Trabectedin: Drug information

(For additional information see "Trabectedin: Patient drug information ")

For abbreviations and symbols that may be used in Lexicomp (show table)

Special Alerts

Yondelis Safety Alert August 2016

Health Canada has completed a safety review and concluded there is a potential risk of capillary leak syndrome with the use of *Yondelis* (trabectedin). Health Canada is recommending updates to the Canadian prescribing information to include the potential risk of capillary leak syndrome with the use of *Yondelis*. At the time of the review, there were no Canadian cases of capillary leak syndrome reported with the use of *Yondelis*; however, international cases were reported.

Further information may be found at http://www.hc-sc.gc.ca/dhp-mps/medeff/reviews-examens/yondelis-eng.php.

Brand Names: US

Yondelis

Brand Names: Canada

Yondelis

Pharmacologic Category

Antineoplastic Agent, Miscellaneous

Dosing: Adult

Note: Prior to each treatment cycle, ANC should be ≥1,500/mm^3, platelets ≥100,000/mm^3 total bilirubin ≤ULN, and alkaline phosphatase, ALT, AST, and CPK ≤2.5 times ULN.

Premedications: Administer dexamethasone 20 mg IV 30 minutes prior to each infusion. Trabectedin is associated with a moderate emetic potential (MASCC 2016); additional antiemetics may be necessary.

Soft tissue sarcoma, unresectable/metastatic: IV: 1.5 mg/m^2 continuous infusion over 24 hours once every 3 weeks; continue until disease progression or unacceptable toxicity (Demetri 2016).

Ovarian cancer, relapsed, platinum sensitive (off-label use): IV: 1.1 mg/m^2 over 3 hours every 3 weeks (in combination with doxorubicin liposomal), continue as long as clinical benefit is demonstrated or until disease progression or confirmed complete response or for 2 or more cycles beyond complete response (Monk 2010; Monk 2012; Poveda 2011). Delay treatment and/or reduce the trabectedin dose (to 0.9 mg/m^2, then to 0.75 mg/m^2) for toxicities (doxorubicin liposomal may also require modification), consider discontinuing if a second dose reduction is not tolerated (Monk 2010).

Dosing: Geriatric

Refer to adult dosing.

Dosing: Renal Impairment

CrCl ≥30 mL/minute: No dosage adjustment is necessary.

CrCl <30 mL/minute or ESRD: There is no dosage adjustment provided in the manufacturer's labeling (has not been studied).

Hemodialysis: Hemodialysis is not expected to enhance elimination of trabectedin.

Dosing: Hepatic Impairment

Hepatic impairment prior to treatment:

Mild impairment (bilirubin 1 to 1.5 times ULN and any AST or ALT): No initial dosage adjustment necessary.

Moderate impairment (bilirubin 1.5 to 3 times ULN and AST or ALT <8 times ULN: Reduce dose from 1.5 mg/m^2 to 0.9 mg/m^2.

Severe impairment: (bilirubin >3 to 10 times ULN and any AST or ALT): Do not administer.

Hepatotoxicity during treatment:

Recommended dose reduction levels in patients with mild or moderate hepatic impairment at baseline (once a dose is reduced it should not be increased in subsequent cycles):

Mild impairment:

First dose reduction: 1.2 mg/m^2 once every 3 weeks.

Second dose reduction: 1 mg/m^2 once every 3 weeks.

Moderate impairment:

First dose reduction: 0.6 mg/m^2 once every 3 weeks.

Second dose reduction: 0.3 mg/m^2 once every 3 weeks.

Total bilirubin >ULN: Delay dose for up to 3 weeks and reduce the next dose by one dose level

AST or ALT >2.5 times ULN: Delay dose for up to 3 weeks

AST or ALT >5 times ULN during prior cycle: Delay dose for up to 3 weeks and reduce the next dose by one dose level

Alkaline phosphatase >2.5 times ULN: Delay dose for up to 3 weeks and reduce the next dose by one dose level

Severe liver dysfunction (bilirubin 2 times ULN and AST or ALT 3 times ULN with alkaline phosphatase <2 times ULN in prior treatment cycle in patients with normal hepatic function at baseline): Permanently discontinue.

Exacerbation of hepatic dysfunction in patients with preexisting moderate impairment: Permanently discontinue.

Adverse reactions with trabectedin administered at 0.3 mg/m^2 (in patients with preexisting moderate hepatic impairment) and requiring further dose reduction: Permanently discontinue.

Dosing: Obesity

ASCO Guidelines for appropriate chemotherapy dosing in obese adults with cancer: Utilize patient's actual body weight (full weight) for calculation of body surface area- or weight-based dosing, particularly when the intent of therapy is curative; manage regimen-related toxicities in the same manner as for nonobese patients; if a dose reduction is utilized due to toxicity, consider resumption of full weight-based dosing with subsequent cycles, especially if cause of toxicity (eg, hepatic or renal impairment) is resolved (Griggs 2012).

Dosing: Adjustment for Toxicity

Soft tissue sarcoma:

Recommended dose reduction levels (once a dose is reduced it should not be increased in subsequent cycles):

First dose reduction: 1.2 mg/m^2 once every 3 weeks

Second dose reduction: 1 mg/m^2 once every 3 weeks

Hematologic toxicity:

ANC <1,500/mm^3: Delay dose for up to 3 weeks

ANC <1,000/mm^3 with fever or infection or <500/mm^3 lasting >5 days during prior cycle: Delay dose for up to 3 weeks and reduce the next dose by one dose level

Platelets <100,000/mm^3: Delay dose for up to 3 weeks

Platelets <25,000/mm^3 during prior cycle: Delay dose for up to 3 weeks and reduce the next dose by one dose level

Nonhematologic toxicity:

Creatine phosphokinase >2.5 times ULN: Delay dose for up to 3 weeks

Creatine phosphokinase >5 times ULN during prior cycle: Delay dose for up to 3 weeks and reduce the next dose by one dose level

Decreased left ventricular ejection fraction (LVEF): Less than the lower limit of normal (LLN) or clinical evidence of cardiomyopathy: Delay dose for up to 3 weeks

Decreased LVEF: Absolute decrease of 10% or more from baseline and less than the LLN or clinical evidence of cardiomyopathy during prior cycle: Delay dose for up to 3 weeks and reduce the next dose by one dose level

Other nonhematologic toxicity: Grade 3 or 4: Delay dose for up to 3 weeks and reduce the next dose by one dose level

Adverse reactions with trabectedin administered at 1 mg/m^2 (in patients with normal hepatic function) or 0.3 mg/m^2 (in patients with preexisting moderate hepatic impairment; refer do dosing in hepatic impairment) and requiring further dose reduction: Permanently discontinue.

Persistent adverse events requiring a delay of more than 3 weeks: Permanently discontinue.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution Reconstituted, Intravenous:

Yondelis: 1 mg (1 ea)

Generic Equivalent Available (US) No

Administration

Trabectedin is associated with a moderate emetic potential; antiemetics are recommended to prevent nausea and vomiting (MASCC 2016).

Infuse through a central line with a 0.2 micron polyethersulfone filter. Infusion must be completed within 30 hours of reconstitution. Premedicate with a corticosteroid (eg, dexamethasone 20 mg IV) 30 minutes prior to treatment; additional antiemetics may be needed.

Soft tissue sarcoma: Single-agent therapy: Infuse as a continuous infusion over 24 hours

Ovarian cancer (off-label use): Combination therapy with doxorubicin liposomal: Administer doxorubicin liposomal first (flush line with D_5W) then follow with trabectedin infusion over 3 hours (Monk 2010).

Vesicant; ensure proper needle or catheter placement prior to and during infusion; avoid extravasation.

Extravasation management: If extravasation occurs, stop infusion immediately and disconnect (leave cannula/needle in place); gently aspirate extravasated solution (do **NOT** flush the line); remove needle/cannula; elevate extremity.

Hazardous Drugs Handling Considerations

Hazardous agent (meets NIOSH 2016 criteria). This medication is not on the NIOSH (2016) list; however, it meets the criteria for a hazardous drug. Drugs are classified as hazardous based on their properties; the properties of a hazardous drug include one or more of the following characteristics: carcinogenic, teratogenic (or other developmental toxicity), reproductive toxicity, organotoxic at low doses, genotoxic, and/or new agents with structural or toxicity profiles similar to existing hazardous agents.

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage.

NIOSH recommends double gloving, a protective gown, ventilated engineering controls (a class II biological safety cabinet or a compounding aseptic containment isolator), and closed system transfer devices (CSTDs) for preparation. Double gloving, a gown, and (if dosage form allows) CSTDs are required during administration (NIOSH 2016).

Use

Soft tissue sarcoma: Treatment of unresectable or metastatic soft tissue sarcoma (liposarcoma or leiomyosarcoma) in patients who have received a prior anthracycline-containing regimen.

Use: Off-Label

Ovarian cancer, relapsed (platinum sensitive)

Medication Safety Issues

High alert medication:

This medication is in a class the Institute for Safe Medication Practices (ISMP) includes among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Adverse Reactions

Note: Adverse reactions as reported for monotherapy and combination therapy with doxorubicin liposomal.

>10%:

Cardiovascular: Phlebitis (monotherapy: 15%)

Central nervous system: Fatigue (45% to 69%), headache (9% to 25%), paresthesia (monotherapy: ≥1% to 11%)

Dermatologic: Palmar-Plantar erythrodysesthesia (24%; grade 3: 4%), alopecia (in combination with liposomal doxorubicin: 12%; monotherapy: 3%), skin rash (11%)

Endocrine & metabolic: Hypophosphatemia (monotherapy: 34%; in combination with liposomal doxorubicin: 1%); hypokalemia (in combination with liposomal doxorubicin: 11%; monotherapy: 2% to 5%)

Gastrointestinal: Nausea (52% to 75%; grade 3: 3% to 10%), vomiting (23% to 56%; grade 3: 2% to 12%; grade 4: <1%), constipation (18% to 37%), decreased appetite (monotherapy: 2% to 37%), diarrhea (14% to 35%), anorexia (in combination with liposomal doxorubicin: 32%; monotherapy: 12% to 19%), abdominal pain (in combination with liposomal doxorubicin: 20%; monotherapy: 2% to 5%), stomatitis (20%), weight gain (monotherapy: 20%; in combination with liposomal doxorubicin: 1%), dyspepsia (5% to 13%), mucosal inflammation (12%)

Hematologic: Anemia (25% to 97% [includes patients anemic at baseline]; grade 3/4: ≤19%), neutropenia (28% to 77%; grade 3/4: 2% to 43%), thrombocytopenia (8% to 59%; grade 3/4: 1% to 23%), leukopenia (in combination with liposomal doxorubicin: 48%; grade 3: 25%; grade 4: 8%; monotherapy: 6% to 12%; grade 3: 2% to 8%; grade 4: 1% to 2%)

Hepatic: Increased serum ALT (90% to 96%; grade 3: 31% to 46%; grade 4: 5%), increased serum AST (84% to 89%, grade 3/4: 2% to 17%), increased alkaline phosphatase (25% to 70%; grade 3/4: ≤2%), hyperbilirubinemia (5% to 25%; grade 3/4: ≤2%)

Local: Catheter site reaction (in combination with liposomal doxorubicin: 14%)

Neuromuscular & skeletal: Increased CPK (10% to 33%; grade 3: 2% to 5%, grade 4: ≤2%),

weakness (6% to 17%), arthralgia (3% to 15%), myalgia (5% to 12%)

Renal: Increased serum creatinine (2% to 46%)

Respiratory: Dyspnea (5% to 25%), cough (in combination with liposomal doxorubicin: 12%)

Miscellaneous: Fever (in combination with liposomal doxorubicin: 20%; monotherapy: 5%)

1% to 10%:

Cardiovascular: Peripheral edema (4% to 28%), pulmonary embolism (5% to <10%), chest pain (monotherapy: 1% to 5%), palpitation (in combination with liposomal doxorubicin: 4%), edema (≥1 to 3%), syncope (in combination with liposomal doxorubicin: 2%), left ventricular dysfunction (in combination with liposomal doxorubicin: 1%; grade 3: <1%)

Central nervous system: Insomnia (2% to 15%), hypoesthesia (monotherapy; <10%), peripheral neuropathy (monotherapy: <10%), peripheral sensory neuropathy (≥1 to 5%), dizziness (monotherapy: 5%)

Dermatologic: Hyperpigmentation (in combination with liposomal doxorubicin: 6%)

Endocrine & metabolic: Dehydration (5%)

Gastrointestinal: Decreased appetite (monotherapy: 2% to 37%), dysgeusia (4% to 8%)

Hematologic: Bleeding complications (in combination with liposomal doxorubicin: 9%), febrile neutropenia (2% to ≤8%, grade 3: 6%, grade 4: 2%), bone marrow failure (in combination with liposomal doxorubicin: 2%; grade 3: <1%; grade 4: 1%), granulocytopenia (in combination with liposomal doxorubicin: 2%; grade 3: 1%; grade 4: <1%), pancytopenia (in combination with liposomal doxorubicin: 2%; grade 3: 2%; grade 4: 1%), neutropenic infection (in combination with liposomal doxorubicin: 1%; grade 3: 1%)

Hepatic: Increased serum transaminases (monotherapy: 2% to 5%; grade 3: 1% to 2%), hepatotoxicity (≤1%)

Hypersensitivity: Hypersensitivity (2%)

Infection: Neutropenic sepsis (1% to 3%; grade 3: <1%; grade 4: <1%)

Local: Catheter pain (in combination with liposomal doxorubicin; 3%), catheter-site erythema (in combination with liposomal doxorubicin; 2%), catheter-site reaction inflammation (in combination with liposomal doxorubicin: 2%)

Neuromuscular & skeletal: Musculoskeletal pain (in combination with liposomal doxorubicin; 4%)

Renal: Renal failure (2% to 3%)

Respiratory: Pulmonary embolism (5% to <10%), pulmonary edema (in combination with liposomal doxorubicin; 1%)

<1%, postmarketing, and/or case reports: Cardiomyopathy, extravasation (with tissue necrosis, requiring debridement), hepatic failure, hepatomegaly, increased heart rate (transient), increased liver enzymes, jaundice, liver pain, multi-organ failure, rhabdomyolysis, septic shock

Contraindications

Known, severe hypersensitivity (including anaphylaxis) to trabectedin or any component of the formulation

Canadian labeling: Additional contraindications (not in the US labeling): Active serious or uncontrolled infection; breast-feeding

Warnings/Precautions

Concerns related to adverse effects:

• Bone marrow suppression: Anemia, neutropenia, and thrombocytopenia commonly occur; neutropenic fever and neutropenic sepsis (with fatalities) have been reported. The median onset for first occurrence of grade 3/4 neutropenia was 16 days (range: 8 days to ~10 months) and median time to recovery was 13 days (range: 3 days to ~2 months). Monitor blood counts prior to each dose and periodically throughout treatment cycle. Withhold treatment for neutrophil count <1,500/mm^3. Reduce dose (permanently) for life-threatening or prolonged severe neutropenia in the preceding cycle.

• Cardiovascular events: Cardiomyopathy, including heart failure, decreased ejection fraction, diastolic dysfunction, or right ventricular dysfunction, has been observed; some events were grades 3 and 4. The median time to development of grades 3 and 4 cardiomyopathy was ~5 months (range: 1 to 15 months). Monitor left ventricular ejection fraction (LVEF) by echocardiogram or MUGA scan prior to treatment initiation and every 2 to 3 months until trabectedin is discontinued. Withhold treatment if LVEF is below the lower limit of normal (LLN); permanently discontinue for symptomatic cardiomyopathy or persistent ventricular dysfunction that does not recover to LLN within 3 weeks. Patients with a history of New York Heart Association class II, III, or IV heart failure or abnormal LVEF were excluded from the sarcoma study.

• Extravasation: Vesicant; ensure proper needle or catheter placement prior to and during infusion. Infuse through a central line. Avoid extravasation. Extravasation of trabectedin with subsequent tissue necrosis requiring debridement has been reported; evidence of necrosis may be delayed up to 1 week after extravasation.

• Gastrointestinal events: Trabectedin is associated with a moderate emetic potential; antiemetics are recommended to prevent nausea and vomiting (MASCC 2016). Nausea and vomiting are common; corticosteroid premedication (eg, dexamethasone) is recommended; other antiemetics may also be needed. Constipation and diarrhea (generally mild) also commonly occur.

• Hepatotoxicity: Hepatotoxicity (including hepatic failure) may occur with trabectedin. Grade 3 and 4 liver function test (LFT) elevations (AST, ALT, total bilirubin, or alkaline phosphatase) occurred in over one-third of patients. The median onset for grade 3/4 ALT or AST elevations was 29 days (range: 3 days to 11.5 months) and the median time to resolution was 13 days (range: 4 days to ~4 months); some patients experienced complete resolution. Drug-induced liver injury (ALT or AST elevation >3 times upper limit of normal [ULN], alkaline phosphatase <2 times ULN, and total bilirubin ≥2 times ULN) and ALT or AST elevations >8 times ULN have been reported. Monitor LFTs prior to each dose (more frequently if clinically indicated); elevated LFTs may require treatment interruption, dose reduction, and/or discontinuation (based on severity and duration). Premedication with dexamethasone (4 mg twice daily the day prior to administration) has been reported to reduce

the incidence of hepatotoxicity (Grosso 2006). Patients with bilirubin above the ULN or AST or ALT >2.5 times the ULN were excluded from the sarcoma clinical trial.

• Hypersensitivity: Symptoms of hypersensitivity reactions have been reported.

• Rhabdomyolysis: Trabectedin may cause rhabdomyolysis and musculoskeletal toxicity (some fatal). Creatine phosphokinase (CPK) elevations occurred in nearly one-third of patients receiving trabectedin; grade 3 and 4 CPK elevations, some complicated by renal failure, occurred. The median time to first occurrence of grade 3 or 4 CPK elevation was 2 months (range: 1 to 11.5 months) and the median time to complete resolution was 14 days (range: 5 to 30 days). Monitor CPK levels prior to each dose; withhold treatment for CPK levels >2.5 times ULN; discontinue permanently if rhabdomyolysis occurs.

• Thromboembolic events: Pulmonary embolism has been reported.

Concurrent drug therapy issues:

• Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

Metabolism/Transport Effects

Substrate of CYP3A4 (major), P-glycoprotein; **Note:** Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

Alcohol (Ethyl): May enhance the hepatotoxic effect of Trabectedin. *Risk X: Avoid combination*

BCG (Intravesical): Immunosuppressants may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

BCG (Intravesical): Myelosuppressive Agents may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

Bosentan: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

CloZAPine: Myelosuppressive Agents may enhance the adverse/toxic effect of CloZAPine. Specifically, the risk for neutropenia may be increased. *Risk C: Monitor therapy*

Coccidioides immitis Skin Test: Immunosuppressants may diminish the diagnostic effect of Coccidioides immitis Skin Test. *Risk C: Monitor therapy*

Conivaptan: May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

CYP3A4 Inducers (Moderate): May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May decrease the serum concentration of Trabectedin. *Risk X: Avoid combination*

CYP3A4 Inhibitors (Moderate): May increase the serum concentration of Trabectedin. *Risk X: Avoid*

combination

CYP3A4 Inhibitors (Strong): May increase the serum concentration of Trabectedin. *Risk X: Avoid combination*

Dabrafenib: May decrease the serum concentration of CYP3A4 Substrates. Management: Seek alternatives to the CYP3A4 substrate when possible. If concomitant therapy cannot be avoided, monitor clinical effects of the substrate closely (particularly therapeutic effects). *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferiprone: Myelosuppressive Agents may enhance the neutropenic effect of Deferiprone. *Risk X: Avoid combination*

Denosumab: May enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased. *Risk C: Monitor therapy*

Dipyrone: May enhance the adverse/toxic effect of Myelosuppressive Agents. Specifically, the risk for agranulocytosis and pancytopenia may be increased *Risk X: Avoid combination*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Fingolimod: Immunosuppressants may enhance the immunosuppressive effect of Fingolimod. Management: Avoid the concomitant use of fingolimod and other immunosuppressants when possible. If combined, monitor patients closely for additive immunosuppressant effects (eg, infections). *Risk D: Consider therapy modification*

Fosaprepitant: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Fusidic Acid (Systemic): May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

HMG-CoA Reductase Inhibitors: May enhance the myopathic (rhabdomyolysis) effect of Trabectedin. *Risk C: Monitor therapy*

Idelalisib: May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

Leflunomide: Immunosuppressants may enhance the adverse/toxic effect of Leflunomide. Specifically, the risk for hematologic toxicity such as pancytopenia, agranulocytosis, and/or thrombocytopenia may be increased. Management: Consider not using a leflunomide loading dose in patients receiving other immunosuppressants. Patients receiving both leflunomide and another immunosuppressant should be monitored for bone marrow suppression at least monthly. *Risk D: Consider therapy modification*

Lenograstim: Antineoplastic Agents may diminish the therapeutic effect of Lenograstim. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Nivolumab: Immunosuppressants may diminish the therapeutic effect of Nivolumab. *Risk D: Consider*

therapy modification

Ocrelizumab: May enhance the immunosuppressive effect of Immunosuppressants. *Risk C: Monitor therapy*

Palbociclib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Palifermin: May enhance the adverse/toxic effect of Antineoplastic Agents. Specifically, the duration and severity of oral mucositis may be increased. Management: Do not administer palifermin within 24 hours before, during infusion of, or within 24 hours after administration of myelotoxic chemotherapy. *Risk D: Consider therapy modification*

P-glycoprotein/ABCB1 Inhibitors: May increase the serum concentration of P-glycoprotein/ABCB1 Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Pimecrolimus: May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Promazine: May enhance the myelosuppressive effect of Myelosuppressive Agents. *Risk C: Monitor therapy*

Ranolazine: May increase the serum concentration of P-glycoprotein/ABCB1 Substrates. *Risk C: Monitor therapy*

Roflumilast: May enhance the immunosuppressive effect of Immunosuppressants. *Risk D: Consider therapy modification*

Sarilumab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Siltuximab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Simeprevir: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Sipuleucel-T: Immunosuppressants may diminish the therapeutic effect of Sipuleucel-T. *Risk C: Monitor therapy*

St John's Wort: May decrease the serum concentration of Trabectedin. *Risk X: Avoid combination*

Stiripentol: May increase the serum concentration of CYP3A4 Substrates. Management: Use of stiripentol with CYP3A4 substrates that are considered to have a narrow therapeutic index should be avoided due to the increased risk for adverse effects and toxicity. Any CYP3A4 substrate used with stiripentol requires closer monitoring. *Risk D: Consider therapy modification*

Tacrolimus (Topical): May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Tertomotide: Immunosuppressants may diminish the therapeutic effect of Tertomotide. *Risk C: Monitor therapy*

Tocilizumab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Tofacitinib: Immunosuppressants may enhance the immunosuppressive effect of Tofacitinib. Management: Concurrent use with antirheumatic doses of methotrexate or nonbiologic disease modifying antirheumatic drugs (DMARDs) is permitted, and this warning seems particularly focused on

more potent immunosuppressants. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Management: Vaccine efficacy may be reduced. Complete all age-appropriate vaccinations at least 2 weeks prior to starting an immunosuppressant. If vaccinated during immunosuppressant therapy, revaccinate at least 3 months after immunosuppressant discontinuation. *Risk D: Consider therapy modification*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants. *Risk X: Avoid combination*

Food Interactions Coadministration with grapefruit or grapefruit juice may increase trabectedin plasma concentrations. Management: Avoid concomitant administration with grapefruit or grapefruit juice.

Pregnancy Implications Animal reproduction studies have not been conducted. Based on the mechanism of action, trabectedin may cause fetal harm if administered during pregnancy. Women of reproductive potential should use effective contraception during and for at least 2 months after treatment. Males with partners of reproductive potential should use effective contraception during and for at least 5 months following treatment. Trabectedin may cause decreased fertility in males and females.

Breast-Feeding Considerations It is not known if trabectedin is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, the manufacturer recommends discontinuing breastfeeding during trabectedin treatment.

Dietary Considerations Avoid grapefruit and grapefruit juice.

Monitoring Parameters CBC with differential (baseline, prior to each dose, and periodically throughout treatment cycles); total bilirubin (prior to each cycle; more frequently if clinically indicated), ALT, AST, and alkaline phosphatase (prior to each cycle; more frequently if clinically indicated); renal function (baseline and during treatment); CPK (prior to each treatment cycle), evaluate LVEF via MUGA or echocardiogram (baseline and every 2 to 3 months); monitor infusion site for signs/symptoms of extravasation

Mechanism of Action Trabectedin is a marine-derived compound (alkylating agent) which blocks the cell cycle at the G_2/M phase by covalently binding to the minor DNA groove, bending the helix toward the major groove and altering DNA transcription (Garcia-Carbonero 2005). Affects activity of DNA binding proteins, transcription factors and DNA repair mechanism, leading to cell death.

Pharmacodynamics/Kinetics

Distribution: V_d: >5,000 L

Protein binding: ~97%; to plasma proteins

Metabolism: Extensively hepatic; via CYP3A4

Half-life elimination: ~175 hours

Excretion: Feces (58%; only negligible amounts as unchanged drug); urine (6%; only negligible amounts as unchanged drug)

Pricing: US

Solution (reconstituted) (Yondelis Intravenous)

1 mg (1): $3304.80

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

International Brand Names

Yondelis (AE, AR, AT, BE, CH, CL, CO, CR, CY, CZ, DE, DK, DO, EC, EE, ES, FR, GB, GR, GT, HK, HN, HR, IE, IL, IN, IS, IT, JO, JP, KR, LB, LT, LU, LV, MT, MY, NI, NL, NO, PA, PL, PT, QA, RO, RU, SA, SE, SG, SI, SK, SV, TH, TR, UA)

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