DRUG NAME: Trabectedin

SYNONYM(S)[1]: Ecteinascidin, Ecteinascidin 743, ET-743

COMMON TRADE NAME(S): YONDELIS®

CLASSIFICATION: miscellaneous

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Trabectedin is an inhibitor of oncogenic transcription. It binds to guanines in the minor groove of DNA, bending the helix toward the major groove. This structural change prevents transcription factors from binding to their recognition sequences, which inhibits oncogenic transcription. In addition, trabectedin degrades transcribing RNA polymerase II and inhibits DNA damage repair, resulting in DNA double strand breaks and tumour cell apoptosis. Trabectedin blocks the cell cycle at the G_2/M phase.[2,3]

PHARMACOKINETICS:

Distribution	extensive distribution to peripheral tissues	
	cross blood brain barrier?	no information found
	volume of distribution	>5000 L
	plasma protein binding	97%
Metabolism	extensively metabolized by CYP 3A4	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	mainly excreted by feces	
	urine	6% (<1% unchanged drug)
	feces	58% (<1% unchanged drug)
	terminal half life	175 h
	clearance	32 L/h
Sex	no clinically significant differences	
Elderly	no clinically significant differences	

Adapted from standard reference[2,4,5] unless specified otherwise.

USES:

Primary uses:

*Soft tissue sarcoma

*Ovarian cancer

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Caution:
- ***premedication*** with dexamethasone is recommended prior to each dose of trabectedin to prevent emesis and protect the liver[2,5]
- risk of ***cardiomyopathy*** is increased in patients with history of cardiovascular disease, reduced left ventricular ejection fraction, and prior anthracycline treatment[2]
- ***alcohol*** consumption may increase the risk of ***hepatotoxicity*** in patients taking trabectedin; concurrent use is not recommended[2,5]

Carcinogenicity: Long-term carcinogenicity studies have not been conducted.[2,5]

Mutagenicity: Trabectedin is genotoxic in both *in vitro* and *in vivo* tests.[2,5]

Fertility: In animal studies, hemorrhage and histopathological signs of degeneration in the testes were observed at exposures approximately 0.2 times the human dose based on body surface area. Based on its mechanism of action (both cytotoxic and mutagenic), trabectedin may impair fertility in male and female patients. Because of the possibility of irreversible infertility, consider sperm preservation for male patients prior to treatment.[2,4]

Pregnancy: Animal reproductive and developmental studies have not been conducted with trabectedin at clinically relevant doses due to dose-limiting maternal toxicity. However, placental transfer of trabectedin has been demonstrated in pregnant rats. Based on its known mechanism of action, trabectedin may cause serious birth defects when administered during pregnancy. Trabectedin also has genotoxic effects which may damage spermatozoa resulting in possible genetic and fetal abnormalities. Pregnancy tests are recommended prior to starting treatment. For females of reproductive potential, contraception is recommended during treatment and for at least 3 months (and up to 8 months) after the last dose of trabectedin. Male patients with female partners of reproductive potential should use contraception for at least 5 months after the last dose.[2,4]

Breastfeeding is not recommended due to the potential secretion into breast milk. Women should not breastfeed during treatment and for 3 months after the last dose of trabectedin.[2]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[6,7]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (27-97%, severe 1%)
	febrile neutropenia (2-5%)[2,4]
	leukopenia (12%, severe 5%)
	neutropenia (49%, severe 35%)
	thrombocytopenia (20%, severe 10%)
cardiac	***cardiomyopathy*** (5-6%, severe 4%)[2,4]; see paragraph following **Side Effects** table
gastrointestinal	*emetogenic potential:* moderate[8]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	abdominal pain (5%, severe 2%)
	constipation (18%)
	diarrhea (15%)
	dyspepsia (5%)
	nausea (72%, severe 4%)
	stomatitis (<10%)[1]
	vomiting (39%, severe 2%)
general disorders and administration site conditions	*extravasation hazard:* vesicant[9]
	asthenia (15%, severe 1%)
	edema, peripheral (5%)
	extravasation (<1%); tissue necrosis reported
	fatigue (53%, severe 5%)
	injection site reaction, phlebitis (15%)
	pyrexia (5%)
hepatobiliary	drug induced liver injury (1%)
	hepatic failure; see paragraph following **Side Effects** table
immune system	hypersensitivity (2%)
infections and infestations	infection; including pneumonia, respiratory tract infection, and catheter site infection
	neutropenic sepsis (3%)[4]; fatalities reported
investigations	alkaline phosphatase increase (28%)
	ALT increase (54%, severe 39%); see paragraph following **Side Effects** table
	AST increase (47%, severe 23%); see paragraph following **Side Effects** table
	blood bilirubin increase (8-23%, severe 2%)
	creatine phosphokinase increase (10-26%, severe 4%); see paragraph following **Side Effects** table
	creatinine increase (5%)
metabolism and nutrition	anorexia (19%, severe 1%)
	appetite decrease (6%)
	dehydration (5%)
	hypoalbuminemia (63%, severe 4%)[4]
	hypokalemia (5%, severe 2%)
musculoskeletal and connective tissue	arthralgia (5-12%, severe 1%)
	myalgia (10%, severe 2%)
	rhabdomyolysis (1%)[4]; see paragraph following **Side Effects** table

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
nervous system	dizziness (5%, severe 1%)
	dysgeusia (8%)
	headache (15%, severe 1%)
	peripheral neuropathy (<10%)[4]
psychiatric	insomnia (6%)
renal and urinary	renal failure (3%)[4]
respiratory, thoracic, and mediastinal	dyspnea (5%, severe 1%)
skin and subcutaneous tissue	alopecia (3%)
vascular	***capillary leak syndrome***; see paragraph following **Side Effects** table
	pulmonary embolism (<10%)[4]

Adapted from standard reference[2,5] unless specified otherwise.

Cardiomyopathy, including cardiac dysfunction and congestive heart failure, has been reported with trabectedin. The median time to onset for grade 3 or 4 cardiomyopathy is 5 months. Trabectedin has also been associated with a transient increase in heart rate and may worsen pre-existing cardiac conditions. Assessment of cardiac function (e.g., LVEF) is recommended prior to initiation of trabectedin and regularly during treatment. Permanently discontinue trabectedin in patients who experience grade 3 or higher cardiac events.[2,5]

Capillary leak syndrome (CLS), including fatal cases, has been reported. Symptoms of CLS may include edema, hypotension, and a rapid decline in albumin level. Withhold trabectedin if CLS is suspected. Permanently discontinue if CLS is confirmed.[2,5]

Extravasation of trabectedin has been reported to cause severe pain, blistering, and tissue necrosis requiring surgical debridement. Tissue necrosis may present days to weeks after extravasation.[11,12] To reduce the risk of extravasation, administration via a central venous line is required.[2,12-14] However, although the incidence of extravasation is decreased with central venous access devices (CVAD), cases of skin and soft tissue damage is still reported. Complications associated with CVAD use (e.g., infections, catheter obstruction) may also lead to extravasation.[11,12] There is no specific antidote for extravasation of trabectedin.[2] For more information on prevention and treatment of extravasation, refer to BC Cancer Systemic Therapy Policy III-20 ***Prevention and Management of Extravasation of Chemotherapy.***

Hepatotoxicity is commonly reported and most frequently presents as transient elevations in transaminases.[2,10] Clinical presentation may include jaundice, hepatomegaly or liver pain. Although rare, severe cases of hepatic failure have been reported. Median time to onset for grade 3 or 4 transaminase elevation is 29 days (range 3 days to 11 months), with usual recovery time of 13 days (range 4 days to 4 months).[4] Liver function tests are assessed at baseline and monitored throughout the treatment. Premedication with dexamethasone prior to each dose of trabectedin is recommended to minimize the incidence and severity of hepatotoxicity, in addition to its antiemetic effects. Trabectedin dose interruption, dose reduction, and/or permanent discontinuation may be required based on severity and duration of hepatotoxicity. Alcohol consumption may increase the risk of hepatotoxicity in patients taking trabectedin; concurrent use is not recommended.[2,4]

Rhabdomyolysis, including severe cases with fatal outcomes, has been reported with trabectedin. Signs and symptoms of rhabdomyolysis may include muscle pain or weakness, elevated creatine phosphokinase (CPK), severe liver function test abnormalities, and renal failure. Median time to onset of grade 3 or higher CPK elevations

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is 2 months (range 1-11 months). Assess CPK levels at baseline and monitor regularly during treatment. Management of rhabdomyolysis may include supportive measures (parenteral hydration, dialysis, urine alkalinisation) and/or trabectedin dose interruption or dose reduction.[2,5]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
ketoconazole[2,4]	66% increase in trabectedin AUC and 21% increase in C_{max}	strong inhibition of CYP 3A4 by ketoconazole	- avoid concurrent use; if concurrent use is unavoidable, consider trabectedin dose reduction and monitor for toxicity - alternately, if ketoconazole will be taken for <14 days, start ketoconazole one week after the trabectedin dose and discontinue it one day before the next trabectedin dose[4]
rifampin[2]	31% decrease in trabectedin AUC and 22% decrease in C_{max}	strong induction of CYP 3A4 by rifampin	avoid concurrent use

Trabectedin is a substrate of CYP 3A4. ***CYP 3A4 inhibitors*** may increase the plasma concentration of trabectedin. Avoid concurrent use with strong CYP 3A4 inhibitors. If concurrent use is unavoidable, consider dose reduction of trabectedin and monitor for toxicity. If a strong CYP 3A inhibitor will be used concurrently with trabectedin short-term (i.e., for less than 14 days), start the inhibitor one week after the trabectedin dose and discontinue it one day before the next trabectedin dose. ***CYP 3A4 inducers*** may decrease the plasma concentration of trabectedin. Avoid concurrent use with strong CYP 3A4 inducers.[2,4]

In vitro, trabectedin is both a substrate and an inhibitor of P-gp. Clinical significance is unknown.[2]

SUPPLY AND STORAGE:

***Injection*:**

Valeo Pharma Inc. supplies trabectedin as 1 mg vials of lyophilized powder. Refrigerate.[5]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Compatibility: consult detailed reference

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PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous	not used due to corrosive nature
Intramuscular	not used due to corrosive nature
Direct intravenous	no information found
Intermittent infusion[2,5]	over 3 hrs; see ***Systemic Therapy Policy III-20: Prevention and Management of Extravasation of Chemotherapy***
Continuous infusion[2,5]	over 24 hr; see ***Systemic Therapy Policy III-20: Prevention and Management of Extravasation of Chemotherapy***
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BC Cancer usual dose noted in ***bold, italics***

Intravenous:

Cycle Length:

3 weeks[2,5,15]: 1.1 mg/m^2 (range 0.75-1.1 mg/m^2) IV for one dose on day 1
(total dose per cycle 1.1 mg/m^2 [range 0.75-1.1 mg/m^2])

3 weeks[2,4,16]: 1.5 mg/m^2 (range 1-1.5 mg/m^2) IV for one dose on day 1
(total dose per cycle 1.5 mg/m^2 [range 1-1.5 mg/m^2])

Concurrent radiation: no information found

Dosage in renal failure:

CrCl ≥30 mL/min: no adjustment required[2,4]
CrCl <30 mL/min: no information found

$$\text{calculated creatinine clearance} = \frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure: refer to protocol by which patient is being treated; if no protocol is available, refer to the following guidelines:
bilirubin ≤1.5 x ULN and any AST/ALT: no information found
bilirubin 1.5-3 x ULN and AST/ALT <8 x ULN: dose reduction is required[4,10]
bilirubin >3 x ULN and any AST/ALT: avoid[4]

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Dosage in dialysis:	no dose adjustment is required; hemodialysis is not expected to enhance elimination of trabectedin[1]
Children:	safety and efficacy have not been established[2]

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