

NDA 20-388/S-010

Page 2

MEDWATCH, HF-2  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21CFR 314.80 and 314.81.

If you have any questions, call Maureen Pelosi, Project Manager, at (301) 594-5778.

Sincerely,

*{See appended electronic signature page}*

Richard Pazdur, M.D.  
Director  
Division of Oncology Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure

1 **PRODUCT INFORMATION**

2 **NAVELBINE®**

3 **(vinorelbine tartrate)**

4 **Injection**

5

6 **WARNING:** NAVELBINE (vinorelbine tartrate) Injection should be administered under the  
7 supervision of a physician experienced in the use of cancer chemotherapeutic agents. This product is  
8 for intravenous (IV) use only. Intrathecal administration of other vinca alkaloids has resulted in death.  
9 Syringes containing this product should be labeled "WARNING – FOR IV USE ONLY. FATAL if  
10 given intrathecally."

11 Severe granulocytopenia resulting in increased susceptibility to infection may occur. Granulocyte  
12 counts should be  $\geq 1000$  cells/mm<sup>3</sup> prior to the administration of NAVELBINE. The dosage should  
13 be adjusted according to complete blood counts with differentials obtained on the day of treatment.

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

18

19 **DESCRIPTION:** NAVELBINE (vinorelbine tartrate) Injection is for intravenous administration.

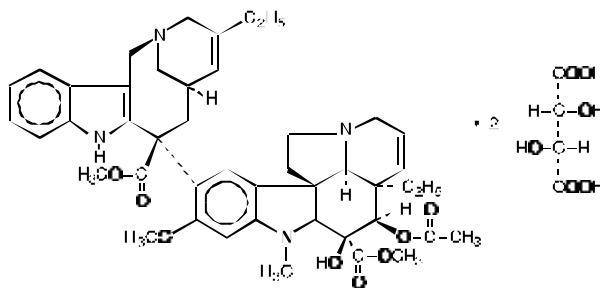
20 Each vial contains vinorelbine tartrate equivalent to 10 mg (1-mL vial) or 50 mg (5-mL vial)  
21 vinorelbine in Water for Injection. No preservatives or other additives are present. The aqueous  
22 solution is sterile and nonpyrogenic.

23 Vinorelbine tartrate is a semi-synthetic vinca alkaloid with antitumor activity. The chemical name is  
24 3',4'-didehydro-4'-deoxy-*C'*'-norvincaloblastine [*R*-(*R*\*,*R*\*)-2,3-dihydroxybutanedioate  
25 (1:2)(salt)].

26 Vinorelbine tartrate has the following structure:

27

## NAVELBINE<sup>®</sup> (vinorelbine tartrate) Injection



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29 Vinorelbine tartrate is a white to yellow or light brown amorphous powder with the molecular  
30 formula  $C_{45}H_{54}N_4O_8 \cdot 2C_4H_6O_6$  and molecular weight of 1079.12. The aqueous solubility is  
31  $>1000$  mg/mL in distilled water. The pH of NAVELBINE Injection is approximately 3.5.

32

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

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

## NAVELBINE<sup>®</sup> (vinorelbine tartrate) Injection

52 0.97 to 1.26 L/h per kg. Steady-state volume of distribution ( $V_{SS}$ ) values range from 25.4 to  
53 40.1 L/kg.

54 Vinorelbine demonstrated high binding to human platelets and lymphocytes. The free fraction was  
55 approximately 0.11 in pooled human plasma over a concentration range of 234 to 1169 ng/mL. The  
56 binding to plasma constituents in cancer patients ranged from 79.6% to 91.2%. Vinorelbine binding  
57 was not altered in the presence of cisplatin, 5-fluorouracil, or doxorubicin.

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

70 The disposition of radiolabeled vinorelbine given intravenously was studied in a limited number of  
71 patients. Approximately 18% and 46% of the administered dose was recovered in the urine and in  
72 the feces, respectively. Incomplete recovery in humans is consistent with results in animals where  
73 recovery is incomplete, even after prolonged sampling times. A separate study of the urinary  
74 excretion of vinorelbine using specific chromatographic analytical methodology showed that 10.9% ±  
75 0.7% of a 30-mg/m<sup>2</sup> intravenous dose was excreted unchanged in the urine.

76 The influence of age on the pharmacokinetics of vinorelbine was examined using data from  
77 44 cancer patients (average age, 56.7 ± 7.8 years; range, 41 to 74 years; with 12 patients ≥60 years  
78 and 6 patients ≥65 years) in 3 studies. CL (the mean plasma clearance),  $t_{1/2}$  (the terminal phase  
79 half-life), and  $V_Z$  (the volume of distribution during terminal phase) were independent of age. A  
80 separate pharmacokinetic study was conducted in 10 elderly patients with metastatic breast cancer

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81 (age range, 66 to 81 years; 3 patients >75 years; normal liver function tests) receiving vinorelbine  
82 30 mg/m<sup>2</sup> intravenously. CL, V<sub>ss</sub>, and t<sub>1/2</sub> were similar to those reported for younger adult patients in  
83 previous studies. No relationship between age, systemic exposure (AUC<sub>0-∞</sub>), and hematological  
84 toxicity was observed.

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

87 **Clinical Trials:** Data from 1 randomized clinical study (211 evaluable patients) with single-agent  
88 NAVELBINE and 2 randomized clinical trials (1044 patients) using NAVELBINE combined with  
89 cisplatin support the use of NAVELBINE in patients with advanced nonsmall cell lung cancer  
90 (NSCLC).

91 **Single-Agent NAVELBINE:** Single-agent NAVELBINE was studied in a North American,  
92 randomized clinical trial in which patients with Stage IV NSCLC, no prior chemotherapy, and  
93 Karnofsky Performance Status ≥70 were treated with NAVELBINE (30 mg/m<sup>2</sup>) weekly or  
94 5-fluorouracil (5-FU) (425 mg/m<sup>2</sup> IV bolus) plus leucovorin (LV) (20 mg/m<sup>2</sup> IV bolus) daily for  
95 5 days every 4 weeks. A total of 211 patients were randomized at a 2:1 ratio to NAVELBINE  
96 (143) or 5-FU/LV (68). NAVELBINE showed improved survival time compared to 5-FU/LV. In  
97 an intent-to-treat analysis, the median survival time was 30 weeks versus 22 weeks for patients  
98 receiving NAVELBINE versus 5-FU/LV, respectively (*P* = 0.06). The 1-year survival rates were  
99 24% (±4% SE) for NAVELBINE and 16% (±5% SE) for the 5-FU/LV group, using the  
100 Kaplan-Meier product-limit estimates. The median survival time with 5-FU/LV was similar to or  
101 slightly better than that usually observed in untreated patients with advanced NSCLC, suggesting that  
102 the difference was not related to some unknown detrimental effect of 5-FU/LV therapy. The  
103 response rates (all partial responses) for NAVELBINE and 5-FU/LV were 12% and 3%,  
104 respectively.

105 **NAVELBINE in Combination with Cisplatin: NAVELBINE plus Cisplatin versus**  
106 **Single-Agent Cisplatin:** A Phase III open-label, randomized study was conducted which  
107 compared NAVELBINE (25 mg/m<sup>2</sup> per week) plus cisplatin (100 mg/m<sup>2</sup> every 4 weeks) to  
108 single-agent cisplatin (100 mg/m<sup>2</sup> every 4 weeks) in patients with Stage IV or Stage IIIb NSCLC  
109 patients with malignant pleural effusion or multiple lesions in more than one lobe who were not

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110 previously treated with chemotherapy. Patients included in the study had a performance status of  
111 0 or 1, and 34% had received prior surgery and/or radiotherapy. Characteristics of the  
112 432 randomized patients are provided in Table 1. Two hundred and twelve patients received  
113 NAVELBINE plus cisplatin and 210 received single-agent cisplatin. The primary objective of this  
114 trial was to compare survival between the 2 treatment groups. Survival (Figure 1) for patients  
115 receiving NAVELBINE plus cisplatin was significantly better compared to the patients who received  
116 single-agent cisplatin. The results of this trial are summarized in Table 1.

### 117 *NAVELBINE plus Cisplatin versus Vindesine plus Cisplatin versus Single-Agent*

118 *NAVELBINE:* In a large European clinical trial, 612 patients with Stage III or IV NSCLC, no  
119 prior chemotherapy, and WHO Performance Status of 0, 1, or 2 were randomized to treatment with  
120 single-agent NAVELBINE (30 mg/m<sup>2</sup> per week), NAVELBINE (30 mg/m<sup>2</sup> per week) plus cisplatin  
121 (120 mg/m<sup>2</sup> days 1 and 29, then every 6 weeks), and vindesine (3 mg/m<sup>2</sup> per week for 7 weeks,  
122 then every other week) plus cisplatin (120 mg/m<sup>2</sup> days 1 and 29, then every 6 weeks). Patient  
123 characteristics are provided in Table 1. Survival was longer in patients treated with NAVELBINE  
124 plus cisplatin compared to those treated with vindesine plus cisplatin (Figure 2). Study results are  
125 summarized in Table 1.

126 *Dose-Ranging Study:* A dose-ranging study of NAVELBINE (20, 25, or 30 mg/m<sup>2</sup> per week)  
127 plus cisplatin (120 mg/m<sup>2</sup> days 1 and 29, then every 6 weeks) in 32 patients with NSCLC  
128 demonstrated a median survival of 10.2 months. There were no responses at the lowest dose level;  
129 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**

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**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
<b>Demographics</b>					
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
<b>Results</b>					
Median survival (months)	7.8	6.2	9.2* <sup>†</sup>	7.4	7.2
<i>P</i> value	<i>P</i> = 0.01		* <i>P</i> = 0.09 vs. vindesine/cisplatin <sup>†</sup> = 0.05 vs. single-agent NAVELBINE		
12-Month survival rate	38%	22%	35%	27%	30%
Overall response	19%	8%	28% <sup>‡§</sup>	19%	14%
<i>P</i> value	<i>P</i> < 0.001		<sup>‡</sup> <i>P</i> = 0.03 vs. vindesine/cisplatin <sup>§</sup> <i>P</i> < 0.001 vs. single-agent NAVELBINE		

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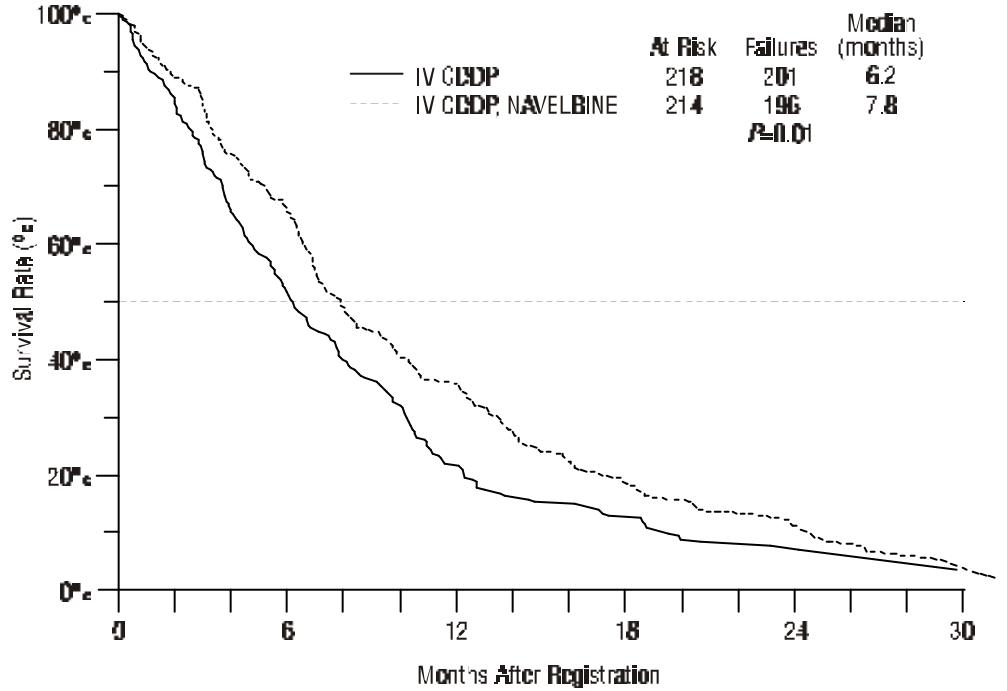
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**Figure 1: Overall Survival**

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#### NAVELBINE/Cisplatin versus Single-Agent Cisplatin



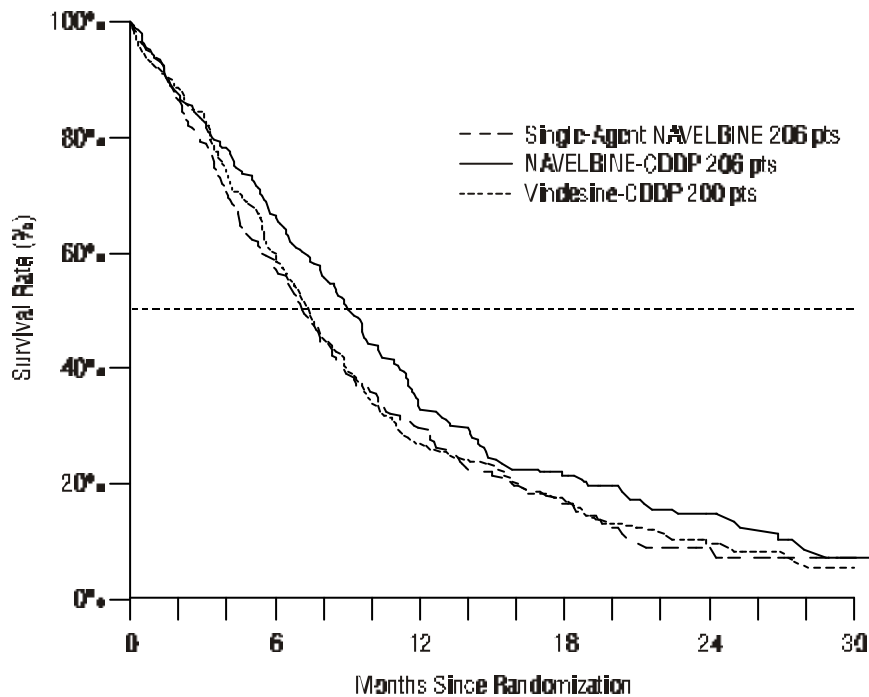
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Figure 2: Overall Survival

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



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

**CONTRAINDICATIONS:** Administration of NAVELBINE is contraindicated in patients with pretreatment granulocyte counts  $<1000$  cells/mm<sup>3</sup> (see WARNINGS).

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

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

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156 Complete blood counts with differentials should be performed and results reviewed prior to  
157 administering each dose of NAVELBINE. NAVELBINE should not be administered to patients  
158 with granulocyte counts  $<1000$  cells/mm<sup>3</sup>. Patients developing severe granulocytopenia should be  
159 monitored carefully for evidence of infection and/or fever. See DOSAGE AND  
160 ADMINISTRATION for recommended dose adjustments for granulocytopenia.

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

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

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

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

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### 182 **PRECAUTIONS:**

183 **General:** Most drug-related adverse events of NAVELBINE are reversible. If severe adverse  
184 events occur, NAVELBINE should be reduced in dosage or discontinued and appropriate

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185 corrective measures taken. Reinstitution of therapy with NAVELBINE should be carried out with  
186 caution and alertness as to possible recurrence of toxicity.

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

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

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

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

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

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

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

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

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

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

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

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

242 **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.

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

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

250

251 **ADVERSE REACTIONS:** The pattern of adverse reactions is similar whether NAVELBINE is  
252 used as a single agent or in combination. Adverse reactions from studies with single-agent and  
253 combination use of NAVELBINE are summarized in Tables 2-4.

254 **Single-Agent NAVELBINE:** Data in the following table are based on the experience of 365  
255 patients (143 patients with NSCLC; 222 patients with advanced breast cancer) treated with IV  
256 NAVELBINE as a single agent in 3 clinical studies. The dosing schedule in each study was  
257 30 mg/m<sup>2</sup> NAVELBINE on a weekly basis.

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

Adverse Event		All Patients (n = 365)	NSCLC (n = 143)
<b>Bone Marrow</b>			
Granulocytopenia	<2000 cells/mm <sup>3</sup>	90%	80%
	<500 cells/mm <sup>3</sup>	36%	29%
Leukopenia	<4000 cells/mm <sup>3</sup>	92%	81%
	<1000 cells/mm <sup>3</sup>	15%	12%
Thrombocytopenia	<100,000 cells/mm <sup>3</sup>	5%	4%
	<50,000 cells/mm <sup>3</sup>	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
<b>Clinical Chemistry Elevations</b>						
Total Bilirubin (n = 351)	13%	9%	4%	3%	3%	2%
SGOT (n = 346)	67%	54%	5%	2%	1%	1%
<b>General</b>						
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%
<b>Digestive</b>						
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.

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† 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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262

263 **Hematologic:** Granulocytopenia is the major dose-limiting toxicity with NAVELBINE. Dose  
264 adjustments are required for hematologic toxicity and hepatic insufficiency (see DOSAGE AND  
265 ADMINISTRATION). Granulocytopenia was generally reversible and not cumulative over time.  
266 Granulocyte nadirs occurred 7 to 10 days after the dose, with granulocyte recovery usually within the  
267 following 7 to 14 days. Granulocytopenia resulted in hospitalizations for fever and/or sepsis in 8% of  
268 patients. Septic deaths occurred in approximately 1% of patients. Prophylactic hematologic growth  
269 factors have not been routinely used with NAVELBINE. If medically necessary, growth factors may  
270 be administered at recommended doses no earlier than 24 hours after the administration of cytotoxic  
271 chemotherapy. Growth factors should not be administered in the period 24 hours before the  
272 administration of chemotherapy.

273 Whole blood and/or packed red blood cells were administered to 18% of patients who received  
274 NAVELBINE.

275 **Neurologic:** Loss of deep tendon reflexes occurred in less than 5% of patients. The development of  
276 severe peripheral neuropathy was infrequent (1%) and generally reversible.

277 **Skin:** Like other anticancer vinca alkaloids, NAVELBINE is a moderate vesicant. Injection site  
278 reactions, including erythema, pain at injection site, and vein discoloration, occurred in approximately  
279 one third of patients; 5% were severe. Chemical phlebitis along the vein proximal to the site of  
280 injection was reported in 10% of patients.

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

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

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

## NAVELBINE<sup>®</sup> (vinorelbine tartrate) Injection

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

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

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

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

### 296 *NAVELBINE in Combination with Cisplatin:*

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

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

302 Four patients on the combination died of granulocytopenia-related sepsis. During this study, the  
303 use of granulocyte colony-stimulating factor ([G-CSF] filgrastim) was permitted, but not mandated,  
304 after the first course of treatment for patients who experienced Grade 3 or 4 granulocytopenia  
305 ( $\leq 1000$  cells/mm<sup>3</sup>) or in those who developed neutropenic fever between cycles of chemotherapy.  
306 Beginning 24 hours after completion of chemotherapy, G-CSF was started at a dose of 5 mcg/kg  
307 per day and continued until the total granulocyte count was  $>1000$  cells/mm<sup>3</sup> on 2 successive  
308 determinations. G-CSF was not administered on the day of treatment.

309 Grade 3 and 4 anemia occurred more frequently in the combination arm compared to control,  
310 24% vs. 8%, respectively. Thrombocytopenia occurred in 6% of patients treated with  
311 NAVELBINE plus cisplatin compared to 2% of patients treated with cisplatin.

312 The incidence of severe non-hematologic toxicity was similar among the patients in both treatment  
313 groups. Patients receiving NAVELBINE plus cisplatin compared to single-agent cisplatin  
314 experienced more Grade 3 and/or 4 peripheral numbness (2% vs. <1%),  
315 phlebitis/thrombosis/embolism (3% vs. <1%), and infection (6% vs. <1%). Grade 3-4 constipation

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316 and/or ileus occurred in 3% of patients treated with combination therapy and in 1% of patients  
317 treated with cisplatin.

318 Seven deaths were reported on the combination arm; 2 were related to cardiac ischemia,  
319 1 massive cerebrovascular accident, 1 multisystem failure due to an overdose of NAVELBINE, and  
320 3 from febrile neutropenia. One death, secondary to respiratory infection unrelated to  
321 granulocytopenia, occurred with single-agent cisplatin.

322 ***NAVELBINE plus Cisplatin versus Vindesine plus Cisplatin versus Single-Agent***  
323 ***NAVELBINE (Table 4):*** Myelosuppression, specifically Grade 3 and 4 granulocytopenia, was  
324 significantly greater with the combination of NAVELBINE plus cisplatin (79%) than with either  
325 single-agent NAVELBINE (53%) or vindesine plus cisplatin (48%),  $P < 0.0001$ . Hospitalization due  
326 to documented sepsis occurred in 4.4% of patients treated with NAVELBINE plus cisplatin; 2% of  
327 patients treated with vindesine and cisplatin, and 4% of patients treated with single-agent  
328 NAVELBINE. Grade 3 and 4 thrombocytopenia was infrequent in patients receiving combination  
329 chemotherapy and no events were reported with single-agent NAVELBINE.

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

**NAVELBINE<sup>®</sup> (vinorelbine tartrate) Injection**

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**Table 3: Selected Adverse Events From a Comparative Trial of  
NAVELBINE plus Cisplatin versus Single-Agent Cisplatin\***

Adverse Event	NAVELBINE 25 mg/m <sup>2</sup> plus Cisplatin 100 mg/m <sup>2</sup> (n = 212)			Cisplatin 100 mg/m <sup>2</sup> (n = 210)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
<b>Bone Marrow</b>						
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%
<b>Febrile neutropenia</b>	N/A	N/A	11%	N/A	N/A	0%
<b>Hepatic</b>						
Elevated transaminase	1%	0%	0%	<1%	<1%	0%
<b>Renal</b>						
Elevated creatinine	37%	2%	2%	28%	4%	<1%
<b>Non-Laboratory</b>						
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%

341

\*Graded according to the standard SWOG criteria.

342

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343 **Table 4: Selected Adverse Events From a Comparative Trial of NAVELBINE Plus**  
344 **Cisplatin versus Vindesine Plus Cisplatin versus Single-Agent NAVELBINE\***

Adverse Event	NAVELBINE/Cisplatin <sup>†</sup>			Vindesine/Cisplatin <sup>‡</sup>			NAVELBINE§		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
<b>Bone Marrow</b>									
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%
<b>Febrile neutropenia</b>	N/A	N/A	4%	N/A	N/A	2%	N/A	N/A	4%
<b>Hepatic</b>									
Elevated bilirubin	6%	NA	NA	5%	NA	NA	5%	NA	NA
<b>Renal</b>									
Elevated creatinine	46%	NA	NA	37%	NA	NA	13%	NA	NA
<b>Non-Laboratory</b>									
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 <sup>¶</sup>	44%	7%	0%	58%	16%	1%	44%	8%	0.5%

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

346 <sup>†</sup>n = 194 to 207; all patients receiving NAVELBINE/cisplatin with laboratory and non-laboratory  
347 data.

348 <sup>‡</sup>n = 173 to 192; all patients receiving vindesine/cisplatin with laboratory and non-laboratory data.

349 <sup>§</sup>n = 165 to 201; all patients receiving NAVELBINE with laboratory and non-laboratory data.

350 Categorical toxicity grade not specified.

351 <sup>¶</sup>Neurotoxicity includes peripheral neuropathy and constipation.

## NAVELBINE<sup>®</sup> (vinorelbine tartrate) Injection

352 **Observed During Clinical Practice:** In addition to the adverse events reported from clinical trials,  
353 the following events have been identified during post-approval use of NAVELBINE. Because they  
354 are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.  
355 These events have been chosen for inclusion due to a combination of their seriousness, frequency of  
356 reporting, or potential causal connection to NAVELBINE.

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

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

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

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

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

372 **Cardiovascular:** Hypertension, hypotension, vasodilation, tachycardia, and pulmonary edema  
373 have been reported.

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

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

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

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380 **Combination Use:** Patients with prior exposure to paclitaxel and who have demonstrated  
381 neuropathy should be monitored closely for new or worsening neuropathy. Patients who have  
382 experienced neuropathy with previous drug regimens should be monitored for symptoms of  
383 neuropathy while receiving NAVELBINE. NAVELBINE may result in radiosensitizing effects with  
384 prior or concomitant radiation therapy (see PRECAUTIONS).

385

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

393

### 394 **DOSAGE AND ADMINISTRATION:**

395 **Single-Agent NAVELBINE:** The usual initial dose of single-agent NAVELBINE is 30 mg/m<sup>2</sup>  
396 administered weekly. The recommended method of administration is an intravenous injection over 6  
397 to 10 minutes. In controlled trials, single-agent NAVELBINE was given weekly until progression or  
398 dose-limiting toxicity.

399 **NAVELBINE in Combination with Cisplatin:** NAVELBINE may be administered weekly at a  
400 dose of 25 mg/m<sup>2</sup> in combination with cisplatin given every 4 weeks at a dose of 100 mg/m<sup>2</sup>.

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

404 NAVELBINE may also be administered weekly at a dose of 30 mg/m<sup>2</sup> in combination with  
405 cisplatin, given on days 1 and 29, then every 6 weeks at a dose of 120 mg/m<sup>2</sup>.

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

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409 ***Dose Modifications for Hematologic Toxicity:*** Granulocyte counts should be  
410  $\geq 1000$  cells/mm<sup>3</sup> prior to the administration of NAVELBINE. Adjustments in the dosage of  
411 NAVELBINE should be based on granulocyte counts obtained on the day of treatment according to  
412 Table 5.

**Table 5: Dose Adjustments Based on Granulocyte Counts**

Granulocytes on Day of Treatment (cells/mm <sup>3</sup> )	Percentage of Starting Dose of NAVELBINE
$\geq 1500$	100%
1000 to 1499	50%
$< 1000$	Do not administer. Repeat granulocyte count in 1 week. If 3 consecutive weekly doses are held because granulocyte count is $< 1000$ cells/mm <sup>3</sup> , 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:	
$\geq 1500$	75%
1000 to 1499	37.5%
$< 1000$	See above

415  
416 ***Dose Modifications for Hepatic Insufficiency:*** NAVELBINE should be administered with  
417 caution to patients with hepatic insufficiency. In patients who develop hyperbilirubinemia during  
418 treatment with NAVELBINE, the dose should be adjusted for total bilirubin according to Table 6.

**Table 6: Dose Modification Based on Total Bilirubin**

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

421

## NAVELBINE<sup>®</sup> (vinorelbine tartrate) Injection

422 ***Dose Modifications for Concurrent Hematologic Toxicity and Hepatic Insufficiency:*** In  
423 patients with both hematologic toxicity and hepatic insufficiency, the lower of the doses based on the  
424 corresponding starting dose of NAVELBINE determined from Table 5 and Table 6 should be  
425 administered.

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

429 ***Dose Modifications for Neurotoxicity:*** If grade  $\geq 2$  neurotoxicity develops, NAVELBINE  
430 should be discontinued.

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

440 As with other toxic compounds, caution should be exercised in handling and preparing the  
441 solution of NAVELBINE. Skin reactions may occur with accidental exposure. The use of gloves is  
442 recommended. If the solution of NAVELBINE contacts the skin or mucosa, immediately wash the  
443 skin or mucosa thoroughly with soap and water. Severe irritation of the eye has been reported with  
444 accidental contamination of the eye with another vinca alkaloid. If this happens with NAVELBINE,  
445 the eye should be flushed with water immediately and thoroughly.

446 Procedures for proper handling and disposal of anticancer drugs should be used. Several  
447 guidelines on this subject have been published.<sup>2-8</sup> There is no general agreement that all of the  
448 procedures recommended in the guidelines are necessary or appropriate.

449 NAVELBINE Injection is a clear, colorless to pale yellow solution. Parenteral drug products  
450 should be visually inspected for particulate matter and discoloration prior to administration whenever

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451 solution and container permit. If particulate matter is seen, NAVELBINE should not be  
452 administered.

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

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

461 5% Dextrose Injection, USP

462 0.9% Sodium Chloride Injection, USP

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

465 5% Dextrose Injection, USP

466 0.9% Sodium Chloride Injection, USP

467 0.45% Sodium Chloride Injection, USP

468 5% Dextrose and 0.45% Sodium Chloride Injection, USP

469 Ringer's Injection, USP

470 Lactated Ringer's Injection, USP

471 **Stability:** Unopened vials of NAVELBINE are stable until the date indicated on the package when  
472 stored under refrigeration at 2° to 8°C (36° to 46°F) and protected from light in the carton.

473 Unopened vials of NAVELBINE are stable at temperatures up to 25°C (77°F) for up to 72 hours.

474 This product should not be frozen.

475

476 **HOW SUPPLIED:** NAVELBINE Injection is a clear, colorless to pale yellow solution in Water for  
477 Injection, containing 10 mg vinorelbine per mL. NAVELBINE Injection is available in single-use,  
478 clear glass vials with elastomeric stoppers and royal blue caps, individually packaged in a carton in  
479 the following vial sizes:

**NAVELBINE<sup>®</sup> (vinorelbine tartrate) Injection**

480 10 mg/1 mL Single-Use Vial, Carton of 1 (NDC 0173-0656-01).

481 50 mg/5 mL Single-Use Vial, Carton of 1 (NDC 0173-0656-44).

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

484

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**NAVELBINE<sup>®</sup> (vinorelbine tartrate) Injection**

509 for



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511 GlaxoSmithKline

512 Research Triangle Park, NC 27709

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