

DRUG NAME: VINOURELBINE**SYNONYM(S):** Vinorelbine tartrate, VRL, VNL, NVB**COMMON TRADE NAME(S):** Navelbine® (notice of compliance,¹ May 1994)**CLASSIFICATION:** Mitotic inhibitor, cytotoxic*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*).² Vinorelbine inhibits cell growth by binding to the tubulin of the mitotic microtubules.³ Like other mitotic inhibitors, vinorelbine also promotes apoptosis in cancer cells.² *In vitro* vinorelbine shows both multidrug and non-multidrug resistance.³ 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.⁴ Vinorelbine is a radiation-sensitizing agent.⁵ It is cell cycle phase-specific (M phase).³

PHARMACOKINETICS:

Interpatient variability	moderate to large interpatient variability ^{6,7}	
Distribution	Widely distributed in the body, mostly in spleen, liver, kidneys, lungs, thymus; moderately in heart, muscles; minimally in fat, brain, bone marrow. ⁴ High levels found in both normal and malignant lung tissue, with slow diffusion out of tumour tissue. ²	
	cross blood brain barrier?	brain and plasma levels comparable in animal studies ²
	volume of distribution	25.4-40.1 L/kg
	plasma protein binding	80-91%
Metabolism	by hepatic cytochrome P450 enzymes ²	
	active metabolite(s)	deacetylvinorelbine
	inactive metabolite(s)	vinorelbine N-oxide ⁴
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 ³ children: 14.7 h ⁸
	clearance	0.97-1.26 L/h/kg
Gender	no information found	
Elderly	no clinically significant difference ⁴	
Children	shorter half life, other parameters similar to adult values ⁸	
Ethnicity	no information found	

Adapted from reference 3 unless specified otherwise.

USES:

Primary uses:

- * Breast cancer⁹
- * Lung cancer, non-small cell¹²

Other uses:

- Cervical cancer^{10,11}
- Lung cancer, small cell^{2,13}
- Ovarian cancer²

*Health Canada Therapeutic Products Programme approved indication

Vinorelbine is currently being studied in children.

SPECIAL PRECAUTIONS:

Inadvertent intrathecal (IT) administration of other vinca alkaloids has resulted in death.^{14,15} It is a medical emergency if vinorelbine is inadvertently given intrathecally. **All** vinorelbine doses dispensed should be labelled with an auxiliary label and a medication label, both stating “**WARNING: FOR INTRAVENOUS USE ONLY – FATAL IF GIVEN BY OTHER ROUTES**”.¹⁶

Neuropathy: Vinorelbine has less neurotoxicity than other vinca alkaloids.⁴ However, patients with a prior history or pre-existing neuropathy should be monitored for new or worsening signs and symptoms while receiving vinorelbine.^{3,17}

Carcinogenicity: No information found.

Mutagenicity: Not mutagenic in Ames test, but mutagenic in mammalian mutation tests.³

Fertility: No information found.

Pregnancy: FDA Pregnancy Category D.⁴ There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Breastfeeding is not recommended due to the potential secretion into breast milk.³

SIDE EFFECTS:

ORGAN SITE	SIDE EFFECT	ONSET			
Dose-limiting side effects are in bold, italics I = immediate (onset in hours to days); E = early (days to weeks); D = delayed (weeks to months); L = late (months to years)					
allergy/immunology	anaphylaxis (rare)	I			
auditory/hearing	auditory deficits (rare)		E	D	
blood/bone marrow febrile neutropenia	anemia (77-87%, severe 1-14%)			D	
	hospitalization for neutropenic complications (8-9%)		E		
	leukopenia (81-99%, severe 12-16%)		E		
	neutropenia (80-96%, severe 28-41%) nadir 7-10 days, recovery within 7-14 days		E		
	neutropenic sepsis, fatal (1%)		E		
	thrombocytopenia (4-6%, severe 1%)		E		

ORGAN SITE	SIDE EFFECT	ONSET			
<p style="text-align: center;">Dose-limiting side effects are in <i>bold, italics</i> I = immediate (onset in hours to days); E = early (days to weeks); D = delayed (weeks to months); L = late (months to years)</p>					
cardiovascular (arrhythmia)	tachycardia (rare)		E	D	
cardiovascular (general)	hypertension (rare)		E	D	
	hypotension (rare)		E	D	
	myocardial infarction (rare)		E	D	
	thromboembolic events (eg, pulmonary embolus, deep vein thrombosis) (rare)		E	D	
	vasodilation (rare)		E	D	
constitutional symptoms	fatigue (25-41%, severe 5-8%)		E	D	
	fever (10-19%, severe 1%) ^{3,7}	I			
dermatology/skin	<i>extravasation hazard: vesicant</i> ³				
	alopecia (12%)		E		
	angioedema (rare)		E		
	injection site pain (13-18%, severe 1-3%)		E		
	injection site reaction (21-38%, severe 2%)	I	E		
	phlebitis (5-10%, severe 1%)		E		
	pruritus (rare)		E	D	
	radiation recall reaction (eg, dermatitis, esophagitis) (rare)		E	D	
	rash (5%)		E	D	
	urticaria (rare)		E	D	
endocrine	flushing (rare)		E		
	syndrome of inappropriate ADH secretion (< 1%) ^{3,18}		E		
gastrointestinal	<i>emetogenic potential: low moderate</i>				
	anorexia (16-19%, severe 1-2%)		E	D	
	constipation (28-38%, severe <2%)		E		
	diarrhea (13-20%, severe 1%) ³	I	E		
	dysphagia (< 5%)		E		
	mucositis (rare)		E		
	nausea (33-50%, severe 1-3%)	I	E		
	stomatitis (15-16%)		E		
	vomiting (14-23%, severe 1-2%) ³	I			
hepatic	transient elevation of bilirubin (9-14%, severe 5-7%)		E		
	transient elevation of AST (54-74%, severe 3-8%)		E		
infection	pneumonia (rare)		E	D	
musculoskeletal	muscle weakness (5-9%, severe 1-3%)		E	D	
neurology	loss of deep tendon reflex (< 5%)		E	D	

ORGAN SITE	SIDE EFFECT	ONSET		
Dose-limiting side effects are in <i>bold, italics</i> I = immediate (onset in hours to days); E = early (days to weeks); D = delayed (weeks to months); L = late (months to years)				
	neuropathy, motor (rare)		E	D
	neuropathy, sensory (21-31%, severe 1-2%)		E	D
pain	abdominal pain (6-12%, severe 1%)		E	D
	arthralgia (< 5%)		E	D
	back pain (rare)		E	D
	chest pain (5-8%, severe 1-2%) ⁶	I		
	headache (< 5%)		E	D
	jaw pain (< 5%)		E	D
	myalgia (< 5%)		E	D
	pain (15-16%, severe 2-3%)		E	D
	pain in tumour-containing tissue (rare) ^{3,19}	I		
pulmonary	dyspnea (3-9%, severe 2%) ^{3,20}	I		
	interstitial pulmonary changes (rare)	I		
	pulmonary edema (rare) ^{3,20}	I	E	
renal/genitourinary	hemorrhagic cystitis (<1%)		E	

Adapted from reference 3 unless specified otherwise.

Injection site reactions: Vinorelbine is a moderate vesicant and can produce extravasation injury (eg, 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.^{3,20,21} 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.⁴ A heat pad on the distal vein may help to minimize injection site reactions.² Hydrocortisone 100 mg IV may be given prior to vinorelbine if the patient experiences pain on administration.^{22,23}

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.³ 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.^{3,24}

Neuropathy: Mild to moderate peripheral neuropathy (paresthesia, hypesthesia) is the most frequently reported neurologic toxicity³ 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.⁴

Alopecia manifests as gradual hair thinning, but total hair loss is uncommon.²⁴ Alopecia is a cumulative toxicity.⁴

Chest pain: 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.^{3,25}

Pain in tumour-containing tissue: 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^{19,26} and may sometimes require narcotic analgesics.

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
cisplatin ^{8,27}	no effect on vinorelbine pharmacokinetics but granulocytopenia, high frequency hearing loss and tinnitus occur more often	unknown	use with caution during concurrent therapy
mitomycin ³	acute dyspnea and severe bronchospasm	unknown	use bronchodilators, corticosteroids and/or oxygen for symptomatic relief
paclitaxel ³	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.²

SOLUTION PREPARATION AND COMPATIBILITY:

Injection: 10 mg, 50 mg vials; each mL contains 10 mg vinorelbine; preservative-free, discard unused portion. Store in the refrigerator, in the original package to protect from light. Avoid freezing. 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.³ Unopened vials are stable for up to 72 hours at room temperature.⁴

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in **bold, italics**

Subcutaneous	not used due to vesicant nature
Intramuscular	not used due to vesicant nature
Direct intravenous	Note: Direct IV injection causes pain on injection. Via small (21 or 23) gauge needle into tubing of running IV. Push slowly, over 6-10 min, so that drip of IV solution does not stop or reverse. Check for blood return before administration and after every 1-2 mL of drug. If no blood return, stop the injection and assess the IV site. Flush with at least 75-125 mL NS or D5W after administration to clear any remaining drug from tubing. ²⁰

Intermittent infusion	in 50 mL NS over 6-10 min.^{21,24} After infusing vinorelbine flush thoroughly with at least 75-125 mL NS.³ <ul style="list-style-type: none"> • Has also been given in 75-125 mL NS or D5W over 10-20 min^{10,13} • For children, dilute to 0.5-2 mg/mL with NS or D5W and infuse IV over 6-10 min.³
Continuous infusion	96-hour continuous IV infusion by a portable pump or diluted in 1000 mL NS, administered through a central venous catheter ⁷
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:

BCCA usual dose noted in **bold, italics**

<i>Intravenous:</i>	Cycle Length:	
	1 week ^{3,4,10} :	30 mg/m ² (range 7.5-35 mg/m ²) IV for one dose on day 1
	2 weeks ²⁸ :	25 mg/m ² IV for one dose on day 1
	3 weeks:	30 mg/m² (range 25-30 mg/m ²) IV for one dose on days 1 and 8 (total dose per cycle 60 mg/m² [range 50-60 mg/m²])²
	3 weeks:	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) ⁷
	4 weeks:	25 mg/m ² IV on days 1 and 8 (total dose per cycle 50 mg/m ²) ¹³

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

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"

Dosage with neurotoxicity: discontinue if moderate or severe neurotoxicity develops³

Dosage in renal failure: no adjustment required³

Dosage in hepatic failure⁴:

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

Dosage in dialysis: 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 patient²⁹

Children:

Vinorelbine is currently being studied in children.³⁰

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