Yondelis

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Yondelis 0.25 mg powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 0.25 mg of trabectedin.

1 ml of reconstituted solution contains 0.05 mg of trabectedin.

Excipients:

Each vial contains 2 mg of potassium and 0.1 g of sucrose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

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 qualified oncologists or other health professionals specialised in the administration of cytotoxic agents.

The recommended 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 receive 20 mg of dexamethasone intravenously 30 minutes prior to Yondelis; 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 $\geq$ 100,000/mm^3
- Bilirubin $\leq$ upper limit of normal (ULN)
- Alkaline phosphatase $\leq$ 2.5 ULN (consider hepatic isoenzymes 5-nucleotidase or GGT, if the elevation could be osseous in origin).
- Albumin $\geq$ 25 g/l.
- Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) $\leq$ 2.5 x ULN

- Creatinine clearance ≥ 30 ml/min
- Creatine phosphokinase (CPK) ≤ 2.5 ULN
- Haemoglobin ≥ 9 g/dl

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

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

The same 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 fulfil the baseline criteria defined above. If any of the following events occur at any time between cycles, the dose must be reduced to 1.2 mg/m^2 for 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 and/or alkaline phosphatase > 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 dose may be further reduced to 1 mg/m^2. In the event that further dose reductions are necessary, treatment discontinuation should be considered.

Duration of treatment

In clinical trials, there were no pre-defined limits to the number of cycles administered. Treatment continued whilst clinical benefit was noted. Trabectedin has been administered for 6 or more cycles in 168 out of 569 (29.5%) patients treated with the proposed dose and schedule. This regime 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

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.

Elderly patients

No specific studies in elderly patients have been performed. Overall 20% of the 1164 patients in the integrated safety analysis 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.

Patients with impaired hepatic function

No studies with the proposed regime have been conducted in patients with liver dysfunction. Thus, data are not available to recommend a lower starting dose in patients with hepatic impairment. However, special caution is advised and dose adjustments may be necessary in these patients since systemic exposure is probably increased and the risk of hepatotoxicity might be increased. Patients with elevated bilirubin must not be treated with Yondelis (see section 4.4).

Patients with impaired renal function

Studies including patients with severe 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). Considering the pharmacokinetic characteristics of trabectedin (see section 5.2), no dose adjustments are warranted in patients with mild or moderate renal impairment.

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

4.3 Contraindications

- Hypersensitivity to trabectedin or to any of the excipients
- Concurrent serious or uncontrolled infection
- Breast-feeding (see section 4.6)
- 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 is probably 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, must be closely monitored and the dose adjusted if needed. Patients with elevated bilirubin must not be treated with trabectedin (see section 4.2).

Renal impairment

Creatinine clearance must be monitored prior to and during treatment. Trabectedin 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 trabectedin 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 section 4.2). Patients who develop fever should promptly seek medical attention. If this occurs, active supportive therapy should be started immediately.

Nausea and vomiting

Anti-emetic prophylaxis with dexamethasone must be administered to all patients (see section 4.2).

Rhabdomyolysis and severe CPK elevations (> 10 x ULN)

Trabectedin must not be used in patients with CPK > 2.5 ULN (see section 4.2). Rhabdomyolysis has been uncommonly reported, 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. 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. Yondelis must not be used in patients with elevated bilirubin. 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.

Others

Co-administration of Yondelis with potent inhibitors of the enzyme CYP3A4 should be avoided (see section 4.5). 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.

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 sections 4.3 and 4.5).

The concomitant use of trabectedin with alcohol must be avoided (see section 4.5).

Men in fertile age 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).

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

In vivo interaction studies have not been performed. Since trabectedin is metabolised mainly by CYP3A4, co-administration of substances that inhibit this isoenzyme e.g. ketoconazole, fluconazole ritonavir or clarithromycin could decrease metabolism and increase trabectedin concentrations. If such combinations are needed, close monitoring of toxicities is required (see section 4.4). Likewise co-administration with potent inducers of this enzyme (e.g. rifampicin, phenorbarbital, Saint John's Wort) may decrease the systemic exposure to 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-gp. Concomitant administration of inhibitors of Pgp, e.g. cyclosporine and verapamil, may alter trabectedin distribution and/or elimination. The relevance of this interaction e.g. 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 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 in fertile age 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 the possibility of genetic counselling should be considered. Genetic counselling 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

Unless otherwise specified, the following safety profile of Yondelis is based on the evaluation in clinical trials of 569 patients treated up to April 2007 with the recommended treatment regime in several cancer types including soft tissue sarcoma, breast cancer, osteosarcoma, ovarian cancer, GIST, melanoma and renal carcinoma.

Approximately 91% of patients can be expected to have adverse reactions of any grade. Around 40% of patients are expected to have 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.

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 frequencies of the adverse reactions reported below are classified as very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1000 to < 1/100).

The table below displays the adverse reactions reported in ≥ 1% of patients according to the standard MedDRA system organ class. Both adverse events 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 in clinical trials at the recommended regime [1.5 mg/m^2, 24 hour infusion every 3 weeks (24-h q3wk)]**
Investigations	**Very Common** Blood creatine phosphokinase increased, Blood creatinine increased, Blood albumin decreased **Common** Weight decreased
Blood and Lymphatic System Disorders	**Very Common** Neutropenia, Thrombocytopenia, Anaemia, Leukopenia **Common** Febrile neutropenia
Nervous System Disorders	**Very Common** Headache **Common** Peripheral sensory neuropathy, Dysgeusia, Dizziness, Paraesthesia
Respiratory, Thoracic and Mediastinal Disorders	**Common** Dyspnoea, Cough
Gastrointestinal disorders	**Very Common** Vomiting , Nausea, Constipation **Common** Diarrhoea , Stomatitis, Abdominal pain, Dyspepsia, Upper abdominal pain
Skin and Subcutaneous Tissue Disorders	**Common** Alopecia
Musculoskeletal and Connective Tissue Disorders	**Common** Myalgia, Arthralgia, Back pain
Metabolism and Nutrition Disorders	**Very Common** Anorexia **Common** Dehydration, Decreased appetite, Hypokalaemia
Infections and Infestations	**Common** Infection
Vascular Disorders	**Common** Hypotension, Flushing
General Disorders and Administration Site Conditions	**Very Common** Fatigue, Asthenia **Common** Pyrexia, Oedema, Oedema peripheral, Injection site reaction

System Organ Class	Adverse reactions reported in ≥ 1% of patients in clinical trials at the recommended regime [1.5 mg/m^2, 24 hour infusion every 3 weeks (24-h q3wk)]
Hepatobiliary Disorders	**Very Common** Hyperbilirubinemia, Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Gamma-glutamyltransferase increased
Psychiatric Disorders	**Common** Insomnia

Most frequent adverse reactions

Blood and Lymphatic system disorders

Neutropenia: Neutropenia occurred in 77% of patients. Grade 3 and 4 neutropenia occurred in 26% and 24% of patients respectively). The analysis per cycle showed that neutropenia of grade 3 and 4 occurred in approximately 19% and 8% of cycles respectively Febrile neutropenia occurred in 2% of patients and in < 1% of cycles.

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 11% and 2% of patients respectively. The analysis per cycle showed that thrombocytopenia of grade 3 and 4 occurred in approximately 3% and < 1% of cycles respectively. Bleeding events associated to thrombocytopenia occurred in < 1% of patients.

Anaemia: Anaemia occurred in 93% of patients although 46% of patients were anaemic at baseline. Grade 3 and 4 anaemia occurred in 10% and 3% of patients respectively. The analysis per cycle showed that anaemia of grade 3 and 4 occurred in approximately 3% and 1% of cycles 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 (see section 4.4). Grade 3 elevations of AST and ALT occurred 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: 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 38.5% of patients respectively. Grade 3-4 *nausea and vomiting were* reported in 6% and 6.5% 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 1% of patients respectively.

Anorexia: Grade 3-4 anorexia occurred in less than 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.

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.

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 = 0.734 CI 0.554-0.974). Median TTP values were 3.7 months (CI: 2.1-5.4 m) in the 24-h q3wk group and 2.3 months (CI: 2.0-3.5 m) in the 3-h qwk group (p=0.0302). No significant differences were detected in overall survival (OS). Median OS with the 24-h q3wk regime was 13.9 months (CI: 12.5-18.6) and 60.2% 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 regime. These trials evaluated a total of 100 patients with lipo and leiomyosarcoma and 83 patients with other types of sarcoma.

This medicinal product has been authorised under "Exceptional Circumstances". This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product.

The European Medicines Agency (EMEA) will review any new information which may become available every year and this SPC will be updated as necessary.

5.2 Pharmacokinetic properties

Systemic exposure after administration as a 24 hour constant rate intravenous infusion is dose proportional at doses up to and including 1.8 mg/m^2. Trabectedin pharmacokinetic profile 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 5000 l.

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.

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 (31.5 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 51% 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), 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 ($\geq$ 34.4 ml/min) present in the patients included in the clinical studies. No data are available in patients with a creatinine clearance of less than 34.4 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

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 (C_{max}), higher than those reached in patients after infusion of 1500 $\mu g/m^2$ 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 section 6.6.

6.3 Shelf life

Unopened vials: 24 months.

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

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 2°C to 8°C, 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 25°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

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 0.25 mg of trabectedin.

Each outer carton contains one vial.

6.6 Special precautions for disposal and other handling

Preparation for intravenous infusion

Appropriate aseptic techniques must be used. Yondelis must be reconstituted and further diluted prior to infusion. Each vial containing 0.25 mg of trabectedin is reconstituted with 5 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 5 ml of sterile water for injections into the vial. Shake the vial until complete dissolution. The reconstituted solution results in a clear, colourless 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 diluent (sodium chloride 9 mg/ml (0.9%) solution for infusion or glucose 50 mg/ml (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 should be added to an infusion bag containing ≥ 1,000 ml of diluent (sodium chloride 9 mg/ml (0.9%) solution for infusion or glucose 50 mg/ml (5%) solution for infusion).

Parenteral solutions should be inspected visually for particles prior to administration. Once the infusion is prepared, it should be administered immediately.

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. 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.

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.

7. MARKETING AUTHORISATION HOLDER

Pharma Mar, S.A.
Avda. de los Reyes 1, Polígono Industrial La Mina
28770 Colmenar Viejo (Madrid)
Spain

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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.

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 qualified oncologists or other health professionals specialised in the administration of cytotoxic agents.

The recommended 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 receive 20 mg of dexamethasone intravenously 30 minutes prior to Yondelis; 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 $\geq$ 100,000/mm^3
- Bilirubin $\leq$ upper limit of normal (ULN)
- Alkaline phosphatase $\leq$ 2.5 ULN (consider hepatic isoenzymes 5-nucleotidase or GGT, if the elevation could be osseous in origin).
- Albumin $\geq$ 25 g/l.
- Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) $\leq$ 2.5 x ULN

- Creatinine clearance ≥ 30 ml/min
- Creatine phosphokinase (CPK) ≤ 2.5 ULN
- Haemoglobin ≥ 9 g/dl

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

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

The same 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 fulfil the baseline criteria defined above. If any of the following events occur at any time between cycles, the dose must be reduced to 1.2 mg/m^2 for 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 and/or alkaline phosphatase> 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 dose may be further reduced to 1 mg/m^2. In the event that further dose reductions are necessary, treatment discontinuation should be considered.

Duration of treatment

In clinical trials, there were no pre-defined limits to the number of cycles administered. Treatment continued whilst clinical benefit was noted. Trabectedin has been administered for 6 or more cycles in 168 out of 569 (29.5%) patients treated with the proposed dose and schedule. This regime 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

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.

Elderly patients

No specific studies in elderly patients have been performed. Overall 20% of the 1164 patients in the integrated safety analysis 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.

Patients with impaired hepatic function

No studies with the proposed regime have been conducted in patients with liver dysfunction. Thus, data are not available to recommend a lower starting dose in patients with hepatic impairment. However, special caution is advised and dose adjustments may be necessary in these patients since systemic exposure is probably increased and the risk of hepatotoxicity might be increased. Patients with elevated bilirubin must not be treated with Yondelis (see section 4.4).

Patients with impaired renal function

Studies including patients with severe 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). Considering the pharmacokinetic characteristics of trabectedin (see section 5.2), no dose adjustments are warranted in patients with mild or moderate renal impairment.

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

4.3 Contraindications

- Hypersensitivity to trabectedin or to any of the excipients
- Concurrent serious or uncontrolled infection
- Breast-feeding (see section 4.6)
- 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 is probably 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, must be closely monitored and the dose adjusted if needed. Patients with elevated bilirubin must not be treated with trabectedin (see section 4.2).

Renal impairment

Creatinine clearance must be monitored prior to and during treatment. Trabectedin 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 trabectedin 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 section 4.2). Patients who develop fever should promptly seek medical attention. If this occurs, active supportive therapy should be started immediately.

Nausea and vomiting

Anti-emetic prophylaxis with dexamethasone must be administered to all patients (see section 4.2).

Rhabdomyolysis and severe CPK elevations (> 10 x ULN)

Trabectedin must not be used in patients with CPK > 2.5 ULN (see section 4.2). Rhabdomyolysis has been uncommonly reported, 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. 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. Yondelis must not be used in patients with elevated bilirubin. 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.

Others

Co-administration of Yondelis with potent inhibitors of the enzyme CYP3A4 should be avoided (see section 4.5). 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.

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 sections 4.3 and 4.5).

The concomitant use of trabectedin with alcohol must be avoided (see section 4.5).

Men in fertile age 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).

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

In vivo interaction studies have not been performed. Since trabectedin is metabolised mainly by CYP3A4, co-administration of substances that inhibit this isoenzyme e.g. ketoconazole, fluconazole ritonavir or clarithromycin could decrease metabolism and increase trabectedin concentrations. If such combinations are needed, close monitoring of toxicities is required (see section 4.4). Likewise co-administration with potent inducers of this enzyme (e.g. rifampicin, phenorbarbital, Saint John's Wort) may decrease the systemic exposure to 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-gp. Concomitant administration of inhibitors of Pgp, e.g. cyclosporine and verapamil, may alter trabectedin distribution and/or elimination. The relevance of this interaction e.g. 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 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 in fertile age 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 the possibility of genetic counselling should be considered. Genetic counselling 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

Unless otherwise specified, the following safety profile of Yondelis is based on the evaluation in clinical trials of 569 patients treated up to April 2007 with the recommended treatment regime in several cancer types including soft tissue sarcoma, breast cancer, osteosarcoma, ovarian cancer, GIST, melanoma and renal carcinoma.

Approximately 91% of patients can be expected to have adverse reactions of any grade. Around 40% of patients are expected to have 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.

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 frequencies of the adverse reactions reported below are classified as very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1000 to < 1/100).

The table below displays the adverse reactions reported in ≥ 1% of patients according to the standard MedDRA system organ class. Both adverse events 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 in clinical trials at the recommended regime [1.5 mg/m^2, 24 hour infusion every 3 weeks (24-h q3wk)]**
Investigations	**Very Common** Blood creatine phosphokinase increased, Blood creatinine increased, Blood albumin decreased **Common** Weight decreased
Blood and Lymphatic System Disorders	**Very Common** Neutropenia, Thrombocytopenia, Anaemia, Leukopenia **Common** Febrile neutropenia
Nervous System Disorders	**Very Common** Headache **Common** Peripheral sensory neuropathy, Dysgeusia, Dizziness, Paraesthesia
Respiratory, Thoracic and Mediastinal Disorders	**Common** Dyspnoea, Cough
Gastrointestinal disorders	**Very Common** Vomiting , Nausea, Constipation **Common** Diarrhoea , Stomatitis, Abdominal pain, Dyspepsia, Upper abdominal pain
Skin and Subcutaneous Tissue Disorders	**Common** Alopecia
Musculoskeletal and Connective Tissue Disorders	**Common** Myalgia, Arthralgia, Back pain
Metabolism and Nutrition Disorders	**Very Common** Anorexia **Common** Dehydration, Decreased appetite, Hypokalaemia
Infections and Infestations	**Common** Infection
Vascular Disorders	**Common** Hypotension, Flushing
General Disorders and Administration Site Conditions	**Very Common** Fatigue, Asthenia **Common** Pyrexia, Oedema, Oedema peripheral, Injection site reaction

System Organ Class	Adverse reactions reported in ≥ 1% of patients in clinical trials at the recommended regime [1.5 mg/m^2, 24 hour infusion every 3 weeks (24-h q3wk)]
Hepatobiliary Disorders	**Very Common** Hyperbilirubinemia, Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Gamma-glutamyltransferase increased
Psychiatric Disorders	**Common** Insomnia

Most frequent adverse reactions

Blood and Lymphatic system disorders

Neutropenia: Neutropenia occurred in 77% of patients. Grade 3 and 4 neutropenia occurred in 26% and 24% of patients respectively). The analysis per cycle showed that neutropenia of grade 3 and 4 occurred in approximately 19% and 8% of cycles respectively Febrile neutropenia occurred in 2% of patients and in < 1% of cycles.

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 11% and 2% of patients respectively. The analysis per cycle showed that thrombocytopenia of grade 3 and 4 occurred in approximately 3% and < 1% of cycles respectively. Bleeding events associated to thrombocytopenia occurred in < 1% of patients.

Anaemia: Anaemia occurred in 93% of patients although 46% of patients were anaemic at baseline. Grade 3 and 4 anaemia occurred in 10% and 3% of patients respectively. The analysis per cycle showed that anaemia of grade 3 and 4 occurred in approximately 3% and 1% of cycles 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 (see section 4.4). Grade 3 elevations of AST and ALT occurred 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: 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 38.5% of patients respectively. Grade 3-4 *nausea and vomiting were* reported in 6% and 6.5% of patients, respectively. Grade 3-4 *diarrhoea* and *constipation were reported* in less than 1% of patients.