Drug Monograph

Drug Name | Mechanism of Action and Pharmacokinetics | Indications and Status | Adverse Effects | Dosing | Administration Guidelines | Special Precautions | Interactions | Recommended Clinical Monitoring | Supplementary Public Funding | References | Disclaimer

A - Drug Name

vinorelbine

COMMON TRADE NAME(S): Navelbine®

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B - Mechanism of Action and Pharmacokinetics

Vinorelbine, a semi-synthetic vinca alkaloid, exerts its anti-tumour activity by binding to tubulin and inhibiting microtubule assembly, thereby preventing cell mitosis and causing cell death. It is cell cycle phase-specific.

Distribution	Initial rapid decline in plasma concentration after IV administration due to distribution to peripheral compartments and metabolism. Widely distributed, with highest amounts found in elimination organs such as liver and kidneys, minimal in heart and brain.	
	Cross blood brain barrier?	minimal
	PPB	80-90%
Metabolism	Largely metabolized via hepatobiliary system (P450, CYP3A4)	
	Active metabolites	yes, deacetylvinorelbine
	Inactive metabolites	yes
Elimination	Mainly eliminated by the liver, with approximately 46% of dose being recovered in the feces.	

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	Urine	18 %
	Half-life	27.7 - 43.6 hours (terminal)

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C - Indications and Status

Health Canada Approvals:

- Advanced non-small cell lung cancer (single agent or in combination)
- Metastatic breast cancer after failure of standard first-line chemotherapy or after relapse within 6 months of anthracycline-based adjuvant therapy

Other Uses:

Refer to ST-QBP regimens for details:

- Ovarian cancer
- Vulva cancer
- Head and neck cancer
- Desmoid tumour
- Hodgkin lymphoma

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D - Adverse Effects

Emetogenic Potential: Minimal

Extravasation Potential: Vesicant

The following adverse events were observed in single-agent treatment (30mg/m^2) in advanced breast cancer patients. Some severe, life-threatening or post-marketing events in other studies are also listed.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Auditory	Hearing impaired (rare; when used with cisplatin)	E
Cardiovascular	Venous thromboembolism (rare)	E
Dermatological	Alopecia (12%) (usually mild)	E

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	Radiation recall reaction (rare)	E
	Rash (<5%)	E
Gastrointestinal	Anorexia (19%)	E
	Constipation (38%) (may be severe)	E
	Diarrhea (20%)	E
	Mucositis (16%)	E
	Nausea, vomiting (50%)	I
General	Fatigue (41%)	E
	Pain (16%) (including chest, abdomen and tumour)	I E
Hematological	Myelosuppression ± infection, bleeding (41% grade 4 neutropenia)	E
Hepatobiliary	↑ LFTs (7% grade 3 or 4)	E
Hypersensitivity	Hypersensitivity (rare)	I
Injection site	Injection site reaction (21%)	I
Metabolic / Endocrine	↑ antidiuretic hormone (<1%)	E
Musculoskeletal	Muscle weakness (9%)	E
Nervous System	Headache (<5%)	E
	Neuropathy (20%) (sensory; motor and autonomic less common)	E
Respiratory	Bronchospasm (3%) (especially with mitomycin)	I
	Dyspnea (9%)	E
	Pneumonitis (rare)	E
Urinary	Hemorrhagic Cystitis (<1%)	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.

** 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 for vinorelbine include nausea, vomiting, fatigue, constipation, injection site reaction, diarrhea, neuropathy, anorexia, mucositis, pain and alopecia.

Granulocytopenia is the major dose-limiting toxicity and results in febrile neutropenia or infections in 8-9% of patients, and is fatal in 1% of patients. It is generally reversible and is not cumulative.

Chest Pain, sometimes accompanied by changes in electrocardiograms, occurs mostly in those with a previous history of cardiovascular disease or the presence of a bulky tumour within the chest.

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Neurotoxicity is generally mild to moderate and reversible on drug discontinuation. Patients with a prior history or pre-existing neuropathy may be at risk. Severe neurotoxicity is seen in less than 1% of patients. Cisplatin does not appear to increase neurotoxicity observed with single agent vinorelbine. Cases of ileus have been reported.

Fatigue, usually mild or moderate, tends to increase with cumulative dosing.

Elevated liver enzymes were usually transient and asymptomatic.

Injection site reactions, such as pain, erythema, or vein discolouration are common, but severe in only 2% of patients. Long infusion times (i.e. more than 20 minutes) may increase the risk of phlebitis and injection site reactions. One study has shown that the incidence of phlebitis can be reduced by infusing dexamethasone IV immediately following the administration of vinorelbine.

Back pain has been reported if infusion duration of vinorelbine is too short (i.e. less than 6 minutes).

Acute shortness of breath and severe bronchospasm have been reported, more commonly when vinorelbine or other vinca alkaloids are combined with mitomycin, and may be acute or subacute. Aggressive treatment of symptoms with bronchodilators, steroids and /or oxygen may be required, especially in patients with pre-existing pulmonary dysfunction.

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E - Dosing

Refer to protocol by which patient is being treated.

Adults:

Intravenous:

- Continuous: 30 mg/m^2 given weekly
- Q 3 weekly: 30 mg/m^2 given on days 1 and 8
- Q 4 weekly: 30 mg/m^2 given on days 1, 8 and 15

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Dosage with Toxicity:

Worst toxicity in previous cycle	Dose (% previous dose)
Febrile neutropenia Thrombocytopenic bleeding ANC < 0.5 and/or grade 4 thrombocytopenia for ≥ 5 to 7 days	75 %*
Grade 2 peripheral neuropathy	Discontinue
Grade 3 peripheral neuropathy	Discontinue
Grade 3 related organ/ non-hematological toxicity	75 %*
Grade 4 related organ/ non-hematological toxicity, OR delay > 3 weeks	Discontinue
*Do not start new cycle until platelets ≥ 100 x 10^9/L, neutrophils ≥ 1.5 x 10^9/L, hemoglobin > 80 g/L and major toxicity has recovered to ≤ grade 2 (may consider administering if neutrophils 1-1.5 x 10^9/L at 50% of planned dose).	

Dose on Day 8, 15 of cycle

Toxicity on Day 8, 15 of cycle					
Non–hematologic (related organ)		Hematologic			Day 8 (or 15) (% day 1 dose)
		ANC (x 10^9/L)		Platelets (x 10^9/L)	
≤ grade 2	and	≥ 1.5	and	≥ 100	100%
≤ grade 2	and	1-1.49	and/or	≥ 100	50%
Grade 3 or 4 related organ	or	< 1	or	<100	Omit

Dosage with Hepatic Impairment:

As vinorelbine undergoes hepatobiliary metabolism and excretion, administer with caution in hepatic insufficiency. Consider adjusting doses with hyperbilirubinemia.

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Suggested adjustments for increases in total bilirubin:

Total Bilirubin (micromol/L)	% Usual dose
< 1.5 x ULN	100%
1.5 to 2 x ULN	50%
> 2 x ULN	25%

Dosage with Renal Impairment:

No adjustment required

Dosage in the elderly:

No dosage adjustments are required for increased age

Children:

Safety and efficacy not established

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F - Administration Guidelines

FOR INTRAVENOUS USE ONLY.

Intrathecal administration of other vinca alkaloids has resulted in death. Syringes containing this product should be labeled "WARNING – FOR INTRAVENOUS USE ONLY. FATAL if given intrathecally."

- Mix in 50mL minibag (D5W, NS) to a final concentration 0.5 - 2mg/mL; infuse over 6-10 minutes through free-flowing IV.

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- Or may push (at final concentration of 1.5 – 3mg/mL) through sidearm of free-flowing IV (D5W, NS); inject over 6-10 minutes.
- After administration is completed, the manufacturer recommends flushing IV line with at least 75 to 125mL of D5W or NS.
- Flushing the line before and after administration of vinorelbine may reduce injection site reactions and phlebitis risk.
- Discontinue the injection if extravasation occurs and the remaining dose should be given into another vein. Warm compresses applied for 15 to 20 minutes 4 times per day for 1-2 days and elevation of affected area for 2-3 days may help disperse the drug and minimize discomfort.
- Refrigerate unopened vials (2-8°C); protect from light and do not freeze.

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G - Special Precautions

Contraindications:

- Patients with known hypersensitivity to vinorelbine
- Patients who have drug-induced severe myelosuppression
- Intrathecal administration is **absolutely contraindicated**

Other Warnings/Precautions:

- Use with extreme caution in patients with compromised marrow reserve
- May result in radiosensitizing effects with prior or concomitant radiation therapy
- Patients with pre-existing neuropathy or prior treatment with other neurotoxic drugs may have increased potential for neurotoxicity

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Mutagenicity: Yes
- Embryotoxicity: Yes
- Fetotoxicity: Yes
  Vinorelbine is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 6 months after the last dose.
- Excretion into breast milk: Probable
  Breastfeeding is not recommended.
- Fertility effects: Probable

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H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Mitomycin	Acute bronchospasm has occurred minutes to hours after administration. Reaction may occur up to 2 weeks after mitomycin.	Unknown	Avoid combination.
Paclitaxel /other neurotoxic / ototoxic compounds	Neuropathy	Additive spindle toxicity (speculated)	Monitor closely, consider dose adjustment
Cisplatin	↑ ototoxicity / vestibular effects and myelosuppression	Additive effects	Monitor closely
CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ neurotoxicity and other toxicity	inhibits vinorelbine metabolism	use with caution; consider vinorelbine dose adjustment when used with azole antifungals

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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 at each dose
Liver function tests	Baseline and before each cycle
Clinical toxicity assessment for signs of neurotoxicity, local toxicity, bleeding, infection, hypersensitivity, thromboembolism, lung or GI toxicity, radiation recall	At each visit

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

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Local site toxicity ratings, if incidence of phlebitis	At each visit

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K - References

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