VINORELBINE INJECTION USP

PRESCRIBING INFORMATION

WARNING: Vinorelbine Injection USP should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. This product is for intravenous (IV) use only. Intrathecal administration of other vinca alkaloids has resulted in death. Syringes containing this product should be labeled "WARNING - FOR IV USE ONLY. FATAL if given intrathecally."

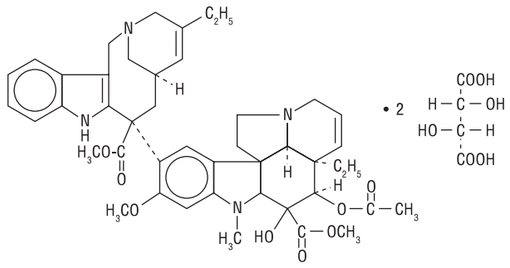
Severe granulocytopenia resulting in increased susceptibility to infection may occur. Granulocyte counts should be ≥ 1,000 cells/mm^3 prior to the administration of **Vinorelbine Injection USP.** The dosage should be adjusted according to complete blood counts with differentials obtained on the day of treatment.

Caution - It is extremely important that the intravenous needle or catheter be properly positioned before **Vinorelbine Injection USP** is injected. Administration of **Vinorelbine Injection USP** may result in extravasation causing local tissue necrosis and/or thrombophlebitis (see DOSAGE AND ADMINISTRATION: Administration Precautions).

DESCRIPTION:

Vinorelbine Injection USP is for intravenous administration. Each vial contains vinorelbine tartrate equivalent to 10 mg (1-mL vial) or 50 mg (5-mL vial) vinorelbine in Water for Injection. No preservatives or other additives are present. The aqueous solution is sterile and nonpyrogenic. Vinorelbine tartrate is a semi-synthetic vinca alkaloid with antitumor activity. The chemical name is 3',4'-didehydro-4'-deoxy-C'-norvincaleukoblastine [R-(R*,R*)-2, 3-dihydroxybutanedioate (1 :2)(salt)].

Vinorelbine tartrate has the following structure:



Vinorelbine tartrate is a white to yellow or light brown amorphous powder with the molecular formula $C_{45}H_{54}N_4O_8.2C_4H_6O_6$ and molecular weight of 1079.12. The aqueous solubility is >1,000 mg/mL in distilled water. The pH of **Vinorelbine Injection USP** is approximately 3.5.

CLINICAL PHARMACOLOGY:

Vinorelbine is a vinca alkaloid that interferes with microtubule assembly. The vinca alkaloids are structurally similar compounds comprised of 2 multiringed units, vindoline and catharanthine. Unlike other vinca alkaloids, the catharanthine unit is the site of structural modification for vinorelbine. The antitumor activity of vinorelbine is thought to be due primarily to inhibition of mitosis at metaphase through its interaction with tubulin. Like other vinca alkaloids, vinorelbine may also interfere with: 1) amino acid, cyclic AMP, and glutathione metabolism, 2) calmodulin-dependent Ca^{++} transport ATPase activity, 3) cellular respiration, and 4) nucleic acid and lipid biosynthesis. In intact tectal plates from mouse embryos, vinorelbine, vincristine and vinblastine inhibited mitotic microtubule formation at the same concentration (2 µM), inducing a blockade of cells at metaphase. Vincristine produced depolymerization of axonal microtubules at 5 µM, but vinblastine and vinorelbine did not have this effect until concentrations of 30 µM and 40 µM, respectively. These data suggest relative selectivity of vinorelbine for mitotic microtubules.

Pharmacokinetics: The pharmacokinetics of vinorelbine were studied in 49 patients who received doses of 30 mg/m^2 in 4 clinical trials. Doses were administered by 15- to 20-minute constant-rate infusions. Following intravenous administration, vinorelbine concentration in plasma decays in a triphasic manner. The initial rapid decline primarily represents distribution of drug to peripheral compartments followed by metabolism and excretion of the drug during subsequent phases. The prolonged terminal phase is due to relatively slow efflux of vinorelbine from peripheral compartments. The terminal phase half-life averages 27.7 to 43.6 hours and the mean plasma clearance ranges from 0.97 to 1.26 L/hr/kg. Steady-state volume of distribution (V_{ss}) values range from 25.4 to 40.1 L/kg.

Vinorelbine demonstrated high binding to human platelets and lymphocytes. The free fraction was approximately 0.11 in pooled human plasma over a concentration range of 234 to 1,169 ng/mL. The binding to plasma constituents in cancer patients ranged from 79.6% to 91.2%. Vinorelbine binding was not altered in the presence of cisplatin, 5-fluorouracil, or doxorubicin.

Vinorelbine undergoes substantial hepatic elimination in humans with large amounts recovered in feces after intravenous administration to humans. Two metabolites of vinorelbine have been identified in human blood, plasma, and urine; vinorelbine N-oxide and deacetylvinorelbine. Deacetylvinorelbine has been demonstrated to be the primary metabolite of vinorelbine in humans, and has been shown to possess antitumor activity similar to vinorelbine. Therapeutic doses of vinorelbine (30 mg/m^2) yield very small, if any, quantifiable levels of either metabolite in blood or urine. The metabolism of vinca alkaloids has been shown to be mediated by hepatic cytochrome P450 isoenzymes in the CYP3A subfamily. This metabolic pathway may be impaired in patients with hepatic dysfunction or who are taking concomitant potent inhibitors of these isoenzymes (see PRECAUTIONS). The effects of renal or hepatic dysfunction on the disposition of vinorelbine have not been assessed, but based on experience with other anticancer vinca alkaloids, dose adjustments are recommended for patients with impaired hepatic function (see DOSAGE AND ADMINISTRATION).

The disposition of radiolabeled vinorelbine given intravenously was studied in a limited number of patients. Approximately 18% and 46% of the administered dose was recovered in the urine and in the feces, respectively. Incomplete recovery in humans is consistent with results in animals where recovery is incomplete, even after prolonged sampling times. A separate study of the urinary excretion of vinorelbine using specific chromatographic analytical methodology showed that 10.9% ± 0.7% of a 30-mg/m^2 intravenous dose was excreted unchanged in the urine.

The influence of age on the pharmacokinetics of vinorelbine was examined using data from 44 cancer patients (average age, 56.7 ± 7.8 years; range, 41 to 74 years; with 12 patients ≥60 years and 6 patients ≥65 years) in 3 studies. CL (the mean plasma clearance), $t_{½}$ (the terminal phase half-life), and Vz (the volume of distribution during terminal phase) were independent of age. A separate pharmacokinetic study was conducted in 10 elderly patients with metastatic breast cancer (age range, 66 to 81 years; 3 patients >75 years; normal liver function tests) receiving vinorelbine 30 mg/m^2 intravenously. CL, V_{ss}, and $t_{½}$ were similar to those reported for younger adult patients in previous studies. No relationship between age, systemic exposure ($AUC_{0-\infty}$), and hematological toxicity was observed.

The pharmacokinetics of vinorelbine are not influenced by the concurrent administration of cisplatin with **Vinorelbine Injection USP** (see PRECAUTIONS: Drug Interactions).

Clinical Trials: Data from 1 randomized clinical study (211 evaluable patients) with single-agent **Vinorelbine Injection USP** and 2 randomized clinical trials (1,044 patients) using **Vinorelbine Injection USP** combined with cisplatin support the use of **Vinorelbine Injection USP** in patients with advanced non-small cell lung cancer (NSCLC).

Single-Agent Vinorelbine Injection USP: Single-agent ***Vinorelbine Injection USP*** was studied in a North American, randomized clinical trial in which patients with Stage IV NSCLC, no prior chemotherapy, and Karnofsky Performance Status ≥ 70 were treated with **Vinorelbine Injection USP** (30 mg/m^2) weekly or 5-fluorouracil (5-FU) (425 mg/m^2 IV bolus) plus leucovorin (LV 20 mg/m^2 IV bolos) daily for 5 days every 4 weeks. A total of 211 patients were randomized at a 2:1 ratio to **Vinorelbine Injection USP** (143) or 5-FU/LV (68). **Vinorelbine Injection USP** showed improved survival time compared to 5-FU/LV. In an intent-to-treat analysis, the median survival time was 30 weeks versus 22 weeks for patients receiving **Vinorelbine Injection USP** versus 5-FU/LV, respectively (P=0.06). The 1-year survival rates were 24% (±4% SE) for **Vinorelbine Injection USP** and 16% (±5% SE) for the 5-FU/LV group, using the Kaplan-Meier product-limit estimates. The median survival time with 5-FU/LV was similar to or slightly better than that usually observed in untreated patients with advanced NSCLC, suggesting that the difference was not related to some unknown detrimental effect of 5-FU/LV therapy. The response rates (all partial responses) for **Vinorelbine Injection USP** and 5-FU/LV were 12% and 3%, respectively.

Vinorelbine Injection USP in Combination with Cisplatin: Vinorelbine Injection USP plus Cisplatin versus Single-Agent Cisplatin: A Phase III open-label, randomized study was conducted which compared **Vinorelbine Injection USP** (25 mg/m^2/week) plus cisplatin (100 mg/m^2 every 4 weeks) to single-agent cisplatin (100 mg/m^2 every 4 weeks) in patients with Stage IV or Stage IIIb NSCLC patients with malignant pleural effusion or multiple lesions in more than one lobe who were not previously treated with chemotherapy. Patients included in the study had a performance status of 0 or 1, and 34% had received prior surgery and/or radiotherapy. Characteristics of the 432 randomized patients are provided in Table 1. Two hundred and twelve patients received **Vinorelbine Injection USP** plus cisplatin and 210 received single-agent cisplatin. The primary objective of this trial was to compare survival between the 2 treatment groups. Survival (Figure 1) for patients receiving **Vinorelbine Injection USP** plus cisplatin was significantly better compared to the-patients who received single-agent cisplatin. The results of this trial are summarized in Table 1.

Vinorelbine Injection USP plus Cisplatin versus Vindesine plus Cisplatin versus Single-Agent Vinorelbine Injection USP: In a large European clinical trial, 612 patients with Stage III or IV NSCLC, no prior chemotherapy, and WHO Performance Status of 0, 1, or 2 were randomized to treatment with single-agent **Vinorelbine Injection USP** (30 mg/m^2/week), **Vinorelbine Injection USP** (30 mg/m^2/week) plus cisplatin (120 mg/m^2 days 1 and 29, then every 6 weeks), and vindesine (3 mg/m^2/week for 7 weeks, then every other week) plus cisplatin (120 mg/m^2 days 1 and 29, then every 6 weeks). Patient characteristics are provided in Table 1. Survival was longer in patients treated with **Vinorelbine Injection USP** plus cisplatin compared to those treated with vindesine plus cisplatin (Figure 2). Study results are summarized in Table 1.

Dose-Ranging Study : A dose-ranging study of **Vinorelbine Injection USP** (20, 25, or 30 mg/m^2/week) plus cisplatin (120 mg/m^2 days 1 and 29, then every 6 weeks) in 32 patients with NSCLC demonstrated a median survival of 10.2 months. There were no responses at the lowest dose level; the response rate was 33% in the 21 patients treated at the 2 highest dose levels.

Table 1: Randomized Clinical Trials of Vinorelbine Injection USP in Combination with Cisplatin in NSCLC

	Vinorelbine Injection USP/ Cisplatin vs. Single-Agent Cisplatin		**Vinorelbine Injection USP** /Cisplatin vs. Vindesine/ Cisplatin vs. Single-Agent Vinorelbine		
	Vinorelbine Injection USP / Cisplatin	Cisplatin	**Vinorelbine Injection USP** / Cisplatin	Vindesine/ Cisplatin	**Vinorelbine Injection USP**
Demographics					
No. of patients	214	218	206	200	206
No. of males	146	141	182	179	188
No. of females	68	77	24	21	18
Median age (years)	63	64	59	59	60
Range (years)	33-84	37-81	32-75	31-75	30-74
Stage of disease					
Stage IIIA	NA	NA	11%	11%	10%
Stage III B	8%	8%	28%	25%	32%
Stage IV	92%	92%	50%	55%	47%
Local recurrence	NA	NA	2%	3%	3 %
Metastatic after surgery	NA	NA	9%	8%	9 %
Histology					
Adenocarcinoma	54%	52%	32%	40%	28%
Squamous	19%	22%	56%	50%	56%
Large cell	14%	14%	13%	11%	16%
Unspecified	13%	13%	NA	NA	NA
Results					
Median survival (months)	7.8	6.2	9.2*†	7.4	7.2
P value	P = 0.01		*P =0.09 vs. vindesine/cisplatin † = 0.05 vs. single-agent **Vinorelbine Injection USP**		
12-Month survival rate	38%	22%	35%	27%	30%
Overall response	19%	8%	28% ‡§	19%	14%
P value	P<0.001		‡P = 0.03 vs. vindesine/cisplatin §P<0.001 vs. single-agent **Vinorelbine Injection USP**		

Figure 1. Overall Survival **Vinorelbine Injection USP** /Cisplatin versus Single-Agent Cisplatin

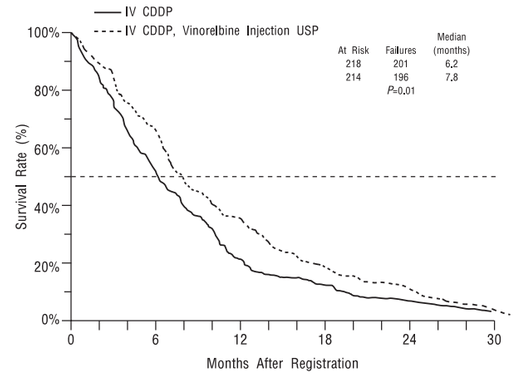
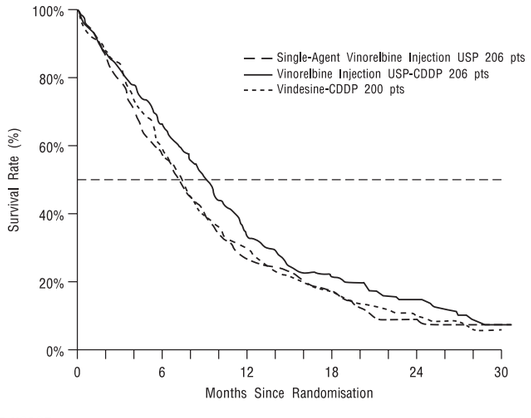


Figure 2. Overall Survival **Vinorelbine Injection USP** /Cisplatin versus Videsine/ Cisplatin versus Single-Agent **Vinorelbine Injection USP.**



INDICATIONS AND USAGE:

Vinorelbine Injection USP is indicated as a single agent or in combination with cisplatin for the first-line treatment of ambulatory patients with unresectable, advanced non-small cell lung cancer (NSCLC). In patients with Stage IV NSCLC, **Vinorelbine Injection USP** is indicated as a single agent or in combination with cisplatin. In Stage III NSCLC, **Vinorelbine Injection USP** is indicated in combination with cisplatin.

CONTRAINDICATIONS:

Administration of **Vinorelbine Injection USP** is contraindicated in patients with pretreatment granulocyte counts <1,000 cells/mm^3 (see WARNINGS).

WARNINGS:

Vinorelbine Injection USP should be administered in carefully adjusted doses by or under the supervision of a physician experienced in the use of cancer chemotherapeutic agents.

Patients treated with **Vinorelbine Injection USP** should be frequently monitored for myelosuppression both during and after therapy. Granulocytopenia is dose-limiting. Granulocyte nadirs occur between 7 and 10 days after dosing with granulocyte count recovery usually within the following 7 to 14 days. Complete blood counts with differentials should be performed and results reviewed prior to administering each dose of **Vinorelbine Injection USP. Vinorelbine Injection USP** should not be administered to patients with granulocyte counts <1,000 cells/mm^3. Patients developing severe granulocytopenia should be monitored carefully for evidence of infection and/or fever. See DOSAGE AND ADMINISTRATION for recommended dose adjustments for granulocytopenia.

Acute shortness of breath and severe bronchospasm have been reported infrequently, following the administration of **Vinorelbine Injection USP** and other vinca alkaloids, most commonly when the vinca alkaloid was used in combination with mitomycin. These adverse events may require treatment with supplemental oxygen, bronchodilators, and/or corticosteroids, particularly when there is pre-existing pulmonary dysfunction.

Reported cases of interstitial pulmonary changes and acute respiratory distress syndrome (ARDS), most of which were fatal, occurred in patients treated with single-agent **Vinorelbine Injection USP.** The mean time to onset of these symptoms after vinorelbine administration was 1 week (range 3 to 8 days). Patients with alterations in their baseline pulmonary symptoms or with new onset of dyspnea, cough, hypoxia, or other symptoms should be evaluated promptly.

Vinorelbine Injection USP has been reported to cause severe constipation (e.g., Grade 3-4), paralytic ileus, intestinal obstruction, necrosis, and/or perforation. Some events have been fatal.

Pregnancy: Pregnancy Category D. **Vinorelbine Injection USP** may cause fetal harm if administered to a pregnant woman. A single dose of vinorelbine has been shown to be embryo- and/or fetotoxic in mice and rabbits at doses of 9 mg/m^2 and 5.5 mg/m^2, respectively (one third and one sixth the human dose). At nonmaternotoxic doses, fetal weight was reduced and ossification was delayed. There are no studies in pregnant women. If **Vinorelbine Injection USP** is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with **Vinorelbine Injection USP.**

PRECAUTIONS:

General: Most drug-related adverse events of **Vinorelbine Injection USP** are reversible. If severe adverse events occur, **Vinorelbine Injection USP** should be reduced in dosage or discontinued and appropriate corrective measures taken. Reinstitution of therapy with **Vinorelbine Injection USP** should be carried out with caution and alertness as to possible recurrence of toxicity.

Vinorelbine Injection USP should be used with extreme caution in patients whose bone marrow reserve may have been compromised by prior irradiation or chemotherapy, or whose marrow function is recovering from the effects of previous chemotherapy (see DOSAGE AND ADMINISTRATION).

Administration of **Vinorelbine Injection USP** to patients with prior radiation therapy may result in radiation recall reactions (see ADVERSE REACTIONS and Drug Interactions).

Patients with a prior history or pro-existing neuropathy, regardless of etiology, should be monitored for new or worsening signs and symptoms of neuropathy while receiving **Vinorelbine Injection USP.**

Care must be taken to avoid contamination of the eye with concentrations of **Vinorelbine Injection USP** used clinically. Severe irritation of the eye has been reported with accidental exposure to another vinca alkaloid. If exposure occurs, the eye should immediately be thoroughly flushed with water.

Information for Patients: Patients should be informed that the major acute toxicities of **Vinorelbine Injection USP** are related to bone marrow toxicity, specifically granulocytopenia with increased susceptibility to infection. They should be advised to report fever or chills immediately. Women of childbearing potential should be advised to avoid becoming pregnant during treatment. Patients should be advised to contact their physician if they experience increased shortness of breath, cough; or other new pulmonary symptoms, or if they experience symptoms of abdominal pain or constipation.

Laboratory Tests: Since dose-limiting clinical toxicity is the result of depression of the white blood cell count, it is imperative that complete blood counts with differentials be obtained and reviewed on the day of treatment prior to each dose of **Vinorelbine Injection USP** (see ADVERSE REACTIONS: Hematologic).

Hepatic: There is no evidence that the toxicity of **Vinorelbine Injection USP** is enhanced in patients with elevated liver enzymes. No data are available for patients with severe baseline cholestasis, but the liver plays an important role in the metabolism of **Vinorelbine Injection USP**. Because clinical experience in patients with severe liver disease is limited, caution should be exercised when administering **Vinorelbine Injection USP** to patients with severe hepatic injury or impairment (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Acute pulmonary reactions have been reported with **Vinorelbine Injection USP** and other anticancer vinca alkaloids used in conjunction with mitomycin. Although the pharmacokinetics of vinorelbine are not influenced by the concurrent administration of cisplatin, the incidence of granulocytopenia with **Vinorelbine Injection USP** used in combination with cisplatin is significantly higher than with single-agent **Vinorelbine Injection USP**. Patients who receive **Vinorelbine Injection USP** and paclitaxel, either concomitantly or sequentially should be monitored for signs and symptoms of neuropathy. Administration of **Vinorelbine Injection USP** to patients with prior or concomitant radiation therapy may result in radio sensitizing effects.

Caution should be exercised in patients concurrently taking drugs known to inhibit drug metabolism by hepatic cytochrome P450 isoenzymes in the CYP3A subfamily, or in patients with hepatic dysfunction. Concurrent administration of vinorelbine tartrate with an inhibitor of this metabolic pathway may cause an earlier onset and/or an increased severity of side effects.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The carcinogenic potential of **Vinorelbine Injection USP** has not been studied. Vinorelbine has been shown to affect chromosome number and possibly structure in vivo (polyploidy in bone marrow cells from Chinese hamsters and a positive micronucleus test in mice). It was not mutagenic in the Ames test and gave inconclusive results in the mouse lymphoma TK Locus assay. The significance of these or other short-term test results for human risk is unknown. Vinorelbine did not affect fertility to a statistically significant extent when administered to rats on either a once-weekly (9 mg/m^2, approximately one third the human dose) or alternate-day schedule (4.2 mg/m^2, approximately one seventh the human dose) prior to and during mating. However, biweekly administration for 13 or 26 weeks in the rat at 2.1 and 7.2 mg/m^2 (approximately one fifteenth and one fourth the human dose) resulted in decreased spermatogenesis and prostate/seminal vesicle secretion.

Pregnancy: Pregnancy Category D. See WARNINGS section.

Nursing Mothers: It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from **Vinorelbine Injection USP**, it is recommended that nursing be discontinued in women who are receiving therapy with **Vinorelbine Injection USP**.

Pediatric Use: Safety and effectiveness of **Vinorelbine Injection USP** in pediatric patients have not been established. Data from a single-arm study in 46 patients with recurrent solid malignant tumors, including rhabdomyosarcoma/undifferentiated sarcoma, neuroblastoma, and CNS tumors, at doses similar to those used in adults, showed no meaningful clinical activity. Toxicities were similar to those reported in adults.

Geriatric Use: Of the total number of patients in North American clinical studies of IV **Vinorelbine Injection USP**, approximately one third were 65 years of age or greater. No overall differences in effectiveness or safety were observed between these patients and younger adult patients. Other reported clinical experience has not identified differences in responses between the elderly and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out.

The phamlacokinetics of vinorelbine in elderly and younger adult patients are similar (see CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS:

The pattern of adverse reactions is similar whether **Vinorelbine Injection USP** is used as a single agent or in combination. Adverse reactions from studies with single-agent and combination use of **Vinorelbine Injection USP** are summarized in Tables 2-4.

Single-Agent Vinorelbine Injection USP: Data in the following table are based on the experience of 365 patients (143 patients with NSCLC; 222 patients with advanced breast cancer) treated with IV **Vinorelbine Injection USP** as a single agent in 3 clinical studies. The dosing schedule in each study was 30 mg/m^2 **Vinorelbine Injection USP** on a weekly basis.

Table 2: Summary of Adverse Events in 365 Patients Receiving Single-Agent Vinorelbine Injection USP *†:

Adverse Event		**All Patients (n=365)**	**NSCLC (n=143)**
Bone Marrow			
Granulocytopenia	<2,000 cells/mm^3	90%	80%
	<500 cells/mm^3	36%	29%
Leukopenia	<4,000 cells/mm^3	92%	81%
	<1,000 cells/mm^3	15%	12%
Thrombocytopenia	<100,000 cells/mm^3	5%	4%
	<50,000 cells/mm^3	1%	1%
Anemia	<11 g/dL	83%	77%
	<8 g/dL	9%	1%
Hospitalizations due to granulocytopenic complications		9%	8%

Adverse Event	All Grades		Grade 3		Grade 4	
	All Patients	NSCLC	All Patients	NSCLC	All Patients	NSCLC
Clinical Chemistry Elevations						
Total Bilirubin (n = 351)	13%	9%	4%	3%	3%	2%
SGOT (n = 346)	67%	54%	5%	2%	1%	1%
General						
Asthenia	36%	27%	7%	5%	0%	0%
Injection Site Reactions	28%	38%	2%	5%	0%	0%
Injection Site Pain	16%	13%	2%	1%	0%	0%
Phlebitis	7%	10%	<1%	1%	0%	0%
Digestive	44%	34% 15%	2%	1%	0%	0%
Nausea	20%	29%	2%	1%	0%	0%
Vomiting	35%	13%	3%	2%	0%	0%
Constipation	17%	20%	1%	1%	0%	0%
Diarrhea	25%	3%	1%	1%	<1%	0%
Peripheral Neuropathy‡	7%	12%	2%	2%	1%	0%
Dyspnea	12%		≤1%	1%	0%	0%
Alopecia						
Non-Laboratory						
Malaise/fatigue/lethargy	67%	12%	0%	49%	8%	0%
Vomiting	60%	7%	6%	60%	10%	4%
Nausea	58%	14%	0%	57%	12%	0%
Anorexia	46%	0%	0%	37%	0%	0%
Constipation	35%	3%	0%	16%	1%	0%
Alopecia	34%	0%	0%	14%	0%	0%
Weight loss	34%	1%	0%	21%	<1%	0%
Fever without infection	20%	2%	0%	4%	0%	0%
Hearing	18%	4%	0%	18%	3%	<1%
Local (injection site reactions)	17%	<1%	0%	1%	0%	0%
Diarrhea	17%	2%	<1%	11%	1%	<1%
Paresthesias	17%	<1%	0%	10%	<1%	0%
Taste alterations	17%	0%	0%	15%	0%	0%
Peripheral numbness	11%	2%	0%	7%	<1%	0%
Myalgia/arthralgia	12%	<1%	0%	3%	<1%	0%
Phlebitis/thrombosis/embolism	10%	3%	0%	<1%	0%	<1%
Weakness	12%	2%	<1%	7%	2%	0%
Dizziness/vertigo	9%	<1%	0%	3%	<1%	0%
Infection	11%	5%	<1%	<1%	<1%	0%
Respiratory infection	10%	4%	<1%	3%	3%	0%

* None of the reported toxicities were influenced by age. Grade based on modified criteria from the National Cancer Institute.
† Patients with NSCLC had not received prior chemotherapy. The majority of the remaining patients had received prior chemotherapy.
‡ Incidence of paresthesia plus hypesthesia.

Hematologic: Granulocytopenia is the major dose-limiting toxicity with **Vinorelbine Injection USP**. Dose adjustments are required for hematologic toxicity and hepatic insufficiency (see DOSAGE AND ADMINISTRATION). Granulocytopenia was generally reversible and not cumulative over time. Granulocyte nadirs occurred 7 to 10 days after the dose, with granulocyte recovery usually within the following 7 to 14 days. Granulocytopenia resulted in hospitalizations for fever and/or sepsis in 8% of patients. Septic deaths occurred in approximately 1% of patients. Prophylactic hematologic growth factors have not been routinely used with **Vinorelbine Injection USP**. If medically necessary, growth factors maybe administered at recommended doses no earlier than 24 hours after the administration of cytotoxic chemotherapy. Growth factors should not be administered in the period 24 hours before the administration of chemotherapy.
Whole blood and/or packed red blood cells were administered to 18% of patients who received **Vinorelbine Injection USP**.
Neurologic: Loss of deep tendon reflexes occurred in less than 5% of patients. The development of severe peripheral neuropathy was infrequent (1%) and generally reversible.
Skin: Like other anticancer vinca alkaloids, **Vinorelbine Injection USP** is a moderate vesicant. Injection site reactions, including erythema, pain at injection site, and vein discoloration, occurred in approximately one third of patients; 5% were severe. Chemical phlebitis along the vein proximal to the site of injection was reported in 10% of patients.
Gastrointestinal: Prophylactic administration of antiemetics was not routine in patients treated with single-agent **Vinorelbine Injection USP**. Due to the low incidence of severe nausea and vomiting with single-agent **Vinorelbine Injection USP**, the use of serotonin antagonists is generally not required.
Hepatic: Transient elevations of liner enzymes were reported without clinical symptoms.
Cardiovascular: Chest pain was reported in 5% of patients. Most reports of chest pain were in patients who had either a history of cardiovascular disease or tumor within the chest. There have been rare reports of myocardial infarction.
Pulmonary: Shortness of breath was reported in 3% of patients; it was severe in 2% (see WARNINGS). Interstitial pulmonary changes were documented.
Other: Fatigue occurred in 27% of patients. It was usually mild or moderate but tended to increase with cumulative dosing.
Other toxicities that have been reported in less than 5% of patients include jaw pain, myalgia, arthralgia, and rash. Hemorrhagic cystitis and the syndrome of inappropriate ADH secretion were each reported in <1% of patients.
Combination Use: Adverse events for combination use are summarized in Tables 3 and 4.

Vinorelbine Injection USP in Combination with Cisplatin:
Vinorelbine Injection USP plus Cisplatin versus Single-Agent Cisplatin (Table 3): Myelosuppression was the predominant toxicity in patients receiving combination therapy, Grade 3 and 4 granulocytopenia of 82% compared to 5% in the single-agent cisplatin arm.
Fever and/or sepsis related to granulocytopenia occurred in 11% of patients on **Vinorelbine Injection USP** and cisplatin compared to 0% on the cisplatin arm. Four patients on the combination died of granulocytopenia-related sepsis. During this study, the use of granulocyte colony-stimulating factor [(G-CSF) filgrastim) was permitted, but not mandated, after the first course of treatment for patients who experienced Grade 3 or 4 granulocytopenia (xl,000 cells/mm^3) or in those who developed neutropenic fever between cycles of chemotherapy. Beginning 24 hours after completion of chemotherapy, G-CSF was started at a dose of 5 mcg/kg per day and continued until the total granulocyte count was >1000 cells/mm^3 on 2 successive determinations. G-CSF was not administered on the day of treatment.
Grade 3 and 4 anemia occurred more frequently in the combination arm compared to control, 24% vs. 8%, respectively. Thrombocytopenia occurred in 6% of patients treated with **Vinorelbine Injection USP** plus cisplatin compared to 2% of patients treated with cisplatin.
The incidence of severe non-hematologic toxicity was similar among the patients in both treatment groups. Patients receiving **Vinorelbine Injection USP** plus cisplatin compared to single-agent cisplatin experienced more Grade 3 and/or 4 peripheral numbness (2% vs. <1%), phlebitis/thrombosis/embolism (3% vs. <1%), and infection (6% vs. <1%). Grade 3-4 constipation and/or ileus occurred in 3% of patients treated with combination therapy and in 1% of patients treated with cisplatin.
Seven deaths were reported on the combination arm; 2 were related to cardiac ischemia, 1 massive cerebrovascular accident, 1 multisystem failure due to an overdose of **Vinorelbine Injection USP**, and 3 from febrile neutropenia. One death, secondary to respiratory infection unrelated to granulocytopenia, occurred with single-agent cisplatin.
Vinorelbine Injection USP plus Cisplatin versus Vindesine plus Cisplatin versus Single-Agent Vinorelbine (Table 4): Myelosuppression, specifically Grade 3 and 4 granulocytopenia, was significantly greater with the combination of **Vinorelbine Injection USP** plus cisplatin (79%) than with either single-agent **Vinorelbine Injection USP** (53%) or vindesine plus cisplatin (48%), P<0.0001. Hospitalization due to documented sepsis occurred in 4.4% of patients treated with **Vinorelbine Injection USP** plus cisplatin: 2% of patients treated with vindesine and cisplatin, and 4% of patients treated with single-agent **Vinorelbine Injection USP**. Grade 3 and 4 thrombocytopenia was infrequent in patients receiving combination chemotherapy and no events were reported with single-agent **Vinorelbine Injection USP**.
The incidence of Grade 3 and/or 4 nausea and vomiting, alopecia, and renal toxicity were reported more frequently in the cisplatin-containing combinations compared to single-agent **Vinorelbine Injection USP**. Severe local reactions occurred in 2% of patients treated with combinations containing **Vinorelbine Injection USP**; none were observed in the vindesine plus cisplatin arm. Grade 3 and 4 neurotoxicity was significantly more frequent in patents receiving vindesine plus cisplatin (17%) compared to **Vinorelbine Injection USP** plus cisplatin (7%) and single-agent vinorelbine (9%) (P<0.005). Cisplatin did not appear to increase the incidence of neurotoxicity observed with single-agent **Vinorelbine Injection USP**.

Table 3: Selected Adverse Events From a Comparative Trial of Vinorelbine Injection USP plus Cisplatin versus Single-Agent Cisplatin*

Adverse Event	**Vinorelbine Injection USP** 25 mg/m^2 plus Cisplatin 100 mg/m^2 (n = 212)			Cisplatin 100 mg/m^2 (n = 210)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Bone Marrow						
Granulocytopenia	89%	22%	60%	26%	4%	1%
Anemia	88%	21%	3%	72%	7%	<1%
Leukopenia	88%	39%	19%	31%	<1%	0%
Thrombocytopenia	29%	4%	1%	21% N/A	1%	<1%
Febrile neutropenia	N/A	N/A	11%		N/A	0%
Hepatic				<1%		
Elevated transaminase	1%	0%	0%		<1%	0%
Renal				28%		
Elevated creatinine	37%	2%	2%		4%	<1%

	Vinorelbine Injection USP / Cisplatin†			Vindesine/Cisplatin‡			**Vinorelbine Injection USP** §		
Adverse Event	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Bone Marrow									
Neutropenia	95%	20%	58%	79%	26%	22%	85%	25%	28%
Leukopenia	94%	40%	17%	82%	24%	3%	83%	26%	6%
Thrombocytopenia	15%	3%	1%	10%	3%	0.5%	3%	0%	0%
Febrile neutropenia	N/A	N/A	4%	N/A	N/A	2%	N/A	N/A	4%
Hepatic									
Elevated bilirubin	6%	N/A	N/A	5%	N/A	N/A	5%	N/A	N/A
Renal									
Elevated creatinine	46%	N/A	N/A	37%	N/A	N/A	13%	N/A	N/A
Non-Laboratory									
Nausea/vomiting	74%	27%	3%	72%	24%	1%	31%	1%	1%
Alopecia	51%	7%	0.5%	56%	14%	0%	30%	2%	0%
Ototoxicity	10%	1%	1%	14%	1%	0%	1%	0%	0%
Local reactions	17%	2%	0.5%	7%	0%	0%	22%	2%	0%
Diarrhea	25%	1.5%	0%	24%	1%	0%	12%	0%	0.5%
Neurotoxicity¶	44%	7%	0%	58%	16%	1%	44%	8%	0.5%

* Grade based on criteria from the World Health Organization (WHO).
† n=194 to 207; all patients receiving **Vinorelbine Injection USP** /cisplatin with laboratory and non-laboratory data.
‡ n=173 to 192; all patients receiving vindesine/cisplatin with laboratory and non-laboratory data.
§ n =165 to 201; all patients receiving **Vinorelbine Injection USP** with laboratory and non-laboratory data.
¶ Neurotoxicity includes peripheral neuropathy and constipation.

Observed During Clinical Practice: in addition to the adverse events reported from clinical trials, the following events have been identified during post-approval use of **Vinorelbine Injection USP.** Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to **Vinorelbine Injection USP**.
Body as a Whole: Systemic allergic reactions reported as anaphylaxis, pruritus, urticaria, and angioedema; flushing; and radiation recall events such as dermatitis and esophagitis (see PRECAUTIONS) have been reported.
Hematologic: Thromboembolic events, including pulmonary embolus and deep venous thrombosis, have been reported primarily in seriously ill and debilitated patients with known predisposing risk factors for these events.
Neurologic: Peripheral neurotoxicities such as, but not limited to, muscle weakness and disturbance of gait; have been observed in patients with and without prior symptoms. There may be increased potential for neurotoxicity in patients with pre-existing neuropathy, regardless of etiology, who receive **Vinorelbine Injection USP**. Vestibular and auditory deficits have been observed with **Vinorelbine Injection USP**, usually when used in combination with cisplatin.
Skin: Injection site reactions, including localized rash and urticaria, blister formation, and skin sloughing have been observed in clinical practice. Some of these reactions may be delayed in appearance.
Gastrointestinal: Dysphagia, mucositis, and pancreatitis have been reported.
Cardiovascular: Hypertension, hypotension, vasodilation, trichycardia, and pulmonary edema have been reported.
Pulmonary: Pneumonia has been reported.
Musculoskeletal: Headache has been reported, with and without other musculosketetal aches and pains.
Other: Pain in tumor-containing tissue, back pain, and abdominal pain have been reported. Electrolyte abnormalities, including hyponatremia with or without the syndrome of inappropriate ADH secretion, have been reported in seriously ill and debilitated patients.
Combination Use: Patients with prior exposure to paclitaxel and who have demonstrated neuropathy should he monitored closely for new or worsening neuropathy. Patients who have experienced neuropathy with previous drug regimens should be monitored for symptoms of neuropathy while receiving **Vinorelbine Injection USP. Vinorelbine Injection USP** may result in radiosensitizing effects with prior or concomitant radiation therapy (see PRECAUTIONS).

OVERDOSAGE:
There is no known antidote for overdoses of **Vinorelbine Injection USP**. Overdoses involving quantities up to 10 times the recommended dose (30 mg/m^2) have been reported. The toxicities described were consistent with those listed in the ADVERSE REACTIONS section including paralytic ileus, stomatitis, and esophagitis. Bone marrow aplasia, sepsis, and paresis have also been reported. Fatalities have occurred following overdose of **Vinorelbine Injection USP**. If overdosage occurs, general supportive measures together with appropriate blood transfusions, growth factors, and antibiotics should be instituted as deemed necessary by the physician.

DOSAGE AND ADMINISTRATION:
Single-Agent Vinorelbine Injection USP: The usual initial dose of single-agent **Vinorelbine Injection USP** is 30 mg/m^2 administered weekly. The recommended method of administration is an intravenous injection over 6 to 10 minutes. In controlled trials, single-agent **Vinorelbine Injection USP** was given weekly until progression or dose-limiting toxicity.
Vinorelbine Injection USP in Combination with Cisplatin: Vinorelbine Injection USP may be administered weekly at a dose of 25 mg/m^2 in combination with cisplatin given every 4 weeks at a dose of 100 mg/m^2.
Blood counts should be checked weekly to determine whether dose reductions of vinorelbine and/or cisplatin are necessary. In the SWOG study, most patients required a 50% dose reduction of **Vinorelbine Injection USP** at day 15 of each cycle and a 50% dose reduction of cisplatin by cycle 3.
Vinorelbine Injection USP may also be administered weekly at a dose of 30 mg/m^2 in combination with cisplatin, given on days 1 and 29, then every 6 weeks with cisplatin at a dose of 120 mg/m^2.
Dose Modifications for Vinorelbine Injection USP: The dosage should be adjusted according to hematologic toxicity or hepatic insufficiency, whichever results in the lower dose for the corresponding starting dose of **Vinorelbine Injection USP (see** Table 5).
Dose Modifications for Hematologic Toxicity: Granulocyte counts should be ≥1,000 cells/mm^3 prior to the administration of **Vinorelbine Injection USP**. Adjustments in the dosage of **Vinorelbine Injection USP** should be based on granulocyte counts obtained on the day of treatment according to Table 5.

Table 5: Dose Adjustments Based on Granulocyte Counts.

Granulocytes on Day of Treatment (cells/mm^3)	Percentage of Starting Dose of **Vinorelbine Injection USP**
≥1,500	100%
1,000 to 1,499	50%
<1,000	Do not administer. Repeat granulocyte count in 1 week. If 3 consecutive weekly doses are held because granulocyte count is <1,000 cells/mm^3, discontinue **Vinorelbine Injection USP**.
Note: For patients who, during treatment with vinorelbine, experienced fever and/or sepsis while granulocytopenic or had 2 consecutive weekly doses held due to granulocytopenia, subsequent doses of vinorelbine should be:	
≥1,500	75%
1,000 to 1,499	37.5%
<1,000	See above

Dose Modifications for Hepatic Insufficiency: **Vinorelbine Injection USP** should be administered with caution to patients with hepatic insufficiency. In patients who develop hyperbilirubinemia during treatment with **Vinorelbine Injection USP**, the dose should be adjusted for total bilirubin according to Table 6.

Table 6. Dose Modification Based on Total Bilirubin

Total Bilirubin (mg/dL)	Percentage of Starting Dose of **Vinorelbine Injection USP**
< 2.0	100%
2.1 to 3.0	50%
>3.0	25%

Dose Modifications for Concurrent Hematologic Toxicity and Hepatic Insufficiency: In patients with both hematologic toxicity and hepatic insufficiency, the lower of the doses based on the corresponding starting dose of **Vinorelbine Injection USP** determined from Table 5 and Table 6 should be administered.
Dose Modifications for Renal Insufficiency: No dose adjustments for **Vinorelbine Injection USP** are required for renal insufficiency. Appropriate dose reductions for cisplatin should be made when **Vinorelbine Injection USP** is used in combination.
Dose Modifications for Neurotoxicity: If Grade ≥2 neurotoxicity develops **Vinorelbine Injection USP** should be discontinued.
Administration Precautions: Caution - **Vinorelbine Injection USP** must be administered intravenously. It is extremely important that the intravenous needle or catheter be properly positioned before any **Vinorelbine Injection USP** is injected. Leakage into surrounding tissue during intravenous administration of **Vinorelbine Injection USP** may cause considerable irritation, local tissue necrosis, and/or thrombophlebitis. If extravasation occurs, the injection should be discontinued immediately, and any remaining portion of the dose should then be introduced into another vein. Since there are no established guidelines for the treatment of extravasation injuries with **Vinorelbine Injection USP**, institutional guidelines may be used. The ONS Chemotherapy Guidelines provide additional recommendations for the prevention of extravasation injuries[1].
As with other toxic compounds, caution should be exercised in handling and preparing the solution of **Vinorelbine Injection USP**. Skin reactions may occur with accidental exposure. The use of gloves is recommended. If the solution of **Vinorelbine Injection USP** contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water. Severe irritation of the eye has been reported with accidental contamination of the eye with another vinca alkaloid. If this happens with **Vinorelbine Injection USP**, the eye should be flushed with water immediately and thoroughly.
Procedures for proper handling and disposal of anticancer drugs should be used. Several guidelines on this subject have been published[2-8].
There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.
Vinorelbine Injection USP is a clear; colorless to pale yellow solution: Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit. If particulate matter is seen, **Vinorelbine Injection USP** should not be administered.
Preparation for Administration: Vinorelbine Injection USP must be diluted in either a syringe or IV bag using one of the recommended solutions. The diluted **Vinorelbine Injection USP** should be administered over 6 to 10 minutes into the side port of a free-flowing IV closest to the IV bag followed by flushing with at least 75 to 125 mL of one of the solutions. Diluted vinorelbine may be used for up to 24 hours under normal room light when stored in polypropylene syringes or polyvinyl chloride bags at 5° to 30°C (41° to 86°F).
Syringe: The calculated dose of **Vinorelbine Injection USP** should be diluted to a concentration between 1.5 and 3.0 mg/mL.
The following solutions may be used for dilution:
5 % Dextrose Injection, USP
0.9 % Sodium Chloride Injection, USP
IV Bag: The calculated dose of **Vinorelbine Injection USP** should be diluted to a concentration between 0.5 and 2 mg/mL.
The following solutions may be used for dilution:
5 % Dextrose Injection, USP
0.9 % Sodium Chloride Injection, USP
0.45 % Sodium Chloride Injection, USP
5 % Dextrose and 0.45% Sodium Chloride Injection, USP
Ringer's Injection, USP
Lactated Ringer's Injection, USP
Stability: Unopened vials of **Vinorelbine Injection USP** are stable until the date indicated on the package when stored under refrigeration at 2° to 8°C (36° to 46°F) and protected from light in the carton. Unopened vials of **Vinorelbine Injection USP** are stable at temperatures up to 25°C (77°F) for up to 72 hours. This product should not be frozen.

HOW SUPPLIED:
Vinorelbine Injection USP is a clear, colorless to pale yellow solution in Water for Injection, containing 10 mg vinorelbine per mL. Vinorelbine Injection is available in single-use, clear glass vials with Omniflex-Plus coated stoppers and light blue caps, individually packaged in a carton in the following vial sizes:
10 mg/1 mL Single-Use Vial, Carton of 1 (NDC 0069-0099-01)
50 mg/5 mL Single-Use Vial, Carton of 1 (NDC 0069-0103-03)

Store the vials under refrigeration at 2° to 8°C (36° to 46°F) in the carton. Protect from light. DO NOT FREEZE.

REFERENCES:

1. ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and Recommendations for Practice. Pittsburgh, Pa: Oncology Nursing Society; 1999: 32-41.
2. Recommendations for the safe handling of parenteral antineoplastic drugs. Washington, DC: Division of Safety, National Institutes of Health; 1983. US Dept of Heath and Human Services, Public Health Service publication NIH 83-2621.
3. AMA Council on Scientific Affairs. Guidelines for handling parenteral antneoplastics. JAMA.1985; 253: 1590-1591.
4. National Study Commission on Cytotoxic Exposure. Recommendations for handling cytotoxic agents. 1987. Available from Louis P Jeffrey, Chairman, National Study Commission on Cytotoxic Exposure. Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115.
5. Clinical Oncological Society of Australia. Guidelines and recommendations for safe handling of antineoplastic agents. Med J Australia. 1983; 1: 426-428.
6. Jones RB, Frank R, Mass T Safe handling of chemotherapeutic agents: a report from the Mount Sinai Medical Center. CA-A Cancer J for Clin. 1983; 33: 258-263.
7. American Society of Hospital Pharmacists. ASHP technical assistance bulletin on handling cytotoxic and hazardous drugs. Am J Hosp Pharm. 1990; 47: 1033-1049.
8. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines.) Am J Health-Syst Pharm. 1996; 53: 1669-1685.

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