

Vinorelbine Injection, USP

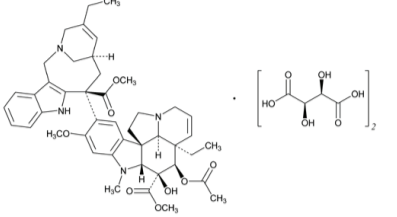


WARNING
Vinorelbine Injection, USP should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. This product is for intravenous (IV) use only. Intrathecal administration of other vinca alkaloids has resulted in death. Syringes containing this product 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 $\geq 1,000$ cells/mm³ prior to the administration of vinorelbine. 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 is injected. Administration of vinorelbine 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 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'-dihydro-4'-deoxy-8-norvincalculoblastine [R-(R₁, R₂)-2,3-dihydroxybutane] di(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 C₂₈H₃₄N₂O₇·2C₄H₈O₆ and molecular weight of 1079.12. The aqueous solubility is $>10,000$ 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 Ca²⁺-translocase activity, 3) cellular respiration, and 4) nucleic acid and lipid biosynthesis. In intact test plates from mouse embryos, vinorelbine, vincristine, and vindesine inhibited mitotic microtubule formation at the same concentration (2 μ M), inducing a blockade of cells at metaphase. Vincristine produced depolymerization of axonal microtubules at 5 μ M, but vindesine and vinorelbine did not have this effect until concentrations of 30 μ M and 40 μ M, 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/m² 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 biphasic 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/m²) 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% \pm 0.7% of a 30-mg/m² 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 \pm 7.8 years; range, 41 to 74 years) with 12 patients \geq 60 years and 6 patients \leq 45 years in 3 studies. Cl (the mean plasma clearance) and t_{1/2} (the terminal phase half-life), and V_d (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/m² intravenously. Cl, V_d, and t_{1/2} were similar to those reported for younger adult patients in previous studies. No interaction between age, systemic exposure (AUC_{0-∞}), and hematology was observed.

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

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

Single-Agent Vinorelbine Tartrate Injection: Single-agent vinorelbine was studied in a North American, randomized clinical trial in which patients with Stage IV NSCLC, no prior chemotherapy, and Karnofsky Performance Status \geq 70 were treated with vinorelbine (30 mg/m²) weekly or 5-Fluorouracil (5-FU) (425 mg/m²) plus leucovorin (LV) (20 mg/m²) IV bolus daily for 5 days every 4 weeks. A total of 211 patients were randomized at a 2:1 ratio to vinorelbine (143) or 5-FU/LV (68). Vinorelbine 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 versus 5-FU/LV, respectively (P = 0.06). The 1-year survival rates were 24% (\pm 4% SE) for vinorelbine and 16% (\pm 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 and 5-FU/LV were 12% and 3%, respectively.

Vinorelbine in Combination with Cisplatin: Vinorelbine plus Cisplatin versus Single-Agent Cisplatin: A Phase III open-label, randomized study was conducted which compared vinorelbine (25 mg/m² per week) plus cisplatin (100 mg/m² every 4 weeks) to single-agent cisplatin (100 mg/m² every 4 weeks) in patients with Stage IV or Stage IIB 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 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 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 plus Cisplatin versus Vindesine plus Cisplatin versus Single-Agent Vinorelbine: In a large European clinical trial, 612 patients with Stage II or IV NSCLC, no prior chemotherapy, and WHO Performance Status of 0, 1, or 2 were randomized to treatment with single-agent vinorelbine (30 mg/m² per week), vinorelbine (30 mg/m² per week) plus cisplatin (120 mg/m² days 1 and 29, then every 6 weeks), and vindesine (3 mg/m² per week for 7 weeks, then every other week) plus cisplatin (120 mg/m² days 1 and 29, then every 6 weeks). Patient characteristics are provided in Table 1. Survival was longer in patients treated with vinorelbine 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 (20, 25, or 30 mg/m² per week) plus cisplatin (120 mg/m² 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 in Combination with Cisplatin in NSCLC

Demographic	Vinorelbine/Cisplatin vs. Single-Agent Cisplatin		Vinorelbine/Cisplatin vs. Vindesine/Cisplatin		Vinorelbine
	Vinorelbine/Cisplatin	Single-Agent Cisplatin	Vinorelbine/Cisplatin	Vindesine/Cisplatin	
Number of patients	214	218	206	200	206
Number of males	146	141	182	179	188
Number 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 IIIB	8%	8%	28%	25%	32%
Stage IV	92%	92%	50%	55%	47%
Local recurrence	NA	NA	2%	3%	3%
Metastatic after surgery	NA	NA	0%	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 ***P = 0.05 vs. single-agent vinorelbine	
12-Month survival rate	38%	22%	35%	27%	30%
Overall response	19%	8%	39%*	19%	14%
P value			P < 0.001	**P = 0.03 vs. vindesine/cisplatin ***P < 0.001 vs. single-agent vinorelbine	

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

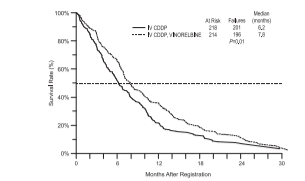
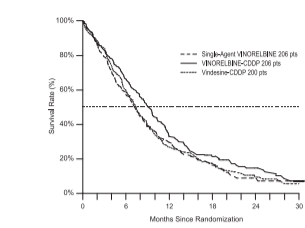


Figure 2. Overall Survival Vinorelbine /Cisplatin versus Vindesine/Cisplatin versus Single-Agent Vinorelbine



INDICATIONS AND USAGE

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

CONTRAINDICATIONS

Administration of Vinorelbine Injection, USP is contraindicated in patients with pretreatment granulocyte counts $<$ 1,000 cells/mm³ (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/mm³. 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 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. 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 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: Teratogenic Effects: Pregnancy Category D:

Vinorelbine 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/m² and 5.5 mg/m², respectively (one third and one sixth the human dose). In nonmaternal studies, fetal weight was reduced and ossification was delayed. There are no studies in pregnant women. If vinorelbine 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.

PRECAUTIONS

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

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

Administration of vinorelbine to patients with prior radiation therapy may result in radiation recall reactions (see ADVERSE REACTIONS and Drug Interactions). Patients with a prior history or pre-existing neuropathy, regardless of etiology, should be monitored for new or worsening signs and symptoms of neuropathy while receiving vinorelbine. Care must be taken to avoid contamination of the eye with concentrations of vinorelbine 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 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 (see ADVERSE REACTIONS: Hematology).

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

Drug Interactions: Acute pulmonary reactions have been reported with vinorelbine 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 used in combination with cisplatin is significantly higher than with single-agent vinorelbine. Patients who receive vinorelbine and paclitaxel, either concomitantly or sequentially, should be monitored for signs and symptoms of neuropathy. Administration of vinorelbine to patients with prior or concomitant radiation therapy may result in radiosensitizing 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 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 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/m²) or approximately one third the human dose) or alternate-day schedule (4.2 mg/m²), 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/m² (approximately one fifteenth and one fourth the human dose) resulted in decreased spermatogenesis and prostate/seminal vesicle secretion.

Pregnancy: Teratogenic Effects: 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, it is recommended that nursing be discontinued in women who are receiving therapy with vinorelbine.

Pediatric Use: Safety and effectiveness of vinorelbine 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 adult patients.

Geriatric Use: Of the total number of patients in North American clinical studies of IV vinorelbine, 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 pharmacokinetics of vinorelbine in elderly and younger adult patients are similar (see CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS

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

Single-Agent Vinorelbine: 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 as a single agent in 3 clinical studies. The dosing schedule in each study was 30 mg/m² vinorelbine on a weekly basis.

Table 2. Summary of Adverse Events in 365 Patients Receiving Single-Agent Vinorelbine*

Adverse Event	All Patients (n = 365)		NSCLC (n = 143)	
	All Patients	NSCLC	All Patients	NSCLC
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) SGO (n = 346)	13%	9%	4%	3%	3%	2%
General	67%	54%	5%	2%	1%	1%
Asthenia	36%	27%	7%	5%	0%	0%
Injection Site Reactions	28%	38%	2%	0%	0%	0%
Injection Site Pain	16%	13%	2%	1%	0%	0%
Phlebitis	7%	10%	$<$ 1%	1%	0%	0%
Digestive						
Nausea	44%	34%	2%	1%	0%	0%
Vomiting	20%	15%	2%	1%	0%	0%
Constipation	35%	29%	3%	2%	0%	0%
Diarrhea	17%	15%	0%	0%	0%	0%
Peripheral Neuropathy*	25%	20%	1%	1%	$<$ 1%	0%
Dyspnea	7%	3%	2%	2%	1%	0%
Allopia	12%	12%	\leq 1%	1%	0%	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. 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. Sepsis deaths occurred in approximately 1% of patients. Prophylactic hematologic growth factors have not been routinely used with vinorelbine. If medically necessary, growth factors may be 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 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. Due to the low incidence of severe nausea and vomiting with single-agent vinorelbine, the use of serotonin antagonists is generally not indicated in patients receiving vinorelbine.

Hepatic: Transient elevations of liver 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 in Combination with Cisplatin:

Vinorelbine 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 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 ($\leq 1,000$ cells/mm³) 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 $>$ 1,000 cells/mm³ 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 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 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 1% 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, and 3 from febrile neutropenia. One death, secondary to respiratory infection unrelated to granulocytopenia, occurred with single-agent cisplatin.

Vinorelbine 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 plus cisplatin (79%) than with either single-agent vinorelbine (53%) or vindesine plus cisplatin (48%). P $<$ 0.0001. Hospitalization due to documented sepsis occurred in 4.4% of patients treated with vinorelbine plus cisplatin; 2% of patients treated with vindesine and cisplatin, and 4% of patients treated with single-agent vinorelbine. Grade 3 and 4 thrombocytopenia was infrequent in patients receiving combination chemotherapy and no events were reported with single-agent vinorelbine.

The incidence of Grade 3 and/or 4 nausea and vomiting, alopecia, and ralopecia were reported more frequently in the cisplatin-containing combinations compared to single-agent vinorelbine. Severe local reactions occurred in 2% of patients treated with combinations containing vinorelbine; none were observed in the vindesine plus single-agent arm. Grade 3 and 4 neurotoxicity was significantly more frequent in patients receiving vindesine plus cisplatin (17%) compared to vinorelbine 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.

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

Adverse Event	Vinorelbine 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%	$<$