ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Yondelis 0.25 mg powder for concentrate for solution for infusion.

Yondelis 1 mg powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Yondelis 0.25 mg

Each vial of powder contains 0.25 mg of trabectedin.

One ml of reconstituted solution contains 0.05 mg of trabectedin.

Excipients with known effect:

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

For the full list of excipients, see section 6.1.

Yondelis 1 mg

Each vial of powder contains 1 mg of trabectedin.

One ml of reconstituted solution contains 0.05 mg of trabectedin.

Excipients with known effect:

Each vial of powder contains 8 mg of potassium and 0.4 g of sucrose.

For the 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 adult 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.

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

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.

Posology

For the treatment of soft tissue sarcoma, 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.

For the treatment of ovarian cancer Yondelis is administered every three weeks as a 3-hour infusion at a dose of 1.1 mg/m^2, immediately after PLD 30 mg/m^2. To minimize the risk of PLD infusion reactions, the initial dose is administered at a rate no greater than 1 mg/minute. If no infusion reaction is observed, subsequent PLD infusions may be administered over a 1-hour period (see also PLD Summary of Product Characteristics [SmPC] for specific administration advice).

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

The following criteria are required to allow treatment with Yondelis:

- Absolute neutrophil count (ANC) ≥ 1,500/mm^3
- Platelet count ≥ 100,000/mm^3
- Bilirubin ≤ upper limit of normal (ULN)
- Alkaline phosphatase ≤ 2.5 x ULN (consider hepatic isoenzymes 5-nucleotidase or gamma glutamyl transpeptidase (GGT), 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 (monotherapy), serum creatinine ≤ 1.5 mg/dl (≤ 132.6 µmol/l) or creatinine clearance ≥ 60 ml/min (combination therapy)
- Creatine phosphokinase (CPK) ≤ 2.5 x 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 one level, according to table 1 below, 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 (monotherapy) or > 5 x ULN (combination therapy), which has not recovered by day 21
- Any other grade 3 or 4 adverse reactions (such as nausea, vomiting, fatigue)

Once a dose has been reduced because of toxicity, dose escalation in the subsequent cycles is not recommended. If any of these toxicities reappear in subsequent cycles in a patient exhibiting clinical benefit, the dose may be further reduced (see below). Colony stimulating factors can be administered for haematologic toxicity according to local standard practice.

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

	Soft tissue sarcoma	**Ovarian cancer**	
	Yondelis	Yondelis	PLD
Starting dose	1.5 mg/m^2	1.1 mg/m^2	30 mg/m^2
First reduction	1.2 mg/m^2	0.9 mg/m^2	25 mg/m^2
Second reduction	1 mg/m^2	0.75 mg/m^2	20 mg/m^2

See the PLD SmPC for more detailed information on PLD dose adjustments.

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

Duration of treatment

In clinical trials, there were no pre-defined limits to the number of cycles administered. Treatment continued whilst clinical benefit was noted. Yondelis has been administered for 6 or more cycles in 29.5% and 52% of patients treated with the monotherapy and combination dose and schedule respectively. The monotherapy and combination regimens have been used for up to 38 and 21 cycles respectively. No cumulative toxicities have been observed in patients treated with multiple cycles.

Paediatric population

Yondelis should not be used in children below 18 years with paediatric sarcomas because of efficacy concerns (see 5.1 for results of paediatric sarcoma study).

Elderly

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

Hepatic impairment

Special caution is advised and dose adjustments may be necessary in patients with hepatic impairment since systemic exposure to trabectedin is increased and the risk of hepatotoxicity might be increased. Patients with elevated serum bilirubin levels at baseline must not be treated with Yondelis. Liver function tests should be monitored during treatment with Yondelis as dose adjustments may be indicated (see Table 1 and section 4.4).

Renal impairment

Studies including patients with renal insufficiency (creatinine clearance < 30 ml/min for the monotherapy, and < 60 ml/min for the combination regimen) have not been conducted and therefore Yondelis must not be used in this patient population (see 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.

Method of administration

Intravenous administration through a central venous line is strongly recommended (see sections 4.4 and 6.6).

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 listed in section 6.1
- 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 the systemic exposure to trabectedin is on average approximately doubled (see section 5.2) due to hepatic impairment and therefore the risk of toxicities 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 serum bilirubin levels must not be treated with trabectedin (see section 4.2).

Renal impairment

Creatinine clearance must be monitored prior to and during treatment. Yondelis monotherapy and combination regimens must not be used in patients with creatinine clearance < 30 ml/min and < 60 ml/min respectively (see section 4.2).

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 section

4.2). 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 section 4.2).

Nausea and vomiting

Anti-emetic prophylaxis with corticosteroids such as dexamethasone must be administered to all patients (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, 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. Yondelis must not be used in patients with elevated bilirubin. Patients with increases in AST, ALT and alkaline phosphatase between cycles may necessitate dose adjustments (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.

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 either alone or in combination with PLD (see sections 4.3 and 4.8).

Cardiac Dysfunction

Patients should be monitored for cardiac-related adverse events or myocardial dysfunction.

A thorough cardiac assessment including determination of left ventricular ejection fraction (LVEF) by echocardiogram or multigated acquisition scan (MUGA) should be conducted before initiation of trabectedin and at 2 to 3-month intervals thereafter until trabectedin is discontinued.

Patients with LVEF less than the lower limit of normal (LVEF < LLN), prior cumulative anthracycline dose of >300mg/m^2, aged > 65 years, or a history of cardiovascular disease (especially in those with cardiac medication) may be at increased risk of cardiac dysfunction at treatment with trabectedin as monotherapy or in combination with doxorubicin.

For patients with Grade 3 or 4 cardiac adverse events indicative of cardiomyopathy or for patients with a LVEF that decreases below the LLN (assessed as either an absolute decrease of LVEF of ≥15% or <LLN with an absolute decrease of ≥5%), trabectedin should be discontinued.

Capillary Leak Syndrome (CLS)

Cases of Capillary Leak Syndrome (CLS) have been reported with trabectedin (including cases with fatal outcomes). If symptoms of possible CLS develop, such as unexplained oedema with or without hypotension, the treating physician should reassess serum albumin level. A rapid decline in serum albumin level may be indicative of CLS. If a diagnosis of CLS is confirmed after exclusion of other causes, the treating physician should discontinue trabectedin and initiate CLS treatment according to institutional guidelines (see sections 4.2 and 4.8).

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 section 4.3).

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

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). Men in fertile age must use effective contraception during treatment and 5 months after treatment (see section 4.6).

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

See also PLD Summary of Product Characteristics for more detailed information on warnings and precautions.

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 Fertility, 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 crossed the placenta when administered to pregnant rats. Trabectedin should not be used during pregnancy. If pregnancy occurs during treatment, 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.

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.

Breast-feeding

It is not known whether trabectedin is excreted in human milk. The excretion of trabectedin in milk has not been studied in animals. Breast-feeding is contraindicated during treatment and 3 months thereafter (see section 4.3).

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

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 adverse reactions during therapy must not drive or operate machines.

4.8 Undesirable effects

Summary of the safety profile

Most patients treated with Yondelis can be expected to have adverse reactions of any grade (91% in monotherapy and 99.4% in combination therapy) and less than one third serious adverse reactions of grade 3 or 4 severity (10% in monotherapy and 25% in combination therapy). The most common adverse reactions of any severity grade were neutropenia, nausea, vomiting, increase in AST/ALT, anaemia, fatigue, thrombocytopenia, anorexia and diarrhoea.

Fatal adverse reactions have occurred in 1.9% and 0.6% of patients treated with the monotherapy and combination regimens respectively. 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 following safety profile of Yondelis is based on adverse reactions reported in clinical trials, post-authorisation safety studies and spontaneous reporting.

The table below displays the adverse reactions reported in patients with soft tissue sarcoma and ovarian cancer that were treated with Yondelis recommended regimen in each indication. Both adverse reactions and laboratory values have been used to provide frequencies.

Adverse reactions are listed by System Organ Class and frequency. The frequencies are classified as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000).

System Organ Class	Very Common	Common	Uncommon	Rare
Infections and Infestations	Neutropenic infection	Sepsis	Septic shock	
Blood and Lymphatic System Disorders	Neutropenia Thrombocytopenia Anaemia Leukopenia	Febrile neutropenia		

System Organ Class	Very Common	Common	Uncommon	Rare
Immune system disorders		Hypersensitivity		
Metabolism and Nutrition Disorders	Decreased appetite	Dehydration Hypokalaemia		
Psychiatric Disorders		Insomnia		
Nervous System Disorders	Headache	Dizziness Dysgeusia Peripheral sensory neuropathy Syncope*		
Cardiac disorders		Palpitations* Left ventricular dysfunction*		
Vascular Disorders		Hypotension Flushing	Capillary leak syndrome	
Respiratory, Thoracic and Mediastinal Disorders	Dyspnoea Cough	Pulmonary embolism*	Pulmonary oedema	
Gastrointestinal disorders	Abdominal pain Nausea Vomiting Constipation Diarrhoea Stomatitis	Dyspepsia		
Hepatobiliary Disorders	Alanine aminotransferase increased Aspartate aminotransferase increased Blood alkaline phosphatase increased Blood bilirubin increased	Gamma-glutamyltransferase increased		Hepatic failure
Skin and Subcutaneous Tissue Disorders	Palmar-plantar erythrodysaesthesia syndrome*	Rash Alopecia Skin hyperpigmentation*		
Musculoskeletal and Connective Tissue Disorders	Back pain Blood creatine phosphokinase increased	Arthralgia Myalgia	Rhabdomyolysis	
General Disorders and Administration Site Conditions	Fatigue Pyrexia Oedema Mucosal inflammation*	Injection site reactions	Extravasation Soft tissue necrosis	
Investigations	Blood creatinine increased Blood albumin decreased	Weight decreased		

* Adverse drug reaction only for Ovarian cancer patients, including data from ET743-OVA-301, a randomized phase 3 study of 672 patients who received either trabectedin (1.1 mg/m^2) and PLD (30 mg/m^2) every 3 weeks or PLD (50 mg/m^2) every 4 weeks; and from study ET743-OVC-3006 which enrolled 576

patients who received either PLD (30 mg/m^2) followed by trabectedin (1.1 mg/m^2) every 3 weeks or PLD alone (50 mg/m^2) every 4 weeks.

In the ET743-OVA-301 Yondelis+PLD arm, non-white (mainly Asian) patients had a higher incidence than white patients in grade 3 or 4 adverse reactions (96% *versus* 87%), and serious adverse reactions (44% *versus* 23% all grades). The differences were mainly observed in relation with neutropenia (93% *versus* 66%), anaemia (37% *versus* 14%) and thrombocytopenia (41% *versus* 19%). However, the incidences of clinical complications related to haematological toxicity such as severe infections or bleeding, or those leading to death or treatment termination, were similar in both subpopulations.

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% and 94% of patients treated with the monotherapy and combination regimens respectively. The percentages of patients anaemic at baseline were 46% and 35% respectively. 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 in both regimens.

Other adverse reactions

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.

Capillary Leak Syndrome (CLS): Cases of Capillary Leak Syndrome (CLS) have been reported with trabectedin (including cases with fatal outcomes) (see section 4.4).

Reporting of suspected adverse reactions

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 deoxyribonucleic acid (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 and safety

The efficacy and safety of trabectedin in soft tissue sarcoma is based in a randomised trial in patients with locally advanced or metastatic lipo- 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, Confidence Interval (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 subjects assessed for OS, the median survival time was 11.9 months (95% CI: 11.2, 13.8). The median survival by histology tumour type was 16.2 months [95% CI: 14.1, 19.5] for subjects with leiomyosarcomas and liposarcomas and 8.4 months [95% CI: 7.1, 10.7] for subjects with other types of sarcomas. The median survival for subjects with liposarcoma was 18.1 months [95% CI: 15.0, 26.4] and for subjects with leiomyosarcoma 16.2 months [95% CI: 11.7, 24.3].

Additional efficacy data are available from a randomized active-controlled phase III study of trabectedin *vs.* dacarbazine (Study ET743-SAR-3007), in patients treated for unresectable or metastatic lipo- or leiomyosarcoma who have been previously treated with at least an anthracycline and ifosfamide containing regimen, or an anthracycline containing regimen and one additional cytotoxic chemotherapy regimen. Patients in the trabectedin arm were required to receive dexamethasone 20 mg intravenous injection prior to each trabectedin infusion. Overall, 384 patients were randomized to the trabectedin group [1.5 mg/m^2 once every 3 weeks (q3wk 24-h)] and 193 patients to the dacarbazine group (1 g/m^2 once every 3 weeks). The median patient age was 56 years (range 17 to 81), 30% were male, 77% Caucasian, 12% African American and 4% Asian. Patients in the trabectedin and dacarbazine arms received a median of 4 and 2 cycles respectively. The primary efficacy endpoint of the study was OS, which included 381 death events (66% of all randomized patients): 258 (67.2%) deaths in the trabectedin group and 123 (63.7%) deaths in the dacarbazine group (HR 0.927 [95% CI: 0.748, 1.150; *p*=0.4920]). The final analysis showed no significant difference with a median survival follow-up of 21.2 months resulted in a median of 13.7 months (95% CI: 12.2, 16.0) for the trabectedin arm and 13.1 months [95% CI: 9.1, 16.2] for the dacarbazine arm. The main secondary endpoints are summarized in the table below:

Efficacy results from Study ET743-SAR-3007

Endpoints / Study population	Trabectedin	Dacarbazine	Hazard Ratio / Odds Ratio	*p* value
Primary endpoint	**n=384**	**n=193**		
Overall survival, n (%)	258 (67.2%)	123 (63.7%)	0.927 (0.748-1.150)	0.4920
Secondary endpoints	**n=345**	**n=173**		
PFS (months; 95% CI)	4.2	1.5	0.55 (0.44, 0.70)	<0.0001
ORR, n (%); Odds ratio (95% CI)	34 (9.9%)	12 (6.9%)	1.47 (0.72, 3.2)	0.33
DOR (months; 95% CI)	6.5	4.2	0.47 (0.17, 1.32)	0.14
CBR, n (%); Odds ratio (95% CI)	34.2%	18.5%	2.3 (1.45, 3.7)	<0.0002

Additional efficacy data are available from a randomized, open-label, multicenter phase II study [JapicCTI-121850] conducted in Japanese patients with translocation-related sarcoma (TRS), most common being myxoid round-cell liposarcoma (n=24), synovial sarcoma (n=18), mesenchymal chondrosarcoma (n=6), and extraskeletal Ewing sarcoma/PNET, alveolar soft part sarcoma, alveolar rhabdomyosarcoma and clear cell sarcoma (n=5 each). The study assessed the efficacy and safety of trabectedin *vs.* best supportive care (BSC) as second-line or later therapy for patients with advanced TRS unresponsive or intolerant to standard chemotherapy regimen. The patients received the trabectedin dose of 1.2 mg/m^2 recommended for Japanese patients [1.2 mg/m^2 once every 3 weeks (q3wk 24-h)]. A total of 76 Japanese patients were enrolled in the study, among which 73 patients were included in the final analysis set. The study primary endpoint was PFS, that showed a statistically significant improvement in favour of trabectedin over BSC [HR=0.07; 95% CI: 0.03-0.16; p<0.0001], with a median PFS in the trabectedin group of 5.6 months [95% CI: 4.1-7.5] and in the BSC group of 0.9 months [95% CI: 0.7-1.0]. The secondary endpoints included objective response analysed using the RECIST and Choi criteria. Using the RECIST criteria the ORR among patients treated with trabectedin was 3 (8.1%; 95% CI: 1.7.21.9%) and 0 (0%, 95% CI: 0.0-9.7%) among patients treated with best supportive care, while the CBR was 24 (64.9%, 95% CI: 47.5-79.9%) versus 0 (0%, 95% CI: 0.0-9.7%), respectively. Using the Choi criteria the ORR among patients treated with trabectedin was 4 (10.8%; 95% CI: 3.0-25.4%) and 0 (0%, 95% CI: 0.0-9.7%) among patients treated with best supportive care, while the CBR was 7 (18.9%, 95% CI: 8.0-35.2%) versus 0 (0%, 95% CI: 0.0-9.7%), respectively.

The efficacy of Yondelis/PLD combination in relapsed ovarian cancer is based on ET743-OVA-301, a randomized phase 3 study of 672 patients who received either trabectedin (1.1 mg/m^2) and PLD (30 mg/m^2) every 3 weeks or PLD (50 mg/m^2) every 4 weeks. The primary analysis of progression free survival (PFS) was performed in 645 patients with measurable disease and assessed by independent radiology review. Treatment with the combination arm resulted in a 21% risk reduction for disease progression compared to PLD alone (HR=0.79, CI: 0.65-0.96, p=0.0190). Secondary analyses of PFS and response rate also favoured the combination arm. The results of the main efficacy analyses are summarised in the table below:

Efficacy analyses from ET743-OVA-301

	Yondelis+PLD	PLD	Hazard/Odds ratio	p-value
Progression Free Survival				
Independent radiology review, *measurable disease* *	**n=328**	**n=317**		
Median PFS (95% CI) (months)	7.3 (5.9-7.9)	5.8 (5.5-7.1)	0.79 (0.65-0.96)	0.0190 [a]
12 months PFS rate (95% CI) (%)	25.8 (19.7-32.3)	18.5 (12.9-24.9)		
Independent oncology review, *all randomised*	**n=336**	**n=335**		
Median PFS (95% CI) (months)	7.4 (6.4-9.2)	5.6 (4.2-6.8)	0.72 (0.60-0.88)	0.0008 [a]
Overall Survival (Final analysis - n=522 events)				
All randomised	**n=337**	**n=335**		
Median OS (95% CI) (months)	22.2 (19.3-25.0)	18.9 (17.1-21.5)	0.86 (0.72-1.02)	0.0835 [a]
Overall survival in platinum-sensitive population (Final analysis n=316 events)				
	n=218	n=212		
Median OS (95% CI) (months)	27.0 (24.1-31.4)	24.1 (20.9-25.9)	0.83 (0.67-1.04)	0.1056 [a]
Overall Response Rate (ORR)				
Independent radiology review, *all randomised*	**n=337**	**n=335**		
ORR (95% CI) (%)	27.6 (22.9-32.7)	18.8 (14.8-23.4)	1.65 (1.14-2.37)	0.0080 [b]

* Primary efficacy analysis

[a] Log rank test

[b] Fisher's test

Based on independent oncology review, patients with platinum-free interval (PFI) < 6 months (35% in Yondelis+PLD and 37% in PLD arm) had similar PFS in the two arms with both showing median PFS of 3.7 months (HR=0.89, CI: 0.67-1.20). In patients with PFI ≥ 6 months (65% in Yondelis+PLD and 63% in PLD arm), median PFS was 9.7 months in the Yondelis+PLD arm compared with 7.2 months in the PLD monotherapy arm (HR=0.66, CI: 0.52-0.85).

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

The benefit in OS with Yondelis plus PLD was not due to the effect of subsequent therapies, which were well balanced between the two treatment arms.

In the multivariate analyses including PFI, treatment effect on overall survival was statistically significant favouring the Yondelis+PLD combination over PLD alone (all randomised: p=0.0285; platinum-sensitive population: p=0.0319).

No statistically significant differences were found between treatment arms in global measures of Quality of Life.

The Yondelis+PLD combination in relapsed ovarian cancer also was evaluated in study ET743-OVC-3006, a phase 3 study in which women with ovarian cancer after failure of a second platinum-containing regimen were randomized to Yondelis (1.1 mg/m^2) and PLD (30 mg/m^2) every 3 weeks or PLD (50 mg/m^2) every 4 weeks. Study participants were required to be platinum sensitive (PFI ≥ 6 months) following their first platinum-containing regimen and have a complete or partial response to a second line platinum-based chemotherapy (without PFI restrictions) meaning that these patients could be either platinum-sensitive (PFI ≥ 6 months) or platinum-resistant (PFI < 6 months) following their second platinum-containing regimen. A post hoc analysis

determined that 42% of enrolled subjects were platinum-resistant (PFI < 6 months) following their last platinum-containing regimen.

The primary endpoint of study ET743-OVC-3006 was OS and secondary endpoints included PFS and ORR. The study was sized to enrol approximately 670 patients in order to observe 514 deaths to detect a HR of 0.78 for OS with 80% power given a two-sided significance level of 0.05 spread across two planned analyses on OS, at interim (60% or 308/514 deaths) and final analysis (514 deaths). Two early unscheduled futility analyses were performed at the request of the Independent Data Monitoring Committee (IDMC). Following the second futility analysis performed at 45% of planned events (232/514 deaths), the IDMC recommended discontinuing the study due to (1) futility of the primary analysis on OS and (2) excessive risk based on imbalance of adverse events not in favour of Yondelis+PLD. At early termination of the study, 9% (52/572 treated) of subjects stopped treatment, 45% (260/576 randomized) stopped follow-up, and 54% (310/576 randomized) were censored from OS assessment, precluding reliable estimates of PFS and OS endpoints.

No data are available comparing Yondelis+PLD to a platinum-based regimen in platinum-sensitive patients.

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/m^2 and 42 with 1.5 mg/m^2. 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 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 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%.

A population pharmacokinetic analysis showed that when administered in combination with PLD, the plasma clearance of trabectedin was decreased by 31%; the plasma pharmacokinetics of PLD were not influenced by the concomitant administration of trabectedin.

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). A population pharmacokinetic analysis showed that plasma trabectedin concentrations observed in the Japanese population at dose level 1.2 mg/m^2 were equivalent to those obtained in the non-Japanese western population at 1.5 mg/m^2.

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

The effect of hepatic impairment on the pharmacokinetics of trabectedin was assessed in 15 cancer patients at doses ranging from 0.58 to 1.3 mg/m^2 administered as 3-hour infusion. The geometric mean dose normalized trabectedin exposure (AUC) increased by 97% (90% CI: 20%, 222%) in 6 patients with moderate hepatic impairment (increased serum bilirubin levels from 1.5 to 3 x ULN and increase of aminotransferases (AST or ALT) < 8 x ULN) following administration of a single trabectedin dose of 0.58 mg/m^2 (n=3) or 0.9 mg/m^2 (n=3) compared to 9 patients with normal liver function following administration of a single trabectedin dose of 1.3 mg/m^2 (see sections 4.2 and 4.4).

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

1,500 μg/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.

Placental transfer of trabectedin and fetal exposure to trabectedin were observed in a study in pregnant rats that received a single i.v. ^{14}C-trabectedin dose at 0.061 mg/kg. Maximum fetal tissue radioactivity concentration was similar to that in maternal plasma or blood.

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

60 months.

After reconstitution

Chemical and physical stability has been demonstrated for 30 hours up to 25 ºC.

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 ºC to 8 ºC, 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 ºC.

6.4 Special precautions for storage

Store in a refrigerator (2 ºC - 8 ºC).

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Yondelis 0.25 mg

Type I colourless glass vial with a butyl rubber stopper covered with an aluminium flip-off seal containing 0.25 mg of trabectedin.

Each carton contains one vial.

Yondelis 1 mg

Type I colourless glass vial with a butyl rubber stopper covered with an aluminium flip-off seal containing 1mg of trabectedin.

Each carton contains one vial.

6.6 Special precautions for disposal and other handling

Preparation for intravenous infusion

Yondelis must be reconstituted and further diluted prior to intravenous infusion. Appropriate aseptic techniques must be used to prepare the infusion solution (see Instructions for reconstitution and for dilution).

When used in combination with PLD the intravenous line should be flushed well with 50 mg/ml (5%) glucose solution for infusion after administration of PLD and before administration of Yondelis. The use of any diluent other than 50 mg/ml (5%) glucose solution for infusion for this line flushing may cause precipitation of PLD (see also PLD Summary of Product Characteristics for specific handling instructions).

Instructions for reconstitution

Yondelis 0.25 mg

Each vial containing 0.25 mg of trabectedin is reconstituted with 5 ml of 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 5 ml of sterile water for injections into the vial. The vial must be shaken 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.

Yondelis 1 mg

Each vial containing 1 mg of trabectedin is reconstituted with 20 ml of 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. The vial must be shaken 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

If administration is to be made through a central venous line, the appropriate amount of reconstituted solution should be withdrawn from the vial and added to an infusion bag containing ≥ 50 ml of diluent (sodium chloride 9 mg/ml (0.9%) solution for infusion or glucose 50 mg/ml (5%) solution for infusion), the concentration of trabectedin in the infusion solution being ≤ 0.030 mg/ml.

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.

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.

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

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)

Yondelis 0.25 mg

EU/1/07/417/001

Yondelis 1 mg

EU/1/07/417/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 September 2007
Date of latest renewal: 03 August 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton – 0.25 mg vial

1. NAME OF THE MEDICINAL PRODUCT

Yondelis 0.25 mg powder for concentrate for solution for infusion
trabectedin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 0.25 mg of trabectedin.
1 ml of reconstituted solution contains 0.05 mg of trabectedin.

3. LIST OF EXCIPIENTS

Also contains: sucrose, potassium dihydrogen phosphate, phosphoric acid and potassium hydroxide.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial of 0.25 mg trabectedin

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution and further dilution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic: handle with caution.

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. For storage conditions after reconstitution and dilution of the medicinal product, see the package leaflet.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard any unused product or waste material in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/417/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial label – 0.25 mg vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Yondelis 0.25 mg powder for concentrate for solution for infusion
trabectedin
IV use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.25 mg trabectedin

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton – 1 mg vial

1. NAME OF THE MEDICINAL PRODUCT

Yondelis 1 mg powder for concentrate for solution for infusion
trabectedin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Also contains: sucrose, potassium dihydrogen phosphate, phosphoric acid and potassium hydroxide.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial of 1 mg trabectedin

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution and further dilution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic: handle with caution.

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. For storage conditions after reconstitution and dilution of the medicinal product, see the package leaflet.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard any unused product or waste material in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/417/002

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial label – 1 mg vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Yondelis 1 mg powder for concentrate for solution for infusion
trabectedin
IV use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mg trabectedin

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Yondelis 0.25 mg powder for concentrate for solution for infusion
Yondelis 1 mg powder for concentrate for solution for infusion
trabectedin

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Yondelis is and what it is used for
2. What you need to know before you are given Yondelis
3. How to use Yondelis
4. Possible side effects
5. How to store Yondelis
6. Contents of the pack and other information

1. What Yondelis is and what it is used for

Yondelis contains the active substance trabectedin. Yondelis is an anti-cancer medicine that works by preventing the tumour cells from multiplying.

Yondelis is used for the treatment of patients with advanced soft tissue sarcoma, when previous medicines have been unsuccessful or the patients are unsuited to receive them. Soft tissue sarcoma is a malignant disease that starts somewhere in the soft tissues, such as the muscles, fat or other tissues (for example cartilages or vessels).

Yondelis in combination with pegylated liposomal doxorubicin (PLD: another anti-cancer medicine) is used for the treatment of patients with ovarian cancer that has come back after at least 1 previous therapy and are not resistant to anti-cancer medicines containing platinum compounds.

2. What you need to know before you are given Yondelis

Do not use Yondelis

- if you are allergic to trabectedin or any of the other ingredients of this medicine (listed in section 6).
- if you have any serious infections.
- if you are breast-feeding.
- if you will receive yellow fever vaccine.

Warnings and precautions

Talk to your doctor before using Yondelis

Yondelis or its combination with PLD must not be used if you have severe liver, kidney or cardiac damage.
Tell your doctor if you know or suspect that you have any of the following before starting the treatment with Yondelis:

- Liver or kidney problems.
- Cardiac problems or a history of cardiac problems.
- Left ventricular ejection fraction (LVEF) under the lower limit of normal.
- Received high anthracycline dose treatment in the past.

You should seek medical attention immediately if any of the following conditions appear:

- If you develop a fever as Yondelis may cause side-effects affecting your blood and liver.
- If you still feel sick, vomit or are unable to drink fluids and therefore pass less urine despite being given anti-sickness medicines.
- If you experience severe muscle pain or weakness as it could be a sign of damage to your muscles (rhabdomyolysis; see section 4).
- If you notice that Yondelis infusion leaks out of your vein while you are being given it. It could lead to damage and death of your tissue cells around the injection site (tissue necrosis, see also section 4) which may require surgery.
- If you have an allergic reaction (hypersensitivity). In this case you may experience one or more of the following signs: fever, difficulty in breathing, redness or flushing of the skin or a rash, feeling sick (nausea) or being sick (vomiting; see section 4).
- If you notice unexplained partial or general swelling (oedema), with possible lightheadedness, dizziness or thirst (low blood pressure). It could be a sign of a condition (capillary leak syndrome) that can cause excessive accumulation of fluid in your tissues, and requires urgent medical evaluation by your doctor.

Children and adolescents

Yondelis should not be used in children below 18 years of age with paediatric sarcomas.

Other medicines and Yondelis

Tell your doctor if you are taking, have recently taken or might take any other medicines.

You must not use Yondelis if you will receive yellow fever vaccine and it is not recommended that you use Yondelis if you will receive a vaccine containing live virus particles. The effect of medicines containing phenytoin (for epilepsy) may be decreased if given together with Yondelis and this is therefore not recommended.

If you use any of the following medicines during your treatment with Yondelis, you need to be closely monitored as the effects of Yondelis are:

- decreased (examples are medicines containing rifampicin (for bacterial infections), phenobarbital (for epilepsy) or St. John's Wort (*Hypericum perforatum*, an herbal medicine for depression)) or

- increased (examples are medicines containing ketoconazole or fluconazole (for fungal infections), ritonavir (for human immunodeficiency virus [HIV] infection), clarithromycin (for bacterial infections), aprepitant (to prevent nausea and vomiting), ciclosporin (inhibit the defensive system of the body) or verapamil (for high blood pressure and heart conditions)).

Thus the use of any of these medicines together with Yondelis should be avoided, if possible.

If you are given Yondelis or the combination Yondelis+PLD together with a medicine that might cause damage to the liver or to the muscles (rhabdomyolysis), you may need to be closely monitored, as there could be an increased risk of liver or muscle damage. Medicines containing statins (for lowering cholesterol levels and preventing cardiovascular disease) is an example of medicines that may cause muscle damage.

Yondelis with alcohol

Alcohol consumption must be avoided during treatment with Yondelis as this may harm the liver.

Pregnancy, breast-feeding and fertility

Pregnancy

Yondelis should not be used during pregnancy. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this medicine.

Adequate contraceptive precautions must be used by women of childbearing potential when receiving Yondelis and for 3 months following the end of treatment.

If a pregnancy should occur you must tell your doctor immediately and genetic counselling is recommended since Yondelis can cause genetic damage.

Breast-feeding

Yondelis must not be given to patients who are breast-feeding. Therefore you must stop breast-feeding before you start your treatment and you must not begin breast-feeding again until your doctor has confirmed that it is safe to do so.

Fertility

Adequate contraceptive precautions must be used by men in fertile age when receiving Yondelis and for 5 months following the end of treatment.

Patients should seek advice on ovules or sperm conservation prior to treatment because of the risk of irreversible infertility due to therapy with Yondelis.

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

Driving and using machines

During your treatment with Yondelis you may feel tired and experience a loss of strength. Do not drive or use any tools or machines if you are experiencing any of these side effects.

Yondelis contains potassium

This medicine contains potassium, less than 1 mmol (39 mg) per vial, and can therefore be considered as essentially "potassium-free".

3. How to use Yondelis

Yondelis is given to you 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 medicines.

For the treatment of soft tissue sarcoma, the usual dose is 1.5 mg/m^2 of body surface area. During the treatment period, your doctor will carefully monitor you and decide the most appropriate dosage of Yondelis to give to you. The recommended dose in Japanese patients is lower than the usual dose for all other races, and is 1.2 mg/m^2 of body surface area.

For the treatment of ovarian cancer, the usual dose is 1.1 mg/m^2 body surface area after the administration of 30 mg/m^2 body surface area of PLD.

Before Yondelis is given to you, it is reconstituted and diluted for intravenous use. Every time you are given Yondelis for the treatment of soft tissue sarcoma, it will take about 24 hours for all of the solution to enter your blood. It will take 3 hours for the treatment of ovarian cancer.

In order to avoid irritation at the site of injection it is recommended that Yondelis is given to you through a central venous line.

You will be given a medicine before and as needed during the treatment with Yondelis in order to protect your liver and to reduce the risk of side effects such as feeling sick (nausea) and vomiting.

The infusion is given to you every 3 weeks, although occasionally your doctor may recommend dose delays to ensure that you receive the most appropriate dose of Yondelis.

The length of your whole treatment period will depend on your progress and how well you feel. Your doctor will tell you how long your treatment lasts. If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine or its combination with PLD can cause side effects, although not everybody gets them.

If you are not sure what the side effects below are, you should ask your doctor to explain them to you in more detail.

Serious side effects caused by the treatment with Yondelis:

Very common: may affect more than 1 in 10 people

- You could have increased levels of the yellow pigment bilirubin in the blood which might cause jaundice (a yellowing of the skin, mucous membranes and eyes).

- Your doctor will order regular blood tests to detect any abnormalities in the blood.

Common: may affect up to 1 in 10 people

- You may also have blood infections (sepsis) if your immune system is greatly compromised. *If you have fever you should seek medical attention immediately.*

- You could also feel pain in your muscles (myalgia). There could also be damage to your nerves which may result in muscle pain, weakness and numbness. You could experience general swelling or swelling of the limbs and a sensation of creeping on the skin.

- You may have a reaction at the site of injection. Yondelis infusion may leak out of your vein while you are being given it, leading to damage and death of your tissue cells around the injection site (tissue necrosis, see also section 2 “Warnings and precautions”) which may require surgery.

- You could have an allergic reaction. In this case you may experience fever, difficulty in breathing, redness or flushing of the skin or a rash, feeling sick (nausea) or being sick (vomiting).

- When Yondelis is used in combination with PLD, you may have syncope also called fainting. Furthermore, you could feel like your heart is beating too hard or too fast in your chest (palpitations), have a weakness in the ventricles, the heart's major pumping chambers (left ventricular dysfunction), or a sudden blockage in a lung artery (pulmonary embolism).

Uncommon: may affect up to 1 in 100 people

- You may feel severe muscle aches and pain, stiffness and muscle weakness. You also may experience a darkening of the urine colour. All the previously described, could be a sign of damage to your muscles (rhabdomyolysis).

- Your doctor may require blood tests in certain situations in order to avoid that you develop muscle damage (rhabdomyolysis). In very severe cases this could lead to kidney failure. *If you experience severe muscle pain or weakness, you should seek medical attention immediately.*

- You may experience difficulty in breathing, irregular heartbeat, decreased urine output, abrupt change in mental status, areas of mottled skin, extremely low blood pressure associated with abnormal laboratory test results (decrease in platelet count). If you get any of the above symptoms or signs, **seek medical care immediately**.

- You may experience an abnormal build-up of fluid in the lungs, which leads to swelling (pulmonary oedema).

- You may notice unexplained partial or general swelling (oedema), with possible lightheadedness, dizziness or thirst (low blood pressure). It could be a sign of a condition

(capillary leak syndrome) that can cause excessive accumulation of fluid in your tissues. If you get the above symptoms or signs, **seek medical care immediately**.

- You may notice that Yondelis infusion leaks out of your vein (extravasation) while you are being given it. Then you will notice some redness, swelling, itchiness and discomfort at the injection site. If you get any of these symptoms or signs, **tell your nurse or doctor immediately.**

  It could lead to damage and death of your tissue cells around the injection site (tissue necrosis) which may require surgery.

  Some of the symptoms or signs of extravasation may not be visible until several hours after it occurred. There may be blistering, peeling and darkening of the skin over the site. It is possible for it to take a few days before the full extent of tissue damage is visible. If you get any of the previous described symptoms or signs, **seek medical care immediately**.

Rare: may affect up to 1 in 1,000 people

- You may experience yellowing of your skin and eyeballs (jaundice), pain in the upper right area of your abdomen, nausea, vomiting, a general sense of not feeling well, difficulty in concentrating, disorientation or confusion, sleepiness. These signs could be indicative of the inability of the liver to perform its normal function. If you get any of the previous described symptoms or signs, **seek medical care immediately**.

<u>Other less serious side effects:</u>

Very common: may affect more than 1 in 10 people

- You may:
  - feel tired
  - feel difficulty breathing and coughing
  - feel pain in your back
  - feel an excess of fluid in the body (oedema)
  - bruise more easily
  - have nose bleeds
  - be more prone to infections. An infection could also give you a raised temperature (fever).

  If you develop any of these symptoms you should seek medical attention immediately.

- You may present some digestive symptoms such as loss of appetite, sick (nausea) or vomit, pain in the abdomen, diarrhoea or constipation. *If you still feel sick, vomit or are unable to drink fluids and therefore pass less urine, despite being given anti-sickness medicine, you should immediately seek medical help.*

- You may experience headache.

- You could have mucosal inflammation as a swelling redness of the inside of the mouth leading to painful ulcers and mouth sores inflammation of the mouth (stomatitis), or as an inflammation of the gastrointestinal tract when Yondelis is used with PLD.

- Patients receiving Yondelis plus PLD for ovarian cancer may also have the hand and foot syndrome. It may present as red skin of the palms, fingers, and soles of the feet that later

may become swollen and violaceous. The lesions may either dry out and desquamate, or blister with ulceration.

Common: may affect up to 1 in 10 people

- You may experience, loss of water from the body, weight loss, digestive discomfort and a change in your sense of taste.
- You may lose hair (alopecia).
- You could also experience dizziness, low blood pressure and flushing or skin rash.
- Higher skin pigmentation could occur in patients receiving Yondelis with PLD for ovarian cancer.
- You may feel pain in joints.
- You may experience sleeping problems.

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Yondelis

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 ºC - 8 ºC).

Information on in-use stability of the reconstituted and diluted solutions is included in the section for medical and healthcare professionals.

Do not use this medicine if you notice visible particles after the reconstitution or dilution of the medicine.

Any unused medicine or waste material should be disposed of in accordance with local requirements for cytotoxic medicines.

6. Contents of the pack and other information

What Yondelis contains

- The active substance is trabectedin.
  Yondelis 0.25 mg: Each vial of powder contains 0.25 mg of trabectedin.

Yondelis 1 mg: Each vial of powder contains 1 mg of trabectedin.

- The other ingredients are sucrose, potassium dihydrogen phosphate, phosphoric acid (for pH-adjustment) and potassium hydroxide (for pH-adjustment).

What Yondelis looks like and contents of the pack

Yondelis is a powder for concentrate for solution for infusion. The powder has a white to off-white colour and comes in a glass vial.

Each carton contains 1 vial of either 0.25 mg or 1 mg of trabectedin.

Marketing Authorisation Holder and Manufacturer

Pharma Mar, S.A.
Avda. de los Reyes 1
Polígono Industrial La Mina
28770 Colmenar Viejo (Madrid)
Spain
Tel: +34 91 846 60 00
Fax: +34 91 846 60 01

For any information about this medicine, please contact the Marketing Authorisation Holder.

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Instructions for use – preparation, handling and disposal

Appropriate procedures for proper handling and disposal of cytotoxic medicines must be followed. Any unused medicine or waste material should be disposed of in accordance with local requirements for cytotoxic medicines.

You should have received training on the correct techniques to reconstitute and dilute Yondelis or its combination with PLD and you should wear protective clothing including mask, goggles and gloves during the reconstitution and dilution. Accidental contact with the skin, eyes or mucous membranes must be treated immediately with copious amounts of water. You should not work with this medicine if you are pregnant.

Preparation for intravenous infusion

Yondelis must be reconstituted and further diluted prior to infusion (see also section 3). *Appropriate aseptic techniques must be used.*

Yondelis must not be administered as a mixture with other medicines in the same infusion apart from the diluent. 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.

When Yondelis is used in combination with PLD, the intravenous line should be flushed well with 50 mg/ml (5%) glucose solution for infusion after administration of PLD and before administration of Yondelis. The use of any diluent other than 50 mg/ml (5%) glucose solution for infusion may cause precipitation of PLD. (See also PLD Summary of Product Characteristics for specific handling instructions).

Instructions for reconstitution

Yondelis 0.25 mg: Inject 5 ml of sterile water for injections into the vial.

Yondelis 1 mg: Inject 20 ml of sterile water for injections into the vial.

A syringe is used to inject the correct amount 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

Dilute the reconstituted solution with sodium chloride 9 mg/ml (0.9%) solution for infusion or glucose 50 mg/ml (5%) solution for infusion. Calculate the required volume as follows:

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

BSA = Body Surface Area

Withdraw the appropriate amount of reconstituted solution from the vial. If intravenous administration is to be made via a central venous line, add the reconstituted solution to an infusion bag containing ≥ 50 ml of diluent (sodium chloride 9 mg/ml (0.9%) solution for infusion or glucose 50 mg/ml (5%) solution for infusion), the concentration of trabectedin in the infusion solution being ≤ 0.030 mg/ml.

If central venous access is not feasible and a peripheral venous line has to be used, add the reconstituted solution 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).

Inspect the parenteral solution visually for particles prior to intravenous administration. Once the infusion is prepared, it should be administered immediately.

<u>In-use stability of the solutions</u>

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

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 solution are the responsibility of the user and would normally not be longer than 24 hours at 2 ºC to 8 ºC, unless reconstitution has taken place in controlled and validated aseptic conditions.

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