

NAVELBINE[®]
(vinorelbine tartrate)
Injection

WARNING

NAVELBINE (vinorelbine tartrate) Injection 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 NAVELBINE. The dosage should be adjusted according to complete blood counts with differentials obtained on the day of treatment.

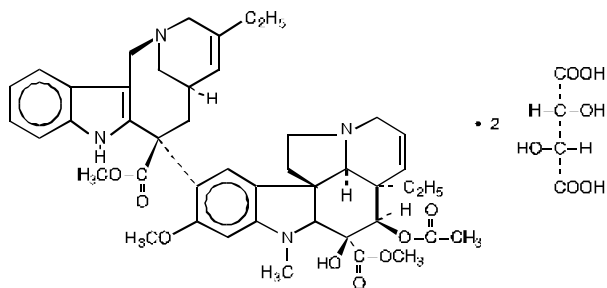
Caution - It is extremely important that the intravenous needle or catheter be properly positioned before NAVELBINE is injected. Administration of NAVELBINE may result in extravasation causing local tissue necrosis and/or thrombophlebitis (see DOSAGE AND ADMINISTRATION: Administration Precautions).

DESCRIPTION

NAVELBINE (vinorelbine tartrate) Injection is for intravenous administration. Each vial contains vinorelbine tartrate equivalent to 10 mg (1-mL vial) or 50 mg (5-mL vial) vinorelbine in Water for Injection. No preservatives or other additives are present. The aqueous solution is sterile and nonpyrogenic.

Vinorelbine tartrate is a semi-synthetic vinca alkaloid with antitumor activity. The chemical name is 3,4-didehydro-4-deoxy-*C*-norvincalculoblastine [*R*-(*R**,*R**)-2,3-dihydroxybutanedioate (1:2)(salt)].

Vinorelbine tartrate has the following structure:



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32 Vinorelbine tartrate is a white to yellow or light brown amorphous powder with the molecular
 33 formula $C_{45}H_{54}N_4O_8 \cdot 2C_4H_6O_6$ and molecular weight of 1079.12. The aqueous solubility is
 34 $>1,000$ mg/mL in distilled water. The pH of NAVELBINE Injection is approximately 3.5.

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36 CLINICAL PHARMACOLOGY

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

49 **Pharmacokinetics:** The pharmacokinetics of vinorelbine were studied in 49 patients who received
 50 doses of 30 mg/m^2 in 4 clinical trials. Doses were administered by 15- to 20-minute constant-rate
 51 infusions. Following intravenous administration, vinorelbine concentration in plasma decays in a
 52 triphasic manner. The initial rapid decline primarily represents distribution of drug to peripheral
 53 compartments followed by metabolism and excretion of the drug during subsequent phases. The
 54 prolonged terminal phase is due to relatively slow efflux of vinorelbine from peripheral
 55 compartments. The terminal phase half-life averages 27.7 to 43.6 hours and the mean plasma

56 clearance ranges from 0.97 to 1.26 L/hr/kg. Steady-state volume of distribution (V_{SS}) values range
57 from 25.4 to 40.1 L/kg.

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

62 Vinorelbine undergoes substantial hepatic elimination in humans, with large amounts recovered in
63 feces after intravenous administration to humans. Two metabolites of vinorelbine have been identified
64 in human blood, plasma, and urine; vinorelbine N-oxide and deacetylvinorelbine.

65 Deacetylvinorelbine has been demonstrated to be the primary metabolite of vinorelbine in humans,
66 and has been shown to possess antitumor activity similar to vinorelbine. Therapeutic doses of
67 NAVELBINE (30 mg/m^2) yield very small, if any, quantifiable levels of either metabolite in blood or
68 urine. The metabolism of vinca alkaloids has been shown to be mediated by hepatic cytochrome P450
69 isoenzymes in the CYP3A subfamily. This metabolic pathway may be impaired in patients with
70 hepatic dysfunction or who are taking concomitant potent inhibitors of these isoenzymes (see
71 PRECAUTIONS). The effects of renal or hepatic dysfunction on the disposition of vinorelbine have
72 not been assessed, but based on experience with other anticancer vinca alkaloids, dose adjustments
73 are recommended for patients with impaired hepatic function (see DOSAGE AND
74 ADMINISTRATION).

75 The disposition of radiolabeled vinorelbine given intravenously was studied in a limited number
76 of patients. Approximately 18% and 46% of the administered dose was recovered in the urine and in
77 the feces, respectively. Incomplete recovery in humans is consistent with results in animals where
78 recovery is incomplete, even after prolonged sampling times. A separate study of the urinary
79 excretion of vinorelbine using specific chromatographic analytical methodology showed that $10.9\% \pm$
80 0.7% of a 30-mg/m^2 intravenous dose was excreted unchanged in the urine.

81 The influence of age on the pharmacokinetics of vinorelbine was examined using data from
82 44 cancer patients (average age, 56.7 ± 7.8 years; range, 41 to 74 years; with 12 patients ≥ 60 years
83 and 6 patients ≥ 65 years) in 3 studies. CL (the mean plasma clearance), $t_{1/2}$ (the terminal phase
84 half-life), and V_Z (the volume of distribution during terminal phase) were independent of age. A
85 separate pharmacokinetic study was conducted in 10 elderly patients with metastatic breast cancer
86 (age range, 66 to 81 years; 3 patients >75 years; normal liver function tests) receiving vinorelbine

87 30 mg/m² intravenously. CL, V_{ss}, and t_{1/2} were similar to those reported for younger adult patients in
88 previous studies. No relationship between age, systemic exposure (AUC_{0-?}), and hematological
89 toxicity was observed.

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

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

96 **Single-Agent NAVELBINE:** Single-agent NAVELBINE was studied in a North American,
97 randomized clinical trial in which patients with Stage IV NSCLC, no prior chemotherapy, and
98 Karnofsky Performance Status ≥70 were treated with NAVELBINE (30 mg/m²) weekly or
99 5-fluorouracil (5-FU) (425 mg/m² IV bolus) plus leucovorin (LV) (20 mg/m² IV bolus) daily for
100 5 days every 4 weeks. A total of 211 patients were randomized at a 2:1 ratio to NAVELBINE (143)
101 or 5-FU/LV (68). NAVELBINE showed improved survival time compared to 5-FU/LV. In an
102 intent-to-treat analysis, the median survival time was 30 weeks versus 22 weeks for patients
103 receiving NAVELBINE versus 5-FU/LV, respectively (*P* = 0.06). The 1-year survival rates were
104 24% (±4% SE) for NAVELBINE and 16% (±5% SE) for the 5-FU/LV group, using the Kaplan-Meier
105 product-limit estimates. The median survival time with 5-FU/LV was similar to or slightly better than
106 that usually observed in untreated patients with advanced NSCLC, suggesting that the difference was
107 not related to some unknown detrimental effect of 5-FU/LV therapy. The response rates (all partial
108 responses) for NAVELBINE and 5-FU/LV were 12% and 3%, respectively.

109 **NAVELBINE in Combination with Cisplatin: NAVELBINE plus Cisplatin versus**

110 **Single-Agent Cisplatin:** A Phase III open-label, randomized study was conducted which
111 compared NAVELBINE (25 mg/m² per week) plus cisplatin (100 mg/m² every 4 weeks) to
112 single-agent cisplatin (100 mg/m² every 4 weeks) in patients with Stage IV or Stage IIIb NSCLC
113 patients with malignant pleural effusion or multiple lesions in more than one lobe who were not
114 previously treated with chemotherapy. Patients included in the study had a performance status of 0 or
115 1, and 34% had received prior surgery and/or radiotherapy. Characteristics of the 432 randomized
116 patients are provided in Table 1. Two hundred and twelve patients received NAVELBINE plus

117 cisplatin and 210 received single-agent cisplatin. The primary objective of this trial was to compare
118 survival between the 2 treatment groups. Survival (Figure 1) for patients receiving NAVELBINE plus
119 cisplatin was significantly better compared to the patients who received single-agent cisplatin. The
120 results of this trial are summarized in Table 1.

121 ***NAVELBINE plus Cisplatin versus Vindesine plus Cisplatin versus Single-Agent***

122 ***NAVELBINE:*** In a large European clinical trial, 612 patients with Stage III or IV NSCLC, no prior
123 chemotherapy, and WHO Performance Status of 0, 1, or 2 were randomized to treatment with
124 single-agent NAVELBINE (30 mg/m² per week), NAVELBINE (30 mg/m² per week) plus cisplatin
125 (120 mg/m² days 1 and 29, then every 6 weeks), and vindesine (3 mg/m² per week for 7 weeks, then
126 every other week) plus cisplatin (120 mg/m² days 1 and 29, then every 6 weeks). Patient
127 characteristics are provided in Table 1. Survival was longer in patients treated with NAVELBINE
128 plus cisplatin compared to those treated with vindesine plus cisplatin (Figure 2). Study results are
129 summarized in Table 1.

130 ***Dose-Ranging Study:*** A dose-ranging study of NAVELBINE (20, 25, or 30 mg/m² per week)
131 plus cisplatin (120 mg/m² days 1 and 29, then every 6 weeks) in 32 patients with NSCLC
132 demonstrated a median survival of 10.2 months. There were no responses at the lowest dose level;
133 the response rate was 33% in the 21 patients treated at the 2 highest dose levels.

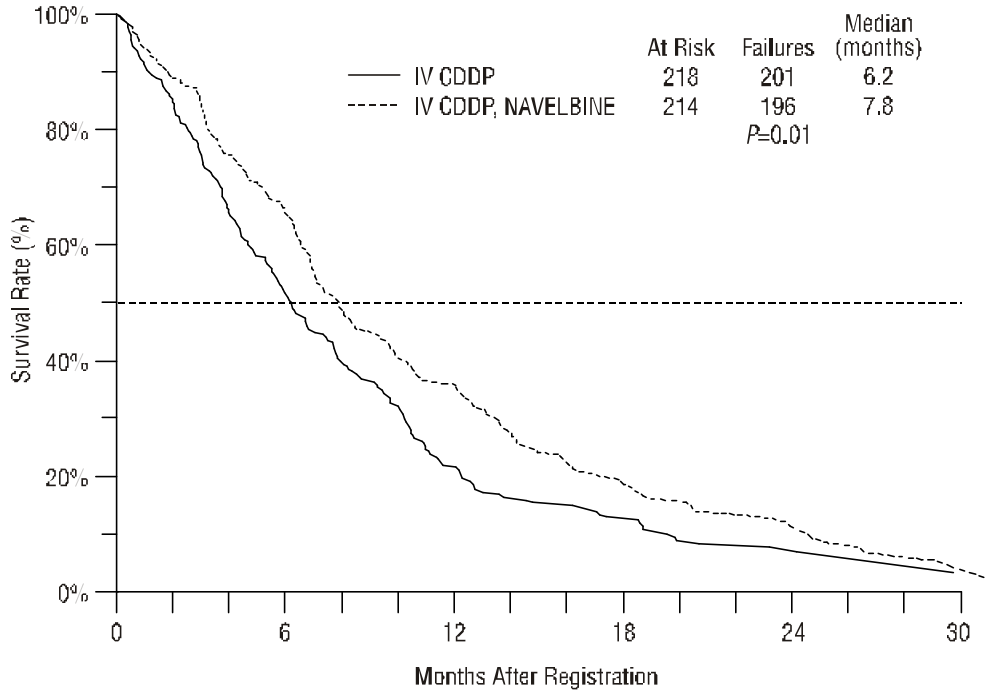
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Table 1. Randomized Clinical Trials of NAVELBINE in Combination with Cisplatin in NSCLC

	NAVELBINE/Cisplatin vs. Single-Agent Cisplatin		NAVELBINE/Cisplatin vs. Vindesine/Cisplatin vs. Single-Agent NAVELBINE		
	NAVELBINE/ Cisplatin	Cisplatin	NAVELBINE/ Cisplatin	Vindesine/ Cisplatin	NAVELBINE
Demographics					
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	9%	8%	9%
Histology					
Adenocarcinoma	54%	52%	32%	40%	28%
Squamous	19%	22%	56%	50%	56%
Large cell	14%	14%	13%	11%	16%
Unspecified	13%	13%	NA	NA	NA
Results					
Median survival (months)	7.8	6.2	9.2* [†]	7.4	7.2
<i>P</i> value	<i>P</i> = 0.01		* <i>P</i> = 0.09 vs. vindesine/cisplatin [†] = 0.05 vs. single-agent NAVELBINE		
12-Month survival rate	38%	22%	35%	27%	30%
Overall response	19%	8%	28% ^{‡§}	19%	14%
<i>P</i> value	<i>P</i> < 0.001		[‡] <i>P</i> = 0.03 vs. vindesine/cisplatin [§] <i>P</i> < 0.001 vs. single-agent NAVELBINE		

137 **Figure 1. Overall Survival**

138 **NAVELBINE/Cisplatin versus Single-Agent Cisplatin**

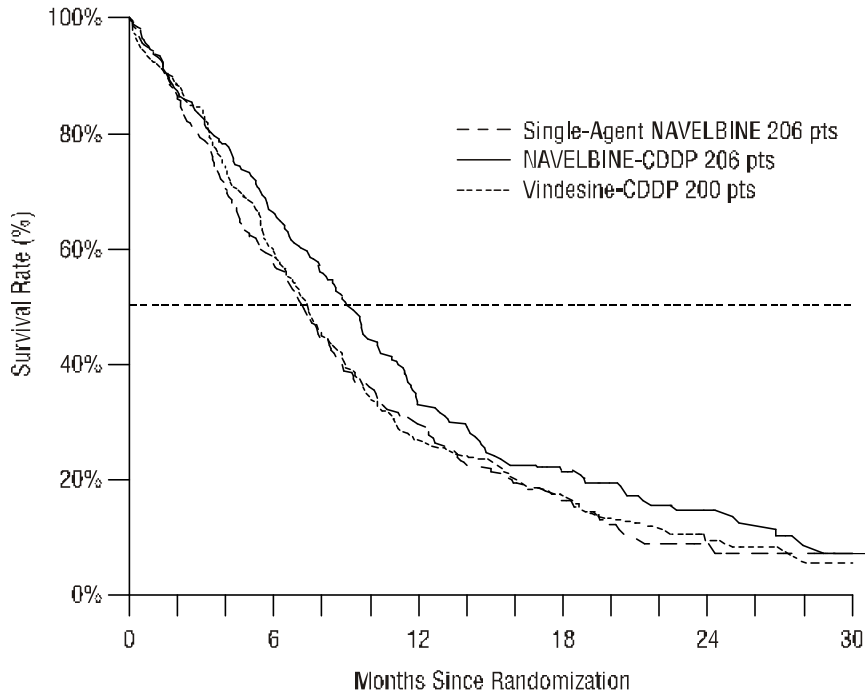


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141 **Figure 2. Overall Survival**

142 **NAVELBINE/Cisplatin versus Vindesine/Cisplatin versus Single-Agent NAVELBINE**



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145 **INDICATIONS AND USAGE**

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

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151 **CONTRAINDICATIONS**

152 Administration of NAVELBINE is contraindicated in patients with pretreatment granulocyte counts
153 $<1,000 \text{ cells/mm}^3$ (see WARNINGS).

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155 **WARNINGS**

156 NAVELBINE should be administered in carefully adjusted doses by or under the supervision of a
157 physician experienced in the use of cancer chemotherapeutic agents.

158 Patients treated with NAVELBINE should be frequently monitored for myelosuppression both
159 during and after therapy. Granulocytopenia is dose-limiting. Granulocyte nadirs occur between 7 and
160 10 days after dosing with granulocyte count recovery usually within the following 7 to 14 days.

161 Complete blood counts with differentials should be performed and results reviewed prior to
162 administering each dose of NAVELBINE. NAVELBINE should not be administered to patients with
163 granulocyte counts $<1,000 \text{ cells/mm}^3$. Patients developing severe granulocytopenia should be
164 monitored carefully for evidence of infection and/or fever. See DOSAGE AND ADMINISTRATION
165 for recommended dose adjustments for granulocytopenia.

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

171 Reported cases of interstitial pulmonary changes and acute respiratory distress syndrome (ARDS),
172 most of which were fatal, occurred in patients treated with single-agent NAVELBINE. The mean time
173 to onset of these symptoms after vinorelbine administration was 1 week (range 3 to 8 days). Patients

174 with alterations in their baseline pulmonary symptoms or with new onset of dyspnea, cough, hypoxia,
175 or other symptoms should be evaluated promptly.

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

178 **Pregnancy:** Pregnancy Category D. NAVELBINE may cause fetal harm if administered to a
179 pregnant woman. A single dose of vinorelbine has been shown to be embryo- and/or fetotoxic in mice
180 and rabbits at doses of 9 mg/m² and 5.5 mg/m², respectively (one third and one sixth the human dose).
181 At nonmaternotoxic doses, fetal weight was reduced and ossification was delayed. There are no
182 studies in pregnant women. If NAVELBINE is used during pregnancy, or if the patient becomes
183 pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.
184 Women of childbearing potential should be advised to avoid becoming pregnant during therapy with
185 NAVELBINE.

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187 **PRECAUTIONS**

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

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

195 Administration of NAVELBINE to patients with prior radiation therapy may result in radiation
196 recall reactions (see ADVERSE REACTIONS and Drug Interactions).

197 Patients with a prior history or pre-existing neuropathy, regardless of etiology, should be
198 monitored for new or worsening signs and symptoms of neuropathy while receiving NAVELBINE.

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

202 **Information for Patients:** Patients should be informed that the major acute toxicities of
203 NAVELBINE are related to bone marrow toxicity, specifically granulocytopenia with increased

204 susceptibility to infection. They should be advised to report fever or chills immediately. Women of
205 childbearing potential should be advised to avoid becoming pregnant during treatment. Patients
206 should be advised to contact their physician if they experience increased shortness of breath, cough,
207 or other new pulmonary symptoms, or if they experience symptoms of abdominal pain or constipation.

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

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

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

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

229 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** The carcinogenic potential of
230 NAVELBINE has not been studied. Vinorelbine has been shown to affect chromosome number and
231 possibly structure in vivo (polyploidy in bone marrow cells from Chinese hamsters and a positive
232 micronucleus test in mice). It was not mutagenic in the Ames test and gave inconclusive results in the
233 mouse lymphoma TK Locus assay. The significance of these or other short-term test results for human

234 risk is unknown. Vinorelbine did not affect fertility to a statistically significant extent when
235 administered to rats on either a once-weekly (9 mg/m², approximately one third the human dose) or
236 alternate-day schedule (4.2 mg/m², approximately one seventh the human dose) prior to and during
237 mating. However, biweekly administration for 13 or 26 weeks in the rat at 2.1 and 7.2 mg/m²
238 (approximately one fifteenth and one fourth the human dose) resulted in decreased spermatogenesis
239 and prostate/seminal vesicle secretion.

240 **Pregnancy:** Pregnancy Category D. See WARNINGS section.

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

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

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

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

257

258 **ADVERSE REACTIONS**

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

262 **Single-Agent NAVELBINE:** Data in the following table are based on the experience of 365
263 patients (143 patients with NSCLC; 222 patients with advanced breast cancer) treated with IV

264 NAVELBINE as a single agent in 3 clinical studies. The dosing schedule in each study was 30 mg/m²
265 NAVELBINE on a weekly basis.

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

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

Adverse Event	All Grades		Grade 3		Grade 4	
	All Patients	NSCLC	All Patients	NSCLC	All Patients	NSCLC
Clinical Chemistry Elevations						
Total Bilirubin (n = 351)	13%	9%	4%	3%	3%	2%
SGOT (n = 346)	67%	54%	5%	2%	1%	1%
General						
Asthenia	36%	27%	7%	5%	0%	0%
Injection Site Reactions	28%	38%	2%	5%	0%	0%
Injection Site Pain	16%	13%	2%	1%	0%	0%
Phlebitis	7%	10%	<1%	1%	0%	0%
Digestive						
Nausea	44%	34%	2%	1%	0%	0%

Vomiting	20%	15%	2%	1%	0%	0%
Constipation	35%	29%	3%	2%	0%	0%
Diarrhea	17%	13%	1%	1%	0%	0%
Peripheral Neuropathy [‡]	25%	20%	1%	1%	<1%	0%
Dyspnea	7%	3%	2%	2%	1%	0%
Alopecia	12%	12%	?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.

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Hematologic: Granulocytopenia is the major dose-limiting toxicity with NAVELBINE. Dose adjustments are required for hematologic toxicity and hepatic insufficiency (see DOSAGE AND ADMINISTRATION). Granulocytopenia was generally reversible and not cumulative over time. Granulocyte nadirs occurred 7 to 10 days after the dose, with granulocyte recovery usually within the following 7 to 14 days. Granulocytopenia resulted in hospitalizations for fever and/or sepsis in 8% of patients. Septic deaths occurred in approximately 1% of patients. Prophylactic hematologic growth factors have not been routinely used with NAVELBINE. 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 NAVELBINE.

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, NAVELBINE is a moderate vesicant. Injection site reactions, including erythema, pain at injection site, and vein discoloration, occurred in

286 approximately one third of patients; 5% were severe. Chemical phlebitis along the vein proximal to
287 the site of injection was reported in 10% of patients.

288 **Gastrointestinal:** Prophylactic administration of antiemetics was not routine in patients treated
289 with single-agent NAVELBINE. Due to the low incidence of severe nausea and vomiting with
290 single-agent NAVELBINE, the use of serotonin antagonists is generally not required.

291 **Hepatic:** Transient elevations of liver enzymes were reported without clinical symptoms.

292 **Cardiovascular:** Chest pain was reported in 5% of patients. Most reports of chest pain were in
293 patients who had either a history of cardiovascular disease or tumor within the chest. There have been
294 rare reports of myocardial infarction.

295 **Pulmonary:** Shortness of breath was reported in 3% of patients; it was severe in 2% (see
296 WARNINGS). Interstitial pulmonary changes were documented.

297 **Other:** Fatigue occurred in 27% of patients. It was usually mild or moderate but tended to increase
298 with cumulative dosing.

299 Other toxicities that have been reported in less than 5% of patients include jaw pain, myalgia,
300 arthralgia, and rash. Hemorrhagic cystitis and the syndrome of inappropriate ADH secretion were
301 each reported in <1% of patients.

302 **Combination Use:** Adverse events for combination use are summarized in Tables 3 and 4.

303 ***NAVELBINE in Combination with Cisplatin:***

304 ***NAVELBINE plus Cisplatin versus Single-Agent Cisplatin (Table 3):***

305 Myelosuppression was the predominant toxicity in patients receiving combination therapy, Grade 3
306 and 4 granulocytopenia of 82% compared to 5% in the single-agent cisplatin arm. Fever and/or sepsis
307 related to granulocytopenia occurred in 11% of patients on NAVELBINE and cisplatin compared to
308 0% on the cisplatin arm.

309 Four patients on the combination died of granulocytopenia-related sepsis. During this study, the use
310 of granulocyte colony-stimulating factor ([G-CSF] filgrastim) was permitted, but not mandated, after
311 the first course of treatment for patients who experienced Grade 3 or 4 granulocytopenia
312 ($< 1,000$ cells/mm³) or in those who developed neutropenic fever between cycles of chemotherapy.
313 Beginning 24 hours after completion of chemotherapy, G-CSF was started at a dose of 5 mcg/kg per
314 day and continued until the total granulocyte count was $>1,000$ cells/mm³ on 2 successive
315 determinations. G-CSF was not administered on the day of treatment.

316 Grade 3 and 4 anemia occurred more frequently in the combination arm compared to control, 24%
317 vs. 8%, respectively. Thrombocytopenia occurred in 6% of patients treated with NAVELBINE plus
318 cisplatin compared to 2% of patients treated with cisplatin.

319 The incidence of severe non-hematologic toxicity was similar among the patients in both treatment
320 groups. Patients receiving NAVELBINE plus cisplatin compared to single-agent cisplatin
321 experienced more Grade 3 and/or 4 peripheral numbness (2% vs. <1%),
322 phlebitis/thrombosis/embolism (3% vs. <1%), and infection (6% vs. <1%). Grade 3-4 constipation
323 and/or ileus occurred in 3% of patients treated with combination therapy and in 1% of patients treated
324 with cisplatin.

325 Seven deaths were reported on the combination arm; 2 were related to cardiac ischemia,
326 1 massive cerebrovascular accident, 1 multisystem failure due to an overdose of NAVELBINE, and 3
327 from febrile neutropenia. One death, secondary to respiratory infection unrelated to granulocytopenia,
328 occurred with single-agent cisplatin.

329 ***NAVELBINE plus Cisplatin versus Vindesine plus Cisplatin versus Single-Agent***

330 ***NAVELBINE (Table 4):*** Myelosuppression, specifically Grade 3 and 4 granulocytopenia, was
331 significantly greater with the combination of NAVELBINE plus cisplatin (79%) than with either
332 single-agent NAVELBINE (53%) or vindesine plus cisplatin (48%), $P < 0.0001$. Hospitalization due
333 to documented sepsis occurred in 4.4% of patients treated with NAVELBINE plus cisplatin; 2% of
334 patients treated with vindesine and cisplatin, and 4% of patients treated with single-agent
335 NAVELBINE. Grade 3 and 4 thrombocytopenia was infrequent in patients receiving combination
336 chemotherapy and no events were reported with single-agent NAVELBINE.

337 The incidence of Grade 3 and/or 4 nausea and vomiting, alopecia, and renal toxicity were reported
338 more frequently in the cisplatin-containing combinations compared to single-agent NAVELBINE.
339 Severe local reactions occurred in 2% of patients treated with combinations containing
340 NAVELBINE; none were observed in the vindesine plus cisplatin arm. Grade 3 and 4 neurotoxicity
341 was significantly more frequent in patients receiving vindesine plus cisplatin (17%) compared to
342 NAVELBINE plus cisplatin (7%) and single-agent NAVELBINE (9%) ($P < 0.005$). Cisplatin did not
343 appear to increase the incidence of neurotoxicity observed with single-agent NAVELBINE.

344

345 **Table 3. Selected Adverse Events From a Comparative Trial of NAVELBINE plus Cisplatin**346 **versus Single-Agent Cisplatin***

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

Non-Laboratory						
Malaise/fatigue/lethargy	67%	12%	0%	49%	8%	0%
Vomiting	60%	7%	6%	60%	10%	4%
Nausea	58%	14%	0%	57%	12%	0%
Anorexia	46%	0%	0%	37%	0%	0%
Constipation	35%	3%	0%	16%	1%	0%
Alopecia	34%	0%	0%	14%	0%	0%
Weight loss	34%	1%	0%	21%	<1%	0%
Fever without infection	20%	2%	0%	4%	0%	0%
Hearing	18%	4%	0%	18%	3%	<1%
Local (injection site reactions)	17%	<1%	0%	1%	0%	0%
Diarrhea	17%	2%	<1%	11%	1%	<1%
Paresthesias	17%	<1%	0%	10%	<1%	0%
Taste alterations	17%	0%	0%	15%	0%	0%
Peripheral numbness	11%	2%	0%	7%	<1%	0%
Myalgia/arthralgia	12%	<1%	0%	3%	<1%	0%
Phlebitis/thrombosis/embolism	10%	3%	0%	<1%	0%	<1%
Weakness	12%	2%	<1%	7%	2%	0%
Dizziness/vertigo	9%	<1%	0%	3%	<1%	0%
Infection	11%	5%	<1%	<1%	<1%	0%
Respiratory infection	10%	4%	<1%	3%	3%	0%

347 *Graded according to the standard SWOG criteria.

348

349 **Table 4. Selected Adverse Events From a Comparative Trial of NAVELBINE Plus Cisplatin**
 350 **versus Vindesine Plus Cisplatin versus Single-Agent NAVELBINE***

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

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

352 [†]n = 194 to 207; all patients receiving NAVELBINE/cisplatin with laboratory and non-laboratory
 353 data.

354 [‡]n = 173 to 192; all patients receiving vindesine/cisplatin with laboratory and non-laboratory data.

355 [§]n = 165 to 201; all patients receiving NAVELBINE with laboratory and non-laboratory data.

356 [†] Categorical toxicity grade not specified.

357 [¶]Neurotoxicity includes peripheral neuropathy and constipation.

358 **Observed During Clinical Practice:** In addition to the adverse events reported from clinical
 359 trials, the following events have been identified during post-approval use of NAVELBINE. Because

360 they are reported voluntarily from a population of unknown size, estimates of frequency cannot be
361 made. These events have been chosen for inclusion due to a combination of their seriousness,
362 frequency of reporting, or potential causal connection to NAVELBINE.

363 **Body as a Whole:** Systemic allergic reactions reported as anaphylaxis, pruritus, urticaria, and
364 angioedema; flushing; and radiation recall events such as dermatitis and esophagitis (see
365 PRECAUTIONS) have been reported.

366 **Hematologic:** Thromboembolic events, including pulmonary embolus and deep venous
367 thrombosis, have been reported primarily in seriously ill and debilitated patients with known
368 predisposing risk factors for these events.

369 **Neurologic:** Peripheral neurotoxicities such as, but not limited to, muscle weakness and
370 disturbance of gait, have been observed in patients with and without prior symptoms. There may be
371 increased potential for neurotoxicity in patients with pre-existing neuropathy, regardless of etiology,
372 who receive NAVELBINE. Vestibular and auditory deficits have been observed with NAVELBINE,
373 usually when used in combination with cisplatin.

374 **Skin:** Injection site reactions, including localized rash and urticaria, blister formation, and skin
375 sloughing have been observed in clinical practice. Some of these reactions may be delayed in
376 appearance.

377 **Gastrointestinal:** Dysphagia, mucositis, and pancreatitis have been reported.

378 **Cardiovascular:** Hypertension, hypotension, vasodilation, tachycardia, and pulmonary edema
379 have been reported.

380 **Pulmonary:** Pneumonia has been reported.

381 **Musculoskeletal:** Headache has been reported, with and without other musculoskeletal aches
382 and pains.

383 **Other:** Pain in tumor-containing tissue, back pain, and abdominal pain have been reported.
384 Electrolyte abnormalities, including hyponatremia with or without the syndrome of inappropriate
385 ADH secretion, have been reported in seriously ill and debilitated patients.

386 **Combination Use:** Patients with prior exposure to paclitaxel and who have demonstrated
387 neuropathy should be monitored closely for new or worsening neuropathy. Patients who have
388 experienced neuropathy with previous drug regimens should be monitored for symptoms of

389 neuropathy while receiving NAVELBINE. NAVELBINE may result in radiosensitizing effects with
390 prior or concomitant radiation therapy (see PRECAUTIONS).

391

392 **OVERDOSAGE**

393 There is no known antidote for overdoses of NAVELBINE. Overdoses involving quantities up to
394 10 times the recommended dose (30 mg/m²) have been reported. The toxicities described were
395 consistent with those listed in the ADVERSE REACTIONS section including paralytic ileus,
396 stomatitis, and esophagitis. Bone marrow aplasia, sepsis, and paresis have also been reported.
397 Fatalities have occurred following overdose of NAVELBINE. If overdosage occurs, general
398 supportive measures together with appropriate blood transfusions, growth factors, and antibiotics
399 should be instituted as deemed necessary by the physician.

400

401 **DOSAGE AND ADMINISTRATION**

402 **Single-Agent NAVELBINE:** The usual initial dose of single-agent NAVELBINE is 30 mg/m²
403 administered weekly. The recommended method of administration is an intravenous injection over 6
404 to 10 minutes. In controlled trials, single-agent NAVELBINE was given weekly until progression or
405 dose-limiting toxicity

406 **NAVELBINE in Combination with Cisplatin:** NAVELBINE may be administered weekly at a
407 dose of 25 mg/m² in combination with cisplatin given every 4 weeks at a dose of 100 mg/m².

408 Blood counts should be checked weekly to determine whether dose reductions of NAVELBINE
409 and/or cisplatin are necessary. In the SWOG study, most patients required a 50% dose reduction of
410 NAVELBINE at day 15 of each cycle and a 50% dose reduction of cisplatin by cycle 3.

411 NAVELBINE may also be administered weekly at a dose of 30 mg/m² in combination with
412 cisplatin, given on days 1 and 29, then every 6 weeks at a dose of 120 mg/m².

413 **Dose Modifications for NAVELBINE:** The dosage should be adjusted according to hematologic
414 toxicity or hepatic insufficiency, whichever results in the lower dose for the corresponding starting
415 dose of NAVELBINE (see Table 5).

416 ***Dose Modifications for Hematologic Toxicity:*** Granulocyte counts should be
417 ?1,000 cells/mm³ prior to the administration of NAVELBINE. Adjustments in the dosage of

418 NAVELBINE should be based on granulocyte counts obtained on the day of treatment according to
419 Table 5.

420

421 **Table 5. Dose Adjustments Based on Granulocyte Counts**

Granulocytes 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. Repeat granulocyte count in 1 week. If 3 consecutive weekly doses are held because granulocyte count is <1,000 cells/mm ³ , discontinue NAVELBINE.
Note: For patients who, during treatment with NAVELBINE, experienced fever and/or sepsis while granulocytopenic or had 2 consecutive weekly doses held due to granulocytopenia, subsequent doses of NAVELBINE should be:	
≥ 1,500	75%
1,000 to 1,499	37.5%
<1,000	See above

422

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

426

427

Table 6. Dose Modification Based on Total Bilirubin

Total Bilirubin (mg/dL)	Percentage of Starting Dose of NAVELBINE
≤2.0	100%
2.1 to 3.0	50%
>3.0	25%

428

429 ***Dose Modifications for Concurrent Hematologic Toxicity and Hepatic***

430 ***Insufficiency:*** In patients with both hematologic toxicity and hepatic insufficiency, the lower of the
431 doses based on the corresponding starting dose of NAVELBINE determined from Table 5 and Table
432 6 should be administered.

433 ***Dose Modifications for Renal Insufficiency:*** No dose adjustments for NAVELBINE are
434 required for renal insufficiency. Appropriate dose reductions for cisplatin should be made when
435 NAVELBINE is used in combination.

436 ***Dose Modifications for Neurotoxicity:*** If Grade ≥2 neurotoxicity develops, NAVELBINE
437 should be discontinued.

438 ***Administration Precautions:*** Caution - NAVELBINE must be administered intravenously. It is
439 extremely important that the intravenous needle or catheter be properly positioned before any
440 NAVELBINE is injected. Leakage into surrounding tissue during intravenous administration of
441 NAVELBINE may cause considerable irritation, local tissue necrosis, and/or thrombophlebitis. If
442 extravasation occurs, the injection should be discontinued immediately, and any remaining portion of
443 the dose should then be introduced into another vein. Since there are no established guidelines for the
444 treatment of extravasation injuries with NAVELBINE, institutional guidelines may be used. The *ONS*
445 *Chemotherapy Guidelines* provide additional recommendations for the prevention of extravasation
446 injuries.¹

447 As with other toxic compounds, caution should be exercised in handling and preparing the solution
448 of NAVELBINE. Skin reactions may occur with accidental exposure. The use of gloves is
449 recommended. If the solution of NAVELBINE contacts the skin or mucosa, immediately wash the skin
450 or mucosa thoroughly with soap and water. Severe irritation of the eye has been reported with

451 accidental contamination of the eye with another vinca alkaloid. If this happens with NAVELBINE,
452 the eye should be flushed with water immediately and thoroughly.

453 Procedures for proper handling and disposal of anticancer drugs should be used. Several
454 guidelines on this subject have been published.²⁻⁸ There is no general agreement that all of the
455 procedures recommended in the guidelines are necessary or appropriate.

456 NAVELBINE Injection is a clear, colorless to pale yellow solution. Parenteral drug products
457 should be visually inspected for particulate matter and discoloration prior to administration whenever
458 solution and container permit. If particulate matter is seen, NAVELBINE should not be administered.

459 **Preparation for Administration:** NAVELBINE Injection must be diluted in either a syringe or IV
460 bag using one of the recommended solutions. The diluted NAVELBINE should be administered over
461 6 to 10 minutes into the side port of a free-flowing IV **closest to the IV bag** followed by flushing
462 with at least 75 to 125 mL of one of the solutions. Diluted NAVELBINE may be used for up to
463 24 hours under normal room light when stored in polypropylene syringes or polyvinyl chloride bags
464 at 5° to 30°C (41° to 86°F).

465 **Syringe:** The calculated dose of NAVELBINE should be diluted to a concentration between 1.5
466 and 3.0 mg/mL. The following solutions may be used for dilution:

467 5% Dextrose Injection, USP

468 0.9% Sodium Chloride Injection, USP

469 **IV Bag:** The calculated dose of NAVELBINE should be diluted to a concentration between 0.5
470 and 2 mg/mL. The following solutions may be used for dilution:

471 5% Dextrose Injection, USP

472 0.9% Sodium Chloride Injection, USP

473 0.45% Sodium Chloride Injection, USP

474 5% Dextrose and 0.45% Sodium Chloride Injection, USP

475 Ringer's Injection, USP

476 Lactated Ringer's Injection, USP

477 **Stability:** Unopened vials of NAVELBINE are stable until the date indicated on the package when
478 stored under refrigeration at 2° to 8°C (36° to 46°F) and protected from light in the carton. Unopened
479 vials of NAVELBINE are stable at temperatures up to 25°C (77°F) for up to 72 hours. This product
480 should not be frozen.

481

482 **HOW SUPPLIED**

483 NAVELBINE Injection is a clear, colorless to pale yellow solution in Water for Injection,
484 containing 10 mg vinorelbine per mL. NAVELBINE Injection is available in single-use, clear glass
485 vials with elastomeric stoppers and royal blue caps, individually packaged in a carton in the
486 following vial sizes:

487 10 mg/1 mL Single-Use Vial, Carton of 1 (NDC 0173-0656-01).

488 50 mg/5 mL Single-Use Vial, Carton of 1 (NDC 0173-0656-44).

489 **Store the vials under refrigeration at 2° to 8°C (36° to 46°F) in the carton. Protect from light.**

490 **DO NOT FREEZE.**

491

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