

NEW ZEALAND DATASHEET

YONDELIS (TRABECTEDIN) POWDER FOR SOLUTION FOR INFUSION

1 PRODUCT NAME

YONDELIS 0.25 mg powder for solution for infusion.

YONDELIS 1 mg powder for solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Powder for solution for infusion.

White to off-white powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

YONDELIS is indicated for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen.

4.2 DOSE 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.

Instructions for handling

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.

Dosage

The recommended dose is 1.5 mg/m² body surface area, administered as an intravenous infusion over 24 hours with a three-week interval between cycles.

All patients must receive corticosteroids e.g. 20 mg of dexamethasone intravenously 30 minutes prior to YONDELIS, not only as anti-emetic prophylaxis, but also because it appears to provide hepatoprotective effects. Additional anti-emetics may be administered as needed.

The following criteria are required to allow treatment with YONDELIS:

- Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$
- Platelet count $\geq 100 \times 10^9/L$
- Bilirubin \leq upper limit of normal (ULN)
- Alkaline phosphatase $\leq 2.5 \times$ 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) $\leq 2.5 \times$ ULN
- Creatinine clearance ≥ 30 mL/min
- Creatine phosphokinase (CPK) $\leq 2.5 \times$ ULN
- Haemoglobin ≥ 90 g/L

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:

- Neutropaenia $< 0.5 \times 10^9/L$ lasting for more than 5 days or associated with fever or infection
- Thrombocytopenia $< 25 \times 10^9/L$
- Increase of bilirubin $> ULN$ and/or alkaline phosphatase $> 2.5 \times ULN$
- Increase of aminotransferases (AST or ALT) $> 2.5 \times ULN$ which has not recovered by day 21
- Any other grade 3 or 4 adverse reactions (such as nausea, vomiting, fatigue)

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

Permanently discontinue YONDELIS for:

- Rhabdomyolysis
- Capillary leak syndrome

- Grade 3 or 4 cardiac adverse events (AEs) indicative of cardiomyopathy or for subjects with an LVEF that decreases below the lower limit of normal

Table 1. Dose modification table

	YONDELIS
Starting dose	1.5 mg/m ²
First reduction	1.2 mg/m ²
Second reduction	1 mg/m ²

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

Duration of treatment

Treatment should be continued until the onset of progressive disease or unacceptable toxicity. In the ET743-SAR-3007 trial long term follow-up, YONDELIS has been administered for 6 or more cycles in 42% of patients. The monotherapy regimen has been used for up to 44 cycles (median 4.0, range: 1-44). No cumulative toxicities have been observed in patients treated with multiple cycles.

Method of administration

Intravenous administration through a central venous line is strongly recommended due to development of a potentially severe injection site reaction when YONDELIS is administered through a peripheral venous line.

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

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).

Instructions for reconstitution

YONDELIS 0.25 mg

Each vial containing 0.25 mg of trabectedin is reconstituted with 5 mL of water for injections.

A syringe is used to inject the 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.

A syringe is used to inject the 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:

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

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 $\geq 1,000$ 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. For infusion times exceeding 4 hours, an infusion set with a 0.2 micron polyethersulfone (PES) in-line filter can be used to further reduce the risk of exposure to adventitious pathogens that may be introduced during solution preparation.

Special populations

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 1,681 patients in an integrated safety analysis of monotherapy clinical trials were aged 65 years or over. In a population pharmacokinetic analysis plasma clearance and distribution volume of trabectedin were not influenced by age. Therefore, dose adjustments based uniquely on age criteria are not routinely recommended.

Japanese population

A population pharmacokinetic analysis showed that plasma trabectedin concentrations observed in Japanese subjects at dose level 1.2 mg/m² were equivalent to those obtained in the non-Japanese western population at 1.5 mg/m².

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) 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.

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

Use in 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 YONDELIS (see section 4.2).

Use in renal impairment

Creatinine clearance must be monitored prior to and during treatment. YONDELIS must not be used in patients with creatinine clearance < 30 mL/min (see section 4.2).

Neutropaenia and sepsis

Neutropaenia and neutropaenic sepsis, including fatal cases, can occur with YONDELIS. Grade 3 or 4 neutropaenia is very common.

A full blood cell count including differential 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 $1.5 \times 10^9/L$. If severe neutropenia ($ANC < 0.5 \times 10^9/L$) lasting more than 5 days or associated with fever or infection occurs, dose reduction is recommended (see section 4.2).

Thrombocytopenia

Grade 3 or 4 thrombocytopenia is also very common following trabectedin administration. Platelet counts should be performed at baseline, weekly for the first two cycles and then once between cycles (see section 4.2). YONDELIS should not be administered to patients with baseline platelets count of less than $100 \times 10^9/L$.

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)

YONDELIS 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 YONDELIS, since the risk of rhabdomyolysis may be increased.

Hepatotoxicity

Hepatotoxicity, including hepatic failure, can occur with YONDELIS. Reversible acute increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) have been reported in most patients, and grade 3 or 4 abnormalities are common.

LFTs should be assessed prior to each administration of YONDELIS and as clinically indicated based on underlying severity of pre-existing hepatic impairment. Patients with increases in AST, ALT and alkaline phosphatase between cycles may necessitate dose adjustments (see section 4.2).

YONDELIS must not be used in patients with elevated bilirubin or those with AST, ALT or alkaline phosphatase > 2.5x ULN.

Caution should be taken if medicinal products associated with hepatotoxicity are administered concomitantly with trabectedin, since the risk of hepatotoxicity may be increased.

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 YONDELIS is administered through a peripheral venous line.

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

Allergic Reactions

During post-marketing experience, hypersensitivity reactions with very rare occurrence of fatal outcome, have been reported in association with YONDELIS administration (see sections 4.3 and 4.8).

Cardiac Dysfunction

Cardiac dysfunction including cardiac failure, congestive heart failure, decreased ejection fraction, diastolic dysfunction, or right ventricular dysfunction can occur with YONDELIS.

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 YONDELIS and at 2 to 3-month intervals thereafter until YONDELIS is discontinued.

Patients with LVEF less than the lower limit of normal (LVEF < LLN), a prior cumulative anthracycline dose of >300 mg/m², aged > 65 years, or a history of cardiovascular disease (especially in those receiving cardiac medication) may be at increased risk of cardiac dysfunction at treatment with YONDELIS.

For patients with Grade 3 or 4 cardiac adverse events indicative of cardiac dysfunction 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%), YONDELIS should be discontinued.

Capillary Leak Syndrome (CLS)

Cases of Capillary Leak Syndrome (CLS) have been reported with YONDELIS (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 YONDELIS 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 YONDELIS should be considered.

Concomitant use of YONDELIS with phenytoin may reduce phenytoin absorption leading to an exacerbation of convulsions. Combination of YONDELIS 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 YONDELIS 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”.

Use in the elderly

No age-related dose adjustment is required for YONDELIS.

Paediatric use

The safety and efficacy of YONDELIS in the paediatric population was studied in SAR-2005 phase I-II study (see section 5.1 Clinical Trials).

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

Effects on laboratory tests

No effects on laboratory tests have been observed.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 CYP3A4 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. 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 YONDELIS due to the hepatotoxicity of the medicinal product (see section 4.4).

Nonclinical 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

Effects on 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.

Fertility studies with trabectedin were not performed in nonclinical studies, 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.

Use in pregnancy - Pregnancy Category D

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. YONDELIS should not be used during pregnancy. If pregnancy occurs during treatment, the patient must be informed of the potential risk to the fetus (see section 5.3) and be monitored carefully. If YONDELIS 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.

Trabectedin was not embryofetotoxic or teratogenic in rats or rabbits at the highest doses tested (15 µg/m²/day and 24 µg/m²/day IV, respectively). These doses were well below the human dose (on a mg/m² basis), but could not be increased because of excessive maternal toxicity.

Use in lactation

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of the ability to drive and to use machines have been performed. However, fatigue and/or asthenia have been reported in patients receiving YONDELIS. Patients who experience any of these adverse reactions during therapy must not drive or operate machines.

4.8 UNDESIRABLE EFFECTS

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at <https://medsafe.govt.nz/profs/adverse/reactions.asp> and drugsafety-STA@stbiopharma.com.

Summary of the safety profile

Most patients treated with YONDELIS can be expected to have adverse reactions of any grade (97.6%) and approximately 63.2% of patients experience serious adverse reactions of grade 3 or 4 severity. The most common adverse reactions of any severity grade were neutropaenia, nausea, vomiting, increase in AST/ALT, anaemia, fatigue, thrombocytopaenia, anorexia and diarrhoea.

Fatal adverse reactions have occurred in 3.8% of patients treated with YONDELIS. They were often the result of a combination of events including pancytopenia, febrile neutropaenia, 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 events and reactions reported in clinical trials, post-authorisation safety studies and spontaneous reporting.

Table 2. Treatment-Emergent Adverse Events regardless of relationship with the study treatment, worst grade per patient (frequency ≥10%); Study ET743-SAR-3007*

System organ class Preferred term	YONDELIS q 3 wk 24-h (1.5 mg/m ²) (N=378) ALL GRADES	YONDELIS q 3 wk 24-h (1.5 mg/m ²) (N=378) GRADES 3-4	Dacarbazine (N=172) ALL GRADES	Dacarbazine (N=172) GRADES 3-4
Gastrointestinal disorders	341 (90.2%)	68 (18.0%)	136 (79.1%)	23 (13.4%)
Nausea	285 (75.4%)	26 (6.9%)	86 (50.0%)	3 (1.7%)
Abdominal pain	68 (18.0%)	16 (4.2%)	36 (20.9%)	10 (5.8%)
Vomiting	173 (45.8%)	22 (5.8%)	37 (21.5%)	2 (1.2%)
Constipation	140 (37.0%)	3 (0.8%)	53 (30.8%)	1 (0.6%)
Diarrhoea	132 (34.9%)	6 (1.6%)	40 (23.3%)	0
Skin and subcutaneous tissue disorders	93 (24.6%)	0	44 (25.6%)	0
General disorders and administration site conditions	324 (85.7%)	57 (15.1%)	121 (70.3%)	10 (5.8%)
Fatigue	261 (69.0%)	31 (8.2%)	89 (51.7%)	3 (1.7%)
Pyrexia	71 (18.8%)	3 (0.8%)	28 (16.3%)	1 (0.6%)
Oedema peripheral	107 (28.3%)	3 (0.8%)	22 (12.8%)	1 (0.6%)
Blood and lymphatic system disorders	230 (60.8%)	140 (37.0%)	77 (44.8%)	44 (25.6%)
Neutropaenia	119 (31.5%)	91 (24.1%)	31 (18.0%)	22 (12.8%)
Leukopaenia	45 (11.9%)	37 (9.8%)	13 (7.6%)	10 (5.8%)
Anaemia	157 (41.5%)	67 (17.7%)	48 (27.9%)	20 (11.6%)
Thrombocytopaenia	74 (19.6%)	40 (10.6%)	34 (19.8%)	18 (10.5%)
Metabolism and nutrition disorders	221 (58.5%)	63 (16.7%)	78 (45.3%)	15 (8.7%)
Decreased appetite	139 (36.8%)	7 (1.9%)	36 (20.9%)	1 (0.6%)
Hypokalaemia	53 (14.0%)	14 (3.7%)	21 (12.2%)	2 (1.2%)
Dehydration	57 (15.1%)	18 (4.8%)	20 (11.6%)	5 (2.9%)
Infections and infestations	157 (41.5%)	46 (12.2%)	50 (29.1%)	6 (3.5%)
Respiratory, thoracic and mediastinal disorders	201 (53.2%)	37 (9.8%)	76 (44.2%)	8 (4.7%)
Cough	85 (22.5%)	1 (0.3%)	36 (20.9%)	0
Dyspnoea	94 (24.9%)	16 (4.2%)	35 (20.3%)	2 (1.2%)
Investigations	281 (74.3%)	202 (53.4%)	80 (46.5%)	38 (22.1%)
Aspartate aminotransferase increased	142 (37.6%)	57 (15.1%)	10 (5.8%)	0
Alanine aminotransferase increased	186 (49.2%)	111 (29.4%)	12 (7.0%)	1 (0.6%)
Blood alkaline phosphatase increased	85 (22.5%)	6 (1.6%)	15 (8.7%)	1 (0.6%)
Blood creatinine increased	48 (12.7%)	8 (2.1%)	3 (1.7%)	0
Blood creatine phosphokinase increased	56 (14.8%)	22 (5.8%)	2 (1.2%)	1 (0.6%)
White blood cell count decreased	97 (25.7%)	75 (19.8%)	20 (11.6%)	15 (8.7%)
Neutrophil count decreased	96 (25.4%)	77 (20.4%)	25 (14.5%)	17 (9.9%)
Platelet count decreased	62 (16.4%)	38 (10.1%)	28 (16.3%)	16(9.3%)
Nervous system disorders	198 (52.4%)	10 (2.6%)	78 (45.3%)	6 (3.5%)

System organ class Preferred term	YONDELIS q 3 wk 24-h (1.5 mg/m ²) (N=378) ALL GRADES	YONDELIS q 3 wk 24-h (1.5 mg/m ²) (N=378) GRADES 3-4	Dacarbazine (N=172) ALL GRADES	Dacarbazine (N=172) GRADES 3-4
Headache	93 (24.6%)	1 (0.3%)	32 (18.6%)	0
Dizziness	46 (12.2%)	1 (0.3%)	21 (12.2%)	0
Musculoskeletal and connective tissue disorders	202 (53.4%)	21 (5.6%)	77 (44.8%)	12 (7.0%)
Back pain	65 (17.2%)	4 (1.1%)	30 (17.4%)	4 (2.3%)
Pain in extremity	47 (12.4%)	5 (1.3%)	15 (8.7%)	4 (2.3%)
Arthralgia	56 (14.8%)	0	14 (8.1%)	2 (1.2%)
Myalgia	47 (12.4%)	0	11 (6.4%)	0
Psychiatric disorders	113 (29.9%)	4 (1.1%)	37 (21.5%)	0
Insomnia	55 (14.6%)	1 (0.3%)	16 (9.3%)	0
Anxiety	40 (10.6%)	0	13 (7.6%)	0
Vascular disorders	84 (22.2%)	23 (6.1%)	33 (19.2%)	3 (1.7%)
Cardiac disorders	51 (13.5%)	17 (4.5%)	21 (12.2%)	3 (1.7%)

* data from Yondelis (trabectedin) Clinical Study Report (CSR) v.16Mar2015

Table 3 below displays the adverse reactions reported in patients with soft tissue sarcoma that were treated with YONDELIS. 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$) and rare ($\geq 1/10,000$ to $< 1/1000$).

Table 3. Adverse reactions that fall below the cut-off by System Organ Classes (SOC) using CIOMS frequencies (uncommon, rare)

System Organ Class	Uncommon	Rare
Infections and Infestations	Septic shock	
Vascular Disorders	Capillary leak syndrome	
Respiratory, Thoracic and Mediastinal Disorders	Pulmonary oedema	
Hepatobiliary Disorders		Hepatic failure
Musculoskeletal and Connective Tissue Disorders	Rhabdomyolysis	
General Disorders and Administration Site Conditions	Extravasation Soft tissue necrosis	

Description of selected adverse reactions

Most frequent adverse reactions

Blood and lymphatic system disorders

Neutropaenia:

Neutropaenia 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 YONDELIS showed neutropaenia of grade 3 and 4 in approximately 19% and 8% of

cycles respectively. In this population febrile neutropaenia occurred in 2% of patients and in < 1% of cycles.

Thrombocytopenia:

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

Anaemia:

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

Hepatobiliary disorders

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.

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 showed grade 3 elevations of AST and ALT in 12% and 20% of cycles respectively. Grade 4 elevations of AST and ALT occurred in 1% and 2% of cycles respectively. Most transaminase elevations improved to grade 1 or to pre-retreatment levels within 15 days, and less than 2% of cycles had recovering times longer than 25 days. ALT and AST increases did not follow a cumulative pattern but showed a tendency towards less severe elevations over time.

Hyperbilirubinemia:

Bilirubin peaks approximately a week after onset and resolves approximately two weeks after onset.

Liver function tests predicting severe toxicity (meeting Hy's law) and clinical manifestations of severe hepatic injury were uncommon with a lower than 1% incidence of individual signs and symptoms including jaundice, hepatomegaly or liver pain. Mortality in the presence of hepatic injury occurred in less than 1% of patients.

Other adverse reactions

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

Post-marketing adverse effects

The following adverse reactions have been identified during post-approval use of YONDELIS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Table 4. Post-marketing adverse reactions by system organ class using CIOMS frequencies

Adverse reactions identified during post-marketing experience with YONDELIS		
System Organ Class	Frequency Category Estimated from Spontaneous Reporting Rates	Frequency Category Estimated from Clinical Trials with YONDELIS
Vascular disorders		
Capillary leak syndrome	Not known	Uncommon

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.

For information on the management of overdose, contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agent, ATC code: L01CX01.

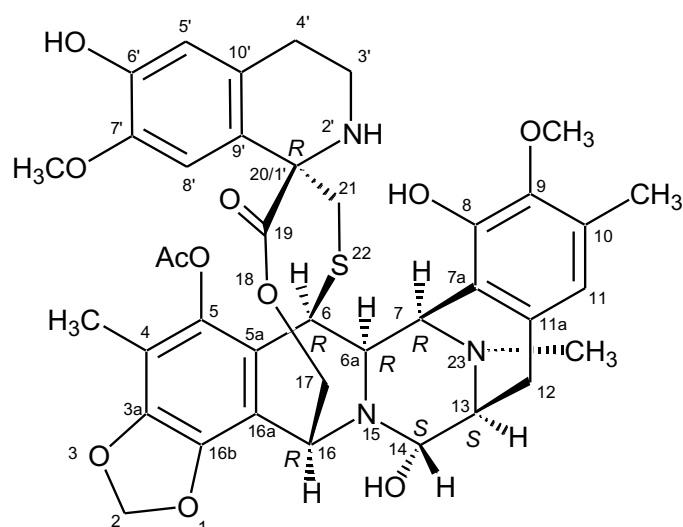
PHYSICOCHEMICAL PROPERTIES

Chemical structure

(1'*R*,6*R*,6*aR*,7*R*,13*S*,14*S*,16*R*)-5-(acetyloxy)-3',4',6,6*a*,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12*H*-1,3-dioxolo[7,8]isoquino[3,2-*b*][3]benzazocine-20,1'(2'*H*)-isoquinolin]-19-one

Molecular Formula: C₃₉H₄₃N₃O₁₁S

Molecular Weight: MW: 761.84



CAS number

114899-77-3

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* 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. *In vivo* activity against tumour xenografts in nude mice has been observed for some tumour types, including some soft tissue sarcomas.

Electrocardiogram (ECG) investigations

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

Clinical trials

The clinical efficacy and safety of YONDELIS in patients with metastatic or recurrent leiomyosarcoma or liposarcoma were demonstrated in the pivotal trial ET743-SAR-3007 (NCT01343277), a randomised (2:1), open-label, active-controlled trial comparing treatment with YONDELIS 1.5 mg/m² as a 24-hour continuous intravenous infusion once every 3 weeks to dacarbazine 1000 mg/m² intravenous infusion (20 to 120 minutes) once every 3 weeks. Treatment continued in both arms until disease progression or unacceptable toxicity; all patients in the YONDELIS arm were required to receive dexamethasone 20 mg intravenous injection prior to each YONDELIS infusion.

Patients were required to have unresectable, locally advanced or metastatic leiomyosarcoma or liposarcoma (dedifferentiated, myxoid round cell, or pleomorphic) and previous treatment with an anthracycline- and ifosfamide-containing regimen or an anthracycline-containing regimen and one additional cytotoxic chemotherapy regimen.

Randomisation was stratified by subtype of soft tissue sarcoma (leiomyosarcoma vs. liposarcoma), ECOG performance status (0 vs. 1), and number of prior chemotherapy regimens (1 vs. ≥ 2). The efficacy outcome measures were investigator-assessed progression-free survival (PFS) according to the Response Evaluation Criteria in Solid Tumours (RECIST v1.1), overall survival (OS), objective response rate (ORR), and duration of response (DOR). Patients in the dacarbazine arm were not offered YONDELIS at the time of disease progression.

A total of 518 patients were randomised, 345 to the YONDELIS arm and 173 patients to the dacarbazine arm. The median patient age was 56 years (range: 17 to 81); 30% were male; 76% White, 12% Black, and 4% Asian; 73% had leiomyosarcomas and 27% liposarcomas; 49% had an ECOG PS of 0; and 89% received ≥ 2 prior chemotherapy regimens. The most common ($\geq 20\%$) pre-study chemotherapeutic agents administered were doxorubicin (90%), gemcitabine (81%), docetaxel (74%), and ifosfamide (59%). Approximately 10% of patients had received pazopanib.

Trial ET743-SAR-3007 demonstrated a statistically significant improvement in PFS. An exploratory analysis of independent radiology committee-determined PFS, in a subgroup consisting of approximately 60% of the total population, provided similar results to the investigator-determined PFS. Efficacy results from Trial ET743-SAR-3007 are presented in [table 5](#) below.

Table 5. Efficacy Results for Trial ET743-SAR-3007

Efficacy Endpoint	YONDELIS N=345	Dacarbazine N=173
Progression-free survival		
PFS Events, n (%)	217 (63%)	112 (65%)
Disease progression	204	109
Death	13	3
Median (95% CI) (months)	4.2 (3.0, 4.8)	1.5 (1.5, 2.6)
HR (95% CI) ^a	0.55 (0.44, 0.70)	
p-value ^b	<0.001	
Overall survival^c		
Events, n (%)	258 (67%)	123 (64%)
Median (95% CI) (months)	13.7 (12.2, 16.0)	13.1 (9.1, 16.2)
HR (95% CI) ^a	0.93 (0.75, 1.15)	
p-value ^b	0.49	
Objective Response Rate (ORR: CR+PR)		
Number of patients (%)	34 (9.9%)	12 (6.9%)
95% CI ^d	(6.9, 13.5)	(3.6, 11.8)
Duration of Response (CR+ PR)		
Median (95% CI) (months)	6.47 (3.58, 7.62)	4.17 (2.14, NE)

^a Cox proportional hazards model with treatment group as the only covariate.

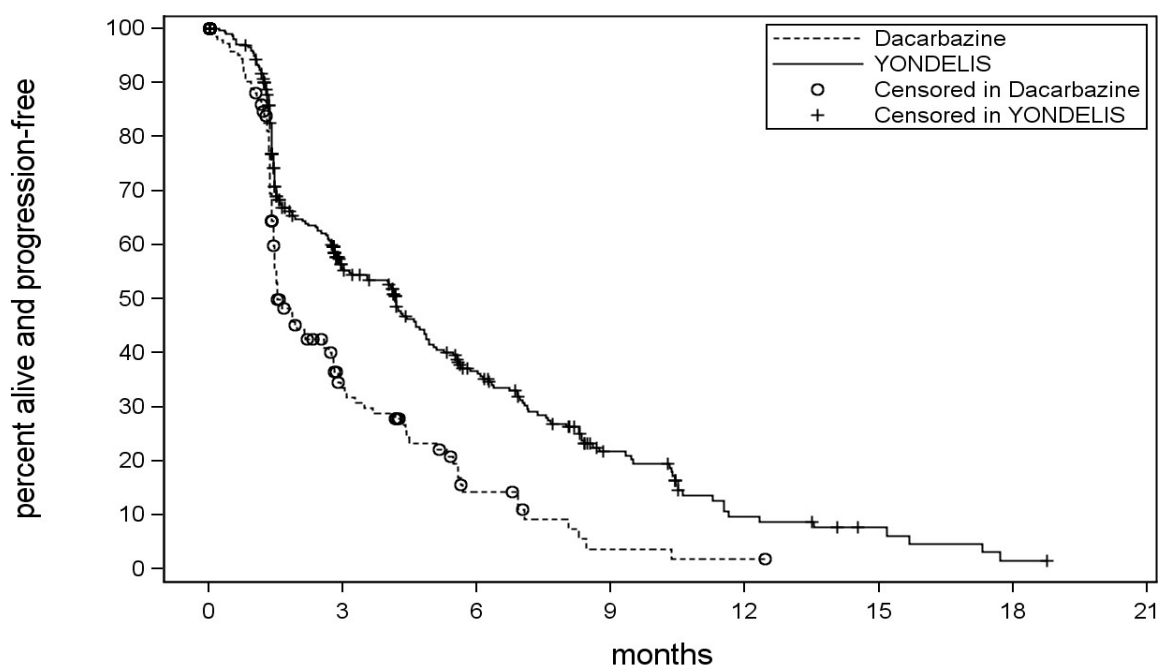
^b Unstratified log rank test.

^c Based on 384 patients randomized to YONDELIS arm and 193 patients randomized to dacarbazine.

^d Fisher's exact CI.

CR = Complete Response; PR = Partial Response; CI = Confidence Interval, HR = hazard ratio, NE = not estimable.

Figure 1. Kaplan-Meier Curves of Progression-Free Survival in Trial ET743-SAR-3007



No. Subjects at Risk

Dacarbazine	173	35	10	2	1	0		
YONDELIS	345	133	71	29	10	5	1	0

Paediatric population

Trabectedin has not been studied in paediatric subjects with leiomyosarcoma or liposarcoma. In a phase I-II study (SAR-2005) in 50 paediatric patients with rhabdomyosarcoma, Ewing sarcoma or non-rhabdomyosarcoma soft tissue sarcoma, the objective response rate was 2.5% (95%CI: 0.1%-13.2%).

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/m². 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.

Metabolism

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

Excretion

Renal elimination of unchanged trabectedin in humans is low (less than 1%). The terminal half-life is long (population value of the terminal elimination phase: 180-hr). After a dose of radiolabelled trabectedin administered to cancer patients, faecal mean (SD) recovery of total radioactivity is 58% (17%), and urinary mean (SD) recovery is 5.8% (1.73%). Based on the population estimate for plasma clearance of trabectedin (30.9 L/h) and blood/plasma ratio (0.89), the clearance of trabectedin in whole blood is approximately 35 L/h. This value is approximately one-half the rate of human hepatic blood flow. Thus the trabectedin extraction ratio can be considered moderate. The inter-patient variability of the population estimate for plasma clearance of trabectedin was 49% and intra-patient variability was 28%.

Special populations

A phase 1 study showed 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 m²).

For information regarding the Japanese population refer to Section 4.2 Dose and Method of Administration, Special Populations.

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/m² administered as 3-hour infusion. The geometric mean dose normalised 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/m² (n=3) or 0.9 mg/m² (n=3) compared to 9 patients with normal liver function following administration of a single trabectedin dose of 1.3 mg/m² (see sections 4.2 and 4.4).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Trabectedin was genotoxic in both *in vitro*, Ames test and lymphoma assays and *in vivo* mouse micronucleus test.

Carcinogenicity

Long-term carcinogenicity studies have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sucrose

monobasic potassium phosphate

phosphoric acid

potassium hydroxide

6.2 INCOMPATIBILITIES

YONDELIS must not be mixed or diluted with other medicinal products except those mentioned in section 4.2.

6.3 SHELF LIFE

Unopened vials

60 months.

After reconstitution

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

From a microbiological point of view, the reconstituted solution should be diluted and used immediately. If not diluted and used immediately, do not store for longer than 24 hours at 2°C to 8°C. For use in one patient on one occasion only. Discard any residue.

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). Refrigerate. Do not freeze.

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

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

Refer to Section 4.2 for Instructions for handling YONDELIS.

7 MEDICINE SCHEDULE

PRESCRIPTION MEDICINE

8 SPONSOR

Specialised Therapeutics Limited
Level 1, The Lane, Botany Town Centre,
588 Chapel Road,
East Tamaki
AUCKLAND 2013

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Fax: +64 9801 0118

www.stbiopharma.com

9 DATE OF FIRST APPROVAL

16 February 2023

10 DATE OF REVISION

N/A

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information