HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VINORELBINE INJECTION safely and effectively. See full prescribing information for VINORELBINE INJECTION.

VINORELBINE injection, for intravenous use
Initial U.S. Approval: 1994

WARNING: MYELOSUPPRESSION

See full prescribing information for complete boxed warning.

Severe myelosuppression resulting in serious infection, septic shock, and death can occur (5.1).
Decrease the dose or withhold vinorelbine in accord with recommended dose modifications (2.2).

----------INDICATIONS AND USAGE----------

Vinorelbine Injection is a vinca alkaloid indicated:

In combination with cisplatin for first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) (1)

As a single agent for first-line treatment of patients with metastatic NSCLC (1)

----------DOSAGE AND ADMINISTRATION----------

In combination with cisplatin: 25 to 30 mg/m^2 as an intravenous injection or infusion once weekly (2.1)

Single agent: 30 mg/m^2 as intravenously once a week (2.1)

Adjust dose in patients with decreased neutrophil counts or elevated serum total bilirubin (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Vinorelbine Injection: 10 mg per 1 mL and 50 mg per 5 mL in single-dose vial (3)

----------CONTRAINDICATIONS----------

None

---------- WARNINGS AND PRECAUTIONS----------

Hepatic Toxicity: Monitor hepatic function prior to initiation and during treatment (5.2)

Severe constipation and bowel obstruction, including necrosis and perforation, occur. Institute a prophylactic bowel regimen to mitigate potential constipation, bowel obstruction and/or paralytic ileus (5.3)

Extravasation can result in severe tissue injury, local tissue necrosis and/or thrombophlebitis. Immediately stop vinorelbine and institute recommended management procedures (5.4)

Neurologic Toxicity: Severe

FULL PRESCRIBING INFORMATION

WARNING: MYELOSUPPRESSION

Severe myelosuppression resulting in serious infection, septic shock, hospitalization and death can occur *[see Warnings and Precautions (5.1)].*
Decrease the dose or withhold vinorelbine in accord with recommended dose modifications *[see Dosage and Administration (2.2)].*

1 INDICATIONS AND USAGE

Vinorelbine Injection is indicated:

- In combination with cisplatin for first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC)
- As a single agent for the treatment of patients with metastatic NSCLC

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

In Combination with Cisplatin 100 mg/m^2

- The recommended dosage of Vinorelbine Injection is 25 mg/m^2 administered as an intravenous injection or infusion over 6 to 10 minutes on Days 1, 8, 15 and 22 of a 28-day cycle in combination with cisplatin 100 mg/m^2 on Day 1 only of each 28-day cycle.

In Combination with Cisplatin 120 mg/m^2

- The recommended dosage of Vinorelbine Injection is 30 mg/m^2 administered as an intravenous injection or infusion over 6 to 10 minutes once a week in combination with cisplatin 120 mg/m^2 on Days 1 and 29, then every 6 weeks.

Single Agent

- The recommended dosage of Vinorelbine Injection is 30 mg/m^2 administered intravenously over 6 to 10 minutes once a week.

2.2 Dosage Modifications

Myelosuppression

Hold or decrease the dose of Vinorelbine Injection in patients with decreased neutrophil counts according to the following schema *[see Warnings and Precautions (5.1)]:*

Neutrophils on Day of Treatment (cells/mm^3)	**Percentage of Starting Dose of Vinorelbine Injection**
	100%
1,000 to 1,499	50%

< 1,000	Do not administer Vinorelbine Injection. Repeat neutrophil count in one week. If three consecutive weekly doses are held because neutrophil count is < 1,000 cells/mm^3, discontinue Vinorelbine Injection
Note: For patients who experience fever and/or sepsis while neutrophil count is < 1,500 cells/mm^3 or had 2 consecutive weekly doses held due to neutropenia, subsequent doses of Vinorelbine Injection should be:	
> 1,500	75%
1,000 to 1,499	37.5%
< 1,000	Do not administer Vinorelbine Injection. Repeat neutrophil count in one week.

Hepatic Impairment/Toxicity

Reduce Vinorelbine Injection dose in patients with elevated serum total bilirubin concentration according to the following schema *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]*:

Serum Total Bilirubin Concentration (mg/dl)	**Percentage of Starting Dose of Vinorelbine Injection**
≤ 2.0	100%
2.1 to 3.0	50%
> 3.0	25%

Concurrent Myelosuppression and Hepatic Impairment/Toxicity

In patients with both myelosuppression

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- Ringer's Injection, USP
- Lactated Ringer's Injection, USP

Stability and Storage Conditions of Diluted Solutions

Diluted Vinorelbine Injection may be used for up to 24 hours under normal room light when stored in polyvinyl chloride bags at 5 °to 30 ℃ (41 °to 86 ℉).

Administration

Administer diluted Vinorelbine Injection over 6 to 10 minutes into the side port of a free-flowing intravenous line followed by flushing with at least 75 to 125 mL of one of the solutions.

Vinorelbine Injection must only be administered intravenously. It is extremely important that the intravenous n

5.6 Pulmonary Toxicity and Respiratory Failure

Pulmonary toxicity, including severe acute bronchospasm, interstitial pneumonitis, acute respiratory distress syndrome (ARDS) occur in patients receiving vinorelbine. Interstitial pneumonitis and ARDS included fatalities. The mean time to onset of interstitial pneumonitis and ARDS after vinorelbine administration was one week (range 3 to 8 days) *[see Adverse Reactions (6.1)]*. Interrupt vinorelbine in patients who develop unexplained dyspnea or have any evidence of pulmonary toxicity. Permanently discontinue vinorelbine for confirmed interstitial pneumonitis or ARDS.

5.7 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, vinorelbine can cause fetal harm when administered to a pregnant woman. In animal reproduction studies in mice and rabbits, embryo and fetal toxicity were observed with administration of vinorelbine at doses approximately 0.33 and 0.18 times the human therapeutic dose, respectively.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with vinorelbine and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with vinorelbine and for 3 months after the final dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Myelosuppression *[see Warnings and Precautions (5.1)]*
- Hepatic Toxicity *[see Warnings and Precautions (5.2)]*
- Severe Constipation and Bowel Obstruction *[see Warnings and Precautions (5.3)]*
- Extravasation and Tissue Injury *[see Warnings and Precautions (5.4)]*
- Neurologic Toxicity *[see Warnings and Precautions (5.5)]*
- Pulmonary Toxicity and Respiratory Failure *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under varying designs and in different patient populations, the adverse reaction rates reported in one clinical trial may not be easily compared to those rates reported in another clinical trial and may not reflect the rates actually observed in clinical practice.

Single Agent

The data below reflect exposure to vinorelbine as a single agent administered at a dose of 30 mg/m^2 on a weekly basis to 365 patients enrolled in 3 controlled studies for metastatic NSCLC and advanced breast cancer. The population included 143 patients with previously untreated metastatic NSCLC (Study 3) who received a median of 8 doses of vinorelbine. The patients were aged 32 to 79 (median 61 years), 71% were male, 91% White, 48%

had adenocarcinoma histology. The data also reflect exposure to vinorelbine in 222 patients with previously treated advanced breast cancer who received a median of 10 doses of vinorelbine. Vinorelbine is not indicated for the treatment of breast cancer.

Selected adverse reactions reported in these studies are provided in Tables 1 and 2. The most common adverse rea vinorelbine were leukopenia, neutropenia, anemia, increased aspartate aminotransferase (AST), nausea, vomiting, constipation, asthenia, injection site reaction and peripheral verse reactions were neutropenia, leukopenia, anemia, increased total bilirubin, increased AST, injection site reaction and asthenia.

Approximately 49% of patients with NSCLC who were treated with vinorelbine experienced at least one dose reduction due to an adverse reaction.

Thirteen percent of patients discontinued vinorelbine due to adverse reactions. The most frequent adverse reactions leading to vinorelbine discontinuation were asthenia, dyspnea, nausea, constipation, anorexia, myasthenia and fever.

Table 1: Hematologic Adverse Reactions Experienced in > 5% of Patients Receiving Vinorelbine :

		All Patients (N=365) (%)	**NSCLC (N=143) (%)**
Laboratory			
Hematologic			
Neutropenia	< 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
Anemia	< 11 g/dl	83	77
	< 8 g/dl	9	1
Hospitalizations due to neutropenic complications		9	8

*Grade based on modified criteria from the National Cancer Institute version 1.

Patients with NSCLC had not received prior chemotherapy. The majority of the remaining patients had received prior chemotherapy.

Table 2: Non-hematologic Adverse Reactions Experienced in 5% of Patients Receiving Vinorelbine :

	All Grades		**Grade 3-4**	
	All Patients (%)	**NSCLC (%)**	**All Patients (%)**	**NSCLC (%)**

AST increased (N=346)	67	54	6	3
Bilirubin increased (N=351)	13	9	7	5
Clinical				
Nausea	44	34	2	1
Asthenia	36	27	7	5
Constipation	35	29	3	2
Injection site reaction	28	38	2	5
Injection site pain	16	13	2	1
Neuropathy peripheral	25	20	<2	1
Vomiting	20	15	2	1
Diarrhea	17	13	1	1
Alopecia	12	12	<1	1
Phlebitis	7	10	<1	1
Dyspnea	7	3	3	2

*Grade based on modified criteria from the National Cancer Institute version 1.
Patients with NSCLC had not received prior chemotherapy. The majority of the remaining patients had received prior chemotherapy.
Incidence of paresthesia plus hypesthesia.

Myelosuppression: In clinical trials, Grade 3-4 neutropenia, anemia and thrombocytopenia occurred in 69%, 9% and 1%, respectively of patients receiving single agent vinorelbine. Neutropenia is the major dose-limiting toxicity.

Neurotoxicity: Neurotoxicity was most commonly manifested as constipation, paresthesia, hyperesthesia and hyporeflexia. Grade 3 and 4 neuropathy was observed in 1% of the patients receiving single agent vinorelbine.

Injection Site Reactions: Injection site reactions, including erythema, pain at injection site and vein discoloration, occurred in approximately one third of patients; 5% were severe. Phlebitis (chemical phlebitis) along the vein proximal to the site of injection was reported in 10% of patients.

Cardiovascular Toxicity: Chest pain occurred in 5% of patients; myocardial infarction occurred in 0.1% of patients.

Pulmonary Toxicity and Respiratory Failure: Dyspnea (shortness of breath) was reported in 3% of patients; it was severe in 2%. Interstitial pulmonary changes were documented.

Other: Hemorrhagic cystitis and the syndrome of inappropriate ADH secretion were each reported in <1% of patients.

In Combination with Cisplatin

vinorelbine treated patients reported in a randomized trial comparing the combination of vinorelbine 25 mg/m^2 administered every week of each 28-day cycle and cisplatin 100 mg/m^2 administered on day 1 of each 28-day cycle versus cisplatin alone at the same dose and schedule in patients with previously untreated NSCLC (Study 1).

Patients randomized to vinorelbine plus cisplatin received a median of 3 cycles of treatment and those randomized to cisplatin alone received a median of 2 cycles of treatment. The incidence of Grade 3 and 4

neutropenia was significantly higher in the vinorelbine plus cisplatin arm (82%) compared to the cisplatin alone arm (5%).

Thirty-five percent of the eligible patients in the combination arm required treatment discontinuation due to an adverse reaction compared to 19% in the cisplatin alone arm.

Four patients in the vinorelbine plus cisplatin arm died of neutropenic sepsis. Seven additional deaths were reported in the combination arm: 2 from cardiac ischemia, 1 cerebrovascular accident, 1 multisystem failure due to an overdose of vinorelbine and 3 from febrile neutropenia.

Table 3: Adverse Reactions Experienced by ≥ 10% of Patients on Vinorelbine plus Cisplatin versus Single Agent Cisplatin*

	Vinorelbine 25mg/m^2 plus Cisplatin 100 mg/m^2 (N=212)		**Cisplatin 100 mg/m^2 (N=210)**	
	All Grades (%)	**Grades 3-4 (%)**	**All Grades (%)**	**Grades 3-4 (%)**
Laboratory				
Hematologic				
Neutropenia	89	82	26	5
Anemia	89	24	72	<8
Leukopenia	88	58	31	<1
Thrombocytopenia	29	5	21	<2
Febrile neutropenia	N/A	11	N/A	0
Renal				
Blood creatinine increased	37	4	28	<5
Clinical				
Malaise/Fatigue/Lethargy	67	12	49	76.944 1

¶Neurotoxicity includes peripheral neuropathy and constipation.

6.2 Postmarketing Experience

Risk Summary

Based on findings from animal studies and its mechanism of action

Males

Vinorelbine may damage spermatozoa *[see Nonclinical Toxicology (13.1)]*. Advise males with female sexual partners of reproductive potential to use effective contraception during treatment with vinorelbine and for 3 months after the final dose.

Infertility

Males

Based on animal findings, vinorelbine may impair fertility in males *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

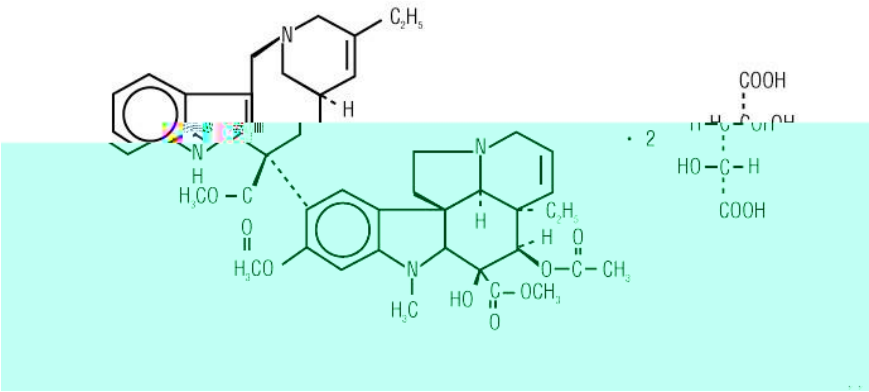
The safety and effectiveness of vinorelbine in pediatric patients have not been established.

Results from a single-arm study of vinorelbine administered at the dose of 33.75 mg/m^2 (for 35 patients) or at the dose of 30 mg/m^2 (for 11 patients) every week for 6 weeks followed by 2 weeks of rest were evaluated (courses of 8 weeks). Forty-six patients age 1 to 25 (median 11 years) with recurrent solid malignant tumors, including rhabdomyosarcoma or undifferentiated sarcoma (N=21 patients), neuroblastoma (N= 4 patients) and central nervous system (CNS) tumors (N=21 patients), were enrolled. The most significant grade 3 or 4

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. If overdosage occurs, general supportive measures together with appropriate blood transfusions, growth factors and antibiotics should be instituted as deemed necessary by the physician.

11 DESCRIPTION

Vinorelbine Injection, USP contains vinorelbine, a semi-synthetic vinca alkaloid. The molecular formula for vinorelbine tartrate is $C_{45}H_{54}N_4O_8$ $_4H_6O_6$. It has a molecular weight of 1079.11. The structural formula is as follows:



Vinorelbine tartrate is a white to light yellow amorphous powder. It is easily soluble in water, very soluble in methanol and practically insoluble in hexane.

Vinorelbine Injection, USP is a sterile nonpyrogenic aqueous solution for intravenous use. Each milliliter of solution contains 10 mg vinorelbine (equivalent to 13.85 mg vinorelbine tartrate) in Water for Injection, USP. The pH of Vinorelbine Injection, USP is approximately 3.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Vinorelbine is a vinca alkaloid that interferes with microtubule assembly. The antitumor activity of vinorelbine is thought to be due primarily to inhibition of mitosis at metaphase through its interaction with tubulin. 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. Vinorelbine inhibited mitotic microtubule formation in intact mouse embryo tectal plates at a concentration of 2

concentration ting a modest selectivity of vinorelbine for mitotic microtubules.

12.3 Pharmacokinetics

The pharmacokinetics of vinorelbine were studied in 49 patients who received doses of 30 mg/m^2 administered as 15- to 20-minute constant-rate infusions. Vinorelbine concentrations in plasma decay in a triphasic manner.

Distribution

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 human plasma over a concentration range of 234 to 1169 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, fluorouracil, or doxorubicin.

Elimination

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.

Metabolism

Vinorelbine undergoes substantial hepatic elimination in humans, with large amounts recovered in feces. 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 vinorelbine is mediated by hepatic CYP3A.

Excretion

After intravenous administration of radioactive vinorelbine, approximately 18% and 46% of administered radioactivity was recovered in urine and feces, respectively. In a different study, 10.9% $\pm$ 0.7% of a 30 mg/m^2 intravenous dose was excreted as parent drug in urine.

Specific Populations

Age has no effect on the pharmacokinetics (CL, V_{SS} and $t_{1/2}$) of vinorelbine.

Drug Interaction Studies

The pharmacokinetics of vinorelbine are not influenced by the concurrent administration of cisplatin.

13 NONCLINICAL TOXICOLOGY

13.1 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.

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 0.14 times the human recommended dose) prior to and during mating. In male rats, administration of vinorelbine twice weekly for 13 or 26 weeks at dose levels of 2.1 and 7.2 mg/m^2 (approximately 0.07 and 0.24 times the recommended human dose), respectively, resulted in decreased spermatogenesis and prostate/seminal vesicle secretion.

14 CLINICAL STUDIES

14.1 Combination Use with Cisplatin

The safety and efficacy of vinorelbine in combination with cisplatin was evaluated in two randomized, multicenter trials.

Cisplatin 100mg/m^2

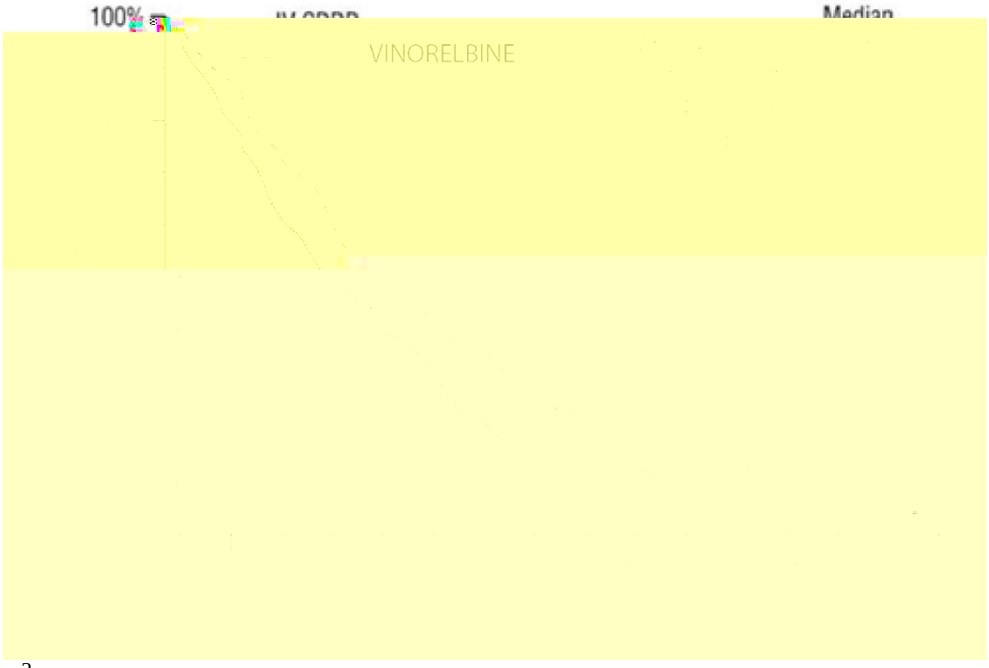
Study 1 was a randomized, multicenter, open-label trial of vinorelbine plus cisplatin and cisplatin alone for the treatment of stage IV or stage IIIb NSCLC in patients with malignant pleural effusion or multiple lesions in more than one lobe of the ipsilateral lung who had not received prior chemotherapy. A total of 432 patients were randomized 1:1 to receive either vinorelbine 25 mg/m^2 on Day 1 then every week of each 28-day cycle plus cisplatin 100 mg/m^2 administered on Day 1 of each 28-day cycle (N=214) or single agent cisplatin 100 mg/m^2 on Day 1 of each 28-day cycle (N=218).

Patient demographics and disease characteristics were similar between arms. Of the overall study population, the median age was 64 (range 33 to 84), 66% were male, 80% were White, 92% had stage IV disease and 8% stage IIIB, 53% had adenocarcinoma, 21% squamous cell, 14% large cell histology. The major efficacy outcome measure was overall survival. The efficacy results are presented in Table 7 and Figure 1.

Table 7. Efficacy Results (Study 1)

	Vinorelbine plus Cisplatin (N=214)	Cisplatin (N=218)
Overall Survival		
Median Survival in months (95% CI)	7.8 (6.9, 9.6)	6.2 (5.4, 7.7)
Unstratified log-rank p-value	0.01	
Overall Response rate (ORR) Evaluable patients ORR (95% CI)	N=206 19% (14%, 25%)	N=209 8% (5%, 13%)
Chi-square test p-value	<0.001	

Figure 1: Overall Survival Vinorelbine / Cisplatin versus Single Agent Cisplatin



Cisplatin 120mg/m^2

Study 2 was a randomized, 3-arm, open-label, multicenter trial of vinorelbine plus cisplatin, vindesine plus cisplatin and vinorelbine as a single agent for the treatment of patients with stage III or IV NSCLC who had not received prior chemotherapy. The study was conducted in Europe. A total of 612 patients were randomized 1:1:1 to receive vinorelbine 30 mg/m^2 every week of a 6-week cycle plus cisplatin 120 mg/m^2 on Day 1 and Day 29, then every 6 weeks thereafter (N=206); and vindesine 3 mg/m^2 for 6 weeks, then every other week thereafter plus cisplatin 120 mg/m^2 on Days 1 and Day 29, then every 6 weeks thereafter (N=200) or vinorelbine 30mg/m^2 every week of a 6-week cycle (N=206). The main efficacy outcome measure was to compare overall survival between vinorelbine plus cisplatin and vindesine plus cisplatin. The other efficacy outcome measure was to compare overall survival in the better of the two combination regimens to that of vinorelbine as a single agent.

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Table 8. Efficacy Results (Study 2)

	Vinorelbine (N=206)	Vinorelbine plus cisplatin (N=206)	Vindesine plus cisplatin (N=200)

25021-204-05	50 mg per 5 mL Single-Dose Vial	1 vial per carton

Vinorelbine Injection, USP is a clear, colorless to pale yellow aqueous solution.

Storage Conditions
Store refrigerated between 2 °and 8 ℃ (36 °and 46 ℉).

Do not freeze.
Protect from light. Retain in carton until time of use.
Discard unused portion.

Unopened vials of Vinorelbine Injection, USP are stable at 25 ℃ (77 ℉) for up to 72 hours. Store diluted solutions of Vinorelbine Injection, USP at 5 °to 30 ℃ (41 °to 86 ℉) *[see Dosage and Administration (2.3)]*.

Vinorelbine Injection, USP is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

Sterile, Nonpyrogenic, Preservative-free.
The container closure is not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

Myelosuppression
Advise patients to contact a healthcare provider for new onset fever, or symptoms of infection *[see Warnings and Precautions (5.1)]*.

Constipation and Bowel Obstruction
Advise patients to follow a diet rich in fibers, drink fluids to stay well hydrated and use stool softeners to avoid constipation. Contact a health care provider for severe constipation, new onset abdominal pain, nausea and vomiting *[see Warnings and Precautions (5.3)]*.

Neurologic Toxicity
Advise patients to contact a health care provider for new onset or worsening of numbness, tingling, decrease sensation or muscle weakness *[see Warnings and Precautions (5.5)]*.

Pulmonary Toxicity
Advise patients to contact a healthcare provider for new onset or worsening of shortness of breath, cough, wheezing or other new pulmonary symptoms *[see Warnings and Precautions (5.6)]*.

Embryo-Fetal Toxicity

- Advise pregnant women of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.1, 8.3)]*.
- Advise females of reproductive potential to use effective contraception during treatment with Vinorelbine Injection and for 6 months after the final dose *[see Use in Specific Populations (8.3)]*.

- Advise males with female partners of reproductive potential to use effective contraception during treatment with Vinorelbine Injection and for 3 months after the final dose *[see Use in Specific Populations (8.3) and Nonclinical Toxicology (13.1)]*.

Lactation

Advise women not to breastfeed during treatment with Vinorelbine Injection and for 9 days after the final dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise males of reproductive potential that Vinorelbine Injection may impair fertility *[see Use in Specific Populations (8.3)]*.

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Revised: April 2020

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