DRUG NAME: Vinorelbine

SYNONYM(S): Vinorelbine tartrate, VRL, VNL, NVB

COMMON TRADE NAME(S): NAVELBINE®

CLASSIFICATION: Mitotic inhibitor

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

MECHANISM OF ACTION:

Vinorelbine is a semisynthetic vinca alkaloid derived from vinblastine. Vinca alkaloids such as vincristine and vinblastine are originally derived from periwinkle leaves (*vinca rosea*). [1] Vinorelbine inhibits cell growth by binding to the tubulin of the mitotic microtubules. [2] Like other mitotic inhibitors, vinorelbine also promotes apoptosis in cancer cells. [1] *In vitro* vinorelbine shows both multidrug and non-multidrug resistance. [2] Microtubules are present in mitotic spindles, neuronal axons, and other cells. Inhibition of mitotic microtubules appears to correlate with antitumour activity, while inhibition of axonal microtubules seems to correlate with neurotoxicity. Compared to vincristine and vinblastine, vinorelbine is more selective against mitotic than axonal microtubules in vitro, which may account for its decreased neurotoxicity. [3] Vinorelbine is a radiation-sensitizing agent. [4] It is cell cycle phase-specific (M phase). [2]

PHARMACOKINETICS:

Interpatient variability	moderate to large interpatient variability [5,6]	
Distribution	Widely distributed in the body, mostly in spleen, liver, kidneys, lungs, thymus; moderately in heart, muscles; minimally in fat, brain, bone marrow. [3] High levels found in both normal and malignant lung tissue, with slow diffusion out of tumour tissue. [1]	
	cross blood brain barrier?	brain and plasma levels comparable in animal studies [1]
	volume of distribution	25.4-40.1 L/kg
	plasma protein binding	80-91%
Metabolism	by hepatic cytochrome P450 enzymes [1]	
	active metabolite(s)	deacetylvinorelbine
	inactive metabolite(s)	vinorelbine N-oxide [3]
Excretion	vinorelbine and its metabolites are excreted in the bile	
	urine	18%, 11% as unchanged drug
	feces	46%
	terminal half life	adults: 28-44 h [2] children: 14.7 h [7]
	clearance	0.97-1.26 L/h/kg
Gender	no information found	
Elderly	no clinically significant difference [3]	
Children	shorter half life, other parameters similar to adult values [7]	
Ethnicity	no information found	

Adapted from reference [2] unless specified otherwise.

USES:

Primary uses:

* Breast cancer [8]
* Lung cancer, non-small cell [11]

Other uses:

Cervical cancer [9,10]

Lung cancer, small cell [1,12]

Ovarian cancer [1]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:

- ***Inadvertent Intrathecal (IT) Administration*** of other vinca alkaloids has resulted in death. [13,14] It is a medical emergency if vinorelbine is inadvertently given intrathecally. Vinorelbine dispensed in a syringe should be labelled with an auxiliary label and a medication label, both stating **"WARNING: FOR INTRAVENOUS USE ONLY – FATAL IF GIVEN BY OTHER ROUTES"**. [15]
- Vinorelbine has less ***neurotoxicity*** than other vinca alkaloids[3]; however, patients with a history or pre-existing neuropathy should be monitored for new or worsening signs and symptoms while receiving vinorelbine. [2,16]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test, but mutagenic in mammalian mutation tests. [2]

Fertility: No deleterious effects on maternal parameters were observed in animal fertility/reproduction studies. [17]

Pregnancy: In animal studies, vinorelbine was found to be embryotoxic and/or fetotoxic. [17]

Breastfeeding is not recommended due to the potential secretion into breast milk. [17]

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.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	anaphylaxis (rare)
auditory/hearing	auditory deficits (rare)
blood/bone marrow febrile neutropenia	anemia (77-87%, severe 1-14%)
	hospitalization for neutropenic complications (8-9%)
	leukopenia (81-99%, severe 12-16%)
	neutropenia (80-96%, severe 28-41%); nadir 7-10 days, recovery within 7-14 days
	neutropenic sepsis, fatal (1%)
	thrombocytopenia (4-6%, severe 1%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
cardiovascular (arrhythmia)	tachycardia (rare)
cardiovascular (general)	hypertension (rare)
	hypotension (rare)
	myocardial infarction (rare)
	thromboembolic events (e.g., pulmonary embolus, deep vein thrombosis) (rare)
	vasodilation (rare)
constitutional symptoms	fatigue (25-41%%, severe 5-8%)
	fever (10-19%, severe 1%) [2,6]
dermatology/skin	extravasation hazard: vesicant [2]
	alopecia (12%)
	angioedema (rare)
	injection site pain (13-18%, severe 1-3%)
	injection site reaction (21-38%, severe 2%)
	phlebitis (5-10%, severe 1%)
	pruritus (rare)
	radiation recall reaction (e.g., dermatitis, esophagitis) (rare)
	rash (5%)
	urticaria (rare)
endocrine	flushing (rare)
	syndrome of inappropriate ADH secretion (<1%) [2,18]
gastrointestinal	emetogenic potential: low moderate
	anorexia (16-19%, severe 1-2%)
	constipation (28-38%, severe <2%)
	diarrhea (13-20%, severe 1%) [2]
	dysphagia (< 5%)
	mucositis (rare)
	nausea (33-50%, severe 1-3%)
	stomatitis (15-16%)
	vomiting (14-23%, severe 1-2%) [2]
hepatic	transient elevation of bilirubin (9-14%, severe 5-7%)
	transient elevation of AST (54-74%, severe 3-8%)
infection	pneumonia (rare)
musculoskeletal	muscle weakness (5-9%, severe 1-3%)
neurology	loss of deep tendon reflex (<5%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	neuropathy, motor (rare)
	neuropathy, sensory (21-31%, severe 1-2%)
pain	abdominal pain (6-12%, severe 1%)
	arthralgia (<5%)
	back pain (rare)
	chest pain (5-8%, severe 1-2%) [5]
	headache (<5%)
	jaw pain (<5%)
	myalgia (<5%)
	pain (15-16%, severe 2-3%)
	pain in tumour-containing tissue (rare) [2,19]
pulmonary	dyspnea (3-9%, severe 2%) [2,20]
	interstitial pulmonary changes (rare)
	pulmonary edema (rare) [2,20]
renal/genitourinary	hemorrhagic cystitis (<1%)

Adapted from reference [2] unless specified otherwise.

Alopecia manifests as gradual hair thinning, but total hair loss is uncommon. [21] Alopecia is a cumulative toxicity. [3]

Most reports of ***chest pain*** are in patients with a history of cardiovascular disease or tumour within the chest. Acute myocardial ischemia has rarely been reported. [2,22]

Acute ***dyspnea and severe bronchospasm*** occur infrequently. The acute reaction resembles an allergic event and may respond to bronchodilators. Risk factor includes concurrent use of mitomycin. [2] Subacute pulmonary reactions occur within one hour after drug administration and may be characterized by cough, dyspnea, hypoxemia and interstitial infiltration. Subacute pulmonary reactions may respond to corticosteroid therapy. Oxygen may provide symptomatic relief. [2,21]

Mild to moderate peripheral ***neuropathy*** (paresthesia, hypesthesia) is the most frequently reported neurologic toxicity [2] and usually reversible on discontinuation of vinorelbine. Cisplatin does not appear to increase the neurotoxic effects of vinorelbine. However, prior treatment with paclitaxel may result in cumulative neurotoxicity. [3]

An acute ***pain syndrome at the tumour site*** can occur during or within 30 minutes after the first dose of vinorelbine. The pain usually lasts for one hour or less, but can continue for two days. Risk factors include locoregional relapse of head and neck cancer. The theory is that prior surgery and/or radiation cause a nervous lesion, and that subsequent vinorelbine causes a neuralgic pain. The pain can be managed with nonsteroidal anti-inflammatory drugs or corticosteroids [19,23] and may sometimes require narcotic analgesics.

Vinorelbine is a moderate ***vesicant*** and can produce extravasation injury (e.g., considerable irritation, local tissue necrosis and/or thrombophlebitis). Injection site reactions occur in about one-third of patients, of which 2% were severe. Reactions include erythema, pain at injection site, vein discoloration, localized rash and urticaria. Chemical phlebitis proximal to the injection site has been reported. The occurrence and severity of venous irritation appear to be reduced when vinorelbine is given as a 6-10 minute infusion with a free-flowing IV fluid and flushing with at least

75-125 mL NS or D5W after administration. [2,20,24] Phlebitis occurs in approximately 5-10% of patients; however, the frequency of phlebitis was notably greater in clinical trials in which vinorelbine was administered over one hour. [3] A heat pad on the distal vein may help to minimize injection site reactions. [1] Hydrocortisone 100 mg IV may be given prior to vinorelbine if the patient experiences pain on administration. [25,26]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
cisplatin [7,27]	no effect on vinorelbine pharmacokinetics but granulocytopenia, high frequency hearing loss and tinnitus occur more often	unknown	use with caution during concurrent therapy
mitomycin [2]	acute dyspnea and severe bronchospasm	unknown	use bronchodilators, corticosteroids and/or oxygen for symptomatic relief
paclitaxel [2]	neuropathy	possibly by cumulative axonal microtubule toxicity	monitor for signs and symptoms of neuropathy

The contribution of cytochrome P450 enzyme activity to vinorelbine metabolism has potential implications in patients receiving other drugs metabolized by this route. [1]

SUPPLY AND STORAGE:

***Injection*:**

Fresenius Kabi Canada Ltd. supplies vinorelbine as 10 mg and 50 mg single-use (preservative free) vials in a concentration of 10 mg/mL. Refrigerate. Protect from light. [17]

Generic Medical Partners Inc. supplies vinorelbine as 10 mg and 50 mg single-use (preservative free) vials in a concentration of 10 mg/mL. Refrigerate. Protect from light. [28]

Teva Canada Limited supplies vinorelbine as 10 mg and 50 mg single-use (preservative free) vials in a concentration of 10 mg/mL. Refrigerate. Protect from light. [29]

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.

Additional information:

- vinorelbine is initially clear and colourless to pale yellow, but may develop a slightly darker yellow to light amber colour in time; this does not indicate a change which should preclude its use [2]

Compatibility: consult detailed reference

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 [30-32]	**NOT USED DUE TO THE RISK OF INADVERTENT INTRATHECAL ADMINISTRATION**
Intermittent infusion [21,24]	***over 6-10 min;*** see ***Systemic Therapy Policy III-20: Prevention and Management of Extravasation of Chemotherapy*** • has also been given in 75-125 mL NS or D5W over 10-20 min [9,12] • for children, dilute to 0.5-2 mg/mL with NS or D5W and infuse IV over 6-10 min [2]
Continuous infusion [6]	96-hour continuous IV infusion by a portable pump or diluted in 1000 mL NS, administered through a central venous catheter
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	**ABSOLUTELY CONTRAINDICATED; INTRATHECAL INJECTION COULD BE FATAL**
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 in patients with other toxicities.

Adults:

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

	Cycle Length:	
Intravenous:	1 week [2,3,9]:	30 mg/m^2 (range 7.5-35 mg/m^2) IV for one dose on day 1 (total dose per cycle 30 mg/m^2 [range 7.5-35 mg/m^2])
	2 weeks [33]:	25 mg/m^2 IV for one dose on day 1 (total dose per cycle 25 mg/m^2)
	3 weeks [1]***:***	***30 mg/m^2*** (range 25-30 mg/m^2) ***IV for one dose on days 1 and 8*** (total dose per cycle 60 mg/m^2 [range 50-60 mg/m^2])
	3 weeks [6]:	8 mg/m^2 IV bolus followed by 8-9 mg/m^2/day over 24 hours for 4 consecutive days (total dose per cycle 40-44 mg/m^2)

4 weeks [12]: 25 mg/m^2 IV on days 1 and 8
(total dose per cycle 50 mg/m^2)

Concurrent radiation: Vinorelbine is currently being studied with concurrent radiation.

Dosage in myelosuppression: modify according to protocol by which patient is being treated;

Dosage with neurotoxicity [2]: discontinue if moderate or severe neurotoxicity develops

Dosage in renal failure: no adjustment required [2]

Dosage in hepatic failure [3]:

Bilirubin (µmol/L)	Dose
<35	100%
36-50	50%
>50	25%

Dosage in dialysis [34]: hemodialysis: reduction from 25 mg/m² to 12.5 mg/m² IV for one dose on day 1 weekly (given after hemodialysis) was reported in one patient

Children: no information found

REFERENCES:

1. Gregory RK, Smith IE. Vinorelbine--a clinical review. Br J Cancer ; 2000;82(12):1907–1913
2. Glaxo Wellcome. NAVELBINE® product monograph. Mississauga, Ontario; 29 October, 1998.
3. USP DI. Volume 1. Drug information for the health care professional. Update monographs. Vinorelbine. Micromedex, Inc.; Accessed 9 August, 2000. Available at: https://www.micromedex.com
4. Gridelli C, Guida C, Barletta E, et al. Thoracic radiotherapy and daily vinorelbine as radiosensitizer in locally advanced non small cell lung cancer: a phase I study. Lung Cancer ; 2000;29(2):131–137
5. Rowinsky EK, Noe DA, Trump DL, et al. Pharmacokinetic, bioavailability, and feasibility study of oral vinorelbine in patients with solid tumors. J Clin Oncol ; 1994;12(9):1754–63
6. Toussaint C, Izzo J, Spielmann M, et al. Phase I/II trial of continuous infusion vinorelbine for advanced breast cancer. J Clin Oncol ; 1994;12(10):2102–2112
7. Leveque D, Jehl F. Clinical pharmacokinetics of vinorelbine [published erratum appears in Clin Pharmacokinet 1997 Apr;32(4):323]. Clin Pharmacokin ; 1996;31(3):184–197
8. Jones S, Winer E, Vogel C, et al. Randomized comparison of vinorelbine and melphalan in anthracycline-refractory advanced breast cancer. J Clin Oncol ; 1995;13(10):2567–74;
9. Morris M, Brader KR, Levenback C, et al. Phase II study of vinorelbine in advanced and recurrent squamous cell carcinoma of the cervix. J Clin Oncol ; 1998;16(3):1094–1098
10. Pignata S, Silvestro G, Ferrari E, et al. Phase II study of cisplatin and vinorelbine as first-line chemotherapy in patients with carcinoma of the uterine cervix. J Clin Oncol ; 1999;17(3):756–760
11. Le Chevalier T, Brisgand D, Douillard JY, et al. Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small-cell lung cancer: results of a European multicenter trial including 612 patients [see comments]. J Clin Oncol ; 1994;12(2):360–367
12. Gridelli C, Perrone F, Ianniello GP, et al. Carboplatin plus vinorelbine, a new well-tolerated and active regimen for the treatment of extensive-stage small-cell lung cancer: a phase II study. Gruppo Oncologico Centro-Sud-Isole. J Clin Oncol ; 1998;16(4):1414–1419
13. McEvoy GK, editor. AHFS 2007 Drug Information. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc.; p. 1225–1228
14. Faulding. Vincristine Sulphate Injection product monograph. Montreal, Quebec; 1995.
15. BCCA Provincial Systemic Therapy Program. Labeling of vinca alkaloid syringes. Policy # V-40. Vancouver, British Columbia: BC Cancer Agency; 27 May , 1999.

16. Dittrich C, Zifko U, Fazeny B, et al. Vinorelbine after paclitaxel in breast cancer: cross resistance and cumulative neurotoxicity? [letter]. Annals of Oncology ; 1994;5(5):473–4
17. Fresenius Kabi Canada Ltd. Vinorelbine Injection product monograph. Toronto, Ontario; August 14, 2023.
18. Garrett CA, A. ST,Jr. Syndrome of inappropriate antidiuretic hormone associated with vinorelbine therapy. Ann Pharmacother ; 1998;32(12):1306–1309
19. Gebbia V, Testa A, Valenza R, et al. Acute pain syndrome at tumour site in neoplastic patients treated with vinorelbine: report of unusual toxicity [letter]. European Journal of Cancer ; 1994;30A(6):889
20. Brogden JM, Nevidjon B. Vinorelbine tartrate (NAVELBINE®): drug profile and nursing implications of a new vinca alkaloid [see comments]. Oncol Nurs Forum ; 1995;22(4):635–46
21. Hohneker JA. A summary of vinorelbine (NAVELBINE®) safety data from North American clinical trials. Sem Oncol ; 1994;21(5 Suppl 10):42–7
22. Karminsky N, Merimsky O, Kovner F, et al. Vinorelbine-related acute cardiopulmonary toxicity. Cancer Chemotherapy and Pharmacology ; 1999;43:180–182
23. Kornek GV, Kornfehl H, Hejna M, et al. Acute tumor pain in patients with head and neck cancer treated with vinorelbine [letter]. Journal of the National Cancer Institute ; 1996;88(21):1593
24. Rittenberg CN, Gralla RJ, Rehmeyer TA. Assessing and managing venous irritation associated with vinorelbine tartrate (Navelbine) [see comments]. Oncol Nurs Forum ; 1995;22(4):707–710
25. BC Cancer Agency Lung Tumour Group. (LUVIN) BCCA protocol summary for treatment of advanced non-small cell lung cancer with vinorelbine in elderly patients. Vancouver, British Columbia: BC Cancer Agency; 01 December , 1999.
26. Ginopoulos P, Mastronikolis NS, Karana A, et al. Use of dexamethasone in the management of phlebitis caused by intravenous administration of vinorelbine (navelbine). Medical Science Research ; 1998;26(6):397–398
27. GlaxoSmithKline. NAVELBINE® product monograph - product monograph revisions. Mississauga, Ontario; 6 April, 2001.
28. Generic Medical Partners Inc. Vinorelbine Injection product monograph. Toronto, Ontario; September 3, 2014.
29. Teva Canada Limited. Vinorelbine tartrate for Injection product monograph. Toronto, Ontario; March 20, 2014.
30. Institute for Safe Medication Practices Canada. 2014-15 Targeted Medication Safety Best Practices for Hospitals - Best Practice #1: Dispense vinCRIStine (and other vinca alkaloids) in a minibag of a compatible solution and not in a syringe. Canada: Institute for Safe Medication Practices Canada; 2014.
31. World Health Organization. Information Exchange System - Vincristine (and other vinca alkaloids) should only be given intravenously via a minibag. Alert No. 115 ed. Geneva, Switzerland: World Health Organization; 18 July , 2007.
32. Institute for Safe Medication Practices Canada. ISMP Safety Bulletin - Published data supports dispensing vincristine in minibags as a system safeguard. Canada: Institute for Safe Medication Practices Canada; 03 October , 2001.
33. Gomez A, Cruz JJ, Garcia-Palomo A, et al. Docetaxel and vinorelbine every 14-days in patients with metastatic breast cancer after using anthracyclines. Final results. Proc Am Soc Clin Oncol ; 2000;19:108a (abstract 418)
34. Rollino C, Milongo R, Schaerer R, et al. Vinorelbine therapy in a hemodialyzed patient [letter]. Nephron ; 1992;61(2):232–3

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