A DRUG NAME: VINORELBINE

SYNONYM(S): didehydrodeoxynorvincaleukoblastine, vinorelbine tartrate

COMMON TRADE NAME(S): Navelbine® (GlaxoSmithKline); Vinorelbine (Mayne)

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.

Oral Absorption	Yes, 40% bioavailable	
Distribution	Initial rapid decline in plasma concentration after IV administration due to distribution to peripheral compartments and metabolism	
	Cross blood brain barrier?	Minimal
	PPB	70-80% (not sure where this comes from)
Metabolism	Largely metabolised via hepatobiliary system (p450, cyp3A4)	
	Active metabolite(s)	Yes, deacetylvinorelbine
	Inactive metabolite(s)	Yes, N-oxide vinorelbine
Excretion	Mainly eliminated by the liver, with approximately 46% of drug being recovered in the feces.	
	Urine	18% (unchanged)
	$T_{1/2}$	27.7 – 43.6 hrs

C INDICATIONS AND STATUS

* Advanced non-small cell lung cancer (single agent or in combination)

* Metastatic breast cancer after standard first-line chemotherapy or after relapse within 6 months of anthracycline-based adjuvant therapy.

* ***Health Canada approved indication***

D ADVERSE EFFECTS

ORGAN SITE	SIDE EFFECT		ONSET
Cardiovascular	Myocardial infarction (rare)		E
	Hypotension, hypertension		E
	Pulmonary Edema (rare)		E
	Thromboembolism (rare)		E
	Chest Pain (5%), tachycardia	I	
Dermatologic	Alopecia (12%),		E
	Radiation recall reaction		E
	Rash (≤5%)		E
Extravasation hazard (refer to **Appendix 2**)	**Vesicant**	I	E
Gastrointestinal	Nausea (33 to 50%*; severe 1-3 %)	I	
	Vomiting (20%)	I	
	Constipation (neurotoxicity; 38%)		E
	Dysphagia (≤5%)	I	
	Anorexia (16-19%*)		E
	Diarrhea (13-20%*)		E
	Stomatitis (15-16%*)		E
Hematologic	Granulocytopenia (Grade 4 : 28-41%*; 8% febrile neutropenia)		E
	Grade 3 or 4 thrombocytopenia (<1%)		E
Hepatic	Increased bilirubin (9-14%*)		E
	Increased transaminases (54-74%*)		E
Injection site	Phlebitis (33%, severe 2%)	I	
Musculoskeletal	Muscle weakness (9%)		E
	Myalgia, arthralgia (<5%)	I	

D ADVERSE EFFECTS (Continued)

ORGAN SITE	SIDE EFFECT	ONSET
Neurologic	Constipation (28-38%*), ileus (2%)	E
	Ototoxicity, vestibular toxicity (rare)	E
	Headache (5%) Jaw pain (< 5%)	E
	Abnormal Gait (rare)	E
	Mild-moderate peripheral neuropathy (10-20%*)	E
Pulmonary	Interstitial pneumonitis (rare)	E
	Shortness of breath (5%, with mitomycin C)	I
	Bronchospasm (3%)	I
Renal/ metabolic	Hemorrhagic cystitis (rare)	
	Syndrome of inappropriate ADH secretion (<1%)	E
General	Anaphylaxis (rare)	I
	Fatigue (25-41%*)	E
	Infection	E
	Tumour pain, pain (15-18%)	I
	Fever (10-19%*)	E

Dose-limiting side effects are underlined.
I = immediate (onset in hours to days); E = early (days to weeks);
D = delayed (weeks to months); L = late (months to years)

*Different toxicity incidences were experienced in treatments of advanced breast cancer and metastatic non-small cell lung cancer, thus percentages of incidence are presented in “range”.

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 reversible and is not cumulative.

Chest Pain, sometimes accompanied by changes in electrocardiograms, is reported in 5% of patients, mostly in those with previous history of cardiovascular disease or presence of a bulky tumour within the chest. There are reports in the literature of myocardial ischemia and infarction possibly related to vinorelbine.

D ADVERSE EFFECTS (Continued)

Neurotoxicity is generally mild to moderate and generally reversible on drug discontinuation. Severe neurotoxicity is seen in less than 1% of patients. Prior treatment with paclitaxel or other neurotoxic drug, or the presence of pre-existing neuropathy of any etiology, may result in increased risk. Ototoxicity and autonomic and motor neuropathies have been reported.

Paralytic ileus and paresthesia have been reported (2% and rarely, respectively). Discontinue vinorelbine if neurotoxicity is moderate or severe. **Asthenia**, usually mild or moderate, tends to increase with cumulative dosing.

Elevated liver enzymes were observed frequently in vinorelbine treatment but are usually transient and asymptomatic.

Injection site reactions, such as pain, erythema, or vein discolouration are common (30% of patients) but severe in only 2% of patients. Phlebitis is seen in approximately 6 % of patients. Long infusion times (i.e. more 20 minutes) may increase the risk of phlebitis and injection site reactions. Flushing the vein before and after administration of vinorelbine can also reduce these 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 (severe in only 2% of patients). Incidence is infrequent but seen more commonly when Vinorelbine or other vinca alkaloids are combined with mitomycin. Aggressive treatment of symptoms with bronchodilators, steroids and /or oxygen may be required, especially in patients with pre-existing pulmonary dysfunction.

E DOSING

Adult:
Intravenous: 30mg/m^2 given once weekly for 2-3 weeks, followed by a one week rest period.

Dosage in myelosuppression:

Absolute neutrophil counts (X10^9/L)	Dose (mg/m^2)	Dose after treatment delay 1-3 weeks or febrile neutropenia (mg/m^2)
≥ 1.5	30	22.5
1 – 1.499	15	11.25
< 1	Hold dose; repeat count each week. Discontinue if no recovery ≥ 3 weeks	

E DOSING (Continued)

Dosage with renal impairment: No adjustment required

Dosage with hepatic impairment: As Vinorelbine undergoes hepatobiliary metabolism and excretion, administer with caution in hepatic insufficiency. Consider adjusting doses with hyperbilirubinemia

Suggested Adjustments for increases in total bilirubin:

Total bilirubin (umol/L)	% usual dose
< 2 x ULN	100%
2-3 x ULN	50%
> 3 x ULN	25%

Dosage with neurotoxicity: Discontinue with mild to moderate neurotoxicity.

Dosage in the elderly: no specific dosage adjustments are required for increased age

***Children*:** safety and efficacy not established

F ADMINISTRATION GUIDELINES (see Appendix 3a)

- Mix in 50mL minibag (D5W, NS) to a final concentration 0.5-2mg/mL; Infuse over 6-10 minutes through free-flowing IV.
- May push (at final concentration of 1.5 – 3mg/mL) through sidearm of free flowing IV (NS); Inject over 6-10 minutes.
- After administration is completed, flush IV line with 200 to 300ml NS or D5W.
- Vinorelbine should be administered only via the iv route; intrathecal administration is fatal.

G SPECIAL PRECAUTIONS

Vinorelbine is contraindicated in patients with known hypersensitivity to vinorelbine, and in patients who have drug-induced severe granulocytopenia or severe thrombocytopenia and should be used with caution in patients with compromised marrow reserve

Vinorelbine may result in radiosensitizing effects with prior or concomitant radiation therapy.

Vinorelbine is potentially **mutagenic** and **carcinogenic**, is embryotoxic and fetotoxic and should not be used in **pregnant** women. **Breast feeding** is not recommended, due to potential for excretion into breast milk.

H INTERACTIONS

AGENT	EFFECT	MECHANISM	MANAGEMENT
Mitomycin	acute pulmonary effects	unknown	avoid combination. Treat vigorously if occurs
Paclitaxel /other neurotoxic /ototoxic compounds	neuropathy	additive spindle toxicity (speculated)	dose adjustment
Cisplatin	increased ototoxicity and myelosuppression	additive effects	dose adjustments
Radiation	sensitises effects – may see radiation recall		use with caution
Inhibitors of cyp 3A4 (Itraconazole etc)	increased neurotoxicity and other toxicity	inhibits vinorelbine metabolism	use with caution and consider dose adjustment

I RECOMMENDED CLINICAL MONITORING

Recommended Clinical Monitoring	**Suggested Clinical Monitoring**
• Monitor blood counts at each visit • Baseline liver function tests • Routine toxicity (especially neurotoxicity and local toxicity) assessment	• Periodic liver function tests • Local site toxicity ratings, if incident of phlebitis

J REFERENCES

BCCA Drug Monograph: Vinorelbine. The Cancer Drug Manual. Vancouver.
http://www.bccancer.bc.ca/HPI/DrugDatabase/DrugIndexPro/Vinorelbine.htm

Compendium of Pharmaceuticals and Specialities. 2006. Navelbine ®.
Canadian Pharmacists Association.

Ginopoulous P, Matronikolis NS, Karana A et .al: Use of dexamethasone in the management of phlebitis caused by intravenous of vinorelbine (Navelbine).
Medical Science Research 1998; 26: 397-8.

Glaxo Wellcome Inc. Navelbine product monograph. Missisauga, Ontario. 1996: May.

Gregory RK, Smith IE. Vinorelbine – a clinical review. British J Cancer (2000) 82(12), 1907-13.

Jones SF, Burris HA. Vinorelbine: A new antineoplastic drug for the treatment of non-small cell lung cancer. Ann Pharmacother 1996; 30: 501-06.

McEnvoy G. (editor): American Hospital Formulary Drug Information 2000.
Bethesda: American Society of Health-System Pharmacists, 1090-4.

Toso C, Lindley C. Vinorelbine: A novel vinca alkaloid.
Am J Health-Syst Pharm. 1995; 52: 1287-304.

Welbanks L. (editor) : Compendium of Pharmaceutical and Specialties .
Ottawa: Canadian Pharmaceutical Association, 2004

Zhou XJ, Rahmani R. Preclinical and clinical pharmacology of vinca alkaloids.
Drugs 44, (Suppl 4): 1-16. 1992.