Drug Monograph

A - Drug Name

trabectedin

COMMON TRADE NAME(S): Yondelis® (Janssen)

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B - Mechanism of Action and Pharmacokinetics

Trabectedin was originally derived from the Caribbean marine tunicate, Ecteinascidia turbinate, and is now produced synthetically. This antineoplastic is a tetrahydroisoquinoline alkaloid which binds to the minor groove of the DNA, bending DNA towards the major groove. The changed conformation interferes with several DNA transcription factors, repair pathways and cell proliferation.

Distribution	Pharmacokinetics are dose-proportional up to 1.8 mg/m^2. No accumulation observed when administered every 3 weeks. Extensively distributed into peripheral tissues	
	PPB	97 %
	Cross blood brain barrier?	No information found.
Metabolism	Extensive metabolism, mainly by CYP 3A4. Does not induce or inhibit major CYP 450 enzymes. No appreciable glucuronidation.	
	Active metabolites	No information found
	Inactive metabolites	Yes
Elimination	Multiple compartment disposition. Mainly fecal elimination, with <1% excreted unchanged. Clearance not influenced by total body weight, body surface area,	

age or gender.	
Half-life	terminal half-life: 175 hours
Urine	(renal) < 9 %
Feces	58 %

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C - Indications and Status

Health Canada Approvals:

- In combination with pegylated liposomal doxorubicin (Caelyx®) for the treatment of platinum-sensitive ovarian cancer patients, for whom one first-line platinum-based chemotherapy (including adjuvant) has failed, and who are not expected to benefit, are ineligible or not willing to receive retreatment with platinum-based chemotherapy.
- For the treatment of patients with metastatic liposarcoma or leiomyosarcoma after failure of prior anthracycline and ifosfamide chemotherapy.

NOTES:

Approval in ovarian cancer was based on progression-free survival benefit; however, overall survival and quality of life benefits have not been demonstrated. Approval in soft tissue sarcoma was based on a progression-free survival in a randomized study comparing 2 doses of trabectedin; survival prolongation was not demonstrated and quality of life was not assessed.

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D - Adverse Effects

Emetogenic Potential: Moderate

Extravasation Potential: Vesicant

These are mainly from single agent studies. Other events that are reported at a higher (>2%) incidence in combination compared to pegylated liposomal doxorubicin (Caelyx®) alone are also reported.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Cardiotoxicity (2%)	E D
	Hypotension (rare)	E
	Palpitations (4%)	E
	Venous thromboembolism (5%)	E
Dermatological	Alopecia (3%) (mostly mild)	E
	Skin hyperpigmentation (6%)	E
Gastrointestinal	Abdominal pain (5%)	E
	Anorexia (19%)	E
	Constipation (18%)	E
	Dehydration (5%)	E
	Diarrhea (15%)	E
	Dyspepsia (5%)	E
	Mucositis (1%)	E
	Nausea, vomiting (72%)	I E
General	Edema (5%)	E
	Fatigue (53%)	E
	Fever (5%)	E
Hematological	Myelosuppression ± infection, bleeding (35%) (severe)	E
Hepatobiliary	↑ LFTs (39%) (severe)	E
Hypersensitivity	Hypersensitivity (2%)	I
Injection site	Phlebitis (15%)	I E
Metabolic / Endocrine	↓ K (5%)	E
Musculoskeletal	Musculoskeletal pain (10%)	E
	↑CPK (26%) (4% severe)	E
	Rhabdomyolysis (<1%)	E
Nervous System	Dizziness (5%)	E
	Dysgeusia (8%)	E
	Headache (15%)	E
	Insomnia (6%)	E
	Peripheral neuropathy (1%)	E
Renal	Creatinine increased (5%) (may be severe)	E
Respiratory	Dyspnea (5%)	E
Vascular	Capillary leak syndrome (rare)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.
Dose-limiting side effects are underlined.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects of trabectedin include **fatigue, myelosuppression, GI effects, headache, musculoskeletal pain, elevated LFTs** or **CPK**. In the pivotal ovarian cancer clinical trial, 42% of patients received filgrastim, and there was an 8% rate of febrile neutropenia (1% fatal).

Grade 3 or 4 LFT elevations are common, usually occur in the first week, and recover prior to the next planned dose. Pretreatment with corticosteroids reduces the incidence. Hepatotoxcity may be cumulative and worsen with successive cycles. Hepatic failure has been reported.

CPK elevations are common; however, rhabdomyolysis is rare, but may be fatal. It is usually associated with myelotoxicity, severe hepatic or renal impairment. Trabectedin should be discontinued and aggressive treatment instituted if rhabdomyolysis occurs.

Phlebitis may occur even when a central line is used.

Hypersensitivity is generally mild to moderate; however, fatal cases have also been reported.

Capillary leak syndrome has been reported and may present with hypotension, edema and rapidly falling albumin.

Clinically significant **cardiac events** were reported in combination with liposomal doxorubicin in patients with ovarian cancer. Cardiac dysfunction was also reported in patients with liposarcoma and leiomyosarcoma who received prior anthracyclines. The incidence was higher in patients who received trabectedin (5%) compared to those who received dacarbazine (2%). Monitoring of LVEF is recommended, especially in patients at risk from previous anthracycline exposure or those with symptoms of cardiac dysfunction.

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E - Dosing

Refer to protocol by which patient is being treated. Premedication with corticosteroids such as dexamethasone 20mg IV 30 minutes before each trabectedin dose is required, for hepatoprotective and anti-emetic effects. Supportive care/colony stimulating factors for myelosuppression should be considered per institutional guidelines.

Adults:

List A:

The following criteria must be met before EACH trabectedin treatment.

- ANC ≥ 1.5 x 10^9/L, Platelets ≥ 100 x 10^9/L, Hemoglobin ≥ 90 g/L
- Bilirubin ≤ ULN, AST and ALT ≤ 2.5 x ULN
- Albumin ≥ 25 g/L
- Creatinine clearance ≥ 30 mL/min (monotherapy)
- Creatinine ≤ 132.6 µmol/L or Creatinine clearance ≥ 60 mL/min (combination therapy)
- ALP (of non-osseous origin) ≤ 2.5 x ULN (consider hepatic isoenzymes 5' nucleotidase or GGT, to distinguish elevations that can be osseous in origin)
- CPK ≤ 2.5 x ULN

Ovarian Cancer:

q3w: 1.1 mg/m^2 IV over 3 hours on day 1, after pegylated liposomal doxorubicin 30 mg/m^2 IV over 90 minutes

Liposarcoma or Leiomyosarcoma

q3w: 1.5 mg/m^2 IV over 24 hours

Dosage with Toxicity:

Reduced doses are not re-escalated. Discontinue if toxicity recurs after 2 dose reductions.

Table A - Dose Levels:

	Liposarcoma or Leiomyosarcoma	**Ovarian Cancer**	
Dose	**Trabectedin**	**Trabectedin**	**Pegylated Liposomal Doxorubicin**
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

Table B - Dose Modifications for Toxicity:

Counts / Toxicity (worst in previous cycles)	**Trabectedin Dose****
Grade 4 ANC≥ 5 days or Febrile neutropenia or Platelets < 25 x 10^9/L	↓ 1 dose level
Alkaline phosphatase > 2.5 x ULN (non-osseous)	↓ 1 dose level
AST/ALT > 2.5 x ULN (monotherapy), or >5 ULN (combination therapy) & not recovered by Day 21 or bilirubin > ULN***	↓ 1 dose level
≥ grade 3 non-hematological/organ toxicity	↓ 1 dose level
Any grade rhabdomyolysis or CPK > 2.5 ULN	Hold until recovery, consider discontinuing
Severe hypersensitivity	Discontinue
Capillary leak syndrome	Hold if suspected; discontinue if confirmed and treat according to institutional practice

**Do not treat until laboratory values meet conditions listed in List A and organ/non-hematologic toxicities have recovered to ≤ grade 2. Delay for a maximum of 3 weeks – if not recovered, discontinue.

***Hold trabectedin until normalizes and restart at reduced dose. If not recovered by day 21, discontinue.

Dosage with Hepatic Impairment:

At baseline:*

Parameter	≥ ULN - < 2.5 x ULN	≥ 2.5 ULN
Bilirubin	Do not treat	Do not treat
AST/ALT	No change	Do not treat
Alkaline Phosphatase	No Change	Do not treat

*Refer to Table B for dose modifications during treatment.

Dosage with Renal Impairment:

CrCl (ml/min	Single Agent Trabectedin	Combination with Pegylated liposomal doxorubicin
30-60	No change	Discontinue
< 30	Discontinue	Discontinue

Dosage in the elderly:

No dose adjustment needed. No differences in safety or effectiveness were seen in patients > 65 years of age versus younger patients.

Dosage based on ethnicity:

Increased myelotoxicity has been reported in Asian patients. Rates of infection were similar between white and Asian cohorts.

Children:

Safety and effectiveness have not been established. A phase II study showed no efficacy in pediatric patients with sarcomas. Trabectedin should not be used in children and adolescents.

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F - Administration Guidelines

- Avoid alcohol intake while on trabectedin treatment to prevent hepatotoxicity.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products (as well as other inhibitors of CYP3A4) during treatment (see Interactions section)
- MUST be administered via central intravenous line.
- Patients must receive corticosteroid premedication 30 minutes before each trabectedin dose (i.e. dexamethasone 20mg IV), as an antiemetic and to protect the liver.
- Reconstitute with sterile water for injection as directed.
- Further dilute in 500mL Normal Saline or D5W.
- Compatible with PVC, glass, polyethylene (PE) containers and tubing.
- After completion of the pegylated liposomal doxorubicin infusion, the IV line should be flushed with D5W before trabectedin administration.
- Do not mix or dilute with other drugs or solutions.
- Refrigerate unopened vials at 2-8°C.

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G - Special Precautions

Contraindications:

- patients who have a hypersensitivity to trabectedin or any of its components
- patients who have active, serious or uncontrolled infections
- patients who have left ventricular injection fraction below the lower limit of normal
- patients with active hepatitis, elevated bilirubin, or who have CPK > 2.5 times the upper limit of normal.

Other Warnings/Precautions:

- exercise caution in patients with a history of ischemic heart disease or tachyarrhythmia, as trabectedin has been associated with transient heart rate increases
- avoid live vaccines
- avoid alcohol, concomitant use of other hepatotoxic drugs or drugs known to cause rhabdomyolysis

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Genotoxicity: Yes
- Mutagenicity: Yes
  Trabectedin is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 3 months after the last dose for females (5 months for males)
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended during treatment and for 3 months after the last dose.
- Fertility effects: Probable

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H - Interactions

Trabectedin does not appear to induce or inhibit major CYP450 enzymes, but is metabolized by CYP3A4.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Pegylated liposomal doxorubicin	↓ trabectedin clearance by 16-31%	Unknown	monitor
CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ trabectedin concentrations and/or toxicity (↑ AUC 66% with ketoconazole)	↓ trabectedin metabolism	Monitor closely; avoid strong CYP3A4 inhibitors if possible or consider dose reduction
CYP3A4 inducers (i.e. phenytoin, rifampin,	↓ trabectedin concentrations and effectiveness (↓ AUC 31% with rifampin)	↑ trabectedin metabolism and clearance	Monitor; avoid strong CYP3A4 inducers if possible

dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)			
P-glycoprotein inducers (i.e. rifampin, dexamethasone, indinavir)	Possibly ↓ trabectedin concentrations and effectiveness	↑ trabectedin metabolism and clearance	Caution
P-glycoprotein inhibitors (i.e. quinidine, verapamil, cyclosporine)	Possibly ↑ trabectedin concentrations and/or toxicity	↓ trabectedin metabolism	Caution
phenytoin (high dose)	↑ free trabectedin concentration (28%)	Displacement of trabectedin from protein binding	Avoid; monitor closely if must use
phenytoin (high dose)	↑ risk of seizures	↓ phenytoin absorption	Avoid; monitor closely if must use
Hepatotoxic drugs (i.e. alcohol, methotrexate, isoniazid, nefazodone)	May ↑ hepatotoxicity	Additive effect	Avoid
Drugs that may cause muscle damage (i.e. statins, levofloxacin)	May ↑ risk of rhabdomyolysis	Additive effect	Caution

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
LVEF	baseline and periodic (especially in patients at risk of cardiac dysfunction)
CBC	baseline, prior to each cycle, and weekly for first 2 cycles, then once between cycles
Liver function tests and CPK	baseline and prior to each cycle, and weekly for the first 2 cycles, then once between cycles
Renal function tests	baseline and regular
Clinical toxicity assessment for cardiac, musculoskeletal, GI, hepatic and local toxicity, as well as VTE, infection and bleeding; regular	At each visit
Albumin	If capillary leak syndrome suspected

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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K - References

Product Monograph: Yondelis® (trabectedin). Janssen-Ortho Inc., April 21, 2017.

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Kim RB. Drugs as p-glycoprotein substrates, inhibitors, or inducers. Drug Metab Rev 2002; 34(1-2): 47-54.

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November 2017 Added description of capillary leak syndrome (CLS) to adverse effects, added CLS to dose modification table, changed monitoring section

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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