Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Trabectedin EVER Pharma 1 mg powder for concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Trabectedin EVER Pharma 1 mg
Each vial of powder contains 1 mg of trabectedin.
One ml of reconstituted solution contains 0.05 mg of trabectedin.

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

Trabectedin EVER Pharma 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.

Trabectedin EVER Pharma 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

Trabectedin EVER Pharma 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 Trabectedin EVER Pharma 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 Trabectedin EVER Pharma (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 Trabectedin EVER Pharma:

- 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 trabectedin (as single agent for soft tissue sarcoma (STS) or in combination for ovarian cancer) and PLD

	Soft tissue sarcoma	**Ovarian cancer**	
	trabectedin	trabectedin	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. Trabectedin 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

Trabectedin EVER Pharma 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 Trabectedin EVER Pharma. Liver function tests should be monitored during treatment with Trabectedin EVER Pharma 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 Trabectedin EVER Pharma 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 Trabectedin EVER Pharma. 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. Trabectedin EVER Pharma 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 Trabectedin EVER Pharma 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.

Trabectedin EVER Pharma 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 Trabectedin EVER Pharma 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. Trabectedin EVER Pharma 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 trabectedin 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).

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

This medicine contains less than 1 mmol sodium (23 mg) per dose that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other substances on trabectedin

Interaction studies have only been performed in adults.

Since trabectedin is metabolised mainly by CYP3A4, the concentrations of trabectedin in plasma are likely to be increased in patients who are co-administered drugs that potently inhibit the activity of this isoenzyme. Similarly, the co-administration of trabectedin with potent inducers of CPY3A4 may increase the metabolic clearance of trabectedin. Two in vivo drug-drug interaction phase 1 studies have confirmed trends toward increased and decreased trabectedin exposures when administered with ketoconazole and rifampicin, respectively.

When ketoconazole was co-administered with trabectedin, the plasma exposure of trabectedin was increased by approximately 21 % for C_{max} and 66 % for AUC, but no new safety concerns were identified. Close monitoring of toxicities is required in patients receiving trabectedin in combination with potent CYP3A4 inhibitors (e.g. oral ketoconazole, fluconazole, ritonavir, clarithromycin or aprepitant) and such combinations should be avoided if possible. If such combinations are needed, appropriate dose adjustments should be applied in the event of toxicities (see sections 4.2 and 4.4).
When rifampicin was co-administered with trabectedin, it resulted in reduced plasma exposure of trabectedin by approximately 22 % for C_{max} and 31 % for AUC. Therefore, the concomitant use of trabectedin with strong CYP3A4 inducers (e.g., rifampicin, phenobarbital, Saint John's Wort) should be avoided if possible (see section 4.4).

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

Preclinical data have demonstrated that trabectedin is a substrate to P-gp. Concomitant administration of inhibitors of P-gp, e.g. cyclosporine and verapamil, may alter trabectedin distribution and/or elimination. The relevance of this interaction e.g. central nervous system (CNS) toxicity has not been established. Caution should be taken in such situations.

4.6 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 Trabectedin EVER Pharma.
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 trabectedin 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 trabectedin 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 trabectedin 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	Febrile neutropenia		

	Anaemia Leukopenia			
Immune system disorders		Hypersensitivity		
Metabolism and nutrition disorders	Decreased appetite	Dehydration Hypokalaemia		
Psychiatric disorders		Insomnia		
Nervous dystem 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/m2) and PLD (30 mg/m2) every 3 weeks or PLD (50 mg/m2) every 4 weeks; and from study ET743-OVC-3006 which enrolled 576 patients who received either PLD (30 mg/m2) followed by trabectedin (1.1 mg/m2) every 3 weeks or PLD alone (50 mg/m2) every 4 weeks.

In the ET743 OVA 301 trabectedin+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 HPRA Pharmacovigilance; Website: www.hpra.ie.

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, other plant alkaloids and natural products;
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 trabectedin/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

	Trabectedin+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,	**n=336**	**n=335**		

all randomised				
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 trabectedin+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 trabectedin+PLD and 63 % in PLD arm), median PFS was 9.7 months in the trabectedin+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 trabectedin+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 trabectedin 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 trabectedin+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 trabectedin+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 trabectedin (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 trabectedin+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 trabectedin+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 14C-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

Citric acid (E330)
Arginine
Phosphoric acid, concentrated (for pH-adjustment) (E338)
Sodium hydroxide (for pH-adjustment) (E524)

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vials
1 mg: 3 years

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

6.5 Nature and contents of container

Trabectedin EVER Pharma 1 mg

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

Each carton contains one vial.

Vials may or may not be sheathed in a protective sleeve.

6.6 Special precautions for disposal and other handling

Preparation for intravenous infusion

Trabectedin EVER Pharma 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 trabectedin. 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

Trabectedin EVER Pharma 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:
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

Trabectedin EVER Pharma 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 Trabectedin EVER Pharma 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

EVER Valinject GmbH
Oberburgau 3
4866 Unterach am Attersee
Austria

8 MARKETING AUTHORISATION NUMBER

PA1774/013/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th March 2026

10 DATE OF REVISION OF THE TEXT

May 2026