Drug Monograph

A - Drug Name

vinBLAStine

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B - Mechanism of Action and Pharmacokinetics

Similar to other vinca alkaloids, vinblastine binds to the microtubular proteins of the mitotic spindle, leading to depolymerization of the microtubule and mitotic arrest at metaphase or cell death. It also has complex effects on nucleic acid and protein synthesis in high concentrations. Vinblastine has some immunosuppressant effects. The vinca alkaloids are considered to be cell cycle phase-specific (M and S phases).

Distribution	Rapid and extensive binding to tissues and to formed elements of peripheral blood. Distributes to the liver.	
	PPB	99%
	Cross blood brain barrier?	poorly
Metabolism	Extensively metabolized in the liver	
	Active metabolites	Yes
	Inactive metabolites	Yes
Elimination	Slowly excreted in urine and feces (via bile).	
	Urine	< 1% unchanged
	Feces	95%

Half-life	25 hours (terminal)

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C - Indications and Status

Health Canada Approvals:

- Frequently responsive:
  - Hodgkin disease
  - Lymphocytic lymphoma
  - Histolytic lymphoma
  - Mycosis fungoides
  - Testicular cancer
  - Kaposi's sarcoma
  - Letterer-Siwe disease (histiocytosis-X)
- Less frequently responsive:
  - Choriocarcinoma resistant to other chemotherapy
  - Breast cancer (unresponsive to endocrine surgery and hormonal therapy)

Other Uses:

- Bladder cancer
- Non-small cell lung cancer
- Desmoid tumour
- CNS cancer

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D - Adverse Effects

Emetogenic Potential: Minimal

Extravasation Potential: Vesicant

The incidences for the adverse effects are based on product monographs where available. Adverse events from other trial data or severe / post-marketing events may also be included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Auditory	Hearing impaired (rare)	E

Cardiovascular	Arterial thromboembolism (in combination with cisplatin and bleomycin)	E
	ECG changes (transient; rare)	E
	Hypertension (≤10%)	I E
Dermatological	Alopecia (>10%) (usually incomplete; re-growth in some cases while on treatment)	E
	Photosensitivity (≤10%)	E
	Rash (≤10%)	E
Gastrointestinal	Abdominal pain (>10%)	E
	Anorexia (>10%)	E
	Constipation (>10%) (may be severe)	E
	Diarrhea (≤10%)	E
	Mucositis (>10%)	E
	Nausea, vomiting (>10%)	I
General	Fatigue (≤10%)	E
	Pain (in tumour-containing tissue, rare)	I
Hematological	Immunosuppression	E
	Myelosuppression ± infection, bleeding (>10%)	E
Hypersensitivity	Hypersensitivity (rare)	I
Injection site	Phlebitis (≤10%)	I E
Metabolic / Endocrine	Hyperuricemia (≤10%) (during periods of active cell lysis)	I
	SIADH (rare)	E
Musculoskeletal	Musculoskeletal pain (≤10%) (including jaw pain, may be severe)	E
Nervous System	Depression (≤10%)	E
	Dysgeusia (>10%)	E
	Headache (≤10%)	E
	Paresthesia (20%) (autonomic, loss of deep tendon reflex, cranial neuropathy - rare)	E
	Seizure (≤10%)	E
Respiratory	Bronchospasm / pneumonitis (or shortness of breath, especially in combination with mitomycin; ≤10%)	I
Vascular	Peripheral ischemia (≤10%) (Raynauds; in combination with cisplatin and bleomycin)	D

* "*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.

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

Myelosuppression and **neurotoxicity** are the main dose-limiting effects of vinblastine.

Hyperuricemia during periods of active cell lysis, which is caused by cytotoxic chemotherapy of highly proliferative tumours of massive burden (e.g. some leukemias and lymphomas), can be minimized with allopurinol and hydration. In hospitalized patients the urine may be alkalinized, by addition of sodium bicarbonate to the IV fluids, if tumour lysis is expected.

Neurotoxicity with the vinca alkaloids is qualitatively similar but quantitatively different (vincristine> vinblastine>vinorelbine). Symptoms tend to be worse with prolonged exposure. Neurotoxicity may manifest as numbness, paresthesia, mental depression, loss of deep tendon reflex, headache, malaise, dizziness, seizures or psychosis. **Cranial nerve neuropathy** may lead to vocal cord paresis or paralysis, oculomotor nerve dysfunction, hearing impairment and facial nerve palsies. Vocal cord effects or facial nerve palsies tend to be bilateral and reversible when treatment with vinblastine is discontinued. High doses (> 20 mg) may be associated with **autonomic neuropathy**, which manifests as constipation, abdominal pain, urinary retention and paralytic ileus.

Severe jaw **pain** or parotid gland pain can occur within a few hours of the first dose of vinblastine. This is not an indication to stop or modify the dose; treat with analgesics.

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E - Dosing

Refer to protocol by which patient is being treated.

Dosage may be reduced and/or delayed in patients with bone marrow depression due to cytotoxic/radiation therapy. Do not re-treat with vinblastine until marrow recovery has occurred.

Adults:

Intravenous: 6 mg/m² Every 1 week
(range 3.7-18.5 mg/m^2; usual weekly dose: 5.5 – 7.4 mg/m^2; maximum weekly dose: 18.5 mg/m^2)
Intravenous: 6 mg/m² on days 1 and 15; every 4 weeks (ABVD)

Intravenous: 0.11 mg/kg days 1 and 2; every 3 weeks (VEIP)

Intravenous: 3 mg/m² day 2 Every 14 days (MVAC(HD))

Dosage with Toxicity:

Modify according to protocol by which patient is being treated.

Suggested:

Worst Toxicity / Counts in Previous Cycle (x 10^9/L)	Dose (% previous dose)*
Febrile neutropenia, grade 4 ANC for ≥ 5-7 days or thrombocytopenic bleeding	75%*
Grade 3 related organ / non-hematologic	Hold, then 75%*
Grade 4 related organ / non-hematologic	Discontinue

*Do not retreat until ANC ≥ 1-1.5 x 10^9L, platelets ≥ 100 x 10^9L and toxicity ≤ grade 2

Dosage with Hepatic Impairment:

Bilirubin	% Usual dose
>1 - 2.5 x ULN	50%
> 2.5 x ULN	25%

Dosage with Renal Impairment:

No adjustment required.

Dosage in the elderly:

Toxicity may be increased; used with caution.

Children:

Refer to protocol being used.

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F - Administration Guidelines

FOR INTRAVENOUS USE ONLY.
Intrathecal administration of other vinca alkaloids has resulted in death. Containers with this product should be labelled:
"**WARNING – FOR INTRAVENOUS USE ONLY. FATAL if given intrathecally.**"

- Direct IV push is not recommended to reduce the risk of inadvertently administering vinca alkaloids via intrathecal route.
- Mix in 50 mL minibag (NS or D5W).
- Dilutions in large volumes (≥ 100mL) and infusions over ≥30-60 minutes are not recommended, since these can increase the risk of vein irritation and extravasation.
- If any signs or symptoms of extravasation occur, the injection or infusion should be immediately terminated and restarted in another vein. Any known or suspected extravasation should be managed promptly according to local guidelines.
- Store unopened vials at 2 to 8ºC; protect from light.

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G - Special Precautions

Contraindications:

- Patients who have hypersensitivity to vinblastine or its formulation
- Patients with severe myelosuppression or infection
- Intrathecal vinblastine administration is **absolutely contraindicated**.

Other Warnings/Precautions:

- Myelosuppressive effects are more marked in patients with bone marrow infiltration, cachexia or skin ulcers
- Use with caution in hepatic impairment due to an increased risk of neurotoxicity.

- Use with caution in patients with ischemic heart disease and in combination with neurotoxic drugs.
- Do not give vinblastine more frequently than once every 7 days.
- Standard doses of vinblastine given for prolonged periods (e.g. daily for 7 days) may result in permanent or fatal neurologic toxicity and should not be used.

Other Drug Properties:

- Carcinogenicity: Yes

Pregnancy and Lactation:

- Mutagenicity: Yes
- Embryotoxicity: Yes
- Teratogenicity: Yes
  Vinblastine is **contraindicated** in pregnancy. Adequate contraception should be used by both sexes during vinblastine treatment and for at least **6 months** after the last dose (general recommendation).
- Breastfeeding:
  Breast feeding is not recommended due to the potential secretion of vinblastine into breast milk.
- Fertility effects: Yes
  Aspermia and amenorrhea have been reported. Recovery of menses is variable.

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H - Interactions

Vinblastine is metabolized by CYP3A4 and is a potent CYP3A4 inhibitor.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Mitomycin	Acute bronchospasm has occurred minutes to hours after administration. Reaction may occur up to 2 weeks after mitomycin.	Unknown	Caution; discontinue vinblastine if this occurs
Phenytoin	↓ serum concentration of phenytoin	Possibly ↓ absorption or increased metabolism of phenytoin	Monitor serum levels of phenytoin and adjust dose as needed
CYP3A4 inhibitors (i.e. ketoconazole, voriconazole, clarithromycin, erythromycin,	↑ risk of neurotoxicity	inhibition of vinblastine metabolism	Avoid concomitant use

ritonavir, fruit or juice from grapefruit, Seville oranges, starfruit or pomegranate)			
CYP3A4 substrates (i.e., aprepitant, tolterodine)	↑ toxicity of CYP3A4 substrates	↓ metabolism of CYP3A4 substrates	Avoid if possible. If must use, monitor or adjust dose.
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ vinblastine effect	↑ metabolism of vinblastine	Caution
Bleomycin +/- cisplatin	Raynaud's phenomenon, nephrotoxicity, neurotoxicity, MI, CVA reported	Unknown	Caution
Ototoxic drugs (i.e., cisplatin, aminoglycosides)	↑ ototoxicity (reported with other vinca alkaloids)	Additive	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
CBC	Baseline and before each dose
Liver function tests	Baseline and before each cycle
Clinical assessment for neurotoxicity, infection, bleeding, GI, local toxicity (i.e. extravasation), hypersensitivity, hyperuricemia	At each visit

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

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K - References

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April 2020 Updated adverse effects, dosing, warnings/precautions, administration, interactions and monitoring sections

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L - Disclaimer

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