive tissue and plasma protein binding (94 to 98% of trabectedin in plasma is protein bound). The distribution volume at steady state of trabectedin in human subjects exceeds 5,000 L.

Biotransformation
Cytochrome P450 3A4 is the major cytochrome P450 isozyme responsible for the oxidative metabolism of trabectedin at clinically relevant concentrations. Other P450 enzymes may contribute to metabolism. Trabectedin does not induce or inhibit major cytochrome P450 enzymes.

Elimination

Renal elimination of unchanged trabectedin in humans is low (less than 1%). The terminal half-life is long (population value of the terminal elimination phase: 180-hr). After a dose of radiolabelled trabectedin administered to cancer patients, faecal mean (SD) recovery of total radioactivity is 58% (17%), and urinary mean (SD) recovery is 5.8% (1.73%). Based on the population estimate for plasma clearance of trabectedin (30.9 l/h) and blood/plasma ratio (0.89), 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). An analysis made on a limited number of patients shows that race and ethnicity are not expected to have clinically significant effects on trabectedin pharmacokinetics.

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 ^{14}C-labelled trabectedin indicates that renal impairment has little influence on the elimination of trabectedin or its metabolites.

Hepatic impairment
Although the population analysis showed no relationship between the serum liver enzymes concentrations and the plasma clearance of trabectedin, systemic exposure to trabectedin may

be increased in patients with hepatic impairment; therefore close monitoring of toxicity is warranted.

5.3 Preclinical safety data
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 ng/ml (C_{max} higher than those reached in patients after infusion of 1,500 μg/m2 for 24 (C_{max} of 1.8 ± 1.1 ng/ml) and similar to those reached after administration of the same dose by 3 hour infusion (C_{max} of 10.8 ± 3.7 ng/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.

Renal toxicological findings were detected in multi-cycle toxicity studies conducted in monkeys. These findings were secondary to severe local reaction at the administration site, and therefore uncertainly attributable to trabectedin; however, caution must be guaranteed 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 *Instructions for Use and Handling and Disposal*.

6.3 Shelf life
See expiry date on the outer pack.

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

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.

6.4 Storage conditions
Store in a refrigerator (2ºC - 8ºC).
For storage conditions of the reconstituted and diluted medicinal product, see *Shelf life*.

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

6.6 Instructions for Use and handling and Disposal

Preparation for intravenous infusion
Yondelis must be reconstituted and further diluted prior to 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.

Instructions for reconstitution
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.

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, colorless or slightly yellowish 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. Personnel should be trained in the correct techniques to reconstitute and dilute the medicinal product and should wear protective clothing including mask, goggles and gloves during the reconstitution and dilution. Pregnant staff must be excluded from working with this medicinal product.

Accidental contact with the skin, eyes or mucous membranes must be treated immediately with copious amounts of water.

No incompatibilities have been observed between Yondelis and type I glass vials, polyvinylchloride (PVC) and polyethylene (PE) bags and tubing, PE and polypropylene mixture bags, polyisoprene reservoirs and titanium or plastic resin implantable vascular access systems.

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

7. MANUFACTURER

Janssen Pharmaceutica NV, Beerse, Belgium

8. LICENSE HOLDER

J-C Health Care Ltd. Kibbutz Shefayim 6099000, Israel