

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-388/S-014

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APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

NDA 20-388/S-014

Trade Name: Navelbine Injection

Generic Name(s): (vinorelbine tartrate)

Sponsor: GlaxoSmithKline

Agent:

Approval Date: November 5, 2002

Indication: Treatment of ambulatory patient with advanced non small cell lung cancer.

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NDA 20-388/S-014

Approval Letter(s)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-388/S-014

SmithKlineBeecham Corporation d/b/a GlaxoSmithKline
2301 Renaissance Boulevard RN0210
Building 510, P.O. Box 61540
King of Prussia, PA 19406-2772

ATTN: Anne-Margaret Martin
Senior Director, US Regulatory Affairs, Oncology

Dear Ms. Martin:

Please refer to your supplemental new drug application dated June 17, 2002, received June 18, 2002, submitted under section 505A of the Federal Food, Drug, and Cosmetic Act for Navelbine (vinorelbine tartrate) Injection.

We acknowledge receipt of your submission dated June 28, 2002.

This supplemental new drug application provides for pediatric study reports and pediatric exclusivity determination.

We have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the September 6, 2002 agreed upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed agreed upon labeling text for the package insert.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated as "FPL for approved supplement NDA 20-388/S-014". Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

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

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

Sincerely,

{See appended electronic signature page}

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

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Richard Pazdur
11/5/02 04:53:30 PM

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NDA 20-388/S-014

Approved Labeling

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PRESCRIBING INFORMATION

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.

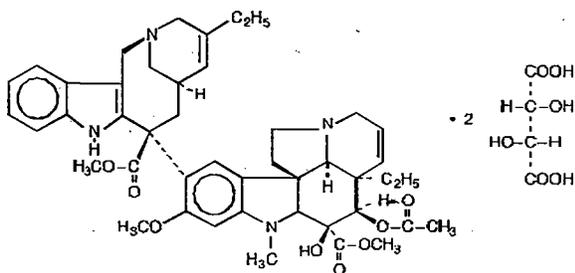
Caution - It is extremely important that the intravenous needle or catheter be properly positioned before NAVELBINE is injected. Administration of NAVELBINE may result in extravasation causing local tissue necrosis and/or thrombophlebitis (see DOSAGE AND ADMINISTRATION: Administration Precautions).

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*-norvincalcoloblastine [*R*-(*R**,*R**)-2,3-dihydroxybutanedioate (1:2)(salt)].

Vinorelbine tartrate has the following structure:



30
31

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.

35

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/m²) 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% ±
80 0.7% of a 30-mg/m² 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.

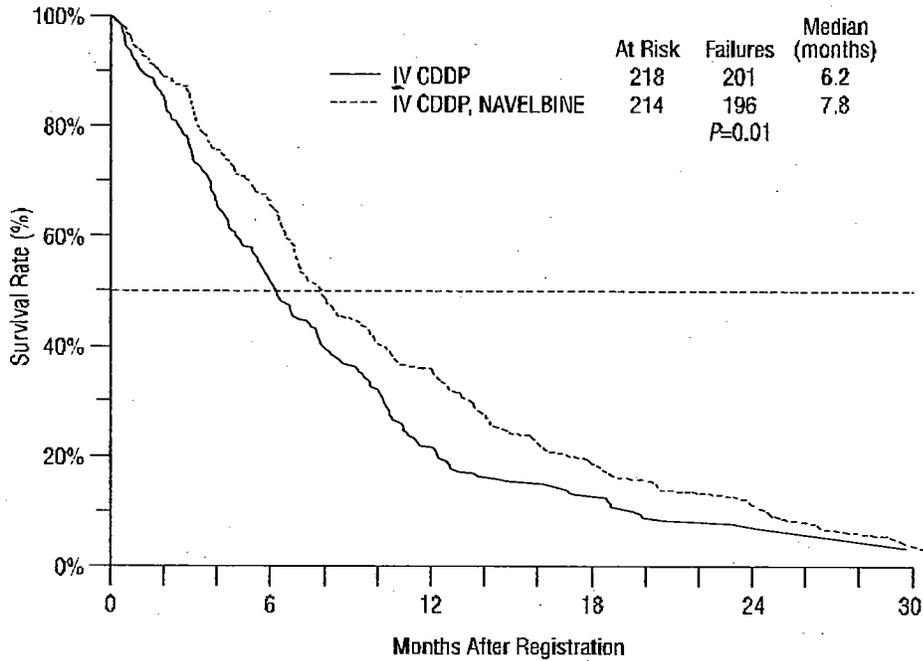
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135 **Table 1. Randomized Clinical Trials of NAVELBINE in Combination with Cisplatin in NSCLC**

	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**

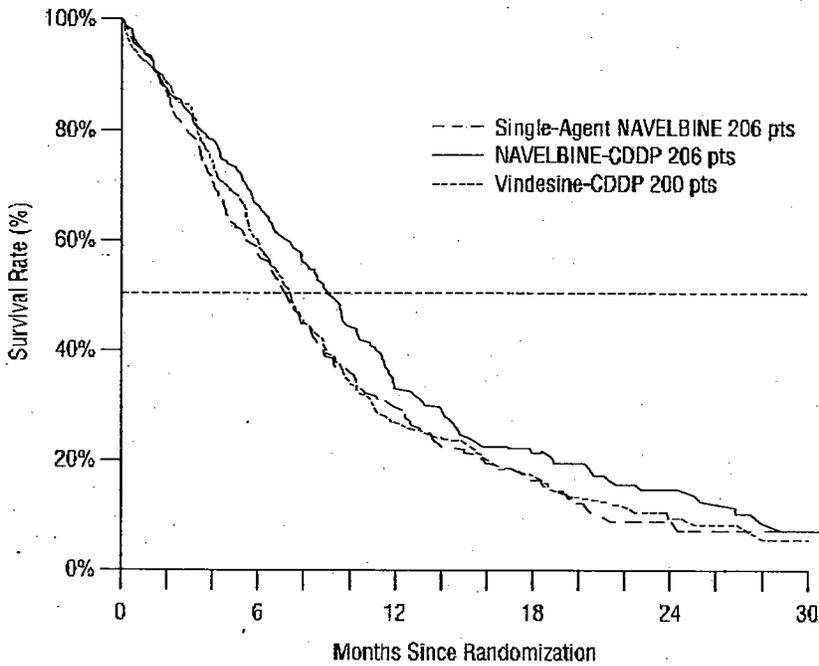


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141 **Figure 2. Overall Survival**

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



143

144

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.

150

151 **CONTRAINDICATIONS**

152 Administration of NAVELBINE is contraindicated in patients with pretreatment granulocyte counts
153 $<1,000$ cells/mm³ (see WARNINGS).

154

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 $<1,000$ cells/mm³. 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.

186

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.

268 [‡] Incidence of paresthesia plus hypesthesia.

269

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

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

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

284 **Skin:** Like other anticancer vinca alkaloids, NAVELBINE is a moderate vesicant. Injection site
 285 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 $\geq 1,000$ 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

492 **REFERENCES**

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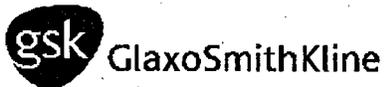
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27 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

X § 552(b)(4) Draft Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-388/S-014

Medical Review(s)

Medical Review: Pediatric Exclusivity Request

NDA:	20-388 SE8-014
Drug:	Navelbine (vinorelbine)
Sponsor:	GlaxoSmithKline
NDA Approval Date:	December 23, 1994
Written Request Proposal Submission Date:	November 15, 2000
Written Request Issue Date:	January 9, 2001
Patent Expiration Date:	July 8, 2002
Date of Submission:	June 17, 2002
Deadline for Submission of Study Reports:	December 31, 2003
Medical Reviewer:	Susan Honig, M.D.
Team Leader:	Grant Williams, M.D.
Review Date:	July 16, 2002

I. Background

On 11/15/00, the sponsor submitted a Proposed Pediatric Study Request for Navelbine. Navelbine is a vinca alkaloid drug that interferes with microtubule assembly and thus inhibits cell growth. It is approved for the treatment of non-small cell lung cancer in adults and is used off-label in multiple malignancies, including breast cancer, ovarian cancer, and lymphoma (Hodgkin's and non-Hodgkin's). Vinorelbine causes myelosuppression but has been reported to cause less neurotoxicity than other vinca alkaloids. Because of the potential for efficacy in children with less neurotoxicity, the sponsor submitted a Proposed Pediatric Study Request. The FDA reviewed the Request and issued a Written Request to the sponsor on 1/9/01. The contents of the Written Request are summarized below. The deadline for submission of the study reports requested in the Written Request was 12/31/03.

In November 2001, the sponsor contacted the project manager and asked to amend the Written Request. According to the sponsor, accrual to the Phase II study was slow and would not be completed until after the sponsor's patent for Navelbine expired on 7/8/02. They requested permission to submit only the Phase I study in response to the Written Request.

The Division had a teleconference 11/29/01 to discuss this issue with the sponsor. We informed them that a Phase I study alone did not constitute meaningful investigation of Navelbine unless the trial demonstrated unacceptable toxicity in children that precluded further study. Because the Phase I trial reportedly identified a safe and potentially effective pediatric dose suitable for Phase II testing, results of the Phase II study are necessary to provide meaningful information for the use of Navelbine in children. An amendment of the Written Request must be based on safety and efficacy concerns, not business concerns.

On June 17, 2002, the sponsor submitted the Phase I study report and a report of the Phase II study, which was closed early (May 24, 2002) because of lack of activity.

II. Summary of regulatory interactions

November 15, 2000	Proposal for a Written Request submitted from the sponsor
January 9, 2001	Written Request issued by FDA
November 29, 2001	Teleconference with sponsor to reinforce the requirements of Written Request
June 17, 2002	Submission of labeling supplement in response to Written Request with request for Pediatric Exclusivity
June 26, 2002	List of deficiencies sent to sponsor by facsimile
June 27, 2002	Teleconference to discuss deficiencies
June 27, 2002	

III. Summary of the clinical trials

The following table summarizes the clinical trial designs.

Table 1. Summary of clinical trial design

Study components	Phase I study	Phase II study
Sponsor	Children's Oncology Group	Children's Oncology Group
Objectives	<ul style="list-style-type: none"> Determine MTD in children Determine toxicities Pharmacokinetics Preliminary efficacy 	<ul style="list-style-type: none"> Determine RR in children Assess toxicity
Indications	Leukemia, lymphoma, solid tumor refractory to usual tx	<ul style="list-style-type: none"> Soft tissue sarcomas Astrocytoma, anaplastic astrocytoma, glioblastoma multiforme Medulloblastoma, peripheral primitive neuroectodermal tumor Other brain tumors Neuroblastoma
Number of patients	3-6/dose level	10-20 per tumor type
Age groups	≤ 21 years ¹	≤ 21 years ¹
Endpoints	<ul style="list-style-type: none"> Toxicity PK Absolute bioavailability Response rate OS 	<ul style="list-style-type: none"> RR in each tumor stratum Survival Toxicity
Timing of assessments	<ul style="list-style-type: none"> Labs Q 1 wk Exam Q 4 wks CT, MRI Q 8 wks 	<ul style="list-style-type: none"> Exam, hematology labs prior to ea. dose Chemistry weeks 1,5 Radiology prior to courses 2 and 3, then Q 2 courses
Entry criteria	<ul style="list-style-type: none"> Confirmed malignancy PS 0-2 Life expectancy ≥ 2 mo Adequate organ function 	<ul style="list-style-type: none"> Confirmed malignancy Measurable disease ≤ 2 prior therapies PS 0-2 Life expectancy ≥ 2 mo Adequate organ function CNS toxicity ≤ grade 2; seizures well-controlled
Dose/schedule	<ul style="list-style-type: none"> Weekly at dose levels of 24, 30, 37.5, 48 mg/m² IV For pts who can swallow capsules, Navelbine given PO on week 1 at 3 x IV dose. All other doses IV Conventional Phase I escalation schema 	<ul style="list-style-type: none"> 33.75 mg/m² IV weekly X 6 wks; repeat every 8 weeks AMENDED to 30 mg/m² IV weekly X 6 wks; repeat every 8 weeks because of grade 4 neutropenia
Drug-specific safety concerns	<ul style="list-style-type: none"> Myelosuppression Neurotoxicity Cardiovascular events Respiratory reactions GI toxicity 	<ul style="list-style-type: none"> Alopecia LFT elevations Injection site reactions Allergic reactions
Statistical design	Usual Phase I	Two-stage study. If the true RR is 30%, test has 88% power to identify a RR of at least 10% with Type I error of 13%
Planned analyses	<ul style="list-style-type: none"> Descriptive statistics for safety Standard PK analysis 	<ul style="list-style-type: none"> RR with 95% CI Descriptive statistics for safety

¹Rationale for age group: Sarcomas have peak incidence in second decade
 Age 18-21 physiologically similar to younger teens
 Pediatric oncologists routinely see patients up to age 21

IV. FDA Evaluation of the Response to the Written Request

The following table summarizes the requirements of the Written Request, the sponsor's submission, and comments from the reviewer about the deficiencies.

Table 2. Summary of the requirements of and response to the Written Request

Written Request Item	Sponsor's Response	FDA Comments
<i>Phase I study</i>		
Study report for the completed study	<ul style="list-style-type: none"> • Protocol, amendments • Data listings • CRFs for all patients • COG draft manuscript • Abbreviated clinical trial report 	<ul style="list-style-type: none"> • Did not submit full study report¹ <ul style="list-style-type: none"> ◆ Supportive data listings and CRFs are sufficient to complete a careful review and draw a meaningful conclusion from the trial
Indications, objectives, age range, statistical design/analysis as in Table 1	<ul style="list-style-type: none"> • Solid tumors n = 25 • Hematologic malignancies n = 4 • Ages 2-17 • Navelbine given PO on week 1, followed by IV on subsequent weeks 	<ul style="list-style-type: none"> • Use of oral drug not specified in original protocol document; no amendment documenting this change submitted • Only 29 patients were considered evaluable; no information submitted for 17 patients <ul style="list-style-type: none"> ◆ Sufficient data available to complete a careful review and draw a meaningful conclusion from the trial • Acceptable mix of indications: no evidence that safety or efficacy will be different in patients with solid tumors and patients with hematologic malignancies • Ages acceptable
MTD required as primary endpoint	<ul style="list-style-type: none"> • MTD = 33.75 mg/m² • 1 PR in patient with rhabdomyosarcoma 	<ul style="list-style-type: none"> • MTD identified
PK measures in blood and CSF as secondary endpoint. Traditional or sparse sampling technique acceptable	<ul style="list-style-type: none"> • Report submitted 	<ul style="list-style-type: none"> • No primary PK data submitted for FDA review²
Must submit separate safety tabulations for oral and IV formulations		<ul style="list-style-type: none"> • Did not submit separate safety tabulations for oral and IV³

<i>Phase II study</i>		
Study report for the study	<ul style="list-style-type: none"> • Protocol, amendments • Data listings • CRF for all patients with data available as of 4/28/02 • Abbreviated clinical trial report 	<ul style="list-style-type: none"> • Did not submit full study report¹
At least 14 pediatric patients per tumor type with refractory or relapsed tumors	<ul style="list-style-type: none"> • CNS tumors n=21 • Soft tissue sarcoma n=21 • Neuroblastoma n=4 	<ul style="list-style-type: none"> • Insufficient numbers enrolled with neuroblastoma
Indications, objectives, age range, statistical design/analysis as in Table 1	<ul style="list-style-type: none"> • Age ≤ 21 • Other parameters as described in study summaries 	<ul style="list-style-type: none"> • Patients up to age 25⁴
RR acceptable primary endpoint	<ul style="list-style-type: none"> • CNS: 0/21 • Sarcoma: 2/21 • Neuroblastoma: 0/4 	<ul style="list-style-type: none"> • Insufficient number of neuroblastoma patients • Did not submit 95% CI for RR⁵
<i>General requirements</i>		
Financial disclosure	Certified that no financial arrangements existed	Reviewed by FDA and found to be satisfactory
Draft labeling		
Postmarketing safety	Not present in original submission	No post-marketing summary ⁶

¹ The sponsor stated that only abbreviated reports were available from COG. They indicated that it is standard practice for COG to write abbreviated reports and publish the findings in the peer-reviewed literature.

² The sponsor can submit primary PK data to FDA on request

³ Because PO Navelbine was given only on week 1 and patients then received weekly IV Navelbine, it is not possible to separate safety tabulations by formulation. The sponsor submitted the safety listings for all patients and organized by toxicity grade, dose, tumor type, presence or absence of bone marrow involvement, and prior history of bone marrow transplant or not.

⁴ Two patients older than age 21 were enrolled, one with soft tissue sarcoma and one with a CNS tumor. Neither were responders.

⁵ 95% CI for RR submitted

⁶ Postmarketing summary for pediatric patients submitted

A teleconference was held with the sponsor about the concerns noted on initial review of the submission. As summarized in the footnotes to the above table, most deficiencies were corrected with subsequent submissions in a timely fashion. The lack of availability of full study reports because of the operational procedures of the Children's Oncology Group was clarified.

The issue for consideration by the Pediatric Board is whether the failure to enroll a sufficient number of patients with neuroblastoma as required by the FDA's Written Request should result in denial of Pediatric Exclusivity for Navelbine. The reviewer would like to discuss this issue to provide background and context for the Board's consideration.

This Phase II study was conducted by the Children's Oncology Group, a cooperative group dedicated to the clinical research of new therapeutic agents in children with cancer. Unlike the adult population, nearly all children with cancer are treated at major academic centers and are preferentially enrolled on clinical trials unless they are ineligible for all available studies or unless the patient and his/her family refuse

participation. Because a small number of children are diagnosed with cancer each year relative to adults, the COG prioritizes its trials to study the most promising agents first. It also monitors studies so that trials of ineffective agents can be closed to avoid exposing pediatric cancer patients to toxic drugs without benefit. Study 9705 met its accrual goals for 2 of the 3 strata of cancer patients. Because of lack of activity (10% response rate in soft tissue sarcoma, 0 in CNS tumors), the study was closed to further accrual on all strata on May 24, 2002. Given the lack of activity in the fully accrued strata and the lack of activity in the 4 neuroblastoma patients entered on study, the action was clinically appropriate. It is unlikely that accrual of 10 more neuroblastoma patients would demonstrate a meaningful benefit given the results to date. Continuation of the study would expose additional patients to an ineffective but toxic drug and would divert accrual from new studies of potentially effective treatments.

According to the submitted documentation, the decision to close the study early was made by the executive committee of the COG and not by the sponsor.

The reviewer believes that the spirit of the Written Request was met. The lack of efficacy of Navelbine in these pediatric cancers is important information that should be included in product labeling.

V. Presentation to the Pediatric Exclusivity Board

This review was presented to the Board on August 15, 2002. Pediatric Exclusivity was granted. The project manager notified the sponsor following the meeting.

Appendix I. FDA review of Phase I study

Title: CCG-0936: A Phase I evaluation of oral and intravenous Navelbine (vinorelbine tartrate) in pediatric cancer patients
Accrual dates: November 1992-December 1997
Report date: June 3, 2002

A. Study design

1. General

This study was a multicenter open-label non-randomized Phase I trial performed at 13 U.S. institutions through the Children's Oncology Group. All patients were aged 18 or younger. The study rationale, objectives, and design are described in Table 1 and follow a classic Phase I dose-escalation schema. Patients who could swallow capsules received PO Navelbine on week 1, followed by 5 weeks of IV therapy; all other patients received 6 weekly IV infusions of Navelbine. Patients remained on therapy until evidence of progressive disease or non-reversible toxicity.

The protocol followed the COG guidelines for Phase I studies, established in 1991, that called for dose-escalation until dose-limiting toxicity (DLT) was reached, following by de-escalation by half-steps to ensure that the maximum tolerated dose (MTD) was tightly defined.

Reviewer Comment:

1. It is acceptable to investigate oral therapy in children. However, the oral dose was selected as 3 times the IV dose. The rationale for dose selection is unclear.
2. The use of one oral dose followed by intravenous dosing on all subsequent treatments precludes a determination of safety and efficacy of this formulation in children.
3. The reported results are most likely to be reflective of the dosing of the IV formulation.

2. Definition of DLT

The protocol was prospectively designed to evaluate dose-limiting toxicity separately for hematologic and non-hematologic events. Patients with leukemia, lymphoma, or with solid tumors metastatic to the bone marrow were not considered evaluable for hematologic DLT and were to be evaluated separately. These patients were to continue therapy regardless of blood counts without dose modification and were to receive supportive care measures. Patients without bone marrow involvement were treated on the basis of day 1 counts with dose modification as outlined in the protocol.

Dose-limiting toxicity was defined as:

- Non-hematologic DLT: Grade 3-4 toxicity except grade 3 nausea, vomiting, or fever, or grade 3 hepatic toxicity which resolved to grade 1 prior to the next scheduled treatment
- Hematologic DLT, patients without BM involvement: grade 4 toxicity lasting ≥ 7 days, or of any duration accompanied by any grade 3-4 non-hematologic toxicity including infection and fever

- Hematologic DLT, patients with BM involvement: Not eligible for this analysis

The manuscript states that patients must have completed 4 of 6 planned weeks of vinorelbine therapy to be evaluated for DLT. However, any patient who had DLT after the first dose of vinorelbine was considered in the MTD assessment.

Reviewer Comment:

1. It is acceptable to calculate DLT separately for patients with and without bone marrow involvement as a sensitivity analysis.

2. Usually, data from all patients entered in a Phase I study are used to calculate DLT and MTD. A significant percentage of patients were excluded from evaluation in this trial.

3. Definition of response

The following definitions of response were used.

a. Hematologic malignancies

- CR: M1 bone marrow (5% blasts) with no circulating blasts or extramedullary disease with recovery of peripheral counts to ANC > 1000/mm³ and platelets > 100,000/mm³ x 4 weeks
- PR: M2 marrow (<25% blasts), no circulating blasts and recovery of counts as per CR
- PD: increase of > 25% in the number of circulating or extramedullary leukemic cells

b. Solid tumors

Standard criteria were used with a requirement for verification in 4 weeks.

4. Pharmacokinetics

The study was designed to evaluate pharmacokinetics after the first oral dose and the second IV dose of vinorelbine. Samples were obtained immediately prior to and at 15, 30, and 45 minutes after oral administration on week 1 day 1, then 1.0, 1.5, 2, 4, 6, 8, 16, 24, 48, 72, and 96 hours after dosing. At week 2, samples were obtained immediately prior to IV administration and at 20 (end of infusion), 25, 30, and 25 minutes and 1, 2, 6, 8, 16, 24, 48, 72, and 96 hours after infusion. Standard analyses were performed.

Reviewer Comments:

1. The results will be evaluated by the Biopharmaceutics reviewers.
2. Raw data were not submitted. The sponsor indicated that these data are available for review if requested.

B. Enrollment and demographics

1. Enrollment

Forty-six patients were enrolled in the study. Twenty-nine patients received at least 4 cycles of vinorelbine and experienced DLT. Four patients experienced DLT at dose level 1 (24 mg/m²), 9 at level 2 (30 mg/m²), 8 at level 3 (37.5 mg/m²), and 8 at level

4 (33.75 mg/m²). Seventeen patients did not experience DLT and did not receive at least 5 of the 6 planned courses. They were not considered eligible for evaluation.

A separate analysis of hematologic toxicity was performed in the subset of patients without bone marrow involvement (n=22).

Twenty-two patients had measurable disease and were included in the efficacy analysis.

Reviewer Comment:

1. Generally, all patients and their toxicity profiles are considered in the evaluation of DLT. The sponsor excluded 37% of the enrolled population and did not provide any information, including demographic and toxicity information, about these patients.

2. Demographics

Twenty-nine patients were considered evaluable. These patients included 19 males and 10 females ranging in age from 2 to 17 years. Most patients had received 1-3 prior chemotherapy regimens and prior radiotherapy. At least half received at least 6 prior chemotherapeutic agents. All had the required PS. Most had CNS, bone, or soft tissue sarcoma tumors.

C. Results: Assessment of DLT

1. Hematologic toxicity

a. Neutropenia

Twenty-five patients did not have bone marrow involvement. Of these, 72% experienced grade 3-4 neutropenia which was dose-dependent and related to duration of therapy. All events were reversible. Eleven of the 25 (44%) required a dose reduction because of neutropenia. Eight of these patients were treated with either 37.5 or 33.75 mg/m².

Table 3. Dose escalation levels

Dose level	Dose
Dose level 1	24 mg/m ²
Dose level 2	30 mg/m ²
Dose level 3	37.5 mg/m ²
Dose level 4	48 mg/m ² [never accrued, because DLT occurred at level 3]
Dose de-escalation level	33.75 mg/m ²

At 30 mg/m², 3 patients had grade 4 neutropenia lasting > 7 days. In 2 of 3 patients, the neutropenia was not considered to be related to Navelbine therapy. One patient received multiple antibiotics for fever and IV acyclovir for herpes zoster. The other developed hematologic toxicity after cycle 6.

At 37.5 mg/m², neutropenia was dose-limiting. Four of 8 patients had grade 4 neutropenia lasting > 7 days with treatment delays or dose reductions. Three of the 4 received all 6 cycles of planned therapy. One was removed because of progressive disease. An additional patient at this dose level developed grade 4 neutropenia, grade 4 mucositis, and vomiting after dose 1, with exacerbation of pre-existing congestive heart failure. This patient recovered and subsequently went off study because of progressive disease and toxicity.

Because DLT was confirmed at a dose of 37.5 mg/m², an intermediate dose level that was ½ step lower was initiated. Eight patients were accrued to an intermediate dose level of 33.75 mg/m². Four of the 8 required dose reductions, but only 3 developed hematologic DLT as defined in the protocol. Therefore, a dose of 33.75 mg/m² was considered as the MTD for patients without bone marrow involvement.

b. Other hematologic toxicity

Seven patients had grade 3 anemia and 2 had grade 4 anemia. Three patients had grade 4 thrombocytopenia. These events were reviewed in the COG's assessment of dose-limiting toxicity.

2. Non-hematologic toxicity

Twenty-nine patients were analyzed for non-hematologic toxicity. Four patients developed grade 3-4 transaminase elevations. One patient experienced grade 4 hyperbilirubinemia. Three to 6 patients developed headaches, fever, diarrhea, abdominal pain and cough. One to 2 patients each developed constipation, hives, fatigue, increased BUN, tachypnea, hematuria, bone pain, and phlebitis. Two patients treated at 30 and 37.5 mg/m² developed peripheral neuropathy (grade 2-3), considered disease-related and not drug-related. One patient treated at 24 mg/m² died of progressive disease.

Reviewer Comment:

1. The reviewer's analysis of these results is presented in the Discussion section below.

D, Results: Efficacy

Twenty-two patients were considered evaluable for efficacy. One patient treated at 33.75 mg/m² had a PR for an overall study response rate of 5%.

Reviewer Comment:

1. Efficacy was not the endpoint of this Phase I study, and responses would not be anticipated in this heavily pretreated population.

2. Review of the database and of the CRF does not provide supporting documentation of this response. The CRF for this patient records tumor size at baseline, but does not contain any subsequent measurements. The attribution of PR was made through an investigator "check" on the CRF.

E. Results: Pharmacokinetics

Pharmacokinetic samples were collected on 31 of the 46 patients entered in this study. Of the 31, pharmacokinetics could be evaluated for the oral formulation in 20 patients (7 patients: PO drug unavailable; 3 patients: unable to swallow pills; 1 patient: insufficient sampling) and for the IV formulation in 26 patients (4 patients with data that did not yield reliable parameters; 1 patient did not receive any dose after the initial oral dose).

The pharmacokinetic results will be evaluated by the Biopharmaceutics reviewers. As reported in the draft manuscript of the study, the mean plasma clearance was slightly higher in children (0.99-2.1 L/h/kg) than in adults (0.97-1.26 L/h/kg). The mean volume of distribution at steady state was less in children (21.1 L/kg) than in adults (range of mean values: 25.4-40.1 L/kg). The mean termination elimination half-life in children was significantly less (16.5 hr) than in adults (range 27.7-43.6 hr). The sponsor and the investigators concluded that the higher systemic clearance in children resulted in a higher maximal tolerated dose than in adults.

Reviewer Comment:

1. Review of the toxicity data does not support this conclusion. Please see the following section. Although the MTD for further study was defined as 33.75 mg/m², this dose was too toxic in the Phase II study. The study was amended to lower the dose to 30 mg/m² weekly, identical to the approved dose in adults.

F. Reviewer analysis and discussion

The following table summarizes the reviewer's interpretation of the toxicity data.

Table 4. Summary of DLT events

N/ Dose-limiting toxicity	Navelbine dose			
	24 mg/m ²	30 mg/m ²	37.5 mg/m ²	33.75 mg/m ²
Hematologic DLT				
N	4	5	8	8
Neutropenia	0	3 (2 called unrelated)	5 (1 called unrelated)	3
Thrombocytopenia	0	1	1	1
Anemia	1 (called unrelated)	1 (called unrelated)	0	0
Non-hematologic DLT				
N	4	9	8	8
Increased transaminases	1	1	1	1
Fever		1		
Diarrhea		1		
Hyperbilirubinemia		1		1
Cough		1		
Peripheral neuropathy		1 (called unrelated)	1 (called unrelated)	

The sponsor evaluated only those adverse events considered to be drug-related (and not disease-related) by the investigator. Use of investigator attribution to analyze a

subset of events tends to overestimate the maximal tolerated dose. Investigators see a few patients at each center, do not have access to the database of events at all sites, and care for patients with serious, refractory, and often symptomatic disease. Drug-related events may not be recognized until all patients have finished treatment and the data are analyzed by a single reviewer. In the current study, Navelbine was already approved in adults for lung cancer, and the spectrum of toxicity was well-established. It is difficult to justify why, for example, peripheral neuropathy was not considered as a drug-related event in this pediatric Phase I trial, even though it is well-documented in adult studies and product labeling that vinorelbine may cause peripheral neuropathy or worsen pre-existing neuropathy. Similarly, neutropenia is a well-recognized adverse event with Navelbine, particularly since the drug is administered weekly, that should have been considered as part of the DLT assessment.

In this study, the MTD may have been exceeded at a dose lower than the one cited in the manuscript. If one looks at hematologic toxicity, 1 of 5 patients without bone marrow involvement treated at dose level 1 (24 mg/m²) experienced DLT (grade 4 anemia; patient 53080). According to the protocol, 1 additional patient should have been entered at this dose level to evaluate this concern. One patient at this dose level had elevated transaminases that met the criteria for DLT according to the manuscript, but this toxicity is not recorded in the submitted database. It is not possible to determine whether 1 of 5 or 2 of 5 patients experienced DLT at this dose.

At dose level 2 (30 mg/m²), 3 of 5 patients without BM involvement met criteria for dose-limiting neutropenia. However, because this event was attributed to disease and not drug in 2 patients, accrual continued. The sponsor's toxicity recording should have halted accrual at this stage and de-escalated by 33%. At dose level 2, 1 patient was reported to have grade 4 anemia (attributed to disease) and 1 was reported to have grade 4 thrombocytopenia. Review of the database, which does not include duration of the event, shows 3 patients with neutropenia (57864, 88800, and 96049). Four patients are recorded with grade 4 thrombocytopenia (patients 55899, 59732, 60483, and 61556). Two patients are recorded with grade 4 anemia (55899 and 57864). Thus, 7 unique patients experienced grade 4 hematologic toxicity that, according to the manuscript, met criteria for DLT.

With respect to non-hematologic toxicity at dose level 2, the sponsor reported that 5 of the 9 patients treated at this level met DLT criteria. A 6th patient had peripheral neuropathy, either grade 2 or grade 3, which was considered to be unrelated to drug therapy by the sponsor. Thus, in the reviewer's judgement, 6 of 9 patients treated with 30 mg/m² met criteria for non-hematologic DLT.

The submitted database was reviewed to evaluate overlap in these two categories of toxicity. The database demonstrated that the patient with peripheral neuropathy also experienced diarrhea, hyperbilirubinemia and grade 4 thrombocytopenia. The patient with elevated transaminases did not have significant hematologic toxicity. Thus, at least 8 unique patients experienced either dose-limiting hematologic or non-hematologic toxicity. According to the protocol, the dose of 30 mg/m² exceeded the MTD.

Escalation continued to dose level 3 (37.5 mg/m²), where MTD was exceeded. The sponsor did not note the episode of grade 4 stomatitis in patient 59900 (who also had dose-limiting neutropenia), the grade 3 episode of hyperbilirubinemia in patient 62253 (grade 4 thrombocytopenia and neutropenia), and the grade 4 episode of constipation in a

patient with grade 4 neutropenia. Constipation and ileus are significant Navelbine-related toxicities well-documented in adults that are likely to be relevant in children as well.

At dose level 4, the de-escalation level of 33.75 mg/m², 3 of 8 patients met DLT criteria for neutropenia. One patient had dose-limiting thrombocytopenia (99660). It is not possible to determine if this patient also had dose-limiting neutropenia because the database did not record duration of event. Two patients had evidence of dose-limiting elevations of transaminases (patient 62643) and bilirubin (patient not found by the reviewer in the submitted database) according to the sponsor. Although this level was deemed the MTD suitable for Phase II testing, the submitted data indicate that this dose level exceeded MTD with at least 4 of 8 patients documented to have DLT. The reviewer's conclusion is supported by the finding that the Phase II study required an amendment lowering the dose from 33.75 to 30 mg/m² because of unacceptable toxicity. It is likely that 30 mg/m² exceeds the MTD as well. In adults, 30 mg/m² weekly is the approved dose, although in clinical practice it is not well-tolerated and the community standard has become 25 mg/m² weekly. The data from this study suggest that a similar dose and schedule are likely to provide optimal dosing in the pediatric children, as in adults.

G. Reviewer Summary

Overestimation of the optimal Phase II dose by considering selected events in the Phase I study may affect toxicity but will not affect efficacy. For cancer chemotherapeutic agents, efficacy is related to use of an optimal threshold dose that is generally selected as the highest tolerable dose. Although the reviewer believes that the current study overestimated MTD, it fulfilled the stated aims of selecting the highest potentially active dose for further study.

Caution should be used in the wording of the pharmacokinetic results in the label if the supplement is approved. Although the sponsor interpreted the pharmacokinetic results as demonstrating that children tolerate higher levels of Navelbine than adults, the clinical trial results do not support this assertion. A dose of 33.75 mg/m² exceeded the MTD (as demonstrated in the Phase II trial). Review of the phase I data suggest a dose of 30 mg/m² exceeded the MTD, and that the optimal dose may lie between 24 and 30 mg/m² weekly. These findings are identical to those reported in adults.

Appendix II FDA review of Phase II trial

Title: CCG A 09705: A Phase II study of Navelbine (vinorelbine tartrate) in children with recurrent or refractory malignancies
Accrual dates: May 18, 1998 to May 24, 2002
Report date: June 4, 2002, with data lock date of April 28, 2002

A. Study design

1. Objectives

This trial was a multicenter study conducted at 26 institutions in children with selected pediatric malignancies. The objectives of the trial were:

- To determine the RR to Navelbine in strata of recurrent solid malignant tumors of childhood
 - ◆ Soft tissue sarcomas, defined as rhabdomyosarcoma, non-rhabdomyosarcoma, and extraosseous Ewing's sarcoma
 - ◆ CNS tumors, defined as PNET, atypical teratoid, rhabdoid tumors, astrocytoma, and ependymoma
 - ◆ Neuroblastoma
- To further assess the toxicity of Navelbine in a larger group of patients treated at the MTD

2. Eligibility

The eligibility criteria include patients aged 21 or younger with the above tumor types and measurable disease (bidimensionally measurable lesion with one dimension at least 0.5 cm). Patients were required to have PS 0-2 and a life expectancy of at least 2 months. Patients could have received up to two prior treatment regimens.

3. Dosage

Patients were enrolled and treated with Navelbine 33.75 mg/m² IV given weekly for 6 weeks followed by a 2-week rest. One course of treatment was defined as an 8-week period. A maximum of 10 courses was planned. All patients were required to have central venous access catheters. Parameters for dose modification were clearly outlined in the protocol.

4. Evaluation and follow-up

Patients were followed with standard assessments. Tumor measurements were obtained with radiographic studies at baseline, prior to courses 2 and 3, then every 2 courses. All assessments were to be repeated when patients were removed from study. Follow-up was to be continued for at least 3 years.

5. Primary endpoint

According to the study synopsis, "disease progression" was the primary endpoint. However, the objectives of the protocol listed response rate as the primary endpoint. Standard response criteria were used. Confirmation of response was required, but the time interval between confirmatory studies was not defined.

Reviewer Comment:

1. The protocol as written provided for a generous assessment of response rate. Only one measurable lesion was required; the minimum diameter in one direction was 0.5 cm instead of the more typical 1 or 2 cm requirement; and the confirmation interval, usually specified as 4 weeks, was required but not defined.

6. Statistical plan (protocol-specified)

It was anticipated that at least 10 patients in each tumor type could be enrolled within 12 months and 20 patients in each subtype in 24 months. The study was designed as a two-stage trial. The following stages and analysis were prespecified to be performed within each of the tumor subtypes.

In stage 1, 10 patients were to be enrolled. If 0 responses were observed, the trial would be closed because of lack of efficacy. If 6 responses were observed, the trial would close because of clear efficacy. If 1-5 responses were observed, the trial would move to stage 2.

In stage 2, an additional 10 patients would be enrolled. If 3 or fewer total responses were observed, the study would close because of lack of efficacy. If 4 or more were observed, the study would close because of clear efficacy.

This design was estimated to have an 88% chance of identifying a true RR of 30% or more for Navelbine and to have a 97% likelihood of stopping the study for a true RR of 10% or less.

All patients who entered the study and received at least 1 dose of Navelbine were evaluable for response as stated in the protocol document. The abbreviated study report considered patients who received at least 2 doses evaluable for response. Patients who died prior to completing course 1 and who were otherwise evaluable were considered non-responders unless criteria for CR or PR are met per protocol.

B. Amendments

After the first 35 patients were enrolled, review of the data demonstrated a high incidence of treatment delays due to neutropenia. The protocol was amended to lower the dose of Navelbine to 30 mg/m².

The study was amended a second time on May 17, 2002 with a closure notice. The memorandum stated that the study would close to accrual on May 24, 2002 "as the trial has accrued a sufficient number of patients in the soft tissue stratum to meet the objectives." All strata were closed simultaneously.

Reviewer Comment:

1. Based on the FDA analysis of the Phase I study, the reviewer agrees that 33.75 mg/m² exceeded the MTD and that the dose reduction was appropriate. It is possible that 30 mg/m² is also too high a dose. Toxicity reports will be evaluated.

C. Enrollment and demographics

Forty-six patients were entered on study. The following table summarizes the distribution of these patients by dose and by tumor type.

Table 5. Tumor type and dose (Table 1 in the abbreviated study report)

Disease type	33.75 mg/m ² N=35	30 mg/m ² N=11	Total N=46
Soft tissue sarcoma	17	4	21
CNS tumors	15	6	21
PNET/medulloblastoma	4	1	5
Astrocytoma, glioma	3	3	6
Other CNS	3	1	4
Brain stem tumor	5	1	6
Neuroblastoma	3	1	4

Although the study was closed early because of sufficient information cited in the soft tissue sarcoma arm, there were sufficient data from the CNS tumor strata to analyze per protocol as well. Although insufficient patients were enrolled in the neuroblastoma arm, the COG Developmental Therapeutics Executive Committee (DTEC) closed all arms of the study because of lack of accrual.

An equal number of males and females were enrolled. The median age was 11 with a range of 1-25. Most patients received 1-2 cycles of the planned 10 cycles. At the time of data analysis, 3 patients remained on study. Two patients were removed because of toxicity. The remaining patients were removed because of progressive disease.

Reviewer Comments:

1. The sponsor submitted the Memorandum of Study Closure from the COG. The reviewer requested the minutes of the meeting of the DTEC in which the decision was made to close all arms of the study.

2. One patient, aged 22 with PNET/medulloblastoma, was enrolled and treated at a dose of 33.75 mg/m². A second patient, aged 25 with soft tissue sarcoma, was enrolled and treated with 33.75 mg/m². Entry of these patients represented protocol violations.

3. These patients will be excluded from the FDA efficacy analysis. After exclusion, there are still sufficient patients in the soft tissue sarcoma and CNS tumor arms to assess efficacy (20 and 20 respectively). The numbers of patients in these strata meet the requirements of the FDA Written Request.

4. The following table summarizes the number of patients on treatment at each course.

Table 6. Number of patients on treatment at each course

Course	33.75 mg/m ² N=35	30 mg/m ² N=11
1	35	11
2	17	2
3	6	2
4	4	0
5	3	0
6	2	0
7	2	0
8	2	0
9	2	0
10	1	0

5. On the higher dose arm, less than half the patients received a second course of treatment (49%). Seventeen percent received a third course. Few patients remained on treatment at course 4.

6. On the lower dose arm, 18% received a second or third course. No patients remained on this arm after course 3.

7. The observation that most patients were removed from study after course 1 (8 weeks) suggests that Navelbine is ineffective treatment for these tumor types. This suggestion is supported by the negligible observed response rate. Alternatively, it is possible that the patients entered on study were heavily pretreated with refractory disease. The database did not record number of prior treatments. It appears that all patients had at least one prior chemotherapy regimen and that most received radiotherapy. Enrollment of heavily pretreated patients is not expected in a well-designed Phase II study performed by a qualified cooperative group.

8. The database recorded off-study information for 39 of the 46 enrolled patients. Thirty-four were removed from study for progressive disease (including 1 patient who completed 10 courses of therapy), 2 were removed for toxicity, 1 by patient choice, 1 by physician choice, and 1 for death not related to Navelbine therapy (recorded as progressive disease in a soft tissue sarcoma patient).

9. Two patients were removed for toxicity. One patient with soft tissue sarcoma had neuralgia and neuropathic pain grade 4. A second patient had grade 4 pneumonitis and hypoxia (brain stem tumor). This patient received 30 mg/m².

D. Results

1. Efficacy

One patient had a PR (30 mg/m²) and 1 had a CR (33.75 mg/m²), both in the soft tissue sarcoma group. This response rate was 9.5% (95% CI 1.2-30.4%). None of the 21 patients with CNS tumors (RR 0; 95% CI 0-16.1%) and none of the 4 with neuroblastoma (RR 0; 95% CI 0-60.2%) had a response.

Reviewer Comments:

1. The protocol and the study report differed on whether patients were evaluable for response after 1 dose of Navelbine or after 2 doses. The database will be reviewed to determine whether this distinction was meaningful in the analysis of this trial.

2. Patient 67897 was reported to have a CR. This patient, as noted, had soft tissue sarcoma and was treated with 33.75 mg/m². The patient was reported to have a CR after courses 1 and 2 and was removed from study because of "physician choice."

3. Patient 36806 was reported to have a PR. Review of the CRF indicated that the patient was recorded as having a PR after course 1 and 2. The patient received courses 3 and 4 (re-evaluation not required). At course 5, the patient had progressive disease and was removed from study.

4. The database records PRs for the following patients that were not assessed as PRs by COG or the sponsor:

- Patient 72614: Recorded as PR after course 1 but developed documented bone marrow involvement shortly after the initiation of course 2
- Patient 600528: Database lists PR; CRF clearly states that the patient had stable disease for two cycles, then went off-study for progressive disease.
- Patient 704468: Called a PR after course 1. However, at the end of course 2 was listed with stable disease, and on day 1 of course 3 (the same day as the end of course 2 evaluation), the patient was listed as having "substantial clinical symptoms from tumor burden." The patient had progressive disease documented at the end of course 3.
- Patient 706606: Database lists a PR, but the CRF indicates only a telephone entry form. No baseline status or treatment recorded.
- Patient 713817: PR listed in database and CRF, but no further treatment or information provided after course 1.

The reviewer agrees with COG and the sponsor that these cases cannot be confirmed as partial responses.

5. It should be noted that the database contains only baseline tumor measurements. No subsequent formal documentation of response was provided. Response was documented by completion of a box on the CRF by the investigator.

6. Most patients received a dose of vinorelbine that exceeded the MTD. The lack of efficacy is not due to suboptimal doses of chemotherapy.

2. Toxicity

The predominant observed toxicities were hematologic. The following table summarizes grade 3-4 hematologic toxicities in individual patients throughout the entire course of treatment. As expected, patients had more than one occurrence of these common chemotherapy-related toxicities during treatment. The sponsor reported that the number of patients with bone marrow involvement at study entry and the number with prior bone marrow transplant were too small to draw conclusions about relative toxicity in these subpopulations. Patterns of toxicity did not appear to vary by tumor subtype.

Table 7. Grade 3-4 hematologic toxicity by dose (derived from toxicity listings)

Adverse event	33.75 mg/m ² N=35	30 mg/m ² N=11	Total N=46
Neutropenia	25 (71%)	7 (64%)	32 (70%)
Febrile neutropenia	3 (9%)	1 (9%)	4 (9%)
Infection w/ gr 3-4 neutropenia	2 (6%)	1 (9%)	3 (7%)
Anemia	10 (29%)	5 (45%)	15 (33%)
Transfusion pRBC	3 (9%)	1 (9%)	4 (9%)
Thrombocytopenia	2 (6%)	0	2 (4%)

Reviewer Comments:

1. It appears that the frequency and severity of neutropenia were decreased by lowering the dose. Febrile neutropenia occurred in the same percentage of patients in both dose groups. However, the number of patients affected was small, and the observed rate of 10% is consistent with febrile neutropenia rates reported in the adult trials.

2. Based on the small number of patients treated at a dose of 30 mg/m², it does not appear that dose reduction appreciably affected the rate of anemia or thrombocytopenia or the need for blood transfusions.

The non-hematologic toxicities reported in greater than 10% of patients are listed in the following table.

Table 8. Grade 3-4 toxicities reported in ≥ 10%, modified from table 3 in the study report

Adverse event	33.75 mg/m ² N=35	30 mg/m ² N=11	Total N=46
Vomiting	4 (11%)	0	4 (9%)
Nausea	3 (9%)	1 (9%)	4 (9%)
Neuropathy			
Motor	5 (14%)	2 (18%)	7 (15%)
Cranial	5 (14%)	1 (9%)	6 (13%)
Sensory	2 (6%)	0	2 (4%)
Dyspnea	4 (11%)	1 (9%)	5 (11%)
Hypoxia	3 (9%)	3 (27%)	6 (13%)
Pneumonitis	1 (3%)	2 (18%)	3 (7%)
Anorexia	2 (6%)	1 (9%)	3 (7%)
Constipation	0	0	0
Ileus	1 (3%)	0	1 (2%)

¹All events grade 1-2; 11%, 9%, 11% respectively

The sponsor reported a trend toward more frequent or severe nausea, vomiting, constipation, and neuropathy in the higher dose arm. The sponsor attributed the greater incidence of pulmonary events on the lower dose arm to comorbid factors.

Reviewer Comment:

1. Navelbine causes an ARDS-like pulmonary toxicity which can easily be confused with pulmonary symptoms from underlying disease. It is possible that the pulmonary events represent drug-related toxicity.

2. Patients on the lower-dose arm received, on average, less drug (i.e., fewer courses) than patients treated on the high-dose arm. The higher incidence of pulmonary toxicity on the lower-dose arm cannot be attributed to higher cumulative drug exposure.

3. Given the small numbers of treated patients, it is difficult to assess whether there is a meaningful difference in the incidence of pulmonary toxicity between treatment arms.

E. Discussion and summary

This phase II trial demonstrated a lack of efficacy for Navelbine in children with soft tissue sarcomas and central nervous system tumors. Adequate numbers of patients with these subtypes were enrolled to evaluate activity. Lack of activity is unlikely to be related to selection of an ineffective dose, since most patients were treated with a high dose of Navelbine. Insufficient numbers of patients with neuroblastoma were enrolled to evaluate activity in this tumor subset. However, based on the negative results in the other two tumor types and in the limited number of patients with neuroblastoma, the possibility of demonstrating clinically meaningful efficacy with further enrollment is low.

The frequency and severity of toxicity in pediatric patients was similar to toxicity observed in adults.

Appendix III. Worldwide marketing reports of toxicity in pediatric patients

The sponsor reported 6 reports of adverse events in pediatric patients treated with Navelbine.

- An infant was exposed to Navelbine in utero and was born with anemia. The anemia resolved. These data were published in a report of 3 pregnant women treated with vinorelbine. The other two babies did not experience adverse effects after birth. At 2-3 years of age, the children were normal for age.
- A 21-year-old complained of pain over the ribs after treatment.
- A 16-year-old female treated with Navelbine, mitoguazone, ifosfamide, and etoposide for recurrent Hodgkin's disease developed capillary leak syndrome with edema, pain, fat necrosis, inflammation, myalgia, dysesthesia, and arthralgia, with elevated CPK, hypoalbuminemia, and neutropenia. Hemorrhage and an abnormal skin biopsy (hypodermic hemorrhagic edema) were reported for this patient. MRI confirmed the presence of painful subcutaneous inflammatory edema. All events were attributed by the investigator to vinorelbine therapy.
- An 18-year-old treated with the same regimen for the same indication had a similar course, with capillary leak syndrome, diffuse erythema and myalgias.
- A 16-year-old developed a maculopapular rash and muscle hemorrhage after treatment with Navelbine, ifosfamide, etoposide, and dichlorhydrate for Hodgkin's disease. After recovery, the events recurred after rechallenge with vinorelbine.
- A 20-year-old female with Hodgkin's disease developed a vascular disorder, myalgia, peripheral edema, and bone pain.

These reports, observed outside of a controlled clinical trial, are similar to those observed and labeled in the adult population.

Appendix IV. Pediatric Exclusivity Board template

Written Request Items	Information Submitted/ Sponsor's response
<p>Types of studies/ Study Design:</p> <p>Study 1: Phase I trial</p> <p>Study 2: Phase II trial</p>	<p>Types of studies:</p> <p>As requested for both trials</p>
<p>Indication to be studied:</p> <p>Phase I: Leukemia, lymphoma, solid tumor refractory to usual therapy</p> <p>Phase II:</p> <ul style="list-style-type: none"> • Soft tissue sarcomas • Brain tumors <ul style="list-style-type: none"> ◆ Astrocytoma, anaplastic astrocytoma, glioblastoma multiforme ◆ Medulloblastoma, peripheral primitive neuroectodermal tumor ◆ Other brain tumors • Neuroblastoma 	<p>Indication studied:</p> <p>As requested for both trials</p>
<p>Age group and population in which study will be performed:</p> <p>Age group ≤ 21 years for both trials</p> <p>Population: see Indications</p>	<p>Age group and population in which study was performed:</p> <p>Age group: For Phase I, ages 2-17 For Phase II, age ≤ 25 (Note: 2 patients over age 21 and one with sarcoma)</p> <p>Population: see Indications</p>

Written Request Items	Information Submitted/ Sponsor's response
<p>Number of patients to be studied or power of study to be achieved:</p> <p>Study 1: 3-6 per dose level</p> <p>Study 2: At least 14 patients per tumor type (grouped by sarcoma, brain tumors, and neuroblastoma)</p>	<p>Number of patients studied or power achieved:</p> <p>Study 1: n=29; 4-9 patients per dose level</p> <p>Study 2: Sarcoma: 21 patients (sufficient even after exclusion of the patient) Brain tumors: 21 patients (sufficient even after exclusion of the patient) Neuroblastoma: 4 patients</p>
<p>Entry criteria:</p> <p>Phase I study</p> <ul style="list-style-type: none"> • Confirmed malignancy • PS 0-2 • Life expectancy \geq 2 mo • Adequate organ function <p>Phase II study</p> <ul style="list-style-type: none"> • Confirmed malignancy • Measurable disease • \leq 2 prior therapies • PS 0-2 • Life expectancy \geq 2 mo • Adequate organ function • CNS toxicity \leq grade 2; seizures well-controlled 	<p>Entry criteria used:</p> <p>As requested</p>

Written Request Items	Information Submitted/ Sponsor's response
<p>Clinical endpoints:</p> <p>Phase I</p> <ul style="list-style-type: none"> • Toxicity • PK • Absolute oral bioavailability • Response rate • OS <p>Maximum tolerated dose (MTD) should be the primary endpoint with PK as secondary endpoints</p> <p>Phase II</p> <ul style="list-style-type: none"> • RR in each tumor stratum • Survival • Toxicity 	<p>Clinical endpoints used:</p> <p>As requested</p>
<p>Timing of assessments:</p> <p>Phase I</p> <ul style="list-style-type: none"> • Labs Q 1 wk • Exam Q 4 wks • CT, MRI Q 8 wks <p>Phase II</p> <ul style="list-style-type: none"> • Exam, hematology labs prior to ea. dose • Chemistry weeks 1,5 • Radiology prior to courses 2 and 3, then Q 2 courses 	<p>Timing of assessments:</p> <p>As requested</p>

Written Request Items	Information Submitted/ Sponsor's response
<p>Drug specific safety concerns:</p> <p>For both studies:</p> <ul style="list-style-type: none"> • Myelosuppression • Neurotoxicity • Cardiovascular events • Respiratory reactions • GI toxicity • Alopecia • LFT elevations • Injection site reactions • Allergic reactions 	<p>Drug specific safety concerns evaluated:</p> <p>Evaluated as requested</p>
<p>Drug information:</p> <p>Phase I</p> <ul style="list-style-type: none"> • Route of administration: IV and oral • Dosage/Regimen: Weekly at dose levels of 24, 30, 37.5, 48 mg/m² IV as tolerated in a classic Phase I dose-escalation schema. For pts who can swallow capsules, Navelbine given PO on week 1 at three times the IV dose. All other doses IV • Formulation: IV injection or soft gelatin capsules <p>Phase II</p> <ul style="list-style-type: none"> • Route of administration: IV • Dosage/regimen: 33.75 mg/m² IV weekly X 6 wks; repeat every 8 weeks • Formulation: IV injection 	<p>Drug information:</p> <p>Phase I as requested</p> <p>Phase II study amended to administer 30 mg/m² IV weekly. Appropriate intervention because of observed grade 4 neut</p>

Written Request Items	Information Submitted/ Sponsor's response
<p>Statistical information (statistical analyses of the data to be performed):</p> <p>Phase I</p> <ul style="list-style-type: none"> • Standard Phase I design and analysis • Descriptive statistics for safety using CTC classification • Standard PK analysis using non-compartmental methods <p>Phase II</p> <ul style="list-style-type: none"> • Two-stage study. If the true RR is 30%, test has 88% power to identify a RR of at least 10% with Type I error of 13% • RR with 95% CI • Descriptive statistics for safety using CTC classification 	<p>Statistical information (statistical analyses of the data to be performed):</p> <p>As requested for Phase I</p> <p>Phase II: stopped early so no analysis for the neuroblastoma sul</p>
<p>Labeling that may result from the studies:</p> <p>May incorporate dosage, pharmacokinetic, and safety findings of the study</p>	<p>Did the sponsor submit proposed labeling?</p> <p>Yes</p>

Written Request Items	Information Submitted/ Sponsor's response
<p>Format of reports to be submitted:</p> <p>Full study reports for the completed trials including full analysis, assessment, and interpretation.</p> <p>Separate safety tabulations of the oral and IV formulations of Navelbine in the Phase I trial</p> <p>Summary of post-marketing experience including safety and efficacy update</p>	<p>Format of reports submitted:</p> <ul style="list-style-type: none"> • Abbreviated study reports only <ul style="list-style-type: none"> ◆ Sponsor states COG does not prepare full study reports ◆ Data listings and CRFs were submitted and are sufficient to draw meaningful conclusions from the data • Submitted PK analysis results, but did not submit primary PK analysis <ul style="list-style-type: none"> ◆ states that these data can be obtained and submitted for review • Unified safety tabulations only <ul style="list-style-type: none"> ◆ Because PO was given on day 1 only followed by IV on day 2, it was not possible to distinguish the toxicity of the two formulations • Not submitted initially, but submitted immediately after the Division's review
<p>Timeframe for submitting reports of the studies:</p> <p>On or before 12/31/03</p>	<p>Date study reports were submitted:</p> <p>6/17/02</p>
<p>Additional Information:</p>	<ul style="list-style-type: none"> • Sponsor submitted minutes of the COG meeting at the Division's meeting, but the meeting was administratively closed because of low accrual. • Insufficient numbers of neuroblastoma patients enrolled, but given the limited number of patients and brain tumor patients, it was not clinically appropriate to continue the trial in the reviewer's opinion.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-388/S-014

Statistical Review(s)

Statistical Review – Pediatric Exclusivity Request

Medical Division: Oncology Drug Products (HFD-150)

Biometrics Division: Division of Biometrics I (HFD-710)

NDA NUMBER: NDA-20-388/ S-014

DRUG NAME: NAVELBINE (vinorelbine tartrate)

INDICATION: Recurrent or Refractory malignancies in pediatric cancer patients

SPONSOR: GlaxoSmithKline

STATISTICAL REVIEWERS: **Rajeshwari Sridhara, Ph.D. (HFD-710)**

STATISTICAL TEAM LEADER: **Gang Chen, Ph.D. (HFD-710)**

CLINICAL REVIEWERS: **Susan Honig, M.D. (HFD-150)**

CLINICAL TEAM LEADER: **Grant Williams, M.D. (HFD-150)**

Deputy Director DODP

PROJECT MANAGER: **Maureen Pelosi (HFD-150)**

Distribution: NDA 20-388

HFD-150/Pelosi

HFD-150/Honig

HFD-150/Williams

HFD-710/Sridhara

HFD-710/Chen

HFD-710/Mahjoob

HFD-710/Chi

HFD-700/Anello

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The sponsor submitted reports of a Phase I study (CCG-0936: A phase I evaluation of oral and intravenous NACELBINE (vinorelbine tartrate in pediatric cancer patients), and a Phase II study (A09705: A phase II study of NAVELBINE (vinorelbine tartrate) in children with recurrent or refractory malignancies), which was closed early because of lack of activity. These reports were submitted as a labeling supplement with a request for Pediatric Exclusivity.

The results of the two studies were presented to the pediatric exclusivity board. In view of the lack of efficacy (< 10% tumor response rates) of NAVELBINE in the various strata of recurrent solid malignant tumors of childhood, the pediatric exclusivity board recommended exclusivity for NAVELBINE in pediatric patients. Because no statistical issues were involved in the two study reports, no formal statistical analysis of data was conducted. Please refer to Medical Review for details.

Rajeshwari Sridhara, Ph.D.
Mathematical Statistician
Date:

Concur: Dr. Chen
Team Leader

Cc:
HFD-150/ Ms. Pelosi
HFD-150/ Dr. Susan
HFD-150/ Dr. Williams
HFD-710/ Dr. Sridhara
HFD-710/ Dr. Chen
HFD-710/ Dr. Mahjoob
HFD-710/ Dr. Chi
HFD-700/ Dr. Anello

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Statistical Review – Pediatric Exclusivity Request

Medical Division: Oncology Drug Products (HFD-150)

Biometrics Division: Division of Biometrics I (HFD-710)

NDA NUMBER: NDA 20-388/ S-014

DRUG NAME: NAVELBINE (vinorelbine tartrate)

INDICATION: Recurrent or Refractory malignancies in pediatric cancer patients

SPONSOR: GlaxoSmithKline

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CLINICAL TEAM LEADER: Grant Williams, M.D. (HFD-150)

Deputy Director DODP

PROJECT MANAGER: Maureen Pelosi (HFD-150)

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HFD-710/ Dr. Mahjooob
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HFD-700/ Dr. Anello

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Clinical Pharmacology and Biopharmaceutics Review: Pediatric Exclusivity Request

I. Project Identification

NDA	20-388/SE8-014
Submission Date	June 17, 2002
Drug Name	Navelbine
Generic Name	vinorelbine tartrate
Dosage Form	IV injection 10 mg/ml and 50 mg/ml single use vial oral capsule (investigational)
Sponsor	GlaxoWellcome PO Box 13398 Five Moore Drive Research Triangle Park, NC 27709-3398
Reviewer	Anne Zajicek, M.D., Pharm.D.
Type of Submission	NDA/supplemental

II. Background

Vinorelbine is a vinca alkaloid that interferes with microtubule assembly. It is approved in adults for first line treatment of unresectable, advanced non-small cell lung cancer, alone (Stage IV), or in combination with cisplatin (Stage III).

III. Purpose of studies

The sponsor submitted two studies, one Phase 1 and one Phase 2 study, in response to a written request issued by FDA, in order to be considered for pediatric exclusivity. The purpose of these studies was to determine the safety, tolerability, pharmacokinetics and efficacy of vinorelbine in children with refractory solid tumors.

IV. Study design

An uncontrolled, open-label, multi-center study entitled "A Phase 1 evaluation of oral and intravenous Navelbine (vinorelbine tartrate) in pediatric cancer patients (CCG-0936)" was submitted in response to the FDA written request for pediatric pharmacokinetic and pharmacodynamic data.

A dosage escalation scheme was used: dose level 1 (24 mg/m², 80% of the adult MTD), level 2 (30 mg/m²), level 3 (37.5 mg/m²), and dose level 4 (48 mg/m²). Six weekly cycles were planned.

The first dose was given orally, at a dose three times the intravenous dose, on an empty stomach.

Blood samples for pharmacokinetic analysis were drawn at:

Following oral dosing: 0 (pre-dose), 15, 30, and 45 minutes, and 1, 1.5, 2, 4, 6, 8, 16, 24, 48, 72, and 96 hours post-dose

Following intravenous administration: 0 (pre-dose), 20 (end of infusion), 30 and 45 minutes, and 1, 2, 6, 8, 16, 24, 48, 72, 96 hours post-dose

Pharmacokinetic parameters were determined using noncompartmental analysis with WinNonlin version 3.0.

V. Results

Forty-six patients, aged 2-17 years, were enrolled. Four patients were treated at dose level 1, nine at level 2, eight at level 3 (37.5 mg/m², a dose which exceeded the MTD), and eight at the adjusted dose level 4 of 33.75 mg/m² (the MTD).

No raw pharmacokinetic data was submitted from the sponsor. Results presented in their abbreviated study report are as follows.

Following intravenous administration, plasma clearance (mean \pm SD) within each dose level ranged from 0.99 (0.2) l/hr/kg to 2.1 (0.78) l/h/kg. Mean plasma clearance across all dose levels was 1.75 (1) l/hr/kg. Volume of distribution at steady state was 21.1 (12.2) l/kg, and the mean terminal elimination half-life after intravenous administration was 16.5 (9.7) hours.

Following oral administration, time to maximum plasma concentrations ranged from 0.25 to 6 hours. The mean absolute bioavailability of vinorelbine in children was approximately 30 %.

In comparison with adult values, the pediatric clearance values appear to be significantly higher (1.75 l/h/kg vs 0.97-1.26 l/hr/kg). Half-life is reportedly shorter (16.5 hr vs 37.9 hr). As vinorelbine is cleared in part by metabolism through the CYP 3A system, these findings are consistent with the higher metabolic capacity of CYP 3A in children.

Bioavailability is reported as 28.5 %, with a standard deviation of 22.5 %; this in contrast to some adult literature suggesting higher bioavailability of > 40 %.

There was no clinical response to vinorelbine, thus no pharmacokinetic/pharmacodynamic relationship could be determined.

No pediatric pharmacokinetic data will appear in the label for the following reasons: lack of clinical effectiveness, and therefore no pediatric indication, and concern that specifics about pediatric dosing and pharmacokinetics might be construed as FDA-approved promotion of off-label use.

V. Recommendation: No action indicated from the Clinical Pharmacology and Biopharmaceutics perspective.

Anne Zajicek, M.D., Pharm.D.
Medical Officer
Division of Pharmaceutical Evaluation 1

N.A.M. Atiqur Rahman, Ph.D.
Team Leader, Oncology
Division of Pharmaceutical Evaluation 1

CC: HFD-150/SHonig, Grant Williams
HFD-860/CSahajwalla, MMehta, PMarroum
HFD-880/ASelen, JLazor

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-388/S-014

**Clinical Pharmacology and Biopharmaceutics
Review**

Clinical Pharmacology and Biopharmaceutics Review: Pediatric Exclusivity Request

I. Project Identification

NDA	20-388/SE8-014
Submission Date	June 17, 2002
Drug Name	Navelbine
Generic Name	vinorelbine tartrate
Dosage Form	IV injection 10 mg/ml and 50 mg/ml single use vial
Sponsor	oral capsule (investigational) GlaxoWellcome PO Box 13398 Five Moore Drive Research Triangle Park, NC 27709-3398
Reviewer	Anne Zajicek, M.D., Pharm.D.
Type of Submission	NDA/supplemental

II. Background

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Following oral administration, time to maximum plasma concentrations ranged from 0.25 to 6 hours. The mean absolute bioavailability of vinorelbine in children was approximately 30 %.

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V. Recommendation: No action indicated from the Clinical Pharmacology and Biopharmaceutics perspective.

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Anne Zajicek
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BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-388/S-014

Administrative/Correspondence

Time Sensitive Patent Information

Patent Information Pursuant to 21 C.F.R. § 314.53
for
NAVELBINE® (vinorelbine tartrate) Injection

NDA 20-388: Supplemental Application - Label Change/Pediatric Exclusivity
Determination Request filed concurrently herewith

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name: NAVELBINE®
Active Ingredient: vinorelbine tartrate
Strength(s): 10 mg and 50 mg
Dosage Form: injection

<u>U.S. Patent</u>	<u>Expiration Date</u>	<u>Type of Patent</u>	<u>Patent Owner</u>	<u>U.S. Agent</u>
4,307,100	8 July 2002 ¹	Drug Substance	Centre National de la Recherche Scientific (CNRS) ²	SmithKline Beecham Corporation

¹ copy of certificate for 1,053 day extension under 35 U.S.C. 156 attached

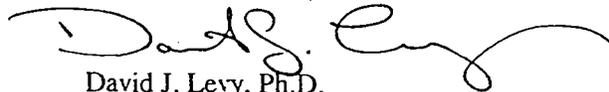
² licensed to SmithKline Beecham Corporation

The undersigned declares that U.S. Patent 4,307,100 covers the drug substance in NAVELBINE® (vinorelbine tartrate). This patent is licensed to SmithKline Beecham Corporation. This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

Please address all communications to:

David J. Levy, Ph.D.
Vice President and Patent Counsel
GlaxoSmithKline - Corporate Intellectual Property Department
Five Moore Drive
Research Triangle Park, NC 27709
(919) 483-2723

Respectfully submitted,



David J. Levy, Ph.D.
Attorney for Applicant

Date: 10 June, 2002

Patent and Exclusivity Search Results from query on 020388 001.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
020388	001	4307100	JUL 08,2002	
020388	001	4307100*PED	JAN 08,2003	

Exclusivity Data

There is no unexpired exclusivity for this product.

Thank you for searching the Electronic Orange Book

[Patent and Exclusivity Terms](#)

[Return to Electronic Orange Book Home Page](#)

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE EXTENDING PATENT TERM
UNDER 35 U.S.C. § 156

PATENT NO. : 4,307,100
ISSUED : December 22, 1981
INVENTOR(S) : Nicole Langlois et al.
PATENT OWNER : Centre National de la Recherche Scientifique (C.N.R.S.)

This is to certify that there has been presented to the

COMMISSIONER OF PATENTS AND TRADEMARKS

an application under 35 U.S.C. § 156 for an extension of the patent term. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

1,053 days

from the date of expiration of the original patent term, August 20, 1999, with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).



I have caused the seal of the Patent and Trademark Office to be affixed this 23rd day of September 1996.

Bruce A. Lehman

Bruce A. Lehman

Assistant Secretary of Commerce and
Commissioner of Patents and Trademarks

EXCLUSIVITY SUMMARY FOR NDA #20-388 SUPPL #014

Trade Name: Navelbine Injection Generic Name: Vinorelbine tartrate

Applicant Name: SmithKlineBeecham DBA GlaxoSmithKline HFD-150

Approval Date If Known 11-5-02

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /___/ NO /X/

b) Is it an effectiveness supplement?

YES /___/ NO /X/

If yes, what type? (SE1, SE2, etc.) SE-8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Negative Study for use in children in various solid tumors

Both studies were done by Children's Cooperative Group with GSK supplying the drug only.

- Efficacy was not an endpoint of CCG-0936, Phase 1 study, an evaluation of NAV in pediatric cancer patients. Responses would not be anticipated in this heavily pretreated population.
- Study CCG A-09705: A Phase 2 study of NAV in children with recurrent or refractory malignancies demonstrated a lack of efficacy for NAV in children with soft tissue sarcomas and central nervous system tumor. Study was stopped early due to lack of response.

cc: Original NDA 20-388/014
Mary Ann Holovac

Division File HFD-150 HFD-93

d) Did the applicant request exclusivity?

YES /___/ NO /x/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

Yes

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /x/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /x/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /x/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-388 Navelbine (vinorelbine tartrate)

NDA# _____

NDA# _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /x/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /X/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /X/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /X/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

CCG-0936: A Phase I evaluation of oral and intravenous Navelbine (vinorelbine tartrate) in pediatric cancer patients

CCG A 09705: A Phase II study of Navelbine (vinorelbine tartrate) in children with recurrent or refractory malignancies

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /X/

Investigation #2

YES /___/

NO /X/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1

YES /___/

NO /X/

Investigation #2

YES /___/

NO /X/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

CCG-0936: A Phase I evaluation of oral and intravenous Navelbine (vinorelbine tartrate) in pediatric cancer patients

CCG A 09705: A Phase II study of Navelbine (vinorelbine tartrate) in children with recurrent or refractory malignancies

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

The phase 1 study and phase 2 were conducted by the Children's Oncology Group under _____ which is held by the University of Texas MD Anderson Cancer Center and cross-referenced to the Glaxo Wellcome INDs _____ and _____ for Navelbine Injection and Navelbine Soft Capsules, respectively.

Investigation #1

IND # _____ NO /___/ Explain: _see above_____

Investigation #2

IND # _____ NO /___/ Explain: _see above_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /_Provided free drug

Investigation #2

YES /Provided free drug

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study?

(Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

Maureen A. Pelosi / January 9, 2003
Project Manager

Grant Williams, MD / January 16, 2002
Deputy Division Director

cc: Original NDA 20-388 SE8-014, Peds Supplement
HFD-150/Division File
/Pelosi
HFD-93 Mary Ann Holovac

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this page is the manifestation of the electronic signature.**

/s/

Grant Williams

1/16/03 05:16:23 PM *

Signed as acting division director for Dr. Pazdur. The
changes to the label are minor. The drug
could be given safely without these changes.

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

DA 20-388 Supplement Type (e.g. SE5): SE8 Supplement Number: 014

Stamp Date: 19 JUN 02 Action Date: 11-5-02 Approval

HFD - 150 Trade and generic names/dosage form: NAVELBINE (vinorelbine tartrate) Injection

Applicant: GlaxoSmithKline Therapeutic Class: Cytotoxic 5010100

Indication(s) previously approved: Non-Small Cell Lung Cancer

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 0

Indication #1: The original application had a full waiver for NSCLC.

Efficacy was not an endpoint of CCG-0936, an evaluation of NAV in pediatric cancer patients. Responses would not be anticipated in this heavily pretreated population.

Study CCG A-09705: A Phase 2 study of NAV in children with recurrent or refractory malignancies and demonstrated a lack of efficacy for NAV in children with soft tissue sarcomas and central nervous system tumors.

Therefore no additional information is required.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
X Disease/condition does not exist in children
Too few children with disease to study
There are safety concerns
Other:

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min kg mo. yr. Tanner Stage
Max kg mo. yr. Tanner Stage

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population

- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Maureen A. Pelosi, RPh
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/Grace Carmouze

NDA ##-###

Page 3

(revised 9-24-02)

PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

Date of Written Request from FDA 01/09/02. Application Written Request was made to: IND _____
NDA 20-388

Timeframe Noted in Written Request for Submission of Studies 12/31/03.

NDA# 20-388 Supplement # 014 Choose one: SE8

Sponsor SmithKlineBeecham D/b/a GlaxoSmithKline

Generic Name vinorelbine tartrate Trade Name Navelbine Injection

Strength 10 mg and 50 mg vials Dosage Form/Route IV (approved) Oral (not approved)

Date of Submission of Reports of Studies 06/17/02 (received 6/18/2)

Pediatric Exclusivity Determination Due Date (90 days from date of submission of studies) 08/16/02.

Was a formal Written Request made for the pediatric studies submitted?	Y <u>X</u> N	N
Were the studies submitted after the Written Request?	Y <u>X</u> N	N
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	Y <u>X</u> N	N
Was the timeframe noted in the Written Request for submission of studies met?	Y <u>X</u> N	N
If there was a written agreement, were the studies conducted according to the written agreement? OR If there was no written agreement, were the studies conducted in accord with good scientific principles?	Y <u>X</u> N	N
Did the studies fairly respond to the Written Request?	Y <u>X</u> N	N

SIGNED Susan Honig, MD [Signature] DATE 07-09/02
 (Reviewing Medical Officer)

Do not enter in DES. FORWARD TO PEDIATRIC EXCLUSIVITY BOARD, BFD-960

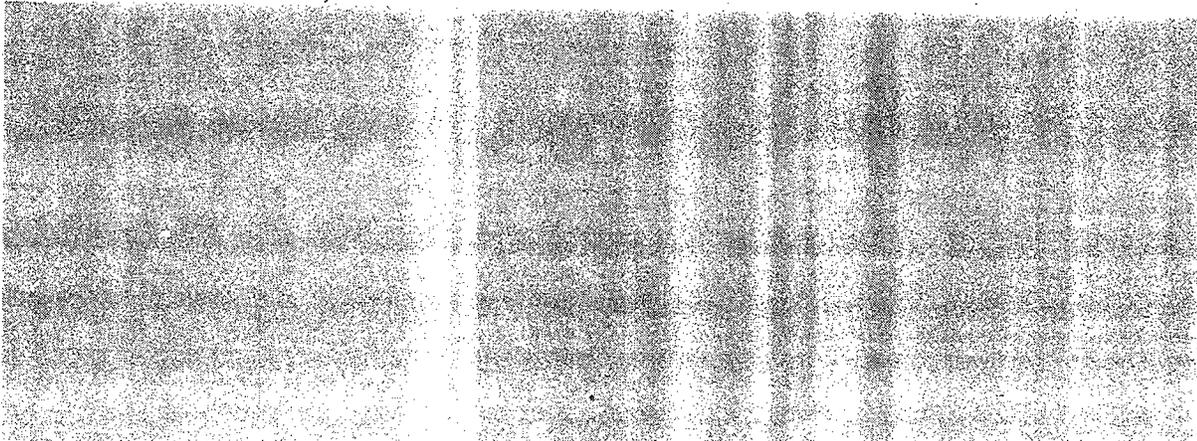
PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity **Granted** **Denied**

Existing Patent or Exclusivity Protection:

NDA/Product #	Eligible Patents/Exclusivity	Current Expiration Date
20-388	4307100	8-JUL-2002

SIGNED [Signature] DATE 8/15/02



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/s/

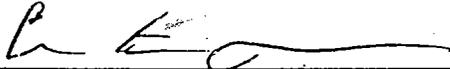
Grace Carmouze
8/19/02 04:39:09 PM

NDA 20-388
NAVELBINE (vinorelbine tartrate) Injection

Supplemental New Drug Application for
Use in Pediatric Patients

DEBARMENT CERTIFICATION

GlaxoSmithKline hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.



Charles E. Mueller
Head, North America Clinical Compliance
World Wide Regulatory Compliance

7 Jul 2002

Date

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

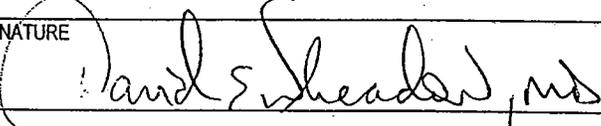
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
David E. Wheadon, M.D.	Senior Vice President, US Regulatory Affairs
FIRM / ORGANIZATION	
SmithKline Beecham Corporation d/b/a GlaxoSmithKline	
SIGNATURE	DATE
	11 June 2002

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-388 / S-014

SmithKlineBeecham Corporation d/b/a/a GlaxoSmithKline
2301 Renaissance Blvd.
Building 510 / MailCode RN0210
P.O. Box 61540
King of Prussia, PA 19406-2772

Attention: Anne-Margaret Martin
Sr. Director, Regulatory Affairs, Oncology

Dear Ms. Martin:

We acknowledge receipt of your December 4, 2002 submission containing final printed labeling in response to our November 5, 2002 letter approving your supplemental new drug application for Navelbine Injection (vinorelbine tartrate) 10 mg/ 1 ml.

We have reviewed the labeling that you submitted in accordance with our November 5, 2002 letter and we find it acceptable.

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

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Dotti Pease
2/3/03 03:44:38 PM
Signing for Richard Pazdur, M.D.

pelosi

USER FEE VALIDATION SHEET

SE8-014-PM

NDA # 20-388

Supp. Type & # SLR-014
(e.g., N000, SLR001, SE1001, etc.)

UFID # 4351

1. YES NO User Fee Cover Sheet Validated? MIS_Elements Screen Change(s):

2. YES NO APPLICATION CONTAINS CLINICAL DATA?
(Circle YES if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).

REF IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION.

3. YES NO SMALL BUSINESS EXEMPTION

4. YES NO WAIVER GRANTED

5. YES NO NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (other than bundling).
If YES, list all NDA #s, review division(s) and those for which an application fee applies.

NDA #	Division	Fee	No Fee
N _____	HFD- _____	Fee	No Fee
N _____	HFD- _____	Fee	No Fee

6. YES NO BUNDLING POLICY APPLIED CORRECTLY? No Data Entry Required
(Circle YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Circle NO if application should be split into more than one application or be submitted as an original instead of a supplement. If NO, list resulting NDA #s and review division(s).

NDA #	Division	NDA #	Division
N _____	HFD- _____	N _____	HFD- _____

7. P S PRIORITY or STANDARD APPLICATION?

Maura Pelosi 7-10-02

PM Signature / Date

Dupont 7-10-02

CPMS Concurrence Signature / Date



NDA 20-388 / S-014

SmithKlineBeecham Corporation d/b/a/a GlaxoSmithKline
2301 Renaissance Blvd.
Building 510 / MailCode RN0210
P.O. Box 61540
King of Prussia, PA 19406-2772

Attention: Anne-Margaret Martin
Sr. Director, Regulatory Affairs, Oncology

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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

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this page is the manifestation of the electronic signature.**

/s/

Dotti Pease
2/3/03 03:44:38 PM
Signing for Richard Pazdur, M.D.

CSO NDA LABELING REVIEW OF PACKAGE INSERT

NDA: 20-388 / SE-8 #014/ FA

DATE OF SUBMISSION: December 4, 2002

DATE OF REVIEW: January 29, 2003

DRUG: Navelbine (vinorelbine tartrate) Injection

**SPONSOR: SmithKlineBeecham Corporation dba GlaxoSmithKline
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101**

This submission contains the labeling changes based upon pediatric study reports and a request for a Pediatric Exclusivity. It includes an electronic version of the PI coded RL1157 (November 2002). The network path location is: \\CDSESUB1\N20388\S_014\2002-12-04.

Labeling changes:

A. _____
This section was deleted as agreed.

B. PRECAUTIONS, Pediatric Use
This section was revised as agreed.

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

C. DOSAGE AND ADMINISTRATION, Single-Agent NAVELBINE
This section was revised as agreed.

DOSAGE AND ADMINISTRATION

I have compared the electronic labeling submitted to the EDR with the labeling attached to our November 5, 2002 approval letter. The FPL is acceptable.

/01-30-03

Maureen A. Pelosi, R.Ph.
Regulatory Project Manager

/

Dotti Pease, SCSO

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this page is the manifestation of the electronic signature.**

/s/

Maureen Pelosi
2/3/03 01:42:01 PM
CSO

Dotti Pease
2/3/03 03:49:47 PM
CSO

Pelosi, Maureen A

From: Pelosi, Maureen A
Sent: Tuesday, November 05, 2002 5:42 PM
To: CDER-APPROVALS; CDER-OND-150-ALL; CDER-OND-150-GROUP; Kolar, Kathleen M
Subject: Navelbine Approval Notification: sNDA 20-388/#014
Importance: High

Today, 11/5/02, the Division of Oncology Drug Products approved a supplement for Navelbine (vinorelbine tartrate) Injection.

Date of Approval: November 5, 2002

NDA #/Supplement: 20-388/S-014

Name of Drug: Navelbine (vinorelbine tartrate) Injection

Name of Applicant: SmithKlineBeecham d/b/a GlaxoSmithKline

Indication: Navelbine is indicated as a single agent or in combination with cisplatin for the first-line treatment of ambulatory patients with unresectable, advanced non-small 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.

Dosage Form: IV

Drug Class/Review Rating: SE-8 /p Priority, Peds Supplement



NAV_AP_014.p AP_letter.doc Label_FDA_clear
df n.doc

Maureen A. Pelosi, RPh
Regulatory Project Manager
FDA, CDER, Oncology HFD-150
phone (301) 594-5778
fax (301) 827-4590
E-mail PELOSIM@CDER.FDA.GOV

Pelosi, Maureen A

From: Meg.A.Martin@gsk.com
Int: Tuesday, November 05, 2002 5:29 PM
S: PELOSIM@cder.fda.gov
Subject: Re: NAV Approved!!



NAV_AP_014.p
df

Dear Maureen,

Many, many thanks. This makes my evening! Take care.

Regards,

Meg Martin, Senior Director
US Regulatory Affairs, Oncology
GlaxoSmithKline Pharmaceuticals
2301 Renaissance Boulevard
Building 510, P.O. Box 61540
Mail Code RN0210
King of Prussia, PA 19406-2772
USA

(Internal) Phone: 8-275-3725, Fax: 8-275-7062

(External) Phone: (610) 787-3725, Fax: (610) 787-7062

"Pelosi,

Maureen A"

<PELOSIM@cder.

fda.gov> To: "Meg.A.Martin

cc:

05-Nov-2002 Subject: NAV Approved!!

17:13

ear Meg,

Dr. Pazdur just signed the NAV-014 letter.

<<NAV_AP_014.pdf>> -

Regards,
Maureen

Maureen A. Pelosi, RPh
Regulatory Project Manager
FDA, CDER, Oncology HFD-150
phone (301) 594-5778
fax (301) 827-4590
E-mail PELOSIM@CDER.FDA.GOV

(See attached file: NAV_AP_014.pdf).

<p>Labeling</p> <p>Appropriate sections of the label may be changed to incorporate the dosage, PK and safety findings of the study.</p>	<p>Additional information regarding the PK (Special Population Section) and a brief description of the clinical trial results are being proposed (Pediatric Use Section).</p>
<p>Format of reports</p> <p>Full study reports addressing the issues outlined in the request with full analysis, assessment, and interpretation. Submit a summary of post-marketing experience including safety and efficacy update.</p>	<p>Only abbreviated study reports are available. No summary of post-marketing experience with Navelbine was submitted.</p>
<p>Timeframe for submission: On or before December 31, 2003. “Keep in mind that pediatric exclusivity attaches to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.”</p>	<p>Granting of exclusivity will only be useful before patent expiration.</p>

6. The summary of post-marketing experience with Navelbine was not submitted.

- This information is included in the Clinical Stat folder.

ACTION ITEMS:

1. GSK to submit the data listings, confidence intervals, and adverse events to the electronic document room.

It was determined that the supplement was fileable.

The meeting concluded at 2:50 PM.

<p>relevant endpoint. Your specified endpoints of proportion of patients in each tumor stratum with a confirmed PR or CR, survival, and toxicity are acceptable.</p>	
<p>Drug Information</p> <p>Dosage form: iv or soft gelatin capsules</p> <p>Route of Administration: iv or oral</p>	<p>Phase 1: The protocol specified treatment consisted of six weeks of iv Navelbine only. According to the study report synopsis, the first treatment week was with oral Navelbine. It was unclear when iv Navelbine was started and how the iv dose was converted.</p>
<p>Safety</p> <p>Please submit separate safety tabulations for the oral and iv formulations of Navelbine.</p>	<p>Safety results were summarized but there was no tabulation according to route of administration.</p>
<p>Statistics:</p> <p>Phase 1: Standard PK parameters using non-parametric methods</p> <p>Phase 2: Analysis of response rates with 95% CI</p>	<p>Phase 1: Only results were submitted. Individual patient PK data is not available for independent analysis.</p> <p>Phase 2: Two responses were observed in the sarcoma group, 0 in CCNS tumors and 0 in neuroblastoma. The analysis of response rate with 95% CI were not shown.</p>

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this page is the manifestation of the electronic signature.**

/s/

Susan Honig

7/23/02 10:04:24 AM

Pelosi, Maureen A

From: CDER DocAdmin, DFS
nt: Tuesday, November 05, 2002 4:59 PM
S: Brubaker, Heidi; Castle Jr, Roy V; Taub, Debra; Carmouze, Grace N; Crescenzi, Terrie L; Jones, Michael D; Locicero, Colleen L; '@cder.fda.gov'; Pelosi, Maureen A; Honig, Susan L; Hsieh, Yung Ao; Wood, Rebecca H; Lostritto, Richard T; Zajicek, Anne; Williams, Grant A; Sridhara, Rajeshwari; Chen, Gang; Pease, Dorothy W; Pazdur, Richard; Treacy, John M; Jenkins, John K
Subject: DFS Email - N 020388 SE8 014 17-Jun-2002 - Supplement Letters



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Document room update the following:

Decision Date Decision Code

N 020388 SE8 014 17-Jun-2002 05-Nov-2002 AP:APPROVAL

N 020388 SE8 014 AM 28-Jun-2002 05-Nov-2002 AP:APPROVAL

Mail paper copy to

DISTRICT OFFICE

Mail paper copy with labeling to

HFI-20/Press Office (with labeling)

Mail labeling to

- HFD-093/DDMS-IST (with labeling)
HFD-013/CDER FOI Team Leader/R.Castle (with labeling)
HFD-013/CDER FOI Team Leader/D.Taub (with labeling)
HF-2/CDER Medwatch Safety Labeling (with labeling)
HFD-430/ODS/DDRE (with labeling)
HFD-613/OGD - Labeling Review Branch (with labeling)
HFD-013/Office Of Regulatory Policy - DIDP (FOI) (with labeling)
HFD-950/OCTAP/ADRA/T.Crescenzi (with labeling)
HFD-101/ADRA (with labeling)
HFD-42/DDMAC (with labeling)
HFD-650/OGD (Bioequivalence) Supervisory PM/L.Sanchez (with labeling)

Document Type: Supplement Letters

Letter Group: Approval Letters

Letter Name: Approval letter based on enclosed/submitted labeling

xt

submission Description: Peds Supplement AP

Author(s)/Discipline(s)

- 1. Maureen Pelosi, CSO
-

Signer(s)

- 1. Maureen Pelosi
05-Nov-2002
2. Dotti Pease
05-Nov-2002
3. Richard Pazdur
05-Nov-2002
-

Supervisory Signer(s)

- 1. Richard Pazdur
05-Nov-2002

Pelosi, Maureen A

From: Meg.A.Martin@gsk.com
nt: Friday, September 06, 2002 10:52 AM
o: PELOSIM@cder.fda.gov
Subject: Re: NAV labeling Comments



Rec_labeling_c
hanges.doc

Dear Maureen,

The team has reviewed Dr. Honig's proposed changes to the Navelbine PI and agrees with her assessment and wording. Please let me know when we might anticipate receiving the approval letter. Many thanks.

Regards,

Meg Martin, Director
North American Regulatory Affairs,
Oncology
GlaxoSmithKline Pharmaceuticals
1250 S. Collegeville Road
P. O. Box 5089, Mail Stop UP4340
Collegeville, PA 19426-0989
USA

(Internal) Phone: 8-282-5494, Fax: 8-282-7665
(External) Phone: (610) 917-5494, Fax: (610) 917-7665

"Pelosi,

Maureen A"

<PELOSIM@cder.

fda.gov>

To: "Meg_A_Martin

cc:

29-Aug-2002

Subject: NAV labeling

16:04

Dear Meg,

Dr. Honig has completed her review and requested that I share her labeling comments with GSK prior to drafting our Action Letter. Approval of this supplement is contingent upon GSK's agreement to the FDA labeling changes detailed in the attachment.

Take your time with this because the supplement is not due until mid-December.

Regards,
Maureen

Maureen A. Pelosi
Regulatory Project Manager
FDA, CDER, Oncology HFD-150
phone (301) 594-5778
fax (301) 827-4590
E-mail PELOSIM@CDER.FDA.GOV

<<Rec_labeling_changes.doc>>

(See attached file: Rec_labeling_changes.doc)

Pelosi, Maureen A

From: Carmouze, Grace N
Sent: Thursday, September 19, 2002 11:05 AM
To: Pelosi, Maureen A
Subject: RE: Navelbine: NDA- 20-388/S014

Maureen,
If you check the Electronic Orange Book, the Peds Exclusivity extension already appears
http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexcl.cfm?Appl_No=020388&Product_No=001&table1=Rx

Grace Carmouze
Regulatory Health Project Manager
Division of Pediatric Drug Development
Office of Counter-terrorism and Pediatric Drug Development
Center for Drug Evaluation and Research
Telephone: 301/594-7337
Fax: 301/827-7727

-----Original Message-----

From: Pelosi, Maureen A
Sent: Thursday, September 19, 2002 10:58 AM
To: Carmouze, Grace N
Subject: FW: Navelbine: NDA- 20-388/S014

Dear Grace,

Any idea of how long it takes before an exclusivity extension appears in the Orange book?
Please see Navelbine question below.

Thanks, Maureen

-----Original Message-----

From: Meg.A.Martin@gsk.com [mailto: Meg.A.Martin@gsk.com]
Sent: Thursday, September 19, 2002 10:46 AM
To: PELOSIM@cder.fda.gov
Subject: RE: Navelbine: NDA- 20-388/S014

Dear Maureen,

I note that on 9/17/02 the FDA granted a tentative approval to Gensia Sicor Pharmaceuticals' ANDA 76-028 for vinorelbine tartrate. Since our proprietary Navelbine patent now has an extension until January 8, 2003, has Gensia been informed? I have been checking the Peds Webpage as well as the electronic Orange Book to see when our exclusivity extension will be listed.

Can you please clarify this for me? Also, let me know approximately when you think we can anticipate your approval letter. Many thanks for everything.

Regards,

Meg Martin, Director
North American Regulatory Affairs,
Oncology
GlaxoSmithKline Pharmaceuticals
1250 S. Collegeville Road
P. O. Box 5089, Mail Stop UP4340
Collegeville, PA 19426-0989
USA

(Internal) Phone: 8-282-5494, Fax: 8-282-7665
(External) Phone: (610) 917-5494, Fax: (610) 917-7665

"Pelosi,

Maureen A"

<PELOSIM@cder.

fda.gov> To: "Meg.A.Martin

cc:

16-Aug-2002 Subject: RE: Navelbine;
NDA- 20-388/S014
09:47

Dear Meg,

The Board determined that they would grant peds exclusivity to Navelbine.

This exclusivity will attach to any existing exclusivities and patents that

GlaxoSmithKline currently has. GSK will receive no other notification re:

granting the pediatric exclusivity. However, this information will be available on the Pediatric Web page shortly (as time permits) and the next monthly update of the Orange Book.

If you need further information, feel free to contact the Project Manager,
Grace Carmouze at 301-594-7337.

Congratulations,

Maureen

-----Original Message-----

From: Meg.A.Martin@sbphrd.com [mailto:Meg.A.Martin@sbphrd.com]
Sent: Thursday, August 15, 2002 2:09 PM
To: pelosim@cder.fda.gov
Subject: Navelbine: NDA- 20-388/S014

Dear Maureen,
Just checking in regarding the pediatric exclusivity submission. Is there anything new I should know?
Many thanks.

Regards,

Meg Martin, Director
North American Regulatory Affairs,
Oncology
GlaxoSmithKline Pharmaceuticals
1250 S. Collegeville Road
P. O. Box 5089, Mail Stop UP4340
Collegeville, PA 19426-0989
USA

(Internal) Phone: 8-282-5494, Fax: 8-282-7665
(External) Phone: (610) 917-5494, Fax: (610) 917-7665

Pelosi, Maureen A

From: CDER DocAdmin, DFS
Int: Thursday, October 31, 2002 10:41 AM
To: Pelosi, Maureen A
Subject: New DFS Email - N 020388 SE8 014 17-Jun-2002 - Forms

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A new DFS document C:\Data\My Documents\Peds
Supp\20388_SE8_014\ActionPkgChecklist.doc has been sent to you by
Maureen Pelosi
Please check your DFS Inbox

Decision Code

N 020388 SE8 014 17-Jun-2002 :

N 020388 SE8 014 AM 28-Jun-2002 :

Document Type: Forms
Form Group: CHECKLIST
Form Name: Action Package Checklist
Submission Description: ~~Action Pkg Checklist~~

Author(s)/Discipline(s)

1. Maureen Pelosi, CSO

Pelosi, Maureen A

From: Meg.A.Martin@gsk.com
nt: Thursday, August 29, 2002 4:14 PM
J: PELOSIM@cder.fda.gov
Subject: Re: NAV labeling Comments



Rec_labeling_c
hanges.doc

Dear Maureen,

Please thank Dr. Honig for completing her review of supplement 014 so rapidly. I will share this information with the team and advise you of our position.

Here's wishing you a nice weekend.

Regards,

Meg Martin, Director
North American Regulatory Affairs,
Oncology
GlaxoSmithKline Pharmaceuticals
1250 S. Collegeville Road
O. Box 5089, Mail Stop UP4340
Collegeville, PA 19426-0989
USA

(Internal) Phone: 8-282-5494, Fax: 8-282-7665
(External) Phone: (610) 917-5494, Fax: (610) 917-7665

"Pelosi,

Maureen A"

<PELOSIM@cder.

fda.gov>

To: "Meg_A_Martin

cc:

29-Aug-2002 Subject: NAV labeling
Comments

Pelosi, Maureen A

From: CDER DocAdmin, DFS
Sent: Monday, August 19, 2002 4:45 PM
To: Crescenzi, Terrie L; Murphy, Dianne; Galson, Steven; Pelosi, Maureen A; Jenkins, John K; Holovac, Mary Ann; Zimmerman, Paul F; Carmouze, Grace N
Subject: DFS Email - N 020388 SE8 014 17-Jun-2002 - Forms



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Document room update the following:

Decision Date Decision Code

N 020388 SE8 014 17-Jun-2002 19-Aug-2002 :

Document Type: Forms

Form Group: CHECKLIST

Form Name: Pediatric Exclusivity Determination Checklist

Submission Description: Peds Exclusivity Determination-Granted

Author(s)/Discipline(s)

1. Grace Carmouze, CSO

Signer(s)

1. Grace Carmouze
19-Aug-2002
2. Grace Carmouze
19-Aug-2002

Supervisory Signer(s)

1. Grace Carmouze
19-Aug-2002

Pelosi, Maureen A

From: Meg.A.Martin@gsk.com
Sent: Tuesday, August 13, 2002 11:12 AM
To: PELOSIM@cder.fda.gov
Subject: RE: Navelbine NDA 20-388: Labeling

*RL-1010 → RL-1095
Editorial changes only
(5/02)*



Navelbine 1095.doc

Dear Maureen,

The editorial changes are basically punctuation marks. I've enclosed an electronic version from Melissa B. for your ready reference that shows all the changes from RL-1010 to RL-1095. These punctuation changes have not yet been made, but Melissa was planning to do so in about a month. Hope this clarifies.

(See attached file: Navelbine 1095.doc)

Regards,

Meg Martin, Director
North American Regulatory Affairs,
Oncology
GlaxoSmithKline Pharmaceuticals
1250 S. Collegeville Road
P. O. Box 5089, Mail Stop UP4340
Collegeville, PA 19426-0989
USA

Internal) Phone: 8-282-5494, Fax: 8-282-7665
(External) Phone: (610) 917-5494, Fax: (610) 917-7665

"Pelosi,

Maureen A"

<PELOSIM@cder.

fda.gov>

To: "Meg.A.Martin

cc:

13-Aug-2002 Subject: RE: Navelbine NDA
20-388: Labeling
10:42

Meg, are the editorial changes contained in RL1095 in use?

Maureen

-----Original Message-----

From: Meg.A.Martin@sbphrd.com [mailto:Meg.A.Martin@sbphrd.com]

Sent: Tuesday, August 13, 2002 9:01 AM

To: pelosim@cder.fda.gov

Subject: Navelbine NDA 20-388: Labeling

Dear Maureen,

I have been informed by Melissa Beaman, our labeling expert, that the changes from RL -1010 to RL-1095 are editorial changes to the insert to change to the new GSK PI format, and that they are annual reportable changes.

Hope this helps.

Regards,

Meg Martin, Director
North American Regulatory Affairs,
Oncology
GlaxoSmithKline Pharmaceuticals
1250 S. Collegeville Road
P.O. Box 5089, Mail Stop UP4340
Collegeville, PA 19426-0989
USA

(Internal) Phone: 8-282-5494, Fax: 8-282-7665

(External) Phone: (610) 917-5494, Fax: (610) 917-7665

Pelosi, Maureen A

From: Pelosi, Maureen A
Sent: Wednesday, August 07, 2002 3:30 PM
To: Carmouze, Grace N
Subject: Navelbine Package for Board #1

Dear Grace,

I have my electronic briefing package for the Board meeting on 8/15 and will send it to you using as many E-mails as it takes. I'll number each one.

This message contains the checklist, cover letter from sNDA 20-388 SE-8 #S-014, and the written request.

Regards, Maureen

  
excklst.doc WRpeds.doc cover_letter.pdf

Maureen A. Pelosi, RPh
Regulatory Project Manager
FDA, CDER, Oncology HFD-150
phone (301) 594-5778
fax (301) 827-4590
mail PELOSIM@CDER.FDA.GOV

Pelosi, Maureen A

From: Pelosi, Maureen A
Sent: Wednesday, August 07, 2002 3:33 PM
To: Carmouze, Grace N
Subject: NAV briefing package, E-mail #2

Grace,

This mail contain the study summaries and filing meeting minutes.
Maureen



Phase I.pdf



Phase II.pdf



Filing_Meeting_
min.doc

Maureen A. Pelosi, RPh
Regulatory Project Manager
FDA, CDER, Oncology HFD-150
phone (301) 594-5778
fax (301) 827-4590
E-mail PELOSIM@CDER.FDA.GOV

Pelosi, Maureen A

From: Pelosi, Maureen A
ent: Wednesday, August 07, 2002 3:35 PM
o: Carmôuze, Grace N
Subject: NAV briefing package #3

Grace,

This message contains the labeling -



Label_annotateLabel_clean.do Label_propose
d.doc c d.doc

Maureen A. Pelosi, RPh
Regulatory Project Manager
FDA, CDER, Oncology HFD-150
phone (301) 594-5778
fax (301) 827-4590
E-mail PELOSIM@CDER.FDA.GOV

Pelosi, Maureen A

From: Pelosi, Maureen A
Sent: Wednesday, August 07, 2002 3:42 PM
To: Carmouze, Grace N
Subject: NAV - briefing package message #4 - final E-mail!

Grace,

This last message contains the medical officer's review and table.



Navelbine-Boar
d_table.doc



Briefing
document.doc

That is it! Let me know if anything else is needed. This was an all electronic NDA. Here is the path in case it



EDR - NDA
38 from GLAXO!

is needed.

Thanks for all your help,
Maureen

Maureen A. Pelosi, RPh
Regulatory Project Manager
FDA, CDER, Oncology HFD-150
phone (301) 594-5778
fax (301) 827-4590
E-mail PELOSIM@CDER.FDA.GOV



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-388 / S-014

SmithKline Beecham Corporation d/b/a/ GlaxoSmithKline
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101

Attention: Anne-Margaret Martin
Director, US Regulatory Affairs

Dear Mrs. Martin:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Navelbine ® (vinorelbine tartrate) Injection

NDA Number: 20-388

Supplement number: S-014

Date of supplement: Jun 17, 2002

Date of receipt: Jun 18, 2002

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on day sixty from the date of receipt of application in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

Via U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products,
HFD-150
5600 Fishers Lane
Rockville, Maryland 20857

Via Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products,
HFD-150
1451 Rockville Pike
Rockville, Maryland 20852-1420

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

Sincerely,

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Maureen Pelosi
7/10/02 02:14:38 PM
signing for Dotti Pease

FILING MEETING MINUTES

MEETING DATE: June 27, 2002 **TIME:** 2 PM **LOCATION:** Conf. Rm B WOC-II

sNDA: 20-388 / SE8-014 Document Submission 6/12/02

DRUG: Navelbine (vinorelbine) for Injection

SPONSOR/APPLICANT: Glaxo Wellcome

TYPE of MEETING:

1. **FILING MEETING for PEDS EXCLUSIVITY SUPPLEMENT**
1. **OTHER – Difficiency telecon with Meg Martin, GSK**

FDA PARTICIPANTS:

Richard Pazdur, MD, Division Director
Grant Williams, MD, Deputy Div Director
Isagani Chico, MD, Team Leader
Susan Honig, M.D, Reviewer
Alla Shapiro, MD and Ramzi Dagher, MD, Peds Representatives
Atik Rahman, PhD, OCPB Team Leader
Maureen Pelosi, RPh, Project Manager

MEETING OBJECTIVES:

1. To determine if the submission is fileable
2. To convey deficiencies identified in preliminary review

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

The supplemental application requesting Pediatric Exclusivity and changes in the label dated June 17, 2002 did not fully meet the requirements of the pediatric Written Request. The specific deficiencies are listed below:

1. The sponsor was required to submit full study reports and not abbreviated summaries.
 - GSK stated that they have supplied all the information they received from COG. They stated that COG wrote only an abbreviated summary.
 - GSK stated that they contacted CTEP about the format and CTEP assured them that abbreviated summaries were common practice.

FDA Comment: In a prior submission, SWOG provided a full study report with full data listings.

2. Only four of the required minimum of 14 patients with neuroblastoma were enrolled in the Phase 2 study.

- GSK stated that although the study was open over 3 years, only 4 patients were able to be enrolled.

FDA Comment: Once it became evident that there were enrollment problems, the FDA is concerned that GSK did not choose to amend the written request last November prior to the study closing and submission of the supplement.

3. The age limit for enrollment was 21 years but patients up to 25 years old were treated on study.

- Patients over age 21 can be excluded from analysis.

4. The adverse event profiles with oral and IV administration of Navelbine were not submitted.

- GSK stated that the Phase 1 study regimen consisted of oral therapy on week 1 only followed by IV therapy on weeks 2 and 3.
- Thus adverse events cannot be attributed to the formulation.
- The data from the oral therapy is only useful for PK and was not submitted because GSK did not believe it would be helpful. However, it is available if FDA wants to review it.

5. The 95% confidence intervals for the analysis of response rate were not shown.

- The 95% CI ranged from 1.2 % to 3.4% per GSK and will be submitted following the teleconference.

_____/7-19-02_____
Maureen Pelosi
Project Manager
Minutes preparer

Concurrence Chair: _____/
Susan Honig, MD
Medical Reviewer

Attachment: Team Leader's Initial Review

TEAM LEADER'S INITIAL REVIEW

Subject: Supplemental Application: Label Change Submission of Pediatric Study Reports
Pediatric Exclusivity Request

Date of Review: June 20, 2002

Reviewer: Isagani M. Chico, MD

Background Information:

NDA Approval Date:	December 23, 1994
Written Request Proposal Submission Date:	November 15, 2000
Written Request Issue Date:	January 9, 2001
Patent Expiration Date:	July 8, 2002
Date of Submission:	June 17, 2002
Deadline for Submission of Study Reports:	December 31, 2003

The table on the following page lists the requirements for pediatric exclusivity stated in the pediatric written request agreement issued in January, 2001 and the contents of the submission. Entries in red print indicate items that were not in compliance with the requirements.

Conclusions:

1. The sponsor performed a Phase 1 and a Phase 2 study in compliance with the type of studies, population and study objectives as agreed in the Pediatric Written Request.
2. Based on initial inspection of the submission, the sponsor did not comply with the written request agreement in the following:
 - Full study reports were not submitted, only abbreviated summaries.
 - Only four of the required 14 patients with neuroblastoma was enrolled in the Phase 2 study. This study was closed after only the enrollment requirement for the other disease groups were met.
 - Patients up to 25 years old were treated on study.
 - The adverse events from oral and iv administration of Navelbine were not presented in the study reports.
 - The 95% confidence intervals for the analysis of response rate were not shown.
 - The summary of post-marketing experience with Navelbine was not submitted.

If the above deficiencies are confirmed after review of the application, the recommendation to the Pediatric Exclusivity Board should be to deny exclusivity. Whether the review should be presented and a decision issued before patent expiration need to be determined.

WRITTEN REQUEST	SUBMISSION
<p>Type of Study</p> <p>Phase 1: A study report for the completed Phase 1 Study.</p> <p>Phase 2 or Pilot Studies: At least 14 pediatric patients per tumor type with refractory or relapsed tumors. Studies should be in facilities with experience, support and expertise to care for children with cancer.</p>	<p>Phase 1 and 2 Studies: There are no full study reports in the submission, only abbreviated study reports (15 pages).</p> <p>Phase 2: Target tumors were: Soft tissue sarcoma (n=21), CNS tumors (n=15), and Neuroblastoma (n=4). The study was conducted by institutions in the Children's Cancer Group and Children's Oncology Group.</p>
<p>Indications</p> <p>Phase 1: Leukemia, Lymphoma and refractory solid tumors</p> <p>Phase 2: Soft tissue sarcomas, astrocytoma/anaplastic astrocytoma/GBM, medulloblastoma/peripheral primitive neuroectodermal tumor, other brain tumors, neuroblastoma</p>	<p>Phase 1: Majority of patients with CNS tumors, bone tumors and soft tissue sarcoma. Three patients with hematologic malignancies</p> <p>Phase 2: See above.</p>
<p>Objectives</p> <p>Phase 1: To determine the MTD, toxicities, PK and antitumor activity of Navelbine in children</p> <p>Phase 2: To determine objective tumor response and toxicity of Navelbine in patients treated at the MTD</p>	<p>Phase 1: As per written request</p> <p>Phase 2: As per written request</p>
<p>Age group: ≤ 21 years</p>	<p>Phase 1: 2 to 17 (median 12)</p> <p>Phase 2: 1 to 25 (median 11)</p>
<p>Study Endpoints:</p> <p>Phase 1: Toxicity, PK, Absolute oral bioavailability, disease response, survival. A traditional or sparse sampling technique may be used to estimate the PK parameters and develop PK/PD relationship</p> <p>Phase 2: Should have disease specific surrogate or clinically</p>	<p>Phase 1: Traditional sparse sampling per protocol. See study report for PK parameters. Twenty-two patients evaluable for response, one patient with rhabdomyosarcoma experienced a PR at the MTD and completed 16 weeks of therapy. MTD in patients without bone involvement is 33.75 mg/m²</p>

<p>relevant endpoint. Your specified endpoints of proportion of patients in each tumor stratum with a confirmed PR or CR, survival, and toxicity are acceptable.</p>	
<p>Drug Information</p> <p>Dosage form: iv or soft gelatin capsules Route of Administration: iv or oral</p>	<p>Phase 1: The protocol specified treatment consisted of six weeks of iv Navelbine only. According to the study report synopsis, the first treatment week was with oral Navelbine. It was unclear when iv Navelbine was started and how the iv dose was converted.</p>
<p>Safety</p> <p>Please submit separate safety tabulations for the oral and iv formulations of Navelbine.</p>	<p>Safety results were summarized but there was no tabulation according to route of administration.</p>
<p>Statistics:</p> <p>Phase 1: Standard PK parameters using non-parametric methods Phase 2: Analysis of response rates with 95% CI</p>	<p>Phase 1: Only results were submitted. Individual patient PK data is not available for independent analysis. Phase 2: Two responses were observed in the sarcoma group, 0 in CCNS tumors and 0 in neuroblastoma. The analysis of response rate with 95% CI were not shown.</p>

<p>Labeling</p> <p>Appropriate sections of the label may be changed to incorporate the dosage, PK and safety findings of the study.</p>	<p>Additional information regarding the PK (Special Population Section) and a brief description of the clinical trial results are being proposed (Pediatric Use Section).</p>
<p>Format of reports</p> <p>Full study reports addressing the issues outlined in the request with full analysis, assessment, and interpretation. Submit a summary of post-marketing experience including safety and efficacy update.</p>	<p>Only abbreviated study reports are available. No summary of post-marketing experience with Navelbine was submitted.</p>
<p>Timeframe for submission: On or before December 31, 2003. “Keep in mind that pediatric exclusivity attaches to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.”</p>	<p>Granting of exclusivity will only be useful before patent expiration.</p>

6. The summary of post-marketing experience with Navelbine was not submitted.
 - This information is included in the Clinical Stat folder.

ACTION ITEMS:

1. GSK to submit the data listings, confidence intervals, and adverse events to the electronic document room.

It was determined that the supplement was fileable.

The meeting concluded at 2:50 PM.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Susan Honig

7/23/02 10:04:24 AM

CSO NDA LABELING REVIEW OF PACKAGE INSERT

NDA: 20-388 / SE-8 #014/

DATE OF SUBMISSION: June 17, 2002

DATE OF REVIEW: August 28, 2002

DRUG: Navelbine (vinorelbine tartrate) Injection

**SPONSOR: SmithKlineBeecham Corporation dba GlaxoSmithKline
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101**

SE8-014 consists of a proposed labeling change submission based upon pediatric study reports and a request for a Pediatric Exclusivity determination.

Below is a chronology of labeling changes:

SLR-011, CBE with FA was approved on 8/24/00, PI was RL-854 dated 7/20/00
SLR-012, CBE with FA was approved 11/29/00, PI was coded RL-872 dated 10/00
SE8 010 (SWOG) was approved 10/2/01 and the PI was coded RL1010 dated 11/28/01
SCM-013 approved 4/3/02 did not include labeling
Y-007 dated 5/1/02 contained the PI coded RL-1010 (Y-007 covered 1/29/01 – 1/28/02)

This supplement includes the PI coded RL1010 as the current labeling. However, I noted that the marked-up label with the proposed pediatric changes was dated May 2002 and coded RL1095.

Meg Martin verified that the RL1095 label differed from the approved RL1010 label in minor editorial changes only and would be mentioned in the January, 2003 annual report. She provided a copy of RL1095 with highlighted editorial changes in a colored font so that I could check the changes against the approved RL1010. I found no changes other than the editorial changes and the proposed pediatric changes that the Medical Officer will review.

/08/28/02

Maureen A. Pelosi, R.Ph.
Regulatory Project Manager

Dotti Pease, SCSO

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this page is the manifestation of the electronic signature.**

/s/

Maureen Pelosi
9/3/02 09:46:56 AM
CSO

Dotti Pease
9/3/02 11:20:36 AM
CSO

Richard Pazdur
9/3/02 12:59:56 PM
MEDICAL OFFICER

34 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

TEAM LEADER'S INITIAL REVIEW

Subject: Supplemental Application: Label Change Submission of Pediatric Study Reports
Pediatric Exclusivity Request

Date of Review: June 20, 2002

Reviewer: Isagani M. Chico, MD

Background Information:

NDA Approval Date:	December 23, 1994
Written Request Proposal Submission Date:	November 15, 2000
Written Request Issue Date:	January 9, 2001
Patent Expiration Date:	July 8, 2002
Date of Submission:	June 17, 2002
Deadline for Submission of Study Reports:	December 31, 2003

The table on the following page lists the requirements for pediatric exclusivity stated in the pediatric written request agreement issued in January, 2001 and the contents of the submission. Entries in red print indicate items that were not in compliance with the requirements.

Conclusions:

1. The sponsor performed a Phase 1 and a Phase 2 study in compliance with the type of studies, population and study objectives as agreed in the Pediatric Written Request.
2. Based on initial inspection of the submission, the sponsor did not comply with the written request agreement in the following:
 - Full study reports were not submitted, only abbreviated summaries.
 - Only four of the required 14 patients with neuroblastoma was enrolled in the Phase 2 study. This study was closed after only the enrollment requirement for the other disease groups were met.
 - Patients up to 25 years old were treated on study.
 - The adverse events from oral and iv administration of Navelbine were not presented in the study reports.
 - The 95% confidence intervals for the analysis of response rate were not shown.
 - The summary of post-marketing experience with Navelbine was not submitted.

If the above deficiencies are confirmed after review of the application, the recommendation to the Pediatric Exclusivity Board should be to deny exclusivity. Whether the review should be presented and a decision issued before patent expiration need to be determined.

1st PK data needed.

WRITTEN REQUEST	SUBMISSION
<p>Type of Study Phase 1: A study report for the completed Phase 1 Study. Phase 2 or Pilot Studies: At least 14 pediatric patients per tumor type with refractory or relapsed tumors. Studies should be in facilities with experience, support and expertise to care for children with cancer.</p>	<p>Phase 1 and 2 Studies: There are no full study reports in the submission, only abbreviated study reports (15 pages). Phase 2: Target tumors were: Soft tissue sarcoma (n=21), CNS tumors (n=15), and Neuroblastoma (n=4). The study was conducted by institutions in the Children's Cancer Group and Children's Oncology Group.</p>
<p>Indications Phase 1: Leukemia, Lymphoma and refractory solid tumors Phase 2: Soft tissue sarcomas, astrocytoma/anaplastic astrocytoma/GBM, medulloblastoma/peripheral primitive neuroectodermal tumor, other brain tumors, neuroblastoma</p>	<p>Phase 1: Majority of patients with CNS tumors, bone tumors and soft tissue sarcoma. Three patients with hematologic malignancies Phase 2: See above.</p>
<p>Objectives Phase 1: To determine the MTD, toxicities, PK and antitumor activity of Navelbine in children Phase 2: To determine objective tumor response and toxicity of Navelbine in patients treated at the MTD</p>	<p>Phase 1: As per written request Phase 2: As per written request</p>
<p>Age group: ≤ 21 years</p>	<p>Phase 1: 2 to 17 (median 12) Phase 2: 1 to 25 (median 11)</p>
<p>Study Endpoints: Phase 1: Toxicity, PK, Absolute oral bioavailability, disease response, survival. A traditional or sparse sampling technique may be used to estimate the PK parameters and develop PK/PD relationship Phase 2: Should have disease specific surrogate or clinically relevant endpoint. Your specified endpoints of proportion of patients in each tumor stratum with a confirmed PR or CR, survival, and toxicity are acceptable.</p>	<p>Phase 1: Traditional sparse sampling per protocol. See study report for PK parameters. Twenty-two patients evaluable for response, one patient with rhabdomyosarcoma experienced a PR at the MTD and completed 16 weeks of therapy. MTD in patients without bone involvement is 33.75 mg/m²</p>

RECOMMENDED REGULATORY ACTION

1. This submission does not meet the terms of the Pediatric Written Request.
2. Please send the following deficiencies to the sponsor by facsimile:

The supplemental application requesting for pediatric exclusivity and changes in the label dated June 17, 2002 did not meet the requirements of the pediatric written request. The specific deficiencies are listed below:

1. The sponsor was required to submit full study reports and not abbreviated summaries.
2. Only four of the required minimum of 14 patients with neuroblastoma was enrolled in the Phase 2 study.
3. The age limit for enrollment was 21 years but patients up to 25 years old were treated on study.
4. The adverse event profiles with oral and iv administration of Navelbine were not submitted.
5. The 95% confidence intervals for the analysis of response rate were not shown.
6. The summary of post-marketing experience with Navelbine was not submitted.

<p>Drug Information Dosage form: iv or soft gelatin capsules Route of Administration: iv or oral</p>	<p>Phase 1: The protocol specified treatment consisted of six weeks of iv Navelbine only. According to the study report synopsis, the first treatment week was with oral Navelbine. It was unclear when iv Navelbine was started and how the iv dose was converted.</p>
<p>Safety Please submit separate safety tabulations for the oral and iv formulations of Navelbine.</p>	<p>Safety results were summarized but there was no tabulation according to route of administration.</p>
<p>Statistics: Phase 1: Standard PK parameters using non-parametric methods Phase 2: Analysis of response rates with 95% CI</p>	<p>Phase 1: Only results were submitted. Individual patient PK data is not available for independent analysis. Phase 2: Two responses were observed in the sarcoma group, 0 in CCNS tumors and 0 in neuroblastoma. The analysis of response rate with 95% CI were not shown.</p>
<p>Labeling Appropriate sections of the label may be changed to incorporate the dosage, PK and safety findings of the study.</p>	<p>Additional information regarding the PK (Special Population Section) and a brief description of the clinical trial results are being proposed (Pediatric Use Section).</p>
<p>Format of reports Full study reports addressing the issues outlined in the request with full analysis, assessment, and interpretation. Submit a summary of post-marketing experience including safety and efficacy update.</p>	<p>No summary of post-marketing experience with Navelbine is submitted.</p>
<p>Timeframe for submission: On or before December 31, 2003. "Keep in mind that pediatric exclusivity attaches to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request."</p>	<p>Granting of exclusivity will only be useful before patent expiration.</p>

16:04

Dear Meg,

Dr. Honig has completed her review and requested that I share her labeling comments with GSK prior to drafting our Action Letter. Approval of this supplement is contingent upon GSK's agreement to the FDA labeling changes detailed in the attachment.

Take your time with this because the supplement is not due until mid-December.

Regards,
Maureen

Maureen A. Pelosi
Regulatory Project Manager
FDA, CDER, Oncology HFD-150
phone (301) 594-5778
fax (301) 827-4590
E-mail PELOSIM@CDER.FDA.GOV

<<Rec_labeling_changes.doc>>

(See attached file: Rec_labeling_changes.doc)

3 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

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/s/

Maureen Pelosi
9/3/02 09:46:56 AM
CSO

Dotti Pease
9/3/02 11:20:36 AM
CSO

Richard Pazdur
9/3/02 12:59:56 PM
MEDICAL OFFICER

Pelosi, Maureen A

From: CDER DocAdmin, DFS
Sent: Tuesday, July 23, 2002 10:09 AM
To: Pelosi, Maureen A; Honig, Susan L; Williams, Grant A; Shapiro, Alla; Dagher, Ramzi; Rahman, Nam Atiqur
Subject: DFS Email - N 020388 SE8 014 17-Jun-2002 - Meeting Minutes



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Document room update the following:

Decision Date Decision Code

N 020388 SE8 014 17-Jun-2002 23-Jul-2002 NR:NO REPLY NECESSARY

N 020388 SE8 014 AM 28-Jun-2002 23-Jul-2002 NR:NO REPLY NECESSARY

Document Type: Meeting Minutes
Submission Description: Peds Supp Filing Meeting

Author(s)/Discipline(s)

1. Maureen Pelosi, CSO

Signer(s)

1. Maureen Pelosi
19-Jul-2002
2. Susan Honig
23-Jul-2002

Supervisory Signer(s)

1. Susan Honig
23-Jul-2002

Pelosi, Maureen A

From: CDER DocAdmin, DFS
Sent: Wednesday, July 10, 2002 2:19 PM
To: Pelosi, Maureen A; Honig, Susan L; Schmidt, Wendelyn J; Hsieh, Yung Ao; Duan, Zongyi J; Wood, Rebecca H; Sridhara, Rajeshwari
Subject: DFS Email - N 020388 SE8 014 17-Jun-2002 - Supplement Letters



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Document room update the following:
Decision Date Decision Code

N 020388 SE8 014 17-Jun-2002 10-Jul-2002 :

N 020388 SE8 014 AM 28-Jun-2002 10-Jul-2002 :

Mail paper copy to

DISTRICT OFFICE

Document Type: Supplement Letters
Letter Group: Acknowledgement Letters
Letter Name: Prior approval supplement acknowledgment letter
Submission Description: acknowleg. letter S-014

Author(s)/Discipline(s)

1. Maureen Pelosi, CSO

Signer(s)

1. Maureen Pelosi
signing for Dotti Pease
10-Jul-2002

Supervisory Signer(s)

1. Maureen Pelosi
signing for Dotti Pease
10-Jul-2002

Appendix V. Labeling Review

The sponsor proposes three sets of labeling changes. Each will be discussed individually.

I. Labeling changes

A. CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations: Pediatrics

(1) The sponsor proposes the following:

Special Populations: Pediatrics: _____

(2) The reviewer recommends the following:
Delete entire section

(3) Rationale:
The Phase II study was negative. The Agency does not include pharmacokinetic information about the dosing of an ineffective drug in labeling.

B. PRECAUTIONS, Pediatric Use

(1) The sponsor proposes the following (this entire section is new):

Pediatric Use: Safety and effectiveness of NAVELBINE in pediatric patients have not been established in controlled clinical trials. Data are available from an uncontrolled, open-label, multicenter study in 46 patients aged 1 to 25 years (median age 11 years) with recurrent solid malignant tumors; 21 patients with rhabdomyosarcoma/undifferentiated sarcoma, 4 patients with neuroblastoma, and 21 with CNS tumors (6 patients with astrocytoma or glioma, 5 patients with primitive neuroectodermal tumor or medulloblastoma, 6 patients with brain stem tumor, and 4 patients with other CNS tumors). NAVELBINE was administered weekly for the first 6 weeks of an 8-week cycle. Up to 10 cycles were administered with the majority of patients receiving 1 to 2 cycles. Starting doses of NAVELBINE were reduced from 33.75 mg/m² to 30 mg/m² after the first cohort of 35 patients was completed due to neutropenia. Toxicities were similar to those reported in adult patients. The most frequent Grade 3/4 hematological toxicity was neutropenia. Some activity was detected in this previously treated patient population.

(2) The reviewer recommends the following (clean copy follows):

Pediatric Use: Safety and effectiveness of NAVELBINE in pediatric patients have not been established in

Clean copy:

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

(3) Rationale:

Navelbine was associated with clinically significant toxicity in children, even after the amendment lowered the dose to 30 mg/m²/week. The statement that the Phase II

study demonstrated "some activity" is misleading. An observed response rate of 9.5% is not clinically meaningful and by classic Phase II design standards is considered indicative of an ineffective therapy.

C. DOSAGE AND ADMINISTRATION, Single-Agent NAVELBINE

(1) The sponsor proposes the following:

DOSAGE AND ADMINISTRATION

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

(2) The reviewer recommends the following:

DOSAGE AND ADMINISTRATION

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

(3) Rationale:

The phase II study did not demonstrate efficacy for Navelbine in the studied pediatric tumors. The label should not include a recommended dose of an inactive therapy.

II. Required regulatory action

The project manager should prepare an Action Letter for this supplement. The project manager should send all of the information contained in the Labeling Review (Appendix V, section I) to the sponsor by facsimile. Approval of this supplement is contingent upon the sponsor's agreement to the FDA labeling changes detailed above.

Susan Flamm Honig, MD
Medical Reviewer

Grant Williams, M.D.
Team Leader/Deputy Division Director

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this page is the manifestation of the electronic signature.**

/s/

Susan Honig
8/22/02 09:38:37 AM
MEDICAL OFFICER

Grant Williams
8/23/02 07:07:59 AM
MEDICAL OFFICER

FILING MEETING MINUTES

MEETING DATE: June 27, 2002 **TIME:** 2 PM **LOCATION:** Conf. Rm B WOC-II

sNDA: 20-388 / SE8-014

Document Submission 6/12/02

DRUG: Navelbine (vinorelbine) for Injection

SPONSOR/APPLICANT: Glaxo Wellcome

TYPE of MEETING:

1. **FILING MEETING for PEDS EXCLUSIVITY SUPPLEMENT**
1. **OTHER – Difficiency telecon with Meg Martin, GSK**

FDA PARTICIPANTS:

Richard Pazdur, MD, Division Director
Grant Williams, MD, Deputy Div Director
Isagani Chico, MD, Team Leader
Susan Honig, M.D, Reviewer
Alla Shapiro, MD and Ramzi Dagher, MD, Peds Representatives
Atik Rahman, PhD, OCPB Team Leader
Maureen Pelosi, RPh, Project Manager

MEETING OBJECTIVES:

1. To determine if the submission is fileable
2. To convey deficiencies identified in preliminary review

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

The supplemental application requesting Pediatric Exclusivity and changes in the label dated June 17, 2002 did not fully meet the requirements of the pediatric Written Request. The specific deficiencies are listed below:

1. The sponsor was required to submit full study reports and not abbreviated summaries.
 - GSK stated that they have supplied all the information they received from COG. They stated that COG wrote only an abbreviated summary.
 - GSK stated that they contacted CTEP about the format and CTEP assured them that abbreviated summaries were common practice.

FDA Comment: In a prior submission, SWOG provided a full study report with full data listings.

2. Only four of the required minimum of 14 patients with neuroblastoma were enrolled in the Phase 2 study.

- GSK stated that although the study was open over 3 years, only 4 patients were able to be enrolled.

FDA Comment: Once it became evident that there were enrollment problems, the FDA is concerned that GSK did not choose to amend the written request last November prior to the study closing and submission of the supplement.

3. The age limit for enrollment was 21 years but patients up to 25 years old were treated on study.

- Patients over age 21 can be excluded from analysis.

4. The adverse event profiles with oral and IV administration of Navelbine were not submitted.

- GSK stated that the Phase 1 study regimen consisted of oral therapy on week 1 only followed by IV therapy on weeks 2 and 3.
- Thus adverse events cannot be attributed to the formulation.
- The data from the oral therapy is only useful for PK and was not submitted because GSK did not believe it would be helpful. However, it is available if FDA wants to review it.

5. The 95% confidence intervals for the analysis of response rate were not shown.

- The 95% CI ranged from 1.2 % to 3.4% per GSK and will be submitted following the teleconference.

_____/7-19-02_____
Maureen Pelosi
Project Manager
Minutes preparer

Concurrence Chair: _____/
Susan Honig, MD
Medical Reviewer

Attachment: Team Leader's Initial Review

TEAM LEADER'S INITIAL REVIEW

Subject: Supplemental Application: Label Change Submission of Pediatric Study Reports
Pediatric Exclusivity Request

Date of Review: June 20, 2002

Reviewer: Isagani M. Chico, MD

Background Information:

NDA Approval Date:	December 23, 1994
Written Request Proposal Submission Date:	November 15, 2000
Written Request Issue Date:	January 9, 2001
Patent Expiration Date:	July 8, 2002
Date of Submission:	June 17, 2002
Deadline for Submission of Study Reports:	December 31, 2003

The table on the following page lists the requirements for pediatric exclusivity stated in the pediatric written request agreement issued in January, 2001 and the contents of the submission. Entries in red print indicate items that were not in compliance with the requirements.

Conclusions:

1. The sponsor performed a Phase 1 and a Phase 2 study in compliance with the type of studies, population and study objectives as agreed in the Pediatric Written Request.
2. Based on initial inspection of the submission, the sponsor did not comply with the written request agreement in the following:
 - Full study reports were not submitted, only abbreviated summaries.
 - Only four of the required 14 patients with neuroblastoma was enrolled in the Phase 2 study. This study was closed after only the enrollment requirement for the other disease groups were met.
 - Patients up to 25 years old were treated on study.
 - The adverse events from oral and iv administration of Navelbine were not presented in the study reports.
 - The 95% confidence intervals for the analysis of response rate were not shown.
 - The summary of post-marketing experience with Navelbine was not submitted.

If the above deficiencies are confirmed after review of the application, the recommendation to the Pediatric Exclusivity Board should be to deny exclusivity. Whether the review should be presented and a decision issued before patent expiration need to be determined.

WRITTEN REQUEST	SUBMISSION
<p>Type of Study</p> <p>Phase 1: A study report for the completed Phase 1 Study. Phase 2 or Pilot Studies: At least 14 pediatric patients per tumor type with refractory or relapsed tumors. Studies should be in facilities with experience, support and expertise to care for children with cancer.</p>	<p>Phase 1 and 2 Studies: There are no full study reports in the submission, only abbreviated study reports (15 pages).</p> <p>Phase 2: Target tumors were: Soft tissue sarcoma (n=21), CNS tumors (n=15), and Neuroblastoma (n=4). The study was conducted by institutions in the Children's Cancer Group and Children's Oncology Group.</p>
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<p>Objectives</p> <p>Phase 1: To determine the MTD, toxicities, PK and antitumor activity of Navelbine in children Phase 2: To determine objective tumor response and toxicity of Navelbine in patients treated at the MTD</p>	<p>Phase 1: As per written request Phase 2: As per written request</p>
<p>Age group: ≤ 21 years</p>	<p>Phase 1: 2 to 17 (median 12) Phase 2: 1 to 25 (median 11)</p>
<p>Study Endpoints:</p> <p>Phase 1: Toxicity, PK, Absolute oral bioavailability, disease response, survival. A traditional or sparse sampling technique may be used to estimate the PK parameters and develop PK/PD relationship Phase 2: Should have disease specific surrogate or clinically</p>	<p>Phase 1: Traditional sparse sampling per protocol. See study report for PK parameters. Twenty-two patients evaluable for response, one patient with rhabdomyosarcoma experienced a PR at the MTD and completed 16 weeks of therapy. MTD in patients without bone involvement is 33.75 mg/m²</p>



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-388 / S-014

SmithKline Beecham Corporation d/b/a/ GlaxoSmithKline
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101

Attention: Anne-Margaret Martin
Director, US Regulatory Affairs

Dear Mrs. Martin:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Navelbine ® (vinorelbine tartrate) Injection

NDA Number: 20-388

Supplement number: S-014

Date of supplement: Jun 17, 2002

Date of receipt: Jun 18, 2002

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on day sixty from the date of receipt of application in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

Via U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products,
HFD-150
5600 Fishers Lane
Rockville, Maryland 20857

Via Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products,
HFD-150
1451 Rockville Pike
Rockville, Maryland 20852-1420

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

Sincerely,

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Maureen Pelosi
7/10/02 02:14:38 PM
signing for Dotti Pease