

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

NAVELBINE® (vinorelbine tartrate) 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 may occur (5.1).
- Decrease the dose or withhold NAVELBINE in accord with recommended dose modifications (2.2).

INDICATIONS AND USAGE

NAVELBINE 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/m² as a single intravenous injection weekly (2.1)
- Single agent: 30 mg/m² as a single intravenous injection weekly (2.1)
- Adjust the dose in patients with decreased neutrophil counts or elevated serum total bilirubin (2.2)

DOSAGE FORMS AND STRENGTHS

- Injection: single use vials of 10 mg/1 mL and 50 mg/5 mL (3)

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

- Hepatic toxicity: monitor liver function during treatment (5.2)

- Severe constipation and bowel obstruction including necrosis and perforation can occur. Institute a prophylactic bowel regimen to mitigate potential constipation. Monitor for abdominal pain and severe constipation (5.3)
- Extravasation can result in severe tissue injury, necrosis and/or thrombophlebitis. Immediately stop NAVELBINE and institute recommended management procedures (5.4)
- Neurologic toxicity: severe sensory and motor neuropathies can occur. Monitor patients for new or worsening signs and symptoms of neuropathy (5.5)
- Pulmonary toxicity and respiratory failure can occur with use of NAVELBINE. Monitor patients respiratory disorders: dyspnea and bronchospasm. Interrupt NAVELBINE in patients who develop unexplained dyspnea (5.6)
- Embryo-fetal toxicity: can cause fetal harm. Advise females of reproductive potential of potential risk to the fetus (5.7, 8.1).

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥ 20%) are neutropenia, anemia, liver enzyme elevation, nausea, vomiting, asthenia, constipation, injection site reaction, and peripheral neuropathy (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pierre Fabre Pharmaceuticals at 1- 855-PFPHARM (1-855-737-4276) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Inhibitors of CYP3A4: increased severity of adverse reactions (7.1)

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: discontinue drug or nursing taking into consideration importance of drug to mother (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 03/2014

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FULL PRESCRIBING INFORMATION

WARNING: MYELOSUPPRESSION

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

1 INDICATIONS AND USAGE

NAVELBINE 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 Dose

In Combination with Cisplatin 100 mg/m²

- The recommended dose of NAVELBINE is 25 mg/m² administered as an intravenous injection or infusion over 6 to 10 minutes on days 1, 8, 15 and 21 of a 28 day cycle in combination with cisplatin 100 mg/m² on day 1 only of each 28 day cycle.

In Combination with Cisplatin 120 mg/m²

- The recommended dose of NAVELBINE is 30 mg/m² administered as an intravenous injection or infusion over 6 to 10 minutes once a week in combination with cisplatin 120 mg/m² on days 1 and 29, then every 6 weeks.

Single-Agent

- The recommended dose of NAVELBINE is 30 mg/m² administered intravenously over 6 to 10 minutes once a week.

2.2 Dose Modifications

Hematologic Toxicity

[see [Warnings and Precautions \(5.1\)](#)]

Hold or decrease the dose of NAVELBINE in patients with decreased neutrophil counts using the following schema.

Neutrophils on Day of Treatment (Cells/mm ³)	Percentage of Starting Dose of NAVELBINE
≥ 1,500	100%
1,000 to 1,499	50%
< 1,000	Do not administer NAVELBINE. Repeat neutrophil count in one week. If three consecutive weekly doses are held because Neutrophil count is < 1,000 cells/mm ³ , discontinue NAVELBINE
Note : For patients who experience fever and/or sepsis while neutrophil count is < 1,500 or had 2 consecutive weekly doses held due to neutropenia, subsequent doses of NAVELBINE should be:	
> 1,500	75%
1,000 to 1,499	37.5%
< 1,000	Do not administer NAVELBINE. Repeat neutrophil count in one week.

Hepatic Impairment/Toxicity

[see [Warnings and Precautions \(5.2\)](#) and [Use in Specific Populations \(8.6\)](#)]

Reduce NAVELBINE dose in patients with elevated serum total bilirubin concentration according to the following schema:

Serum total bilirubin concentration (mg/dl)	Percentage of Starting Dose of NAVELBINE
≤ 2.0	100%
2.1 to 3.0	50%
> 3.0	25%

Concurrent Hematologic Toxicity and Hepatic Impairment

In patients with both hematologic toxicity and hepatic impairment, administer the lower of the doses based on the corresponding starting dose of NAVELBINE determined from the above schemas.

Neurologic Toxicity

[see [Warnings and Precautions \(5.5\)](#)]

Discontinue NAVELBINE for NCI CTCAE Grade 2 or higher peripheral neuropathy or autonomic neuropathy causing constipation.

2.3 Preparation and Administration

Preparation of NAVELBINE

Dilute NAVELBINE in either a syringe or intravenous bag using one of the recommended solutions.

Syringe

Dilute to a concentration between 1.5 and 3 mg/mL. The following solutions may be used for dilution:

- 5% Dextrose Injection, USP
- 0.9% Sodium Chloride Injection, USP

Intravenous Bag

Dilute 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

Diluted NAVELBINE 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).

Administration

Administer diluted NAVELBINE 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.

NAVELBINE must only be administered intravenously. It is extremely important that the intravenous needle or catheter be properly positioned before any NAVELBINE is injected.

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, NAVELBINE should not be administered.

Management of Suspected Extravasation

- If NAVELBINE leakage into surrounding tissue occurs or is suspected, immediately stop administration of NAVELBINE and initiate appropriate management measures in accordance with institutional policies. [see [Warnings and Precautions \(5.4\)](#).]

2.4 Procedures for Proper Handling and Disposal

Handle and dispose NAVELBINE consistent with recommendations for the handling and disposal of hazardous drugs².

Exercise caution in handling and preparing the solution of NAVELBINE. The use of gloves is recommended. If the solution of NAVELBINE contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water.

Avoid contamination of the eye with NAVELBINE. If exposure occurs, flush the eyes with water immediately and thoroughly.

3 DOSAGE FORMS AND STRENGTHS

NAVELBINE Injection

Clear colorless to pale yellow solution in single use vials:

1 mL (10 mg/ 1 mL)

5 mL (50 mg/ 5 mL)

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Myelosuppression manifested by neutropenia, anemia and thrombocytopenia occur with NAVELBINE® as a single agent and in combination with cisplatin [see *Adverse Reactions (6.1 and 6.2)*]. Neutropenia is the major dose-limiting toxicity with NAVELBINE. Grade 3-4 neutropenia occurred in 53% of patients treated with NAVELBINE at 30 mg/m² per week. Dose adjustment due to myelosuppression occurred in 51% of patients (Study 2). In clinical trials with NAVELBINE administered at 30 mg/m² per week, neutropenia resulted in hospitalizations for pyrexia and/or sepsis in 8% of patients. Death due to sepsis occurred in 1% of patients.

Neutropenia nadirs occur between 7 and 10 days after dosing with neutropenia count recovery usually occurring within the following 7 to 14 days.

Monitor complete blood counts prior to each dose of NAVELBINE. Do not administer NAVELBINE to patients with neutrophil counts $<1,000$ cells/mm³. Adjustments in the dosage of NAVELBINE should be based on neutrophil counts obtained on the day of treatment [*see [Dosage and Administration \(2.2\)](#)*].

5.2 Hepatic Toxicity

Drug-induced liver injury manifest by elevations of aspartate aminotransferase and bilirubin can occur in patients receiving NAVELBINE alone or in combination with cytotoxic agents. Assess hepatic function prior to initiation of NAVELBINE and periodically during treatment. Reduce the dose of NAVELBINE for patients who develop elevations in total bilirubin ≥ 2 times upper limit of normal [*see [Dosage and Administration \(2.2\)](#) and [Use in Specific Populations \(8.5\)](#)*].

5.3 Severe Constipation and Bowel Obstruction

Severe and fatal paralytic ileus, constipation, intestinal obstruction, necrosis, and perforation occur with NAVELBINE administration. Institute a prophylactic bowel regimen to mitigate potential constipation, bowel obstruction and/or paralytic ileus, considering adequate dietary fiber intake, hydration, and routine use of stool softeners.

5.4 Extravasation and Tissue Injury

Extravasation of NAVELBINE can result in severe irritation, local tissue necrosis and/or thrombophlebitis. If signs or symptoms of extravasation occur, immediately stop administration of NAVELBINE and institute recommended management procedures. [*see [Dosage and Administration \(2.2\)](#) and [Adverse Reaction \(6.1\)](#)*]

5.5 Neurologic Toxicity

Sensory and motor neuropathies, including severe neuropathies, occur in patients receiving NAVELBINE. Monitor patients for new or worsening signs and symptoms of neuropathy such as paresthesia, hyperesthesia, hyporeflexia and muscle weakness while receiving NAVELBINE. Discontinue NAVELBINE for NCI CTCAE Grade 2 or greater neuropathy [*see [Dosage and Administration \(2.2\)](#) and [Adverse Reaction \(6.1\)](#)*]

5.6 Pulmonary Toxicity and Respiratory Failure

Pulmonary toxicity, including severe acute bronchospasm, interstitial pneumonitis, acute respiratory distress syndrome (ARDS) occurs with use of NAVELBINE. 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 NAVELBINE in patients who develop unexplained dyspnea, or have any evidence of pulmonary toxicity. Permanently discontinue NAVELBINE for confirmed interstitial pneumonitis or ARDS.

5.7 Embryo-Fetal Toxicity

NAVELBINE 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. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus. Advise females of reproductive potential to use highly effective contraception during therapy with NAVELBINE [*see [Use in Specific Populations \(8.1, 8.7\)](#)*].

6 ADVERSE REACTIONS

The following serious adverse reactions, which may include fatalities, are discussed in greater detail in other sections of the label:

- Myelosuppression [*see Warnings and Precautions (5.1)*]
- Pulmonary Toxicity and Respiratory Failure [*see Warnings and Precautions (5.2)*]
- Constipation and Bowel Obstruction [*see Warnings and Precautions (5.3)*]
- Extravasation Tissue Injury [*see Warnings and Precautions (5.4)*]
- Neurologic Toxicity [*see Warnings and Precautions (5.5)*]
- Hepatic Toxicity [*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 NAVELBINE as a single agent administered at a dose of 30 mg/m² on a weekly basis to 365 patients enrolled in 3 controlled studies for metastatic NSCLC and advanced breast cancer. The population included 143 previously untreated metastatic NSCLC patients (Study 3) who received a median of 8 doses of NAVELBINE. The patients were aged 32 to 79 (median 61 years), 71% were male, 91% Caucasian, 48% had adenocarcinoma histology. The data also reflect exposure to NAVELBINE in 222 patients with previously treated advanced breast cancer who received a median of 10 doses of NAVELBINE. NAVELBINE 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 reactions ($\geq 20\%$) of single agent NAVELBINE were leukopenia, neutropenia, anemia, Aspartate aminotransferase (AST) elevation, nausea, vomiting, constipation, asthenia, injection site reaction, and peripheral neuropathy. The most common ($\geq 5\%$) Grade 3 or 4 adverse reactions were neutropenia, leukopenia, anemia, increased total bilirubin, AST elevation, injection site reaction and asthenia. Approximately 49% of NSCLC patients treated with Navelbine experienced at least one dose reduction due to an adverse reaction. Thirteen percent of patients discontinued NAVELBINE due to adverse reactions. The most frequent adverse reactions leading to NAVELBINE discontinuation were asthenia, dyspnea, nausea, constipation, anorexia, myasthenia and fever.

Table 1: Hematologic Adverse Reactions Experienced in > 5% of Patients Receiving NAVELBINE*†:

		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%
Anaemia	< 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 NAVELBINE*†:

	All grades		Grades 3+4	
	All Patients	NSCLC	All Patients	NSCLC
Laboratory Hepatic				
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.

‡ Incidence of paresthesia plus hypesthesia.

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

Myelosuppression: In clinical trials, Grade 3-4 neutropenia, anemia, and thrombocytopenia occurred in 69%, 9% and 1%, respectively of patients receiving single-agent NAVELBINE. 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 NAVELBINE.

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 less than 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

Table 3 presents the incidence of selected adverse reactions, occurring in $\geq 10\%$ of NAVELBINE treated patients reported in a randomized trial comparing the combination of NAVELBINE 25 mg/m² administered every week of each 28-day cycle and cisplatin 100 mg/m² 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 NAVELBINE plus cisplatin received a median of 3 cycles of treatment and those randomized to cisplatin alone received a median of 2 cycles of treatment. 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. The incidence of Grade 3 and 4 neutropenia was significantly higher in the NAVELBINE plus cisplatin arm (82%) compared to the cisplatin alone arm (5%). Four patients in the NAVELBINE 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 NAVELBINE, and 3 from febrile neutropenia.

Table 3: Adverse Reactions Experienced by $\geq 10\%$ of Patients on NAVELBINE plus Cisplatin versus Single-Agent Cisplatin*

	NAVELBINE 25mg/m ² plus Cisplatin 100 mg/m ² (n=212)		Cisplatin 100mg/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%	8%
Vomiting	60%	13%	60%	14%
Nausea	58%	14%	57%	12%
Decreased appetite	46%	0%	37%	0%
Constipation	35%	3%	16%	1%
Alopecia	34%	0%	14%	0%
Weight decreased	34%	1%	21%	<1%
Fever without infection	20%	2%	4%	0%
Hearing impaired	18%	4%	18%	<4%
Injection site reaction	17%	<1%	1%	0%
Diarrhea	17%	<3%	11%	<2%
Paraesthesia	17%	<1%	10%	<1%
Taste alterations	17%	0%	15%	0%
Peripheral numbness	11%	2%	7%	<1%
Myalgia/Arthralgia	12%	<1%	3%	<1%
Phlebitis/Thrombosis/Embolism	10%	3%	<1%	<1%
Weakness	12%	<3%	7%	2%
Infection	11%	<6%	<1%	<1%
Respiratory tract infection	10%	<5%	3%	3%

* Graded according to the standard SWOG criteria version 1.

* Categorical toxicity grade not specified

Table 4 presents the incidence of selected adverse reactions, occurring in $\geq 10\%$ of NAVELBINE treated patients reported in a randomized trial of NAVELBINE plus cisplatin, vindesine plus cisplatin and NAVELBINE alone in patients with stage III or IV NSCLC who had not received prior chemotherapy. A total of 604 patients received either NAVELBINE 30 mg/m² every week plus cisplatin 120 mg/m² on Day 1 and Day 29, then every 6 weeks thereafter (N=207), vindesine 3 mg/m² for 6 weeks, then every other week thereafter plus cisplatin 120 mg/m² on Days 1 and Day 29, then every 6 weeks thereafter (N=193) or NAVELBINE 30mg/m² every week (N=204).

Patients randomized to NAVELBINE plus cisplatin received a median of 15 weeks of treatment, vindesine plus cisplatin 12 weeks and NAVELBINE received 13 weeks. Study discontinuation due to an adverse reaction was required in 27, 22 and 10% of the patients randomized to NAVELBINE plus cisplatin, vindesine plus cisplatin and cisplatin alone arms, respectively. Grade 3 and 4 neutropenia was significantly greater in the NAVELBINE plus cisplatin arm (78%) compared to vindesine plus cisplatin (48%) and NAVELBINE alone (53%). Neurotoxicity, including peripheral neuropathy and constipation was reported in 44% (Grades 3-4, 7%) of the patients receiving NAVELBINE plus cisplatin, 58% (Grades 3-4, 17%) of the patients receiving vindesine and cisplatin and 44% (Grades 3-4, 8.5%) of the patients receiving NAVELBINE alone.

Table 4: Adverse Reactions Experienced by $\geq 10\%$ of Patients from a Comparative Trial of NAVELBINE Plus Cisplatin versus Vindesine Plus Cisplatin versus Single-Agent NAVELBINE*

	NAVELBINE/Cisplatin†		Vindesine/Cisplatin‡		NAVELBINE§	
	All Grades	Grades 3+4	All Grades	Grades 3+4	All Grades	Grades 3+4
Laboratory						
Hematologic						
Neutropenia	95%	78%	79%	48%	85%	53%
Leukopenia	94%	57%	82%	27%	83%	32%
Thrombocytopenia	15%	4%	10%	3.5%	3%	0%
Renal						
Blood creatinine increased †	46%	N/A	37%	N/A	13%	N/A
Clinical						
Nausea/Vomiting	74%	30%	72%	25%	31%	2%
Alopecia	51%	7.5%	56%	14%	30%	2%
Neurotoxicity ¶	44%	7%	58%	17%	44%	8.5%
Diarrhoea	25%	1.5%	24%	1%	12%	0.5%
Injection site reaction	17%	2.5%	7%	0%	22%	2%
Ototoxicity	10%	2%	14%	1%	1%	0%

* Grade based on criteria from the World Health Organization (WHO).

† n=194 to 207; all patients receiving NAVELBINE/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 NAVELBINE with laboratory and non-laboratory data.

† Categorical toxicity grade not specified.

¶ Neurotoxicity includes peripheral neuropathy and constipation.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of NAVELBINE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections and infestations: pneumonia

Immune system disorders: anaphylactic reaction, pruritus, urticaria, angioedema

Nervous system disorders: loss of deep tendon reflexes, muscular weakness, gait disturbance, headache

Ear and labyrinth disorders: vestibular disorder, hearing impaired

Cardiac disorders: tachycardia

Respiratory disorders: pulmonary edema

Vascular disorders: pulmonary embolism, deep vein thrombosis, hypertension, hypotension, flushing, vasodilatation

Gastrointestinal disorders: mucosal inflammation, dysphagia, pancreatitis

Skin disorders: generalized cutaneous reactions (rash)

Musculoskeletal and connective tissue disorders: jaw pain, myalgia, arthralgia

General disorders and administration site conditions: injection site rash, urticaria, blistering, sloughing of skin

Injury, poisoning and procedural complications: radiation recall phenomenon, dermatitis, esophagitis

Laboratory abnormalities: electrolyte imbalance including hyponatremia

Other: tumor pain, back pain, abdominal pain

7 DRUG INTERACTIONS

7.1 CYP3A Inhibitors

Exercise caution in patients concurrently taking drugs known to inhibit drug metabolism by hepatic cytochrome P450 isoenzymes in the CYP3A subfamily. Concurrent administration of NAVELBINE with an inhibitor of this metabolic pathway may cause an earlier onset and/or an increased severity of adverse reactions.

8 USE IN SPECIFIC POPULATION

8.1 Pregnancy

Pregnancy Category D

Risk Summary

NAVELBINE 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. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus.

Animal Data

In a mouse embryofetal development study, administration of a single dose of vinorelbine at a dose level of 9 mg/m² or greater (approximately 0.33 times the recommended human dose based on body surface area) was embryotoxic and fetotoxic. Vinorelbine was embryotoxic and fetotoxic to pregnant rabbits when administered every 6 days during the period of organogenesis at doses of 5.5 mg/m² (approximately 0.18 times the recommended human dose based on body surface area) or greater. At doses that did not cause maternal toxicity in either species, vinorelbine administration resulted in reduced fetal weight and delayed ossification.

8.3 Nursing Mothers

It is not known whether this drug is present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from vinorelbine, a decision should be made whether to discontinue nursing or discontinue the drug taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of NAVELBINE in pediatric patients have not been established. Results from a single-arm study of NAVELBINE administered at the dose of 33.75 mg/m² (for 35 patients) or at the dose of 30mg/m² (for 11 patients) every week during 6 weeks followed by 2 weeks of rest was 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 hematological adverse reactions were neutropenia (70%) and anemia (33%). The most significant grade 3 or 4 non-hematological toxicity adverse reactions were motor (15%) or cranial (13%) neuropathy, hypoxia (13%) and dyspnea (11%). Objective tumor response was observed in 2 out of 21 patients with rhabdomyosarcoma or undifferentiated sarcoma. No objective tumor response was observed in patients with CNS tumors (N=21) or neuroblastoma (N=4).

8.5 Geriatric Use

Of the 769 number of patients who received NAVELBINE alone and NAVELBINE in combination with Cisplatin in studies 1, 2 and 3, 247 patients were 65 years of age or older. No overall differences in safety, efficacy and pharmacokinetic parameters were observed between these patients and younger patients. [*see [Clinical Pharmacology \(12.3\)](#)*].

8.6 Hepatic Impairment

The influence of hepatic impairment on the pharmacokinetics of NAVELBINE has not been evaluated, but the liver plays an important role in the metabolism of NAVELBINE. Elevations of aspartate aminotransferase occur in > 60% of the patients receiving NAVELBINE alone (6% Grade 3-4). Therefore, exercise caution in patients with hepatic impairment. Reduce the dose of NAVELBINE for patients with bilirubin elevation [*see [Dosage and Administration \(2.2\)](#) and [Warnings and Precautions \(5.2\)](#)*].

8.7 Females and Males of Reproductive Potential

Contraception

Females

NAVELBINE can cause fetal harm when administered to a pregnant woman [*see [Use in Specific Populations \(8.1\)](#)*]. Advise female patients of reproductive potential to use highly effective contraception during therapy with NAVELBINE.

Males

NAVELBINE may damage spermatozoa [*see [Nonclinical Toxicology \(13.1\)](#)*]. Males with female sexual partners of reproductive potential should use highly effective contraception during and for 3 months after therapy with NAVELBINE.

Fertility

Males

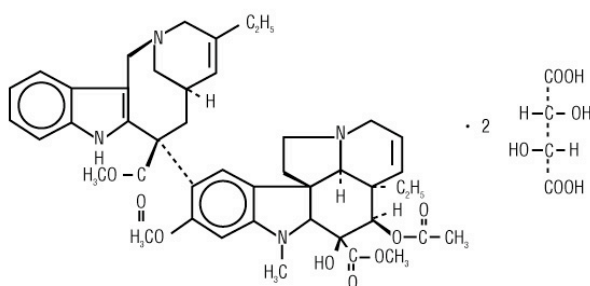
Based on animal findings, NAVELBINE may cause decreased fertility in males [see *Nonclinical Toxicology (13.1)*]

10 OVERDOSAGE

There is no known antidote for overdoses of NAVELBINE. Overdoses involving quantities up to 10 times the recommended dose (30 mg/m²) 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 NAVELBINE. 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

NAVELBINE (vinorelbine tartrate) is a semi-synthetic vinca alkaloid for intravenous injection. Chemically, vinorelbine tartrate is 3',4'-didehydro-4'-deoxy-C'-norvincalcoloblastine [R-(R*,R*)-2, 3-dihydroxybutanedioate (1:2)(tartrate)] and has the following structure:



C₄₅H₅₄N₄O₈ · 2C₄H₆O₆
M.W. 1079.12.

NAVELBINE Injection is a sterile nonpyrogenic aqueous solution. Each milliliter of solution contains 10 mg vinorelbine tartrate in Water for Injection. The pH of NAVELBINE Injection 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 μM inducing a blockade of cells at metaphase, but produced depolymerization of axonal microtubules at a concentration 40 μM, suggesting 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/m² administered as 15- to 20-minute constant-rate infusions. Vinorelbine concentrations in plasma decay in a triphasic manner. 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.

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, 5-fluorouracil, or doxorubicin.

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/m²) yield very small, if any, quantifiable levels of either metabolite in blood or urine. The metabolism of vinorelbine is mediated by hepatic cytochrome P450 isoenzymes in the CYP3A subfamily.

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% ± 0.7% of a 30-mg/m² intravenous dose was excreted as parent drug in urine.

Specific Populations

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

Drug Interactions

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 NAVELBINE 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/m², approximately one third the human dose) or alternate-day schedule (4.2 mg/m², 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/m² (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 NAVELBINE in combination with cisplatin was evaluated in two randomized, multicenter trials.

Cisplatin 100mg/m²

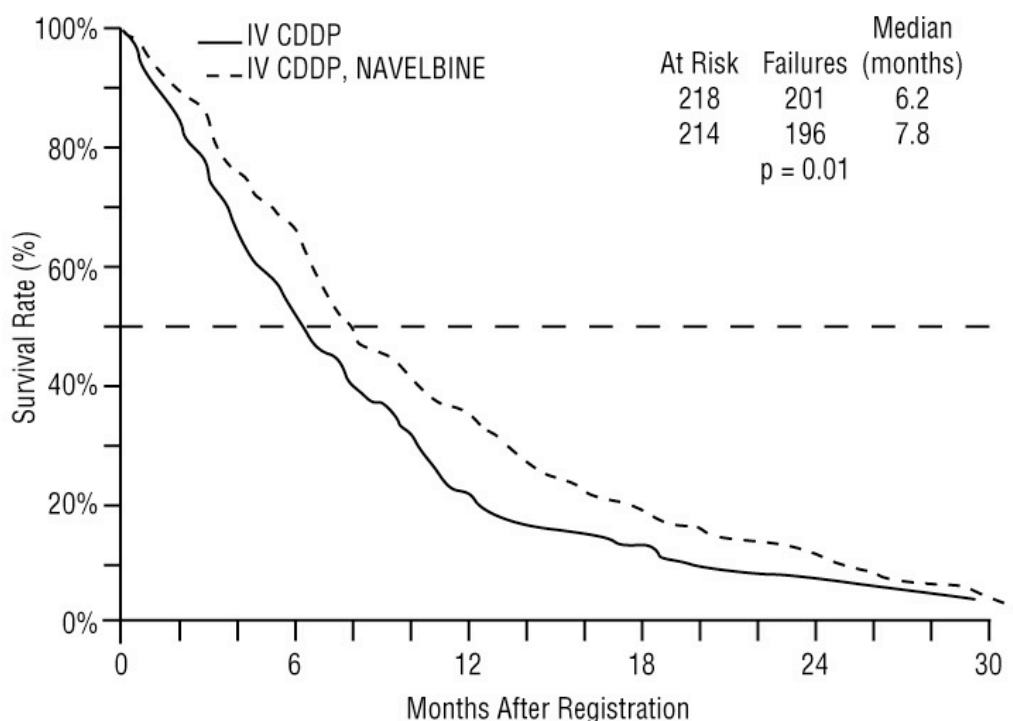
Study 1 was a randomized, multicenter, open-label trial of NAVELBINE plus cisplatin and cisplatin alone for the treatment of stage IV or stage IIIB NSCLC patients with malignant pleural effusion or multiple lesions in more than one lobe of the ipsilateral lung who had not received prior chemotherapy. A total of 432 patients were randomized 1:1 to receive either NAVELBINE 25 mg/m² on Day 1 then every week of each 28-day cycle with cisplatin 100 mg/m² administered on Day 1 of each 28-day cycle (N=214) or cisplatin 100 mg/m² 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 33-84), 66% were male, 80% were Caucasian, 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)

	NAVELBINE plus Cisplatin (N=214)	Cisplatin Alone (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	N = 206	N=209
ORR (95% CI)	19% (14%, 25%)	8% (5%, 13%)
Chi-square test p-value	<0.001	

Figure 1: Overall Survival NAVELBINE / Cisplatin versus Single-Agent Cisplatin



Cisplatin 120mg/m²

Study 2 was a randomized, 3-arm, open-label, multicenter trial of NAVELBINE plus cisplatin, vindesine plus cisplatin and NAVELBINE alone 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 NAVELBINE 30 mg/m² every week of a 6-week cycle plus cisplatin 120 mg/m² on Day 1 and Day 29, then every 6 weeks thereafter (N=206); and vindesine 3 mg/m² for 6 weeks, then every other week thereafter plus cisplatin 120 mg/m² on Days 1 and Day 29, then every 6 weeks thereafter (N=200) or NAVELBINE 30mg/m² every week of a 6-week cycle (N=206). The main efficacy outcome measure was to compare overall survival between NAVELBINE 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 NAVELBINE alone.

Patient demographics were in general similar between arms: the median age of the overall population was 60 years (range 30 to 75), 90% were male, 78% had WHO performance status of 0 or 1. Tumor characteristics were in general similar with the exception of histologic subtype of NSCLC. Adenocarcinoma was the histologic subtype in 32% of patients in the NAVELBINE plus cisplatin arm, 40% of patients in vindesine plus cisplatin arm and 28% of patients on the NAVELBINE alone arm. Ten percent of the patients had stage IIIA disease, 28% stage IIIB and 50% stage IV. Twelve percent of the patients had received prior surgery or radiotherapy.

The efficacy results of Study 2 are presented in Table 8.

Table 8. Efficacy Results (Study 2)

	NAVELBINE Alone (N=206)	NAVELBINE plus cisplatin (N=206)	Vindesine plus cisplatin (N=200)
Median survival in months (99.5% CI)	7.2 (5.4-9.1)	9.2 (7.4-11.1)	7.4 (6.1-9.1)
Unstratified log-rank p-value	n/a ¹	0.087	
	0.05		n/a
Overall Response (ORR) Evaluable Patients ORR (95% CI)	N=205 14% (10%, 20%)	N=203 28% (22%, 35%)	N=198 19% (14%, 25%)
Chi-square test p-value	n/a	0.03	
	< 0.001		n/a

¹n/a = not applicable

14.2 Single Agent

The safety and efficacy of NAVELBINE as a single agent was evaluated in one randomized multi-center trial.

Study 3 was a randomized, open-label clinical trial of NAVELBINE or 5-Fluorouracil (5-FU) plus leucovorin (LV) in patients with Stage IV NSCLC who had not received prior chemotherapy. A total of 211 patients were randomized 2:1 to receive NAVELBINE 30 mg/m² weekly of a 8-week cycle (N=143) or 5-FU 425 mg/m² bolus intravenously plus LV 20 mg/m² bolus intravenously daily for 5 days of a 4-weeks cycle (N=68).

Patient demographics and disease characteristics were in general similar between arms. In the overall population, the median age was 61 years (range 32 - 83), 74% were male, 88% were Caucasian, 46% had adenocarcinoma histology. Fifty percent of the patients had Karnofsky performance status \geq 90 in the NAVELBINE arm compared to 38% in the 5-FU and LV arm.

The primary efficacy outcome of the study was overall survival. The median survival time was 30 weeks versus 22 weeks for patients receiving NAVELBINE versus 5-FU/LV, respectively (P=0.06). Partial objective responses were observed in 11.1% (95% CI=6.2%, 17.9%) and 3.5% (95% CI=0.4%, 11.9%) of patients who received NAVELBINE and 5-FU/LV, respectively.

15 REFERENCES

1. OSHA. <http://www.osha.gov/SLTC/hazardousdrugs/index.html>

16 HOW SUPPLIED/STORAGE AND HANDLING

NAVELBINE Injection is a clear, colorless to pale yellow aqueous solution available in single-dose vials with royal blue caps, individually packaged in a carton as:

- 10 mg/1 mL (NDC 64370-532-01).
- 50 mg/5 mL (NDC 64370-532-02).

Store the vials at 2° to 8°C (36° to 46°F) in the carton. Protect from light. DO NOT FREEZE. Unopened vials of NAVELBINE are stable at 25°C (77°F) for up to 72 hours.

NAVELBINE is a cytotoxic drug. Follow applicable special handling and disposal procedures.¹

17 PATIENT COUNSELING INFORMATION

Inform patients of the following:

- 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)*]
- Females and Males of Reproductive Potential
 - o NAVELBINE can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use highly effective contraception during treatment with NAVELBINE, and to contact their healthcare provider if they become pregnant, or if pregnancy is suspected [*see Warnings and Precautions (5.7) and Use in Specific Populations (8.7)*].
 - o NAVELBINE may damage sperm. Advise males to use highly effective contraception during and for 3 months after therapy [*see Use in Specific Population (8.7) and Nonclinical Toxicology (13.1)*].
 - o NAVELBINE, may cause decreased fertility in males [*see Nonclinical Toxicology (13.1)*].



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