

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

Approval Package for:

APPLICATION NUMBER:

76-028

Generic Name: Vinorelbine Tartrate Injection,
10mg/1mL and 50mg/5mL
Single-dose Vials

Sponsor: Gensia Sicor Pharmaceuticals, Inc.

Approval Date: February 3, 2003

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APPLICATION NUMBER:

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APPROVAL LETTER

ANDA 76-028

FEB 3 2003

Gensia Sicor Pharmaceuticals, Inc.
Attention: Elvia O. Gustavson
19 Hughes
Irvine, CA 92618-1902

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated November 17, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Vinorelbine Tartrate Injection, 10 mg (base)/mL, packaged in 10 mg/1 mL and 50 mg/5 mL single-dose vials.

Reference is also made to your amendments dated August 21, 2001, November 13, 2002, and January 9, January 14, and January 29, 2003.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Vinorelbine Tartrate Injection, 10 mg (base)/mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Navelbine[®] Injection, 10 mg (base)/mL of GlaxoSmithKline).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.

Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies that may be identified.

Sincerely yours,

ISI

Gary Buehler 2/3/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-028

**TENTATIVE APPROVAL
LETTER**

ANDA 76-028

SEP 17 2002

Gensia Sicor Pharmaceuticals, Inc.
Attention: Elvia O. Gustavson
19 Hughes
Irvine, CA 92618-1902

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated November 17, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Vinorelbine Tartrate Injection, 10 mg (base)/mL packaged in 10 mg/1 mL and 50 mg/5 mL single-dose vials.

Reference is also made to your amendments dated August 21, 2001, June 27, July 2, July 24, August 27, and September 16, 2002.

We have completed the review of this abbreviated application and have concluded that based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Although we are unable to grant final approval at this time due to exclusivity issues noted below, the application is **tentatively approved**. This determination is based upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). The determination is subject to change on the basis of new information that may come to our attention.

The reference listed drug product (RLD) upon which you have based your application, Navelbine® Injection of GlaxoSmithKline, is currently subject to a period of patent protection. As noted in the current edition of the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book", U.S. Patent No. 4,307,100 (the '100 patent) was due to expire on July 8, 2002. However, Section 111 of Title I of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act) created Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a). Section 505A

permits the sponsor of the RLD to obtain an additional six months of marketing exclusivity (pediatric exclusivity) if, in accordance with the requirements of the statute, the sponsor of the RLD submits data previously requested by the agency relating to the use of the drug in the pediatric population.

GlaxoSmithKline has submitted data to the agency to support the use of Navelbine Injection in a pediatric population. Consequently, the expiration of the '100 patent has been effectively extended until January 8, 2003. Your application contains a Paragraph III Certification to the '100 patent under Section 505(j)(2)(A)(vii)(III) of the Act stating that you will not market this drug product prior to the expiration of this patent. Therefore, final approval of your application may not be made effective pursuant to 21 U.S.C. 355(j)(5)(B)(ii) of the Act until the additional period of marketing exclusivity attached to the '100 patent has expired, i.e., January 8, 2003.

In order to reactivate your application prior to final approval, please submit a MINOR AMENDMENT - FINAL APPROVAL REQUESTED. This should be submitted between 60 to 90 days prior to the date you believe your application will be eligible for final approval. This amendment should identify changes, if any, in the conditions under which the product was tentatively approved, and should include updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made. In addition to this amendment, the Agency may request at any time prior to the final date of approval that you submit an additional amendment containing the information described above.

Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to Agency review before final approval of the application will be made.

Please note that this drug product may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d).

Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the "Orange Book". Should you believe that there are grounds for issuing the final approval letter prior to January 8, 2003, you should amend your application accordingly.

For further information on the status of this application and prior to submitting any amendments, please should contact Peter Chen, R.Ph., Project Manager, at (301) 827-5848.

Sincerely yours,

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Gary Buehler

9/17/02

Director

Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-028

FINAL PRINTED LABELING

Vinorelbine Tartrate Injection

WARNING

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 ≥ 1000 cells/mm³ prior to the administration of vinorelbine. The dosage should be adjusted according to complete blood counts with differentials obtained on the day of treatment.

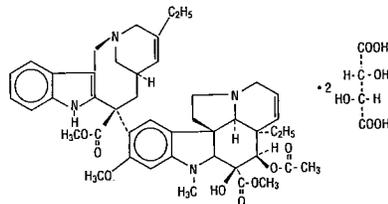
Caution - It is extremely important that the intravenous needle or catheter be properly positioned before vinorelbine tartrate is injected. Administration of vinorelbine tartrate injection may result in extravasation causing local tissue necrosis and/or thrombophlebitis (see **DOSE AND ADMINISTRATION: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

DESCRIPTION

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'-dihydro-4'-deoxy-C'-norvincalkekoblastine [R-(R*,R*)-2,3-dihydroxybutanedioate (1:2)(salt)].

Vinorelbine tartrate has the following structure:



Vinorelbine tartrate is a white to yellow or light brown amorphous powder with the molecular formula C₄₅H₅₄N₄O₈·2C₄H₆O₆ and molecular weight of 1079.12. The aqueous solubility is >1000 mg/mL in distilled water. The pH of Vinorelbine Tartrate Injection is approximately 3.5.

CLINICAL PHARMACOLOGY

Vinorelbine is a vinca alkaloid that interferes with microtubule assembly. The vinca alkaloids are structurally similar compounds comprised of 2 multiringed units, vindoline and catharanthine. Unlike other vinca alkaloids, the catharanthine unit is the site of structural modification for vinorelbine. The antitumor activity of vinorelbine is thought to be due primarily to inhibition of mitosis at metaphase through its interaction with tubulin. Like other vinca alkaloids, vinorelbine may also interfere with: 1) amino acid, cyclic AMP, and glutathione metabolism, 2) calmodulin-dependent Ca²⁺-transport ATPase activity, 3) cellular respiration, and 4) nucleic acid and lipid biosynthesis. In intact tectal plates from mouse embryos, vinorelbine, vincristine, and vinblastine inhibited mitotic microtubule formation at the same concentration (2 μM), inducing a blockade of cells at metaphase. Vincristine produced depolymerization of axonal microtubules at 5 μM, but vinblastine and vinorelbine did not have this effect until concentrations of 30 μM and 40 μM, respectively. These data suggest relative selectivity of vinorelbine for mitotic microtubules.

Pharmacokinetics: The pharmacokinetics of vinorelbine were studied in 49 patients who received doses of 30 mg/m² in 4 clinical trials. Doses were administered by 15- to 20-minute constant-rate infusions. Following intravenous administration, vinorelbine concentration in plasma decays in a triphasic manner. The initial rapid decline primarily represents distribution of drug to peripheral compartments followed by metabolism and excretion of the drug during subsequent phases. The prolonged terminal phase is due to relatively slow efflux of vinorelbine from peripheral compartments. The terminal phase half-life averages 27.7 to 43.6 hours and the mean plasma clearance ranges from 0.97 to 1.26 L/h per kg. Steady-state volume of distribution (V_{ss}) values range from 25.4 to 40.1 L/kg.

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

Vinorelbine undergoes substantial hepatic elimination in humans, with large amounts recovered in feces after intravenous administration to humans. Two metabolites of vinorelbine have been identified in human blood, plasma, and urine; vinorelbine N-oxide and deacetylvinorelbine. Deacetylvinorelbine has been demonstrated to be the primary metabolite of vinorelbine in humans, and has been shown to possess antitumor activity similar to vinorelbine. Therapeutic doses of vinorelbine (30 mg/m²) yield very small, if any, quantifiable levels of either metabolite in blood or urine. The metabolism of vinca alkaloids has been shown to be mediated by hepatic cytochrome P450 isoenzymes in the CYP3A subfamily. This metabolic pathway may be impaired in patients with hepatic dysfunction or who are taking concomitant potent inhibitors of these isoenzymes (see **PRECAUTIONS**). The effects of renal or hepatic dysfunction on the disposition of

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

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

Table 1
Randomized Clinical Trials of Vinorelbine Tartrate in Combination with Cisplatin in NSCLC

	Vinorelbine/Cisplatin vs. Single-Agent Cisplatin		Vinorelbine/Cisplatin vs. Vindesine/Cisplatin vs. Single-Agent Vinorelbine		
	Vinorelbine/Cisplatin	Cisplatin	Vinorelbine/Cisplatin	Vindesine/Cisplatin	Single-Agent Vinorelbine
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	N/A	N/A	11%	11%	10%
Stage IIIB	8%	8%	28%	25%	32%
Stage IV	92%	92%	50%	55%	47%
Local recurrence	N/A	N/A	2%	3%	3%
Metastatic after surgery	N/A	N/A	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%	N/A	N/A	N/A
Results					
Median survival (months)	7.8	6.2	9.2*†	7.4	7.2
P value	P = 0.01		*P = 0.09 vs. vindesine/cisplatin †P = 0.05 vs. single-agent vinorelbine		
12-Month survival rate	38%	22%	35%	27%	30%
Overall response	19%	8%	28%‡§	19%	14%
P value	P < 0.001		‡P = 0.03 vs. vindesine/cisplatin §P < 0.001 vs. single-agent vinorelbine		

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

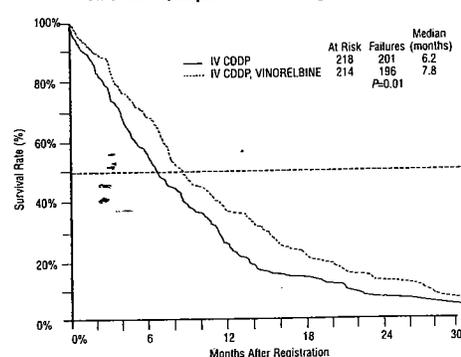
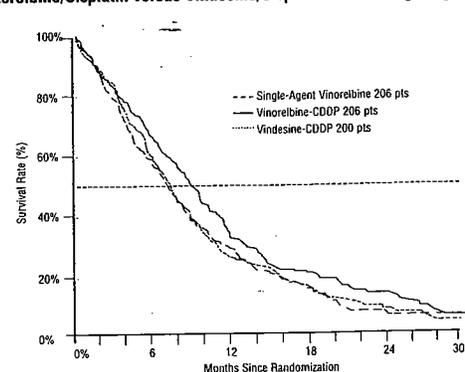


Figure 2
Overall Survival
Vinorelbine/Cisplatin versus Vindesine/Cisplatin versus Single-Agent Vinorelbine



concentrations of 30 µM and 40 µM, respectively. These data suggest relative selectivity of vinorelbine for mitotic microtubules.

Pharmacokinetics: The pharmacokinetics of vinorelbine were studied in 49 patients who received doses of 30 mg/m² in 4 clinical trials. Doses were administered by 15- to 20-minute constant-rate infusions. Following intravenous administration, vinorelbine concentration in plasma decays in a triphasic manner. The initial rapid decline primarily represents distribution of drug to peripheral compartments followed by metabolism and excretion of the drug during subsequent phases. The prolonged terminal phase is due to relatively slow efflux of vinorelbine from peripheral compartments. The terminal phase half-life averages 27.7 to 43.6 hours and the mean plasma clearance ranges from 0.97 to 1.26 L/h per kg. Steady-state volume of distribution (V_{ss}) values range from 25.4 to 40.1 L/kg.

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The disposition of radiolabeled vinorelbine given intravenously was studied in a limited number of patients. Approximately 18% and 46% of the administered dose was recovered in the urine and in the feces, respectively. Incomplete recovery in humans is consistent with results in animals where recovery is incomplete, even after prolonged sampling times. A separate study of the urinary excretion of vinorelbine using specific chromatographic analytical methodology showed that 10.9% ± 0.7% of a 30-mg/m² intravenous dose was excreted unchanged in the urine.

The influence of age on the pharmacokinetics of vinorelbine was examined using data from 44 cancer patients (average age, 56.7 ± 7.8 years; range, 41 to 74 years; with 12 patients ≥60 years and 6 patients ≥65 years) in 3 studies. CL (the mean plasma clearance), t_{1/2} (the terminal phase half-life), and V₂ (the volume of distribution during terminal phase) were independent of age. A separate pharmacokinetic study was conducted in 10 elderly patients with metastatic breast cancer (age range, 66 to 81 years; 3 patients >75 years; normal liver function tests) receiving vinorelbine 30 mg/m² intravenously. CL, V_{ss}, and t_{1/2} were similar to those reported for younger adult patients in previous studies. No relationship between age, systemic exposure (AUC_{0-∞}), and hematological toxicity was observed.

The pharmacokinetics of vinorelbine are not influenced by the concurrent administration of cisplatin with vinorelbine tartrate injection (see **PRECAUTIONS: Drug Interactions**).

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

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

Vinorelbine in Combination with Cisplatin: Vinorelbine plus Cisplatin versus Single-Agent Cisplatin: A Phase III open-label, randomized study was conducted which compared vinorelbine (25 mg/m² per week) plus cisplatin (100 mg/m² every 4 weeks) to single-agent cisplatin (100 mg/m² every 4 weeks) in patients with Stage IV or Stage IIIB NSCLC patients with malignant pleural effusion or multiple lesions in more than one lobe who were not previously treated with chemotherapy. Patients included in the study had a performance status of 0 or 1, and 34% had received prior surgery and/or radiotherapy. Characteristics of the 432 randomized patients are provided in Table 1. Two hundred and twelve patients received vinorelbine plus cisplatin and 210 received single-agent cisplatin. The primary objective of this trial was to compare survival between the 2 treatment groups. Survival (Figure 1) for patients receiving vinorelbine plus cisplatin was significantly better compared to the patients who received single-agent cisplatin. The results of this trial are summarized in Table 1.

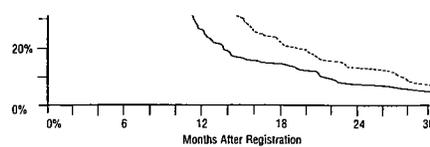
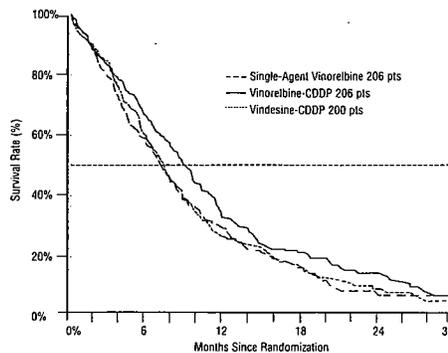


Figure 2
Overall Survival
Vinorelbine/Cisplatin versus Vinorelbine/Cisplatin versus Single-Agent Vinorelbine



INDICATIONS AND USAGE

Vinorelbine tartrate injection is indicated as a single agent or in combination with cisplatin for the first-line treatment of ambulatory patients with unresectable, advanced nonsmall cell lung cancer (NSCLC). In patients with Stage IV NSCLC, vinorelbine is indicated as a single agent or in combination with cisplatin. In Stage III NSCLC, vinorelbine is indicated in combination with cisplatin.

CONTRAINDICATIONS

Administration of vinorelbine tartrate injection is contraindicated in patients with pretreatment granulocyte counts <1000 cells/mm³ (see **WARNINGS**).

WARNINGS

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

Patients treated with vinorelbine should be frequently monitored for myelosuppression both during and after therapy. Granulocytopenia is dose-limiting. Granulocyte nadirs occur between 7 and 10 days after dosing with granulocyte count recovery usually within the following 7 to 14 days. Complete blood counts with differentials should be performed and results reviewed prior to administering each dose of vinorelbine. Vinorelbine should not be administered to patients with granulocyte counts <1000 cells/mm³. Patients developing severe granulocytopenia should be monitored carefully for evidence of infection and/or fever. See **DOSE AND ADMINISTRATION** for recommended dose adjustments for granulocytopenia.

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

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

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

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

PRECAUTIONS

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

Rx only

Vinorelbine
Tartrate Injection

Rx only

Vinorelbine
Tartrate Injection

Y36-000-PLC

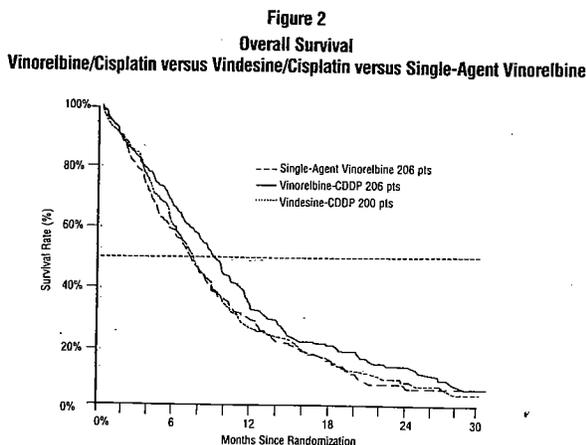
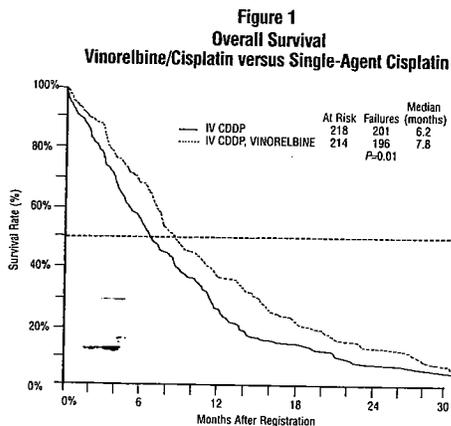
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GENSIASTICOR

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

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

	Vinorelbine/Cisplatin vs. Single-Agent Cisplatin		Vinorelbine/Cisplatin vs. Vindesine/Cisplatin vs. Single-Agent Vinorelbine		
	Vinorelbine/Cisplatin	Cisplatin	Vinorelbine/Cisplatin	Vindesine/Cisplatin	Vinorelbine
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	N/A	N/A	11%	11%	10%
Stage IIIB	8%	8%	28%	25%	32%
Stage IV	92%	92%	50%	55%	47%
Local recurrence	N/A	N/A	2%	3%	3%
Metastatic after surgery	N/A	N/A	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%	N/A	N/A	N/A
Results					
Median survival (months)	7.8	6.2	9.2*†	7.4	7.2
P value	P = 0.01		*P = 0.09 vs. vindesine/cisplatin †P = 0.05 vs. single-agent vinorelbine		
12-Month survival rate	38%	22%	35%	27%	30%
Overall response	19%	8%	28%‡§	19%	14%
P value	P < 0.001		‡P = 0.03 vs. vindesine/cisplatin §P < 0.001 vs. single-agent vinorelbine		



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

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

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

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

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

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

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

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility: The carcinogenic potential of vinorelbine has not been studied. Vinorelbine has been shown to affect chromosome number and possibly structure *in vivo* (polyploidy in bone marrow cells from Chinese hamsters and a positive micronucleus test in mice). It was not mutagenic in the Ames test and gave inconclusive results in the mouse lymphoma TK Locus assay. The significance of these or other short-term test results for human risk is unknown. Vinorelbine did not affect fertility to a statistically significant extent when administered to rats on either a once-weekly (9 mg/m², approximately one third the human dose) or alternate-day schedule (4.2 mg/m², approximately one seventh the human dose) prior to and during mating. However, biweekly administration for 13 or 26 weeks in the rat at 2.1 and 7.2 mg/m² (approximately one fifteenth and one fourth the human dose) resulted in decreased spermatogenesis and prostate/seminal vesicle secretion.

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

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

Pediatric Use: Safety and effectiveness of vinorelbine tartrate injection 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.

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

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

ADVERSE REACTIONS

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

Single-Agent Vinorelbine: Data in the following table are based on the experience of 365 patients (143 patients with NSCLC; 222 patients with advanced breast cancer) treated with IV vinorelbine as a single agent in 3 clinical studies. The dosing schedule in each study was 30 mg/m² vinorelbine on a weekly basis.

Adverse Event	All Patients (n = 365)	NSCLC (n = 143)
Bone Marrow		
Granulocytopenia	<2000 cells/mm ³	90%
	<500 cells/mm ³	36%
Leukopenia	<4000 cells/mm ³	92%
	<1000 cells/mm ³	15%
Thrombocytopenia	<100,000 cells/mm ³	5%
		4%

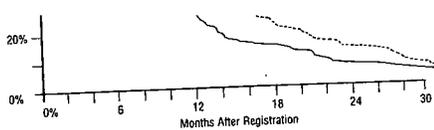
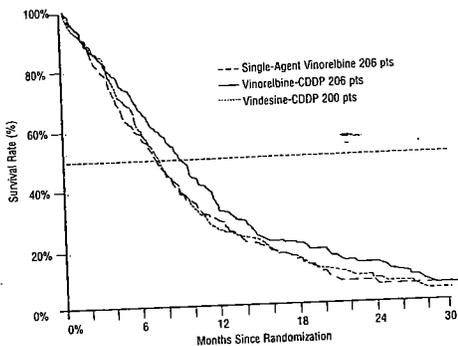


Figure 2

Overall Survival

Vinorelbine/Cisplatin versus Vindesine/Cisplatin versus Single-Agent Vinorelbine



INDICATIONS AND USAGE

Vinorelbine tartrate injection 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, vinorelbine is indicated as a single agent or in combination with cisplatin. In Stage III NSCLC, vinorelbine is indicated in combination with cisplatin.

CONTRAINDICATIONS

Administration of vinorelbine tartrate injection is contraindicated in patients with pretreatment granulocyte counts <1000 cells/mm³ (see WARNINGS).

WARNINGS

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

Patients treated with vinorelbine should be frequently monitored for myelosuppression both during and after therapy. Granulocytopenia is dose-limiting. Granulocyte nadirs occur between 7 and 10 days after dosing with granulocyte count recovery usually within the following 7 to 14 days. Complete blood counts with differentials should be performed and results reviewed prior to administering each dose of vinorelbine. Vinorelbine should not be administered to patients with granulocyte counts <1000 cells/mm³. Patients developing severe granulocytopenia should be monitored carefully for evidence of infection and/or fever. See DOSAGE AND ADMINISTRATION for recommended dose adjustments for granulocytopenia.

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

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

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

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

PRECAUTIONS

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

Other reported clinical experience has not identified differences in responses between the elderly and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out.

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

ADVERSE REACTIONS

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

Single-Agent Vinorelbine: Data in the following table are based on the experience of 365 patients (143 patients with NSCLC; 222 patients with advanced breast cancer) treated with IV vinorelbine as a single agent in 3 clinical studies. The dosing schedule in each study was 30 mg/m² vinorelbine on a weekly basis.

Table 2
Summary of Adverse Events in 365 Patients Receiving Single-Agent Vinorelbine Tartrate Injection*†

Adverse Event	All Patients (n = 365)		NSCLC (n = 143)	
	All Patients	NSCLC	All Patients	NSCLC
Bone Marrow				
Granulocytopenia	<2000 cells/mm ³	90%	80%	
	<500 cells/mm ³	36%	29%	
Leukopenia	<4000 cells/mm ³	92%	81%	
	<1000 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 All Patients		Grade 3 All Patients		Grade 4 All Patients	
	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%
Phebitis	7%	10%	<1%	1%	0%	0%
Digestive						
Nausea	44%	34%	2%	1%	0%	0%
Vomiting	20%	15%	2%	1%	0%	0%
Constipation	35%	29%	3%	2%	0%	0%
Diarrhea	17%	13%	1%	1%	0%	0%
Peripheral Neuropathy†	25%	20%	1%	1%	<1%	0%
Dyspnea	7%	3%	2%	2%	1%	0%
Alopecia	12%	12%	≤1%	1%	0%	0%

* None of the reported toxicities were influenced by age. Grade based on modified criteria from the National Cancer Institute.

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

‡ Incidence of paresthesia plus hypesthesia.

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

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

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

Skin: Like other anticancer vinca alkaloids, vinorelbine is a moderate vesicant. Injection site reactions, including erythema, pain at injection site, and vein discoloration, occurred

Rx only

Vinorelbine Tartrate Injection

Rx only

Vinorelbine Tartrate Injection

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

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

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

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

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

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

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

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

Vinorelbine in Combination with Cisplatin:

Vinorelbine plus Cisplatin versus Single-Agent Cisplatin (Table 3):

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

Four patients on the combination died of granulocytopenia-related sepsis. During this study, the use of granulocyte colony-stimulating factor ((G-CSF) filgrastim) was permitted, but not mandated, after the first course of treatment for patients who experienced Grade 3 or 4 granulocytopenia (≤ 1000 cells/mm³) or in those who developed neutropenic fever between cycles of chemotherapy. Beginning 24 hours after completion of chemotherapy, G-CSF was started at a dose of 5 mcg/kg per day and continued until the total granulocyte count was >1000 cells/mm³ on 2 successive determinations. G-CSF was not administered on the day of treatment.

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

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

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

Vinorelbine plus Cisplatin versus Vindesine plus Cisplatin versus Single-Agent Vinorelbine (Table 4):

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

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

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

Adverse Event	Vinorelbine 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%

!Categorical toxicity grade not specified.

*Neurotoxicity includes peripheral neuropathy and constipation.

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

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

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

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

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

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

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

Pulmonary: Pneumonia has been reported.

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

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

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

Single-Agent Vinorelbine: The usual initial dose of single-agent vinorelbine 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 vinorelbine was given weekly until progression or dose-limiting toxicity.

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

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

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

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

Dose Modifications for Hematologic Toxicity: Granulocyte counts should be ≥ 1000 cells/mm³ prior to the administration of vinorelbine. Adjustments in the dosage of vinorelbine should be based on granulocyte counts obtained on the day of treatment according to Table 5.

Table 5
Dose Adjustments Based on Granulocyte Counts

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

Note: For patients who, during treatment with Vinorelbine, experienced fever and/or sepsis while granulocytopenic or had 2 consecutive weekly doses held due to granulocytopenia, subsequent doses of vinorelbine should be:

Dose Modifications for Hepatic Insufficiency: Vinorelbine should be administered with caution to patients with hepatic insufficiency. In patients who develop

Selected Adverse Events From a Comparative Trial of Vinorelbine plus Cisplatin versus Single-Agent Cisplatin*

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	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/arthritis	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%

*Graded according to the standard SWOG criteria.

corresponding starting dose of vinorelbine (see Table 5).

Dose Modifications for Hematologic Toxicity: Granulocyte counts should be ≥ 1000 cells/mm³ prior to the administration of vinorelbine. Adjustments in the dosage of vinorelbine should be based on granulocyte counts obtained on the day of treatment according to Table 5.

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Dose Adjustments Based on Granulocyte Counts

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≥ 1500	75%
1000 to 1499	37.5%
<1000	See above

Note: For patients who, during treatment with Vinorelbine, experienced fever and/or sepsis while granulocytopenic or had 2 consecutive weekly doses held due to granulocytopenia, subsequent doses of vinorelbine should be:

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

Table 6
Dose Modification Based on Total Bilirubin

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

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

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

Dose Modifications for Neurotoxicity: If grade ≥ 2 neurotoxicity develops, vinorelbine should be discontinued.

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

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

Procedures for proper handling and disposal of anticancer drugs should be used. Several guidelines on this subject have been published.²⁻⁶ There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Vinorelbine tartrate injection is a clear, colorless to pale yellow solution. Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit. If particulate matter is seen, vinorelbine should not be administered.

Table 4
Selected Adverse Events From a Comparative Trial of Vinorelbine Plus Cisplatin versus Vindesine Plus Cisplatin versus Single-Agent Vinorelbine*

Adverse Event	Vinorelbine/Cisplatin [†]			Vindesine/Cisplatin [‡]			Vinorelbine §		
	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 II	6%	N/A	N/A	5%	N/A	N/A	5%	N/A	N/A
Renal									
Elevated creatinine II	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%

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

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

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

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

II Categorical toxicity grade not specified.

[†]Neurotoxicity includes peripheral neuropathy and constipation.

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

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

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

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

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

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

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

Pulmonary: Pneumonia has been reported.

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

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

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

Single-Agent Vinorelbine: The usual initial dose of single-agent vinorelbine 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 vinorelbine was given weekly until progression or dose-limiting toxicity.

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

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

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

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

Dose Modifications for Hematologic Toxicity: Granulocyte counts should be ≥ 1000 cells/mm³ prior to the administration of vinorelbine. Adjustments in the dosage of vinorelbine should be based on granulocyte counts obtained on the day of treatment according to Table 5.

Table 5
Dose Adjustments Based on Granulocyte Counts

Granulocytes on Day of Treatment (cells/mm ³)	Percentage of Starting Dose of Vinorelbine
≥ 1500	100%
1000 to 1499	50%
< 1000	Do not administer. Repeat granulocyte count in 1 week. If 3 consecutive weekly doses are held because granulocyte count is < 1000 cells/mm ³ , discontinue vinorelbine.

Note: For patients who, during treatment with Vinorelbine, experienced fever and/or sepsis while granulocytopenic or had 2 consecutive weekly doses held due to granulocytopenia, subsequent doses of vinorelbine should be:

≥ 1500	75%
1000 to 1499	37.5%
< 1000	See above

Dose Modifications for Hepatic Insufficiency: Vinorelbine should be administered with caution to patients with hepatic insufficiency. In patients who develop

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

Syringe: The calculated dose of vinorelbine should be diluted to a concentration between 1.5 and 3.0 mg/mL. The following solutions may be used for dilution:
5% Dextrose Injection, USP
0.9% Sodium Chloride Injection, USP

IV Bag: The calculated dose of vinorelbine should be diluted to a concentration between 0.5 and 2 mg/mL. The following solutions may be used for dilution:
5% Dextrose Injection, USP
0.9% Sodium Chloride Injection, USP
0.45% Sodium Chloride Injection, USP
5% Dextrose and 0.45% Sodium Chloride Injection, USP
Ringer's Injection, USP
Lactated Ringer's Injection, USP

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

HOW SUPPLIED:

Vinorelbine Tartrate Injection is a clear, colorless to pale yellow solution in water for injection, containing 10 mg vinorelbine per mL. Vinorelbine Tartrate Injection is available as follows:

NDC Number	Total Contents	Package
0703-4182-01	10 mg/1 mL	1 Single-Dose Vial per Carton
0703-4183-01	50 mg/5 mL	1 Single-Dose Vial per Carton

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

REFERENCES

1. ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines: Recommendations for practice. Pittsburgh, PA: Oncology Nursing Society; 1999: 32-41.
2. Recommendations for the safe handling of parenteral antineoplastic drugs. Washington, DC: Division of Safety, National Institutes of Health; 1983. US Dept of Health and Human Services, Public Health Service publication NIH 83-2621.
3. AMA Council on Scientific Affairs. Guidelines for handling parenteral antineoplastics. *JAMA*. 1985;253:1590-1591.
4. National Study Commission on Cytotoxic Exposure. Recommendations for handling cytotoxic agents. 1987. Available from Louis P. Jeffrey, Chairman, National Study Commission on Cytotoxic Exposure. Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115.
5. Clinical Oncological Society of Australia. Guidelines and recommendations for safe handling of antineoplastic agents. *Med J Australia*. 1983;1:426-428.
6. Jones RB, Frank R, Mass T. Safe handling of chemotherapeutic agents: a report from the Mount Sinai Medical Center. *CA-A Cancer J for Clin*. 1983;33:258-263.
7. American Society of Hospital Pharmacists. ASHP technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm*. 1990;47:1033-1049
8. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines.) *Am J Health-Syst Pharm*. 1996;53:1669-1685.

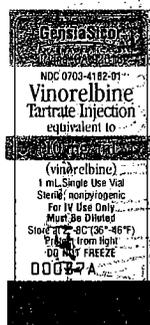
Issued: November 2002
Gensia Sior Pharmaceuticals, Inc.
Irvine, CA 92618

Manly

Gensia Sicor Pharmaceuticals, Inc.
VINORELBINE TARTRATE INJECTION
ANDA 76-028

Response to the Agency's Facsimile Dated May 10, 2001

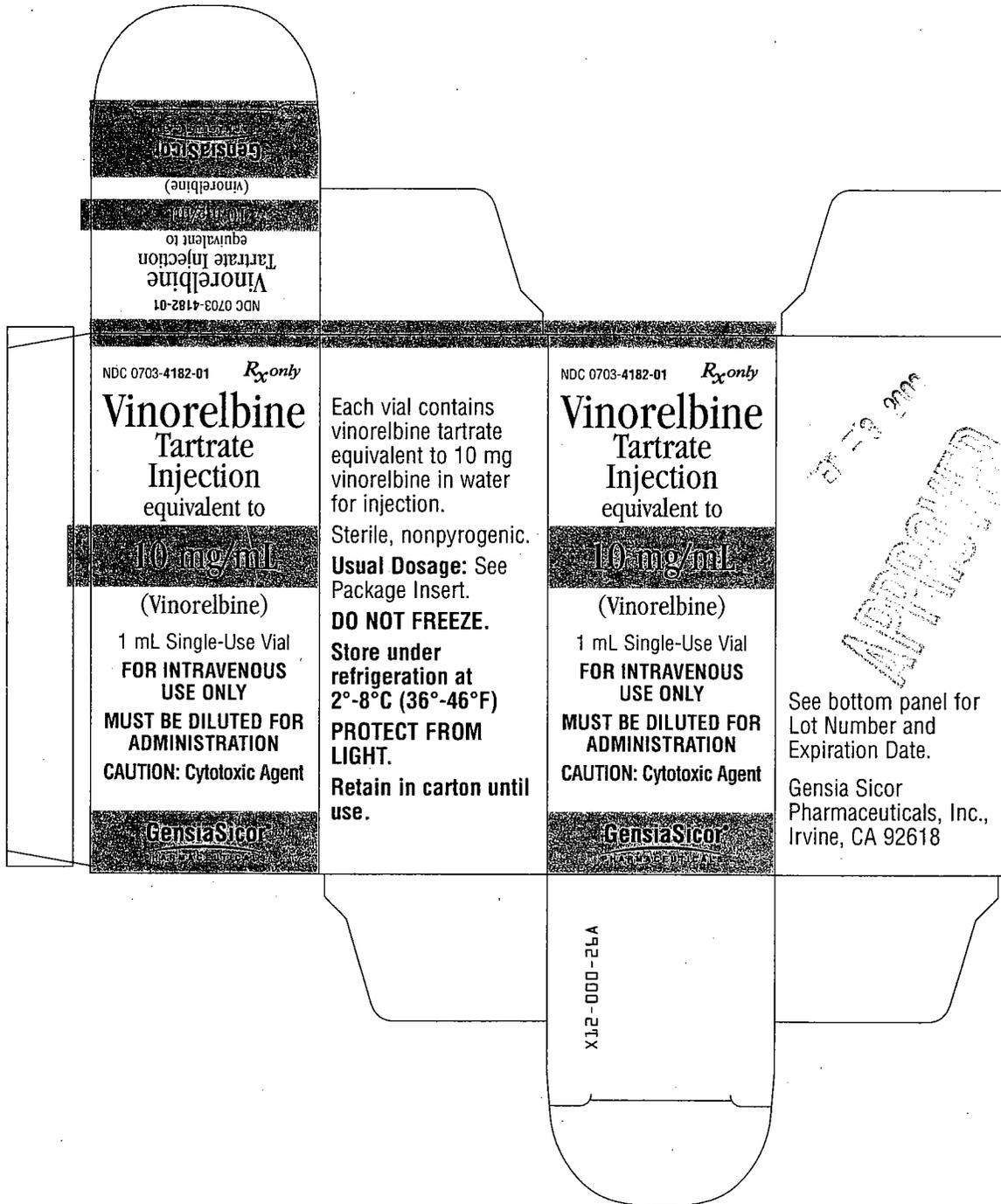
1 mL VIAL LABEL--Part # Y29-000-57A



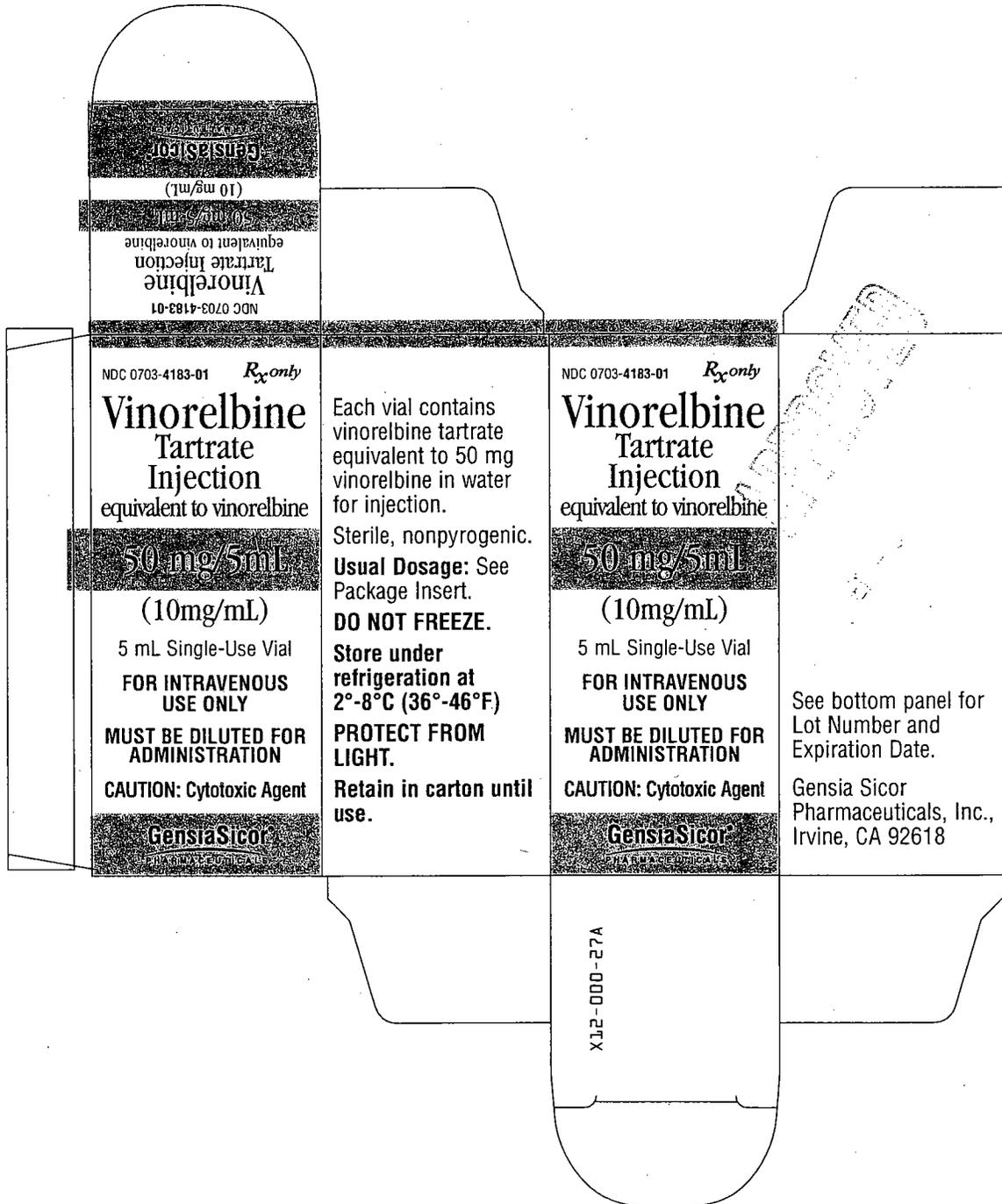
5 mL VIAL LABEL--Part # Y29-000-58A



1 mL UNIT CARTON--Part # X12-000-26A



5 mL UNIT CARTON--Part # X12-000-27A



**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-028

CSO LABELING REVIEW(S)

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 76-028

Date of Submission: Nov 17, 2000

Applicant's Name: GensiaSicor

Established Name: Vinorelbine Tartrate Injection, 10 mg (base) / mL, 1 mL and 5 mL vials

Labeling Deficiencies:

1. GENERAL COMMENTS:

- a. We note you did not model your insert labeling after the latest approved labeling for the reference listed drug Navelbine (NDA 20-388/S-012, Glaxo Wellcome Inc., Approved Nov. 29, 2000, Revised Oct. 2000). We have enclosed a copy of the innovator's labeling for your convenience.
- b. Please use the mock-up labeling for the use of Vinorelbine vs Vinorelbine Trtrate vs Vinorelbine Trtrate Injection throughout the insert labeling.

2. CONTAINER :

- a. 1 mL – Add complete storage recommendations. Do not bold “ 1 mL single Use Vial Sterile, nonpyrogenic”.
- b. 5 mL- express the full equivalency statement – add “equivalent to vinorelbine”. In addition add “**MUST BE DILUTED**” just after “for IV use Only” on the main panel.

3. CARTON 1 mL and 5 mL

1 mL Insert “equivalent to” just after the product strength or make it consistent with your container label. Please place the following in bold print “For Intravenous...Must Be diluted”.

Please revise your labels and labeling, as instructed above, and submit draft labels and labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed Navelbine labeling.

A. A. 1
IS
Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

(Enclosure)

Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			X
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			x
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST: none

FOR THE RECORD:

- The reference listed drug for this product is Navelbine (vinorelbine tartrate injection, Glaxo, NDA 20388/S-012, approved Nov 26,2000 revised Oct. 00).
- The patent for this product # is 4307100 expire July 8, 2002. There are no exclusivity issues. Firm certifies to the above information. Paragraph III in jacket
- The product will be manufactured by Gensia Sicor Pharmaceutical Inc. . Corp address 19 hughes, Irvin CA 92618-1902..
- No outside firms are used.
- Container/Closure: Amber glass tubing
- Product line: — (1 mL fill)and 5 mL vials. 1 per carton
- Components/Composition
RLD—vinorelbine tartrate and Water for injection. No preservatives.
Applicant : same
- Storage/Dispensing Conditions:
RLD: Store the vials under refrigeration at 2 to 8C(36 to 46 F) in the carton.Protect from light.DO NOT FREEZE.
Applicant: same

Date of Review: 02/05/01
Primary Reviewer: A Payne
Team Leader:

Date of Submission: Nov. 17, 2000
Date:
Date:

cc: ANDA 76-028
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
V:firmsam/Gensia/let&revs/76028na1.l
Review

ISI 02-08-01

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval): Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:

Container Labels: 10 mg/1 mL and 50mg/5mL

Carton Labeling: 1 mL and 5 mL

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Navelbine

NDA Number: 20-388

NDA Drug Name: Vinorelbine tartrate Injection

NDA Firm: Glaxo Welcome

Date of Approval of NDA Insert and supplement #: S-012 approved Nov. 29,00 revised Oct. 00

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

If yes, give date of labeling guidance:

Basis of Approval for the Container Labels: Navelbine

Basis of Approval for the Carton Labeling: Navelbine

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)			X
Labeling(continued)			
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			

**APPROVAL SUMMARY
 REVIEW OF PROFESSIONAL LABELING
 DIVISION OF LABELING AND PROGRAM SUPPORT
 LABELING REVIEW BRANCH**

ANDA Number	76-028
Date of Submission	July 2, 2002
Applicant	GensiaSicor
Drug Name	Vinorelbine Tartrate Injection,
Strength(s)	10 mg (base)/ mL, 1 mL and 5 mL vials

FPL Approval Summary

Container Labels		Submitted
10 mg/1 mL	10 mg/1 mL and 50 mg/5 mL	Jul. 20, 2001, Vol. A&B, 2.1 attachment 11.
Carton labeling		
10 mg and 50 mg	1 mL and 5 mL	Jul. 20, 2001, Vol. A&B, 2.1 attachment 11.
Package Insert Labeling	#Y36-000-21A Rev. Jun. 2002	July, 2, 2002 Vol. A 3.1 FPL

BASIS OF APPROVAL:

Patent Data For NDA 20-388

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4307100	Jul. 8, 2002		Nor bis-indole compounds usable as medicaments	PIII	Same As

Exclusivity Data For NDA XX-XXX

Code/sup	Expiration	Description	Labeling impact
None	None	None	

Reference Listed Drug

RLD on the 356(h) form	Navelbine
NDA Number	20-388
RLD established name	Vinorelbine tartrate Injection
Firm	Glaxo Welcome
Currently approved PI	S-010
AP Date	Approved 10/02/01

Note. I called the firm on 9/16/02 at (949)455-4724 Elvia Gustavson to request that the HOW SUPPLIED section citing _____ vial size be changed to 1 mL. The _____ The fill volume is 1 mL. Firm commits to revising the HOW SUPPLIED section.

**APPEARS THIS WAY
 ON ORIGINAL**

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)			X
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			X
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			x
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	

Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST: none

FOR THE RECORD:

- The reference listed drug for this product is Navelbine (vinorelbine tartrate injection, Glaxo, NDA 20388/S-010, Approved 10/02/01).
- The **patent** for this product # is 4307100 expires July 8, 2002. There are no **exclusivity** issues. Firm certifies to the above information. Paragraph III in jacket .
- The product will be manufactured by Gensia Sicor Pharmaceutical Inc. . Corp address 19 hughes, Irvin CA 92618-1902..
- No outside firms are used.
- Container/Closure: Amber glass tubing
- Product line: — (1 mL fill)and 5 mL vials. 1 per carton
- Components/Composition
RLD—vinorelbine tartrate and Water for injection. No preservatives.
Applicant : same
- Storage/Dispensing Conditions:
RLD: Store the vials under refrigeration at 2 to 8C(36 to 46 F) in the carton.Protect from light.DO NOT FREEZE.
Applicant: same

Date of Review: 07/19/02

Date of Submission: July 2, 2002

cc: ANDA: 76-028
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
V:firmsam/Gensia/let&revs/76028ap.Lab
Review

Handwritten:
ISI 7/28/02
ISI 8/2/2002
U

**APPEARS THIS WAY
ON ORIGINAL**

Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)			X
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			X
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			x
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST: none

FOR THE RECORD:

- The reference listed drug for this product is Navelbine (vinorelbine tartrate injection, Glaxo, NDA 20388/S-012, approved Nov 26,2000 revised Oct. 00).
- The **patent** for this product # is 4307100 expires July 8, 2002. There are no **exclusivity** issues. Firm certifies to the above information. Paragraph III in jacket
- The product will be manufactured by Gensia Sicor Pharmaceutical Inc. . Corp address 19 hughes, Irvin CA 92618-1902..**
- No outside firms are used.
- Container/Closure: Amber glass tubing
- Product line: — (1 mL fill)and 5 mL vials. 1 per carton
- Components/Composition
RLD—vinorelbine tartrate and Water for injection. No preservatives.
Applicant : same
- 9.Storage/Dispensing Conditions:
RLD: Store the vials under refrigeration at 2 to 8C(36 to 46 F) in the carton.Protect from light.DO NOT FREEZE.
Applicant: same

Date of Review: 09/05/01

Date of Submission: July 20, 2001

cc: ANDA: 76-028
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
V:firmsam/Gensia/let&revs/76028TA.L
Review

ISI

9/12/2001

APPEARS THIS WAY
ON ORIGINAL

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-028

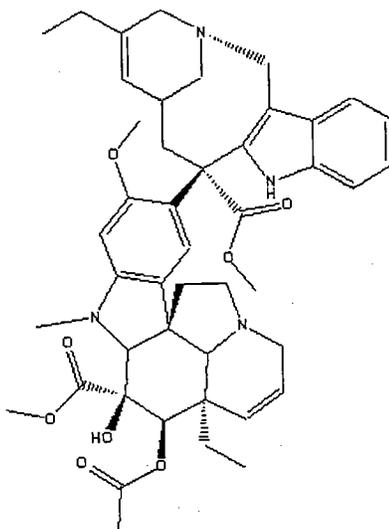
CHEMISTRY REVIEW(S)

DMF number	DMF type	DMF holder
_____	Type III	_____
_____	Type II	_____

13. DOSAGE FORM: Injection (10 mg/mL); 1 mL in _____ vial, and 5 mL in 5 mL vial)

14. POTENCY: 10 mg (vinorelbine)/mL

15. CHEMICAL NAME AND STRUCTURE



2 HOOC-CHOH-CHOH-COOH

Vinorelbine Tartrate $C_{45}H_{54}N_4O_8 \cdot 2C_4H_6O_6$ 1079.12
 Vinorelbine $C_{45}H_{54}N_4O_8$ 778.94)

16. RECORDS AND REPORTS n/a

17. COMMENTS

- EERs: Pending (need update EER).
- Labeling review: Deficient 2/14/01
- Bio-review: Waiver Granted (2/26/01)
- Micro: Pending (4/23/01)
- Method Validation; Awaiting finalized methods
- Container-closure system differs from innovator; Amber Vial
- Major CMC deficiencies; Refer to Item 38.

18. CONCLUSIONS AND RECOMMENDATIONS: NA MAJOR

19. REVIEWER: Kenneth J. Furnkranz
DATE COMPLETED: 4/27/01 DATE REVISED: 5/2/01

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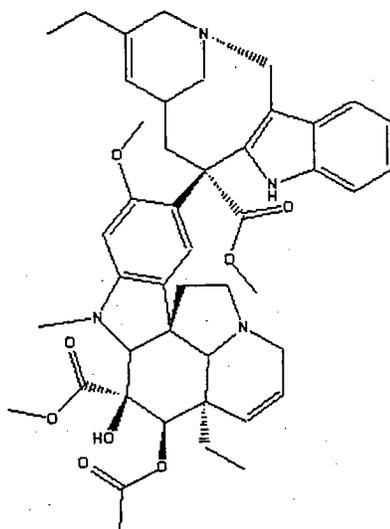
12. RELATED IND/NDA/DMF(s)

DMF number	DMF type	DMF holder
_____	Type III	_____
_____	Type II	_____

13. DOSAGE FORM: Injection (10 mg/mL); 1 mL in _____ vial, and 5 mL in 5 mL vial)

14. POTENCY: 10 mg (vinorelbine)/mL

15. CHEMICAL NAME AND STRUCTURE



2 HOOC-CHOH-CHOH-COOH

Vinorelbine Tartrate $C_{45}H_{54}N_4O_8 \cdot 2C_4H_6O_6$ 1079.12
 Vinorelbine $C_{45}H_{54}N_4O_8$ 778.94

16. RECORDS AND REPORTS n/a

17. COMMENTS

- EERs: Acceptable on 8/29/01 as per D. Ambrogio.
- Labeling review: Satisfactory 9/12/01
- Bio-review: Waiver Granted (2/26/01)
- Micro: Pending Review
- Method Validation; To be sent concurrent with this Chemistry Review.

18. CONCLUSIONS AND RECOMMENDATIONS: NA MINOR **Refer to**
Item 38.

19. REVIEWER: Kenneth Furnkranz DATE COMPLETED: 1/28/02
DATE REVISED: 2/1/02

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1. CHEMISTRY REVIEW NO.: 3
2. ANDA # 76-028
3. NAME AND ADDRESS OF APPLICANT:
 Gensia Sicor Pharmaceuticals, Inc.
 19 Hughes
 Irvine, CA 92618
 Attention: Elvia O. Gustavson
4. LEGAL BASIS FOR SUBMISSION:
 Innovator Product: Navelbine® (vinorelbine tartrate)
 Innovator Company: Glaxo Wellcome
 Manufactured by: Pierre Fabre Medicament Production
 NDA#: 20-388
 Patent Expiration Date: 07/08/2002 (Paragraph III)
 Exclusivity: None
- Gensia states that their drug product has the same active and inactive ingredients, dosage form, strength, route of administration and conditions of use, as the Reference Listed Drug; Glaxo Wellcome; Navelbine® (refer to p. 100015 for a comparison chart).
5. SUPPLEMENT(s): N/A
6. PROPRIETARY NAME: None
7. NONPROPRIETARY NAME: Vinorelbine Tartrate Injection
8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A
9. AMENDMENTS AND OTHER DATES:

Gensia Sicor Pharmaceuticals Inc.	
11/17/00	Original
7/20/01	ANDA MAJOR Amendment
8/21/01	ANDA Microbiology Amendment
4/3/02	ANDA MINOR Chemistry Amendment
FDA	
12/29/00	Acknowledge letter (accept for filing)
2/14/01	Labeling is Deficient
2/26/01	Bio-waiver granted (no further questions).
5/10/01	N/A MAJOR Chemistry/Labeling Deficiencies
7/30/01	TA Labeling Summary
8/16/01	N/A Microbiology Deficiencies
2/12/02	N/A MINOR Chemistry Deficiencies
Other	
2/4/02	Method Validation Request to HFD-140

10. PHARMACOLOGICAL CATEGORY: Treatment of ambulatory patients with unresectable, advanced, non-small cell lung cancer

11. Rx or OTC: Rx

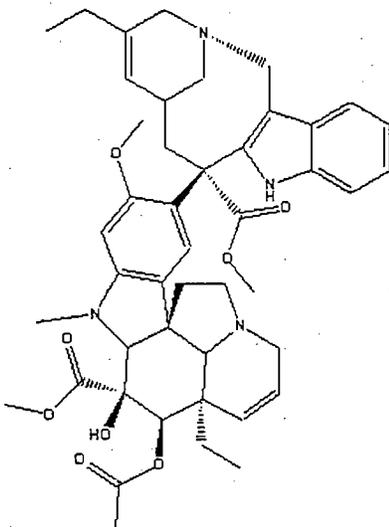
12. RELATED IND/NDA/DMF(s)

DMF number	DMF type	DMF holder
_____	Type III	_____
_____	Type II	_____

13. DOSAGE FORM: Injection (10 mg/mL); 1 mL in _____ vial, and 5 mL in 5 mL vial)

14. POTENCY: 10 mg (vinorelbine)/mL

15. CHEMICAL NAME AND STRUCTURE



2 HOOC-CHOH-CHOH-COOH

Vinorelbine Tartrate $C_{45}H_{54}N_4O_8$ $2C_4H_6O_6$ 1079.12

Vinorelbine $C_{45}H_{54}N_4O_8$ 778.94

16. RECORDS AND REPORTS n/a

17. COMMENTS

- EERs: Acceptable on 8/29/01 as per D. Ambrogio.
- Labeling review: Satisfactory as per TA Labeling Summary dated 9/12/01
- Bio-review: Waiver Granted (2/26/01)
- Micro: Pending Review
- Method Validation; Sent 2/4/02. Awaiting report

at this time.

18. CONCLUSIONS AND RECOMMENDATIONS: NA/MINOR Amendment
(Micro and MV are also pending).

19. REVIEWER: Kenneth Furnkranz DATE COMPLETED: 4/26/02
DATE REVISED: 5/1/02

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1. CHEMISTRY REVIEW NO.: 4
2. ANDA # 76-028
3. NAME AND ADDRESS OF APPLICANT:
 Gensia Sicor Pharmaceuticals, Inc.
 19 Hughes
 Irvine, CA 92618
 Attention: Elvia O. Gustavson
4. LEGAL BASIS FOR SUBMISSION:
 Innovator Product: Navelbine® (vinorelbine tartrate)
 Innovator Company: Glaxo Wellcome
 Manufactured by: Pierre Fabre Medicament Production
 NDA#: 20-388
 Patent Expiration Date: 07/08/2002 (Paragraph III)
 Exclusivity: None
- Gensia states that their drug product has the same active and inactive ingredients, dosage form, strength, route of administration and conditions of use, as the Reference Listed Drug; Glaxo Wellcome; Navelbine®.
5. SUPPLEMENT: N/A
6. PROPRIETARY NAME: None
7. NONPROPRIETARY NAME: Vinorelbine Tartrate Injection
8. SUPPLEMENT(S) PROVIDE(S) FOR: N/A
9. AMENDMENTS AND OTHER DATES:

Gensia Sicor Pharmaceuticals Inc.	
11/17/00	Original
7/20/01	ANDA MAJOR Amendment
8/21/01	ANDA Microbiology Amendment
4/3/02	ANDA MINOR Chemistry Amendment
*6/27/02	ANDA MINOR Chemistry Amendment
7/2/02	Unsolicited Labeling Amendment
FDA	
12/29/00	Acknowledge letter (accept for filing)
2/14/01	Labeling is Deficient
2/26/01	Bio-waiver granted (no further questions).
5/10/01	N/A MAJOR Chemistry/Labeling Deficiencies
7/30/01	TA Labeling Summary
8/16/01	N/A Microbiology Deficiencies
2/12/02	N/A MINOR Chemistry Deficiencies
5/7/02	N/A MINOR Chemistry Deficiencies
Other	
2/4/02	Method Validation Request to HFD-140

* - subject of this review

10. PHARMACOLOGICAL CATEGORY: Treatment of ambulatory patients with unresectable, advanced, non-small cell lung cancer

11. Rx or OTC: Rx

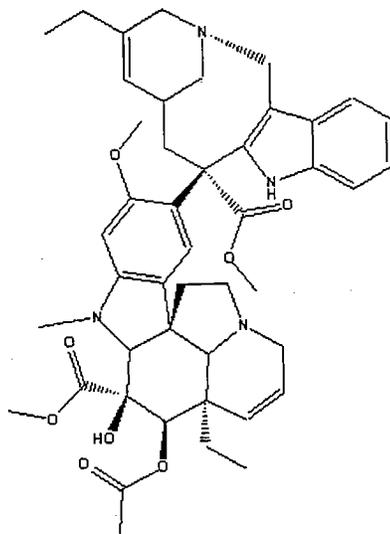
12. RELATED IND/NDA/DMF(s)

DMF number	DMF type	DMF holder
_____	Type III	_____
_____	Type II	_____

13. DOSAGE FORM: Injection (10 mg/mL); 1 mL in _____ vial, and 5 mL in 5 mL vial)

14. POTENCY: 10 mg (vinorelbine)/mL

15. CHEMICAL NAME AND STRUCTURE



HOOC-CHOH-CHOH-COOH

Vinorelbine Tartrate $C_{45}H_{54}N_4O_8 \cdot 2C_4H_6O_6$ 1079.12
Vinorelbine $C_{45}H_{54}N_4O_8$ 778.94

16. RECORDS AND REPORTS n/a

17. COMMENTS

- EERs: Acceptable on 8/29/01 as per D. Ambrogio.
- Bio-review: Waiver Granted (2/26/01)
- Micro Recommended the ANDA for Approval on the basis of Sterility Assurance as per L. Shelton/N. Sweeney on 6/25/02

- Revised Labeling (based on recent Innovator Labeling revisions) are currently under review
- Method Validation; Sent 2/4/02. Samples received 4/5/02. Awaiting report at this time.
- Categorical Exclusion from performing an Environmental Assessment request was requested to be sent to Nancy Sager's group for consult on 7/17/02 (appropriate information was given to H. Greenberg for transmittal).

18. CONCLUSIONS AND RECOMMENDATIONS: **Chemistry Closed**
(pending MV, EA Consult and Labeling).

19. REVIEWER: Kenneth Furnkranz DATE COMPLETED: 7/19/02
DATE REVISED: 7/22/02

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1. CHEMISTRY REVIEW NO.: 4 (Addendum)
2. ANDA 76-028
3. NAME AND ADDRESS OF APPLICANT:
Gensia Sicor Pharmaceuticals, Inc.
19 Hughes
Irvine, CA 92618
Attention: Elvia O. Gustavson
4. LEGAL BASIS FOR SUBMISSION:
Innovator Product: Navelbine® (vinorelbine tartrate)
Innovator Company: Glaxo Wellcome
Manufactured by: Pierre Fabre Medicament Production
NDA#: 20-388
Patent Expiration Date: 07/08/2002 (Paragraph III)
Exclusivity: Pediatric Exclusivity granted on 8/15/02.
Length of exclusivity TBD

Gensia states that their drug product has the same active and inactive ingredients, dosage form, strength, route of administration and conditions of use, as the Reference Listed Drug; Glaxo Wellcome; Navelbine®
5. SUPPLEMENT: N/A
6. PROPRIETARY NAME: None
7. NONPROPRIETARY NAME: Vinorelbine Tartrate Injection
8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A
9. AMENDMENTS AND OTHER DATES:

**APPEARS THIS WAY
ON ORIGINAL**

- Gensia Sicor Pharmaceuticals Inc.	
11/17/00	Original
7/20/01	ANDA MAJOR Amendment
8/21/01	ANDA Microbiology Amendment
4/3/02	ANDA MINOR Chemistry Amendment
6/27/02	ANDA MINOR Chemistry Amendment
*7/2/02	Unsolicited Labeling Amendment
*7/24/02	ANDA MINOR Chemistry Amendment
FDA	
12/29/00	Acknowledge letter (accept for filing)
2/14/01	Labeling is Deficient
2/26/01	Bio-waiver granted (no further questions).
5/10/01	N/A MAJOR Chemistry/Labeling Deficiencies
7/30/01	TA Labeling Summary
8/16/01	N/A Microbiology Deficiencies
2/12/02	N/A MINOR Chemistry Deficiencies
5/7/02	N/A MINOR Chemistry Deficiencies
7/22/02	Chemistry Closed pending EA, MV & Labeling
Other	
2/4/02	Method Validation Request to HFD-140

* - subject of this review

10. PHARMACOLOGICAL CATEGORY: Treatment of ambulatory patients with unresectable, advanced, non-small cell lung cancer

11. Rx or OTC: Rx

12. RELATED IND/NDA/DMF(s)

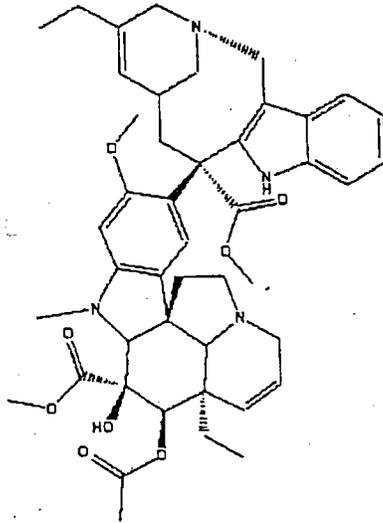
DMF number	DMF type	DMF holder
 	Type III	
 	Type II	

13. DOSAGE FORM: Injection (10 mg/mL); 1 mL in vial, and 5 mL in 5 mL vial)

14. POTENCY: 10 mg (vinorelbine)/mL

15. CHEMICAL NAME AND STRUCTURE

APPEARS THIS WAY
ON ORIGINAL



HOOC-CHOH-CHOH-COOH

Vinorelbine Tartrate $C_{45}H_{54}N_4O_8$ $2C_4H_6O_6$ 1079.12
 Vinorelbine $C_{45}H_{54}N_4O_8$ 778.94

16. RECORDS AND REPORTS n/a

17. COMMENTS

- EERs: Acceptable on 8/29/01 as per D. Ambrogio.
- Bio-review: Waiver Granted (2/26/01)
- Micro Recommended the ANDA for Approval on the basis of Sterility Assurance as per L. Shelton/N. Sweeney on 6/25/02
- Revised Labeling (based on recent Innovator Labeling revisions) submitted on 7/2/02 was found acceptable as per DLPS (A.Payne/J.Grace) on 8/2/02
- A justified Categorical Exclusion request from performing an Environmental Assessment was granted as per N. Sager (see attached e-mail dated 8/2/02) based on amendment dated 7/24/02
- Method Validation; Sent 2/4/02. Samples received by S.J. Lab on 4/5/02. Awaiting MV report at this time.

18. CONCLUSIONS AND RECOMMENDATIONS: Tentative Approval due to Pediatric Exclusivity issues. **(with MV outstanding)**.

19. REVIEWER: Kenneth Furnkranz DATE COMPLETED: 8/21/02
DATE REVISED:

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-028 APPLICANT: Gensia Sicor

DRUG PRODUCT: Vinorelbine Tartrate Injection, 10 mg/mL

There are no additional Chemistry, Manufacturing and Controls deficiencies remaining. MVP is outstanding.

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 76-028
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-625/K.Furnkranz/8/21/
HFD-625/M.Smela, TL/8/21/02
~~HFD-617/P.Chen, PM/8/26/02~~

ISI 8/28/02
ISI

8/28/02

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F/T by: gp/8/26/02

CHEMISTRY REVIEW - Tentative Approval (with MV outstanding)

APPEARS THIS WAY
ON ORIGINAL

11. Rx or OTC: Rx

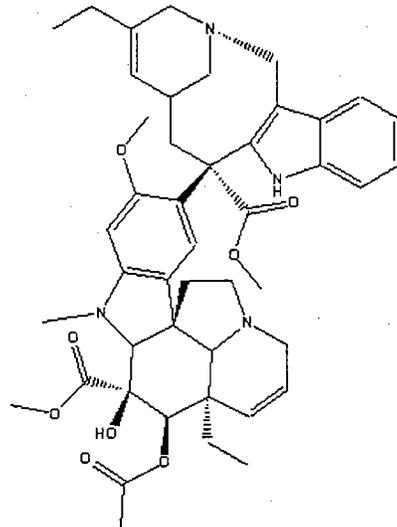
12. RELATED IND/NDA/DMF(s)

DMF number	DMF type	DMF holder
_____	Type III	_____
_____	Type II	_____

13. DOSAGE FORM: Injection (10 mg/mL); 1 mL in _____ vial, and 5 mL in 5 mL vial)

14. POTENCY: 10 mg (vinorelbine)/mL

15. CHEMICAL NAME AND STRUCTURE



HOOC-CHOH-CHOH-COOH

Vinorelbine Tartrate $C_{45}H_{54}N_4O_8 \cdot 2C_4H_6O_6$ 1079.12

Vinorelbine $C_{45}H_{54}N_4O_8$ 778.94

16. RECORDS AND REPORTS n/a

17. COMMENTS

- ANDA was Tentatively Approved on 9/17/02. No CMC changes have been reported since then. No new information has been submitted except for FPL, which is pending review.
- MV was sent 2/4/02. Samples received by S.J. Lab on 4/5/02. MVP is still pending at this time.
- A Proposed USP Monograph was published in the PF (Sept/Oct 2001). Differences are not significant

(refer to Section 24 for a comparison of the proposed USP specifications and the current Gensia Sicor specifications..

18. CONCLUSIONS AND RECOMMENDATIONS: **Chemistry Closed**
(with MV outstanding).

19. REVIEWER: Kenneth Furnkranz DATE COMPLETED: 1/8/03
DATE REVISED:

**APPEARS THIS WAY
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1. CHEMISTRY REVIEW NO.: 5 (Addendum)
2. ANDA 76-028
3. NAME AND ADDRESS OF APPLICANT:
Gensia Sicor Pharmaceuticals, Inc.
19 Hughes
Irvine, CA 92618
Attention: Elvia O. Gustavson
4. LEGAL BASIS FOR SUBMISSION:
Innovator Product: Navelbine® (vinorelbine tartrate)
Innovator Company: Glaxo Wellcome
Manufactured by: Pierre Fabre Medicament Production
NDA#: 20-388
Patent Expiration Date: 01/08/2003
5. SUPPLEMENT: N/A
6. PROPRIETARY NAME: None
7. NONPROPRIETARY NAME: Vinorelbine Tartrate Injection
9. AMENDMENTS AND OTHER DATES:

Gensia Sicor Pharmaceuticals Inc.	
Firm	
11/17/00	Original
7/20/01	ANDA MAJOR Amendment
8/21/01	ANDA Microbiology Amendment
4/3/02	ANDA MINOR Chemistry Amendment
6/27/02	ANDA MINOR Chemistry Amendment
7/2/02	Unsolicited Labeling Amendment
7/24/02	ANDA MINOR Chemistry Amendment
8/27/02	Exclusivity Amendment
9/16/02	ANDA TELEPHONE Amendment
11/13/02	ANDA MINOR Amendment
*1/14/03	ANDA TELEPHONE Amendment
*1/29/03	ANDA TELEPHONE Amendment
FDA	
12/29/00	Acknowledge letter (accept for filing)
2/14/01	Labeling is Deficient
2/26/01	Bio-waiver granted (no further questions).
5/10/01	N/A MAJOR Chemistry/Labeling Deficiencies
7/30/01	TA Labeling Summary
8/16/01	N/A Microbiology Deficiencies
2/12/02	N/A MINOR Chemistry Deficiencies
5/7/02	N/A MINOR Chemistry Deficiencies
7/22/02	Chemistry Closed pending EA, MV & Labeling
8/28/02	CR #4A; Chemistry Closed
9/17/02	ANDA Tentatively Approved; MV outstanding
1/9/03	CR #5; Chemistry Closed
Other	
2/4/02	Method Validation Request to HFD-140
1/13/03	Telecon with G/S
1/27/03	Telecon with G/S
1/29/03	Telecon with G/S

* - subject of this review

10. PHARMACOLOGICAL CATEGORY: Treatment of ambulatory patients with unresectable, advanced, non-small cell lung cancer

11. Rx or OTC: Rx

12. RELATED IND/NDA/DMF(s)

DMF number	DMF type	DMF holder
_____	Type III	_____
_____	Type II	_____

13. DOSAGE FORM: Injection (10 mg/mL); 1 mL in _____ vial, and 5 mL in 5 mL vial)

14. POTENCY: 10 mg (vinorelbine)/mL

15. CHEMICAL NAME AND STRUCTURE: See Previous Chemistry Reviews.

16. RECORDS AND REPORTS n/a

17. COMMENTS

- ANDA was Tentatively Approved on 9/17/02.
- FPL is Acceptable.
- MV is still pending at this time.
- A Monograph was published in USP 26 (effective 1/1/03). Firm has adopted the USP monograph tests, however, the related Compound A Reference Standard is not available. G/S has committed to perform both their in-house method as well as the USP Related Compounds method (once the Related Compound A Reference Standard becomes available). Gensia/Sicor will submit a supplement if they wish to eliminate either of the Related Compounds tests after demonstrating equivalence of the two methods. The revised specifications for the Vinorelbine Tartrate drug substance are as indicated in the table below:

New Gensia/Sicor Specifications reflecting the USP Monograph and the results of testing of Lot #K2902553		
Test	New Gensia Sicor Specifications	Results of testing Lot #K2902553
Description	White to beige powder	Conforms
Identification IR	Conforms to Ref. Std.	Conforms
ID- _____	Responds to the test for _____	Conforms
ID- _____	Conforms to Reference Standard	Conforms
% Water (KF)	NMT _____	_____
Clarity of Solution	Clear (solution of 138.5 mg Vinorelbine Tartrate in 10mL of water)	Clear
	NMT _____ (solution of 138.5 mg Vinorelbine Tartrate in 10mL of water)	_____
pH (1 mg/mL)	_____	_____
Res. On Ignition	NMT _____	0.0%
Heavy Metals	NMT _____	_____
Specific Rotation	_____	_____

Non-Aqueous Titration Assay	(on " " Basis)	
Related Compounds (In-House)	Single Largest Ind: NMT Total: NMT	Sngl Lgst: Total Imps: Not Performed
Related Compounds (USP)	Single Largest Other: NMT (RRT " ", : NMT Total (excluding NMT	
Residual solvents:	NMT NMT NMT	ppm ND ND
Bact. Endotoxins:	NMT	
Bioburden (CFU/g):	Total NMT Total : NMT	
Microbial Limits:	Absent Absent Absent Absent	Absent Absent Absent Absent

18. CONCLUSIONS AND RECOMMENDATIONS: Approve ANDA (with MV outstanding) .

19. REVIEWER: Kenneth Furnkranz DATE COMPLETED: 1/29/03
DATE REVISED:

cc: ANDA 76-028
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-625/K. Furnkranz/1/29/03

HFD-625/M. Smela, TL/1/30/03

HFD-617/P. Chen, PM/1/30/03

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F/T by: gp/1/30/03

CHEMISTRY REVIEW - Approve ANDA (with MV outstanding)

TEJ/ST 1/31/03
1/31/03
1/31/03

**APPEARS THIS WAY
ON ORIGINAL**

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 76-028

FIRM: GensiaSicor Pharmaceuticals, Inc.

DOSAGE FORM: Injection

STRENGTHS: 10 mg/mL, 1 mL and 5 mL vials

DRUG: Vinorelbine Tartrate Injection

CGMP STATEMENT/EIR UPDATED STATUS: EER status for all facilities listed in Section # 33 of the Chemistry Review #4 is acceptable on 8/29/01 per D. Ambrogio of HFD-324.

BIOEQUIVALENCE STATUS: Acceptable. Bioequivalence waiver granted 2/26/01.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Methods Validation is outstanding at this time (samples received by the lab on 4/5/02). A commitment has been made to expeditiously resolve MV issues that may develop post-approval..

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION? Containers used in the stability studies are identical to those listed in container section. Product is packaged in _____ or 5 mL amber glass vials with _____ stopper and flip-off seals. Acceptable.

LABELING: FPL - acceptable per review completed by A.Payne/J.Grace on 1/27/03.

STERILIZATION VALIDATION (IF APPLICABLE): Product is _____
Validation of the _____ process was found acceptable as per L.Shelton/N.Sweeney on 6/25/02.

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?): Gensia Sicor manufactured a pilot plant scale batch of _____ (Batch #X00H602 and X00H602F1). For production, GensiaSicor will manufacture each fill size separately in batch size of _____

Gensia Sicor has submitted a blank master batch production record for a _____ production size of the 1 mL and 5 mL fill sizes.

The Vinorelbine Tartrate drug substance is manufactured by _____ The DMF was last reviewed on July 22, 2002 as a result of a DMF Update, and was found adequate. No new information has been submitted since this last review (COMIS checked 1/30/03).

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?): The exhibit lots were utilized for the stability studies. Bioequivalence studies were waived for this drug product.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY? The manufacturing process for the production batches is the same. Production batch size is _____s. The exhibit batch was: _____

MISCELLANEOUS ISSUES: A USP Monograph for Vinorelbine Tartrate drug substance became official in USP 26 (effective 1/1/03). The Tests/Specifications established in the USP Vinorelbine Tartrate monograph differed slightly from those previously established by Gensia/Sicor. G/S was asked to update their tests and specs to be consistent with the USP Monograph and provide data to demonstrate that their product meets the USP specifications.

G/S informed us that they cannot provide comparative data for the USP Vinorelbine Tartrate Related Compounds test, since the USP Related Compound A Reference Standard is not available, and may not be available for some time.

As a result, we contacted G/S and informed them that they should:

- Revise their Vinorelbine Tartrate drug substances tests and specifications to include both their in-house Related Substances method/specifications as well as the USP method/specifications for Related Compounds.
- Commit to test all lots of their drug substance using both methods at such time as the USP makes the Related Compound A Reference Standard available.
- Provide validation data, when the USP Related Compound A Reference Standard becomes available, to demonstrate that their in-house method can detect and quantitate the related substances identified and quantitated by the USP method.
- Supplement their application at such time as they wish to delete either the in-house method or the USP method (the USP method will still be the regulatory method).

G/S provided a Telephone Amendment response addressing the above issues and their response was deemed adequate.

cc: ANDA #76-028
HFD-600/Reading File

Endorsements:

HFD-625/K.Furnkranz

HFD-625/M.Smela/1/30/03

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F/T by: gp/1/30/03

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1/31/03

ISI
1/31/03

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 76-028

FIRM: GensiaSicor Pharmaceuticals, Inc.

DOSAGE FORM: Injection

STRENGTHS: 10 mg/mL, 1 mL and 5 mL vials

DRUG: Vinorelbine Tartrate Injection

CGMP STATEMENT/EIR UPDATED STATUS: EER status for all facilities listed in Section # 33 of the Chemistry Review #4 is acceptable on 8/29/01 per D. Ambrogio of HFD-324.

BIOEQUIVALENCE STATUS: Acceptable. Bioequivalence waiver granted 2/26/01.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): Methods Validation is outstanding at this time (samples received by the lab on 4/5/02). A commitment has been made.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION? Containers used in the stability studies are identical to those listed in container section. Product is packaged in _____ or 5 mL amber glass vials with _____ stopper and flip-off seals. Acceptable.

LABELING: FPL - acceptable per review completed by A.Payne/J.Grace on 8/2/02.

STERILIZATION VALIDATION (IF APPLICABLE): Product is _____ Validation of the _____ process was found acceptable as per L.Shelton/N.Sweeney on 6/2/02.

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?): Gensia Sicor manufactured a pilot plant scale batch of _____ (Batch #X00H602 and X00H602F1). For production, GensiaSicor will manufacture each fill size separately in batch size of _____

Gensia Sicor has submitted a blank master batch production record for a _____ production size of the 1 mL and 5 mL fill sizes.

The Vinorelbine Tartrate drug substance is manufactured by _____ The DMF was last reviewed on July 22, 2002 as a result of a DMF Update, and was found adequate. No new information has been submitted since this last review (COMIS checked 8/21/02).

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?): The exhibit lots were utilized for the stability studies. Bioequivalence studies were waived for this drug product.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY? The manufacturing process for the production batches is the same.
Production batch size is _____ The exhibit batch was _____

cc: ANDA #76-028
HFD-600/Reading File

Endorsements:

HFD-625/K.Furnkranz/8/21/02

HFD-625/M.Smela/8/21/02

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F/T by: gp/8/26/02

ISI 8/28/02
ISI

8/28/02

APPEARS THIS WAY
ON ORIGINAL

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-028

MICROBIOLOGY REVIEW

OFFICE OF GENERIC DRUGS, HFD-620
Microbiology Review #1
August 16, 2001

- A. 1. **ANDA** **76-028**
- APPLICANT Gensia Sicor Pharmaceuticals
 19 Hughes
 Irvine, CA 92618-1902
2. PRODUCT NAME: Vinorelbine Tartrate Injection
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 10 mg
 base/mL packaged as 1 mL/—, vial and 5 mL/5 mL vial,
 single dose, liquid, intravenous injection
4. METHOD(S) OF STERILIZATION: _____
5. PHARMACOLOGICAL CATEGORY: Neoplastic Chemotherapeutic
 Agent
- B. 1. DATE OF INITIAL SUBMISSION: November 17, 2000
 **Subject of this Review (Received November 20,
 2000)**
2. DATE OF AMENDMENT: None
3. RELATED DOCUMENTS:
 DMF _____
 DMF _____
4. ASSIGNED FOR REVIEW: June 18, 2001
- C. REMARKS: The subject drug product will be _____
 _____ at the Irvine, CA
 manufacturing facility.
- D. CONCLUSIONS: The submission is **not recommended** for
 approval on the basis of sterility assurance. Specific
 comments regarding the _____ process are provided
 in "E. Review Notes" and "Microbiology Comments to be
 Provided to the Applicant."

Lisa S. G. Shelton, Ph.D.

8/16/01

cc: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy

②84
8/16/01

Drafted by L. Shelton, HFD-620 v:\microrev\76-028.doc
Initialed by M. Fanning/ A. High

APPEARS THIS WAY
ON ORIGINAL

E. REVIEW NOTES:

1. General Drug and Processing Descriptions. Each mL of Vinorelbine Tartrate Injection contains 13.85 mg vinorelbine tartrate (equivalent to 10 mg vinorelbine base) and water for injection (WFI) (p. 100046, vol. 1.1). The subject drug product is light and oxygen sensitive (p. 100096, vol. 1.1). The recommended storage condition is 2-8°C, protected from light. Vinorelbine Tartrate Injection is packaged in 10 mg/mL and 50 mg/5 mL single use vials (pp. 100039 and 100041, vol. 1.1).

The subject drug product solution is

2. Facility and Environmental Control Descriptions. The finished drug product is manufactured at

Gensia Sicor Pharmaceuticals, Inc.
 21 Hughes
 Irvine, CA 92718

Testing of the finished product will be performed in _____ (p. 100092, vol. 1.1).

Floor plans with component/product flow indicated on them are provided on pp. 100107-100109, vol. 1.1 and pp. 300020-300022, vol. 1.3.

_____ and the adjacent areas are shown schematically on p. 300153, vol. 1.3. A floor plan indicating room classifications is provided on p. 300052, vol. 1.3.

The _____ The
 applicant states that _____



are provided (pp. 300035 and 300038, vol. 1.3).

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commercial

information

_____ (pp. 300130-300131, vol. 1.3). The endotoxin limit is _____. The calculated MVD is 1:2073 for 10 mg/mL product. Validation of the endotoxin test shows no inhibition or enhancement of the _____ using a _____ of the subject drug product (pp. 200283-200288, vol. 1.2 and pp. 300167-300172, vol. 1.3).

- c. Stability Protocol. The applicant commits to placing the first three commercial production lots of each product size (container/closure system) into the stability program (p. 200359, vol. 1.2). Stored vials of the finished drug product will be tested for sterility and bacterial endotoxin at the _____ time point (pp. 200351-200352, 200367-200368, vol. 1.2). Container/ closure integrity will be verified by performing the microbial ingress test on media-filled vials at _____ time points (p. 200354, vol. 1.2).

Not acceptable

APPEARS THIS WAY
ON ORIGINAL

Microbiology Comments to be Provided to the Applicant

ANDA: 76-028 APPLICANT: Gensia Sicor Pharmaceuticals, Inc.

DRUG PRODUCT: Vinorelbine Tartrate Injection, 10 mg base/mL

Microbiology Deficiencies:

1. With regard to the acceptance criteria for the Revalidation of Equipment Sterilization Cycle (p. 300059, vol. 1.3), you stated "the cumulative F_0 value must be _____ minutes for the entire cycle"; however, there is no further mention of the F_0 value and whether this acceptance criteria was met. Please provide an explanation regarding the F_0 and results addressing this acceptance criteria.

2. Regarding _____, please provide production parameters for comparison with the _____ parameters, _____ and the _____

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,



Mary Fanning, M.D., Ph.D.
 Associate Director of Medical Affairs
 Office of Generic Drugs
 Center for Drug Evaluation and Research

Product Quality Microbiology Review

Review for HFD-620

25 June 2002

ANDA: 76-028

Drug Product Name

Proprietary: N/A

Non-proprietary: Vinorelbine Tartrate

Drug Product Classification: Neoplastic Chemotherapeutic Agent

Review Number: #2

Subject of this Review

Submission Date: August 21, 2001

Receipt Date: August 22, 2001

Consult Date: N/A

Date Assigned for Review: May 16, 2002

Submission History (for amendments only)

Date(s) of Previous Submission(s): November 17, 2000

Date(s) of Previous Micro Review(s): August 16, 2001

Applicant/Sponsor

Name: Gensia Sicor Pharmaceuticals

Address: 19 Hughes, Irvine, CA 92618-1902

Representative: Elvia Gustavson

Telephone: 949-455-4724

Name of Reviewer: Lisa S.G. Shelton

Conclusion: The submission is recommended for approval on the basis of sterility assurance.

Executive Summary

I. Recommendations

A. Recommendation on Approvability –

The submission is **recommended** for approval on the basis of sterility assurance. Specific comments regarding the _____ process are provided in the “Product Quality Microbiology Assessment”.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assesments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –

The subject drug product is _____ into _____ and 5 mL single dose vials in _____, at the Irvine, CA manufacturing facility.

B. Brief Description of Microbiology Deficiencies - None

C. Assessment of Risk Due to Microbiology Deficiencies - None

III. Administrative

A. Reviewer's Signature _____

ISI

B. Endorsement Block

Microbiologist, Lisa S.G. Shelton, Ph.D. *LS 6/25/02*
 Microbiology Supervisor/Team Leader, Neal Sweeney, Ph.D.

C. CC Block

cc:
 Original ANDA 76-028
 HFD- 600/Division File/ANDA 76-028
 filename: V:\MICROREV\76-028a1.doc

ISI
6/25/02

Product Quality Microbiology Assessment

The applicant has responded to the Microbiology Deficiencies and Comments in the letter dated August 21, 2001. The original questions are italicized.

A. Microbiology Deficiencies:

- With regard to the acceptance criteria for the Revalidation of Equipment Sterilization Cycle (p. 300059, vol. 1.3), you stated "the cumulative F₀ value must be _____ for the entire cycle"; however, there is no further mention of the F₀ value and whether this acceptance criteria was met. Please provide an explanation regarding the F₀ and results addressing this acceptance criteria.*

Response: The applicant states the F₀ should have read _____, rather than _____, and supplies a corrected page for acceptance criteria. The applicant adds F₀ results in the following table:

Thermocouples and RTDs	Temperature, °C	
	Minimum Load	Maximum Load
Sterilization Set Point	_____	_____
Penetration TCs – Range	_____	_____
Distribution TCs – Range	_____	_____
Distribution TCs at drain – Range	_____	_____
Drain RTD – Range	_____	_____
Fo Range for Entire Cycle, minutes	_____	_____

Acceptable

- Regarding _____, please provide production parameters for comparison with the _____ parameters, _____*

Response: The applicant states that the a bracketing approach is used for _____ to include all products filled on any _____. The _____ is bracketed by _____ representing the worst case challenge for handling and generation of particulate matter, and the largest vial at the slowest speed, resulting in maximum exposure. The applicant provides the following information:

Parameter	Media Fills – _____	Production of Vinorelbine
Line Speed	_____ vials/minute and _____ vials/minute	_____ minute and _____/minute
Number of vials filled	Minimum: _____ 2 mL vials Minimum: _____ (100 mL) vials	Maximum: _____ (1 mL/ _____ mL) Maximum: _____ (5 mL/5 mL)
Maximum duration of filling	_____	_____

Acceptable

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-028

**BIOEQUIVALENCE
REVIEW(S)**

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #76-028 APPLICANT: Gensia Sicor

DRUG PRODUCT: Vinorelbine Tartrate Injection, 10 mg/ml,
single-use vials, 1 ml and 5 ml

The Division of Bioequivalence has completed its review
and has no further questions at this time.

Please note that the bioequivalency comments provided in
this communication are preliminary. These comments are
subject to revision after review of the entire
application, upon consideration of the chemistry,
manufacturing and controls, microbiology, labeling, or
other scientific or regulatory issues. Please be
advised that these reviews may result in the need for
additional bioequivalency information and/or studies, or
may result in a conclusion that the proposed formulation
is not approvable.

Sincerely yours,



Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Vinorelbine Tartrate Injection
10 mg/ml, single-use vials (1 ml & 5 ml)
ANDA #76-028
Reviewer: Nhan L. Tran

Gensia Sicor
Irvine, CA
Submission Date:
November 17, 2000

REVIEW OF A WAIVER REQUEST

I. Background

1. The firm has requested a waiver of an in vivo bioequivalence study requirement for its proposed product, Vinorelbine Tartrate Injection, 10 mg/ml, single-use vials (1 ml and 5 ml vials). The reference listed product is Navelbine^R (Vinorelbine Tartrate) Injection, 10 mg/ml, single-use vials, 1 ml and 5 ml, manufactured by GlaxoWellcome
2. Vinorelbine Tartrate Injection, a semi-synthetic vinca alkaloid, is indicated for the treatment of nonsmall cell lung cancer.
3. The test and the reference listed product are both administered intravenously.

II. Formulation comparison

The test and reference formulations are compared as shown below:

Ingredients	Navelbine ^R Injection 10 mg/ml, single-use vial	Vinorelbine Tartrate Injection 10 mg/ml, single-use vial
Vinorelbine Tartrate	equi to 10mg/ml base	13.85mg/ml (13.85mg Vinorelbine Tartrate equivalent to 10mg Vinorelbine base)
Water for Injection, USP	QS to 1 ml	QS to 1 ml

III. Comments

1. The test product, Vinorelbine Tartrate Injection, 10 mg/ml, single-use vials (1 ml and 5 ml), contains the same active and inactive ingredients in the same concentration and dosage form as the reference product, Navelbine^R (Vinorelbine Tartrate) Injection, 10 mg/ml, single-use, 1 ml and 5 ml vials.
2. A waiver is granted under 21 CFR 320.22 (b) (1).

IV. Recommendation

The Division of Bioequivalence agrees that the information submitted by Gensia Sicor on its parenteral product, Vinorelbine Tartrate Injection, 10 mg/ml, single-use vials (1 ml and 5 ml) falls under 21 CFR section 320.22 (b) (1) of the Bioavailability/Bioequivalence Regulations. The waiver of an in vivo bioequivalence study for the drug is granted. The Division of Bioequivalence deems the test product, Vinorelbine Tartrate Injection, 10 mg/ml, single-use vials (1 ml and 5 ml), bioequivalent to the reference product, Navelbine^R (Vinorelbine Tartrate) Injection, 10 mg/ml, single-use vials (1 ml and 5 ml), manufactured by GlaxoWellcome.

/S/

Nhan L. Tran, Ph.D.
Division of Bioequivalence
Review Branch II

for
RD INITIALED BY SNERURKAR
FT INITIALED BY SNERURKAR

/S/ ; Date: 2/6/01

Concur: C **/S/**
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

7 Date: 2/26/01

Cc: ANDA 76-028 (original), HFD 650 (Tran, Nerurkar), Drug File, Division File

**APPEARS THIS WAY
ON ORIGINAL**

CC: ANDA #76-028
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Reviewer
HFD-655/ Bio team leader

v:\FIRMSam\Gensia Sicor\ltrs&rev\76028w.N00

Endorsements: (Final with Dates)

HFD-655/ Reviewer *SW 2-6*
for HFD-655/ Bio team Leader *MS 2/6/01*
HFD-617/ Project Manager
HFD-650/ D. Conner *DC 2/26/01*

BIOEQUIVALENCY - ACCEPTABLE

Submission date: 11/17/2000

✓ 1. WAIVER (WAI)

Strength: 10 mg/ml

Outcome: AC

Outcome Decisions: AC - Acceptable

WinBio Comments: A waiver is granted

APPEARS THIS WAY
ON ORIGINAL

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APPLICATION NUMBER:

76-028

**ADMINISTRATIVE
DOCUMENTS**

Document Listing for N 020388 9/12/01

Type	No.	Sub.	Letter Date	Stamp Date Date	Status Code	Status Date
Annual Report	001		10/16/96	10/18/96		
Annual Report	002		06/17/97	06/17/97		
Annual Report	003		04/17/98	04/20/98		
Annual Report	004		04/30/99	05/03/99		
Annual Report	005		04/27/00	04/28/00		
Annual Report	006		04/27/01	04/30/01		
Original	000		08/27/93	08/27/93	AP	12/23/94
Original	000	Min Amend-Chemist	10/13/93	10/19/93		
Original	000	Min Amend-Biopharm	11/09/93	11/10/93		
Original	000	Min Amend-Chemist	11/17/93	11/18/93		
Original	000	Min Amend-Clinical	11/24/93	11/29/93		
Original	000	Min Amend-Clinical	12/09/93	12/09/93		
Original	000	Maj Amend-Mlty Dis	12/22/93	12/23/93		
Original	000	Min Amend-Mlty Dis	01/13/94	01/13/94		
Original	000	Safety Update	02/01/94	02/03/94		
Original	000	Min Amend-Statists	02/01/94	02/03/94		
Original	000	Min Amend-Chemist	02/16/94	02/17/94		
Original	000	Min Amend-Chemist	03/15/94	03/15/94		
Original	000	Min Amend-Chemist	04/21/94	04/22/94		
Original	000	Min Amend-Microbio(NDA)	04/21/94	04/22/94		
Original	000	Maj Amend-Chemist	04/29/94	04/29/94		
Original	000	Min Amend-Chemist	04/29/94	04/29/94		
Original	000	Min Amend-Chemist	05/31/94	06/03/94		
Original	000	Min Amend-Drft Lab	06/02/94	06/03/94		
Original	000	Maj Amend-Drft Lab	06/06/94	06/06/94		
Original	000	Min Amend-Microbio(NDA)	06/24/94	06/24/94		
Original	000	Min Amend-Chemist	06/27/94	06/29/94		
Original	000	Maj Amend-Chemist	06/28/94	07/01/94		
Original	000	Min Amend-Chemist	07/07/94	07/12/94		
Original	000	Min Amend-Clinical	07/14/94	07/14/94		
Original	000	Safety Update	08/04/94	08/05/94		
Original	000	Maj Amend-Drft Lab	10/21/94	10/24/94		
Original	000	Maj Amend-Fpl	10/28/94	10/31/94		
Original	000	Safety Update	11/09/94	11/10/94		
Original	000	Maj Amend-Fpl	11/14/94	11/15/94		
Original	000	Min Amend-Drft Lab	11/16/94	11/17/94		
Original	000	Maj Amend-Drft Lab	11/30/94	12/02/94		
Original	000	Min Amend-Drft Lab	12/02/94	12/07/94		
Original	000	Min Amend-Chemist	11/28/94	12/12/94		
Original	000	FDA Initiated Action - Minor	11/21/95	11/21/95		
Original	000	FDA Initiated Action - Minor	11/28/95	11/28/95		
Original	000		11/15/00	11/16/00		
Periodic Safety Report	001		05/15/95	05/17/95		
Periodic Safety Report	002		08/14/95	08/17/95		

Periodic Safety Report	003		12/05/95	12/11/95		
Periodic Safety Report	004		01/30/96	02/01/96		
Periodic Safety Report	005		04/30/96	05/03/96		
Periodic Safety Report	006		07/26/96	07/30/96		
Periodic Safety Report	007		10/29/96	10/31/96		
Periodic Safety Report	008		01/27/97	01/30/97		
Periodic Safety Report	009		04/23/97	04/25/97		
Periodic Safety Report	010		07/31/97	08/04/97		
Periodic Safety Report	011		10/23/97	10/24/97		
Periodic Safety Report	012		01/27/98	01/29/98		
Periodic Safety Report	013		04/28/98	04/29/98		
Periodic Safety Report	014		02/10/99	02/11/99		
Periodic Safety Report	015		02/16/00	02/17/00		
Periodic Safety Report	016		02/05/01	02/06/01		
Suppl.-Labeling Revision	001		01/30/96	01/31/96	AP	02/22/96
Suppl.-Labeling Revision	002		04/17/96	04/18/96	AP	05/24/96
Suppl.-Labeling Revision	003		07/02/97	07/03/97	AP	08/29/97
Suppl.-Labeling Revision	005		12/15/97	12/16/97	AP	01/06/98
Suppl.-Labeling Revision	007		07/13/98	07/15/98	AP	10/16/98
Suppl.-Labeling Revision	008		08/24/99	08/30/99	AP	06/08/00
Suppl.-Labeling Revision	008	Maj Amend-Drft Lab	04/10/00	04/11/00		
Suppl.-Labeling Revision	009		12/17/99	12/20/99	AP	05/12/00
Suppl.-Labeling Revision	009	Min Amend-Drft Lab	01/06/00	01/07/00		
Suppl.-Labeling Revision	011		07/31/00	08/01/00	AP	08/25/00
Suppl.-Labeling Revision	012		11/03/00	11/06/00	AP	11/29/00
Suppl.-Manuf. Change/Addtn.	004		07/23/97	07/24/97	AP	04/16/98
Suppl.-Manuf. Change/Addtn.	004	Maj Amend-Chemist	02/11/98	02/12/98		
Suppl.-Package Change	006		04/08/98	04/10/98	AP	09/16/98
Supplement-Pediatric	010		04/06/00	04/07/00	AE	08/17/01
Supplement-Pediatric	010	Min Amend-Drft Lab	07/18/00	07/19/00		
Supplement-Pediatric	010	Min Amend-Clinical	08/09/00	08/10/00		
Supplement-Pediatric	010	Min Amend-Clinical	11/01/00	11/02/00		
Supplement-Pediatric	010	Min Amend-Drft Lab	11/03/00	11/06/00		
Supplement-Pediatric	010	Maj Amend-Drft Lab	02/16/01	02/20/01		

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	

Exclusivity Data

There is no unexpired exclusivity for this product.

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Patent and Exclusivity Terms

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Smela Jr, Michael

From: Smela Jr, Michael
t: Monday, May 06, 2002 3:43 PM
Ouderkirk, Larry A; Hsieh, Yung Ao
Cc: Wood, Rebecca H; Patel, Rashmikant M
Subject: RE: Impurity (Related Compounds) Limits proposed for Vinorelbine Tartrate DS

Larry....These limits are **MUCH** tighter than what has been approved for Glaxo (). If the limits came to USP from Glaxo, I would wonder if they are trying something. Nonetheless, GSP and their supplier have much tighter limits than Glaxo. I would be comfortable for us to recommend that the limit for other individual impurities and total impurities should be relaxed slightly.

As an aside, this drug has There should be a test and limit for

Mike

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

From: Ouderkirk, Larry A
Sent: Monday, May 06, 2002 11:35 AM
To: Hsieh, Yung Ao; Smela Jr, Michael
Cc: Wood, Rebecca H
Subject: Impurity (Related Compounds) Limits proposed for Vinorelbine Tartrate DS

Dear Colleagues,

Shawn Dressman of USP has requested our help with the Related Compounds limits proposed for Vinorelbine Tartrate in the Sept-Oct 2001 issue of PF (pp. 3054-3057). There seem to be some issues regarding the ability of the proposed method to resolve some of the RC's, so it was necessary to word the limits differently than is usual. Shawn wanted our general comments on the limits proposed (too high, too low, etc.). He understands that the actual approved values for the limits are not releasable to USP. The issues here are somewhat similar to those for the Paclitaxel monograph.

Our approved NDA 20-388 is for Navelbine Injection by Glaxo-Smithkline. There is also an ANDA 76-028 pending review submitted by Gensia Sicor Pharm.

I am faxing a copy of the proposal to Mike and am delivering copies to Yung-Ao and Rebecca (in this building). Please review at your earliest convenience because USP needs input from us this week if possible (publication deadline is 5/15).

Thanks very much,

Larry Ouderkirk
Compendial Operations Staff

Smela Jr, Michael

From: Smela Jr, Michael
Sent: Thursday, January 09, 2003 12:37 PM
To: Chen, Peter
Cc: Furnkranz, Kenneth J
Subject: 76028/Vinorelbine

PC....Please add to AP matrix. MVP and Labeling review are pending.

Michael J. Smela, Jr.
Team Leader, ANDA Review Branch 2
Division of Chemistry 1
Office of Generic Drugs
Voice 301-827-5775
Facsimile 301-594-0180

**APPEARS THIS WAY
ON ORIGINAL**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 76028/000**
Stamp: **20-NOV-2000** Regulatory Due:
Applicant: **GENSIA SICOR PHARMS**
19 HUGHES
IRVINE, CA 926181902

Priority:
Action Goal:
Brand Name:
Established Name: **VINORELBINE TARTRATE**
Generic Name:
Dosage Form: **INJ (INJECTION)**
Strength: **10MG/ML**

Org Code: **600**
District Goal: **20-OCT-2001**

FDA Contacts: **M. DILLAHUNT (HFD-613) 301-827-5848 , Project Manager**
M. SMELA JR (HFD-625) 301-827-5848 , Team Leader

Overall Recommendation:

ACCEPTABLE on 29-AUG-2001 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: **2027158**
GENSIA SICOR PHARMACEUTICALS
19 HUGHES
IRVINE, CA 926181902

DMF No:
AADA No:

Profile: **SVS** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **29-AUG-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE
MANUFACTURER**

Establishment: _____

DMF No: _____
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **23-AUG-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: _____

**APPEARS THIS WAY
ON ORIGINAL**

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**

FOR FDA USE ONLY

(Title 21, Code of Federal Regulations, 314 & 601)

APPLICATION NUMBER
76-028

APPLICANT INFORMATION

NAME OF APPLICANT Gensia Sicor Pharmaceuticals, Inc.	DATE OF SUBMISSION June 27, 2002
TELEPHONE NO. (Include Area Code) (949) 455-4724	FACSIMILE (FAX) Number (Include Area Code) (949) 583-7351
APPLICANT ADDRESS (Number, Street, City, State, Country, Zip Code or Mail Code, and U.S. License number if previously issued): 19 Hughes Irvine, CA 92618-1902	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, Zip Code, telephone & FAX number) IF APPLICABLE N/A

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) N/A		
ESTABLISHED NAME (e.g., Proper name USP/USAN name) Vinorelbine Tartrate Injection	PROPRIETARY NAME (trade name) IF ANY ---	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) 3',4"-didehydro-4'-deoxy- C' -norvincal leukoblastine [R-(R*,R*)-2,3-dihydroxybutanedioate (1:2)(salt)].		CODE NAME (if any) N/A
DOSAGE FORM: Liquid	STRENGTHS: 10 mg/mL	ROUTE OF ADMINISTRATION: Intravenous

(PROPOSED) INDICATIONS (S) FOR USE:
Vinorelbine tartrate injection 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, vinorelbine tartrate is indicated as a single agent or in combination with cisplatin. In Stage III NSCLC, vinorelbine tartrate is indicated in combination with cisplatin.

APPLICATION INFORMATION

APPLICATION TYPE (check one)	<input type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)	<input checked="" type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
	<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)	

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE	<input type="checkbox"/> 505 (b) (1)	<input type="checkbox"/> 505 (b) (2)	<input type="checkbox"/> 507
------------------------------------------	--------------------------------------	--------------------------------------	------------------------------

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION	Name of Drug Navelbine® Injection	Holder of Approved Application Glaxo Wellcome
------------------------------------------------------------------------------------------------------	---------------------------------------------	---------------------------------------------------------

TYPE OF SUBMISSION (check one)	<input type="checkbox"/> ORIGINAL APPLICATION	<input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION	<input type="checkbox"/> RESUBMISSION
	<input type="checkbox"/> PRESUBMISSION	<input type="checkbox"/> ANNUAL REPORT	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT
	<input type="checkbox"/> EFFICACY SUPPLEMENT	<input type="checkbox"/> LABELING SUPPLEMENT	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT
			<input type="checkbox"/> SUPAC SUPPLEMENT
			<input type="checkbox"/> OTHER

REASON FOR SUBMISSION
Amendment – Response to Chemistry Deficiency Facsimile Dated May 7, 2002

PROPOSED MARKETING STATUS (check one)	<input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx)	<input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
---------------------------------------	---------------------------------------------------------------	---------------------------------------------------------

NUMBER OF VOLUMES SUBMITTED N/A	THIS APPLICATION IS	<input checked="" type="checkbox"/> PAPER	<input type="checkbox"/> PAPER AND ELECTRONIC	<input type="checkbox"/> ELECTRONIC
----------------------------------------	---------------------	-------------------------------------------	-----------------------------------------------	-------------------------------------

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

All functions described herein occur at the applicant address listed above and has been assigned the central facility number 2027158. This facility is ready for inspection at the time this application is submitted.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

DMF _____
DMF _____

RECEIVED
JUN 28 2002

This application contains the following items: (Check all that apply)

1. Index
2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
3. Summary (21 CFR 314.50 (c))
4. Chemistry section
A. Chemistry, Manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
B. Samples (21 CFR 314.50 (e) (1) , 21 CFR 601.2 (a)) (Submit only upon FDA's request)
C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
15. Establishment description (21 CFR Part 600, if applicable)
16. Debarment certification (FD&C Act 306 (k) (1))
17. Field copy certification (21 CFR 314.50 (k) (3))
18. User Fee Cover Sheet (Form FDA 3397)
X 19. OTHER (Specify) Amendment – Response to Chemistry Deficiency Facsimile Dated May 7, 2002

CERTIFICATION

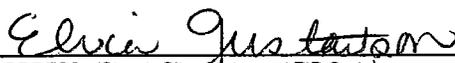
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but no limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulation on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Elvia Gustavson Director, Regulatory Affairs	DATE June 27, 2002
ADDRESS (Street, City, State, and ZIP Code) 19 Hughes, Irvine, CA 92618-1902	Telephone Number (949) 455-4724	

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHSS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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Smela Jr, Michael

From: Smela Jr, Michael
Sent: Monday, July 22, 2002 3:25 PM
To: Chen, Peter
Cc: Furnkranz, Kenneth J
Subject: 76028

PC...I am closing this. Pls add to AP Matrix. Pending are:

1. Labeling review of unsolicited amendment of 7/2/02.
2. EA consult (pages 5-7, 11-26) of 6/27/02 amendment.
3. MVP. Issued to DFS.

Michael J. Smela, Jr.
Team Leader, ANDA Review Branch 2
Division of Chemistry 1
Office of Generic Drugs
Voice 301-827-5775
Facsimile 301-594-0180

**APPEARS THIS WAY
ON ORIGINAL**

kranz, Kenneth J

Furnkranz, Kenneth J
Wednesday, July 17, 2002 10:54 AM
Greenberg, Harvey A
Smela Jr, Michael

Subject: Request for Categorical Exclusion from performing an EA for ANDA 76-028; Vinorelbine Tartrate Injection; Gensia Sicor

Harvey.

Gensia Sicor submitted a request for Categorical Exclusion from performing an Environmental Assessment for ANDA #76-028; Vinorelbine Tartrate Injection; Gensia Sicor. Based on the information submitted,

the country (which would not necessarily make them cultivated plants). Could you send the appropriate submission information over to Nancy Sager's group for consult (I have copied the appropriate information from the 6/27/02 ANDA Amendment (p. 5 and pp. 11-26)?)

Thanks,

Ken Furnkranz
7-5772
HFD-625
Rm E-231

76028

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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	REQUEST FOR CONSULTATION
--------------------------------------------------------------------------------------------------	--------------------------

TO (Division/Office) Nancy Sager HFD-357 CDR/OPS/CPS	FROM: Office of Generic Drugs(OGD)/RSB
------------------------------------------------------------	-------------------------------------------

DATE: July 24, 2002	IND NO.	ANANDA NO. 76-028	TYPE OF DOCUMENT Original Application	DATE OF DOCUMENT June 27, 2002
NAME OF DRUG Vinorelbine Tartrate Injection		PRIORITY CONSIDERATION Medium	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE September 24, 2002

NAME OF FIRM Gensia Sicor

REASON FOR REQUEST

- I. GENERAL
- | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE/ADDITION
<input type="checkbox"/> MEETING PLANNED BY _____ | <input type="checkbox"/> PRE NDA MEETING
<input type="checkbox"/> END OF PHASE II MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY/EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICPENY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input checked="" type="checkbox"/> OTHER (specify below) |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

II. BIOMETRICS

- | | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| STATISTICAL EVALUATION BRANCH | STATISTICAL APPLICATION BRANCH |
| <input type="checkbox"/> TYPE A OR B NDA REVIEW
<input type="checkbox"/> END OF PHASE II MEETING
<input type="checkbox"/> CONTROLLED STUDIES
<input type="checkbox"/> PROTOCOL REVIEW
<input type="checkbox"/> OTHER | <input type="checkbox"/> CHEMISTRY
<input type="checkbox"/> PHARMACOLOGY
<input type="checkbox"/> BIOPHARMACEUTICS
<input type="checkbox"/> OTHER |

III. BIOPHARMACEUTICS

- | | |
|------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> PROTOCOL- BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE IV STUDIES |
|------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|

IV. DRUG EXPERIENCE

- | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS(List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

V. SCIENTIFIC INVESTIGATIONS

- CLINICAL
 PRECLINICAL

COMMENTS
 Nancy, Gensia has amended their original application and the chemist is requesting a determination of the categorical exclusion, please attached
 Please return completed to review:
 Harvey Greenberg
 HFD-615

Categorical exclusion provided in July 24, 2002 amendment is accepted 8/2/02

SIGNATURE OF REQUESTER Harvey Greenberg	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
--------------------------------------------	-----------------------------------------------------------------------------------------------

SIGNATURE OF RECEIVER <i>TSI 8/2/02</i>	SIGNATURE OF DELIVERER
--------------------------------------------	------------------------

Peter

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Smela Jr, Michael

From: West, Robert L
Sent: Tuesday, August 20, 2002 8:38 AM
To: Chen, Peter
Cc: Smela Jr, Michael; Furnkranz, Kenneth J; Dillahunt, Michelle; Buehler, Gary J
Subject: FW: Peds Exclusivity Granted

Peter:

See below. Pediatric exclusivity was granted to this product which is currently appearing on the approvals matrix. Please revise the approval letter to a tentative approval letter referencing the pediatric exclusivity. We won't need FPL for the tentative approval.

Thanks,

Bob

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

From: Buehler, Gary J
Sent: Monday, August 19, 2002 5:11 PM
To: Rickman, William P; West, Robert L
Subject: FW: Peds Exclusivity Granted

Peter and Bob

I think that we have an application on the approvals matrix for this product.

Gary

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

From: Carmouze, Grace N
Sent: Monday, August 19, 2002 4:47 PM
To: Buehler, Gary J; Parise, Cecelia M; West, Robert L; Rickman, William P; Holovac, Mary Ann
Cc: Hixon, Dena R
Subject: Peds Exclusivity Granted

Pediatric Exclusivity was granted for Navelbine (vinorelbine) on August 15, 2002.

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: 301/827-7738

Chen, Peter

From: West, Robert L
Sent: Tuesday, August 20, 2002 8:38 AM
To: Chen, Peter
Cc: Smela Jr, Michael; Furnkranz, Kenneth J; Dillahunt, Michelle; Buehler, Gary J
Subject: FW: Peds Exclusivity Granted

Peter:

See below. Pediatric exclusivity was granted to this product which is currently appearing on the approvals matrix. Please revise the approval letter to a tentative approval letter referencing the pediatric exclusivity. We won't need FPL for the tentative approval.

Thanks,

Bob

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

From: Buehler, Gary J
Sent: Monday, August 19, 2002 5:11 PM
To: Rickman, William P; West, Robert L
Subject: FW: Peds Exclusivity Granted

Peter and Bob

I think that we have an application on the approvals matrix for this product.

ty

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

From: Carmouze, Grace N
Sent: Monday, August 19, 2002 4:47 PM
To: Buehler, Gary J; Parise, Cecelia M; West, Robert L; Rickman, William P; Holovac, Mary Ann
Cc: Hixon, Dena R
Subject: Peds Exclusivity Granted

Pediatric Exclusivity was granted for Navelbine (vinorelbine) on August 15, 2002.

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: 301/827-7738

RECORD OF TELEPHONE CONVERSATION
Office of Generic Drugs
Division of Chemistry 1
Team 2 HFD-625

FROM: Michael J. Smela, Jr. Team Leader DATE:1/13/03

NAME/TITLE OF INDIVIDUAL(S): Elvia Guftavson, Reg
Affairs
FIRM: Gensia Sicor
PRODUCT NAME: Vinorelbine Tartrate ANDA 76028
TEL #: 9494572808

Notes of Conversation: I advised that I was seeking a telephone amendment to address the recent inclusion of the DS in USP26. I asked that the following be addressed:

pH test changed to match USP
Color of Solution test changed to match USP
Total Impurities limit tightened to match USP
Clarity of Solution test added per USP

I asked the above changes be submitted in revised specification sheet.

I asked GSP to acknowledge that the USP methods are regulatory.

I asked GSP to also submit CoFA of representative lot showing compliance with new USP monograph.

I asked for fax copy of amendment to me at 3015940180.

Elvia agreed to all above.

SIGNATURE OF OGD REPRESENTATIVES: . . .

MS
1/13/03

Location of Electronic Copy: V:\firmsan\gensia\telecons\011303

**APPROVAL SUMMARY
 REVIEW OF PROFESSIONAL LABELING
 DIVISION OF LABELING AND PROGRAM SUPPORT
 LABELING REVIEW BRANCH**

ANDA Number	76-028
Date of Submission	January 9, 2003 and Nov. 13, 2002
Applicant	GensiaSicor
Drug Name	Vinorelbine Tartrate Injection,
Strength(s)	10 mg (base)/ mL, 1 mL and 5 mL vials

FPL Approval Summary

Container Labels		Submitted
10 mg/1 mL	10 mg/1 mL and 50 mg/5 mL	Jul. 20, 2001, Vol. A&B, 2.1 attachment 11.
Carton labeling		
10 mg and 50 mg	1 mL and 5 mL	Jul. 20, 2001, Vol. A&B, 2.1 attachment 11.
Package Insert Labeling	#Y36-000-21C Rev. Nov. 2002	Jan, 9, 2003 Vol. A 3.1 FPL

BASIS OF APPROVAL:

Patent Data For NDA 20-388

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4307100	Jul. 8, 2002 <i>Des! Jan 8, 2003</i>		Nor bis-indole compounds usable as medicaments	PIII	Same As

Exclusivity Data For NDA XX-XXX

Code/sup	Expiration	Description	Labeling impact
None	None	None	

Reference Listed Drug

RLD on the 356(h) form	Navelbine
NDA Number	20-388
RLD established name	Vinorelbine tartrate Injection
Firm	Glaxo Welcome
Currently approved PI	S-014
AP Date	Approved 11/5/02

Note. S-014 contains pediatric text that did not get the 3 year W/H exclusivity. This generic labeling is the same as the RLD.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N/A
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)			X
Labeling(continued)			
	Yes	No	N/A
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by..." statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			X
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			x
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	

Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST: none

FOR THE RECORD:

1. The reference listed drug for this product is Navelbine (vinorelbine tartrate injection, Glaxo, NDA 20388/S-014, Approved 11/5/02).
2. The **patent** for this product # is 4307100 expires July 8, 2002. There are no **exclusivity** issues. Firm certifies to the above information. Paragraph III in jacket
3. The product will be manufactured by Gensia Sicor Pharmaceutical Inc. . Corp address 19 Hughes, Irvin CA 92618-1902..
4. No outside firms are used.
5. Container/Closure: Amber glass tubing
6. Product line: _____ (1 mL fill)and 5 mL vials. 1 per carton
7. Components/Composition
RLD-vinorelbine tartrate and Water for injection. No preservatives.
Applicant : same
8. Storage/Dispensing Conditions:
RLD: Store the vials under refrigeration at 2 to 8C(36 to 46 F) in the carton.Protect from light. DO NOT FREEZE.
Applicant: same

Date of Review: 01/13/03

Date of Submission: Jan 9, 2003 and Nov. 13, 2002

cc: ANDA: 76-028
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
V:firmsam/Gensia/let&revs/76028ap2.Lab
Review

Handwritten:
S/S 1/13/02
S/S 1/27/2003

**APPEARS THIS WAY
ON ORIGINAL**

GensiaSicor™

PHARMACEUTICALS

A GensiaSicor Company

Gensia Sicor Pharmaceuticals
19 Hughes
Irvine, California 92618-1902

**REGULATORY AFFAIRS
FAX COVER SHEET**

DATE: January 14, 2003

TO: Mike Smela – Team Leader, Division of
Chemistry I, FDA, OGD

PHONE: (301) 827-5848
FAX: (301) 594-0180

FROM: Elvia O. Gustavson 
Director, Regulatory Affairs

PHONE: (949) 455-4724
FAX: (949) 583-7351

RE: Vinorelbine Tartrate Injection (ANDA No. 76-028)

Number of pages including cover sheet:

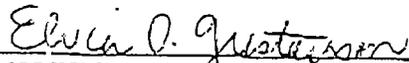
Message-

Pursuant to our telephone conversation, attached is our Telephone Amendment for Vinorelbine Tartrate Injection, ANDA 76-028.

The original is being sent today via FedEx (Tracking No. 7901 8519 4407).

**APPEARS THIS WAY
ON ORIGINAL**

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		Form Approved: OMB No. 0910-0398 Expiration Date: March 31, 2003 See OMB Statement on page 2.	
APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE <i>(Title 21, Code of Federal Regulations, Parts 314 & 601)</i>		FOR FDA USE ONLY	
		APPLICATION NUMBER 76-028	
APPLICANT INFORMATION			
NAME OF APPLICANT Gensia Sicor Pharmaceuticals, Inc.		DATE OF SUBMISSION 1/14/03	
TELEPHONE NO. (Includes Area Code) (949) 455-4724		FACSIMILE (FAX) Number (Include Area Code) 949-583-7351	
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 19 Hughes Irvine, CA 92618-1902		AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE N/A	
PRODUCT DESCRIPTION			
NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)			
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Vinorelbine Tartrate Injection		PROPRIETARY NAME (trade name) IF ANY N/A	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) 3',4"-didehydro-4'-deoxy- C' -norvincal leukoblastine [R-(R*,R*)-2,3-dihydroxybutanedioate (1:2)(salt)].		CODE NAME (if any) N/A	
DOSAGE FORM: Liquid	STRENGTHS: 10 mg/mL	ROUTE OF ADMINISTRATION: Intravenous	
(PROPOSED) INDICATION(S) FOR USE: Vinorelbine tartrate injection 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, vinorelbine tartrate is indicated as a single agent or in combination with cisplatin. In Stage III NSCLC, vinorelbine tartrate is indicated in combination with cisplatin.			
PRODUCT DESCRIPTION			
APPLICATION TYPE (check one) <input type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input checked="" type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)			
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)			
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION			
Name of Drug Navelbine® Injection		Holder of Approved Application Glaxo Wellcome	
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER			
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A			
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)			
REASON FOR SUBMISSION Telephone Amendment - Chemistry			
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)			
NUMBER OF VOLUMES SUBMITTED N/A THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC			
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.			
All functions described herein occur at the applicant address listed above and has been assigned the Central Facility Number 2027158. This facility is ready for inspection at the time this application is submitted.			
Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)			

This application contains the following items: (Check all that apply)		
	1. Index	
	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling	
	3. Summary (21 CFR 314.50 (c))	
	4. Chemistry section	
	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)	
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)	
	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)	
	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)	
	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))	
	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)	
	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)	
	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)	
	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)	
	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)	
	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))	
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))	
	15. Establishment description (21 CFR Part 600, if applicable)	
	16. Debarment certification (FD&C Act 306 (k)(1))	
	17. Field copy certification (21 CFR 314.50 (l)(3))	
	18. User Fee Cover Sheet (Form FDA 3397)	
	19. Financial Information (21 CFR Part 54)	
XX	20. OTHER (Specify) Telephone Amendment - Chemistry	
CERTIFICATION		
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:		
<ol style="list-style-type: none"> 1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820. 2. Biological establishment standards in 21 CFR Part 600. 3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809. 4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202. 5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12. 6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81. 7. Local, state and Federal environmental impact laws. 		
If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.		
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.		
Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.		
SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT		TYPED NAME AND TITLE
		Elvia O. Gustavson Director, Regulatory Affairs
		DATE: January 14, 2003
ADDRESS (Street, City, State, and ZIP Code)		Telephone Number
19 Hughes, Irvine, CA 92630		(949) 455-4724
Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:		
Department of Health and Human Services Food and Drug Administration DER, HFD-99 401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CBER, HFM-94 12420 Parklawn Dr., Room 3046 Rockville, MD 20852	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.



January 14, 2003

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: Vinorelbine Tartrate Injection
ANDA 76-028

TELEPHONE AMENDMENT

Dear Mr. Buehler:

Reference is made to Gensia Sicor's ANDA 76-028 for Vinorelbine Tartrate Injection, 10 mg/mL, which was submitted to the Agency on November 17, 2000. Reference is also made to the telephone conversation with Mr. Mike Smela on January 13, 2003 discussing revisions to the active pharmaceutical ingredient (raw material) specifications.

In accordance with the provisions of Section 314.96(a)(1) of the *Code of Federal Regulations, Title 21*, we hereby amend our application. The following information is included.

- Executed raw material testing specification and data sheet for raw material lot K2902553 which demonstrates conformance with USP 26 specifications for Vinorelbine Tartrate, USP
- Updated blank raw material testing specification and data sheet which demonstrates conformance with USP 26 specifications for Vinorelbine Tartrate, USP
- Acknowledgement that the USP will be considered the regulatory method in cases where the GSPI test methods differ from the USP method.

We trust that the information provided in this amendment is satisfactory for your review and approval. Should you have any additional questions regarding our application, please feel free to contact me at (949) 457-4724 or by facsimile at (949) 583-7351.

Sincerely,


Elvia O. Gustavson
Director, Regulatory Affairs

S:\Vinorelbine76028\Amend6\Amend6 Labeling.doc

cc: Mr. Alonza Cruse, District Director
FDA, Los Angeles District
19900 MacArthur Blvd., Suite 300, Irvine, CA 92612

Redacted 9

Page(s) of trade

secret and /or

confidential

commercial

information

RECORD OF TELEPHONE CONVERSATION
Office of Generic Drugs
Division of Chemistry 1
Team 2 HFD-625

FROM: Michael J. Smela, Jr. Team Leader DATE: 1/27/03
Kenneth J. Furnkranz, Review Chemist

NAME/TITLE OF INDIVIDUAL(S): Elvia Guftavson, Reg Affairs
FIRM: Gensia Sicor
PRODUCT NAME: Vinorelbine Tartrate ANDA 76028
TEL #: 9494572808

Notes of Conversation: We called as a follow-up to our Telecon dated 1/13/03 and the subsequent 1/14/03 ANDA Amendment regarding the new USP Monograph for Vinorelbine Tartrate in USP 26 (effective 1/1/03).

The firm provided information requested in the 1/13/01 telecon, however, the information was reviewed by this reviewer, and it was noted that G/S tested the Vinorelbine Tartrate by their in-house related substances method, and not by the USP method. As a result, it was not possible to tell whether the methods are comparable or whether the drug substance meets the USP monograph.

G/S was asked to submit a CoFA for the lot of Vinorelbine Tartrate drug substance (#K2902553) using the USP method for Related Substances. G/S was also asked to either show that the in-house method detects the impurities identified by the USP method, or withdraw the in-house method and agree to test their drug substance using the USP method.

SIGNATURE OF OGD REPRESENTATIVES

[Handwritten signature]
1/27/03

[Handwritten signature] 1/27/03

Location of Electronic Copy: V:\firmsan\gensia\telecons\012703

RECORD OF TELEPHONE CONVERSATION
Office of Generic Drugs
Division of Chemistry 1
Team 2 HFD-625

FROM: Kenneth J. Furnkranz, Review Chemist DATE:1/29/03

NAME/TITLE OF INDIVIDUAL(S):Sonia Hernandez, Reg Affairs
FIRM:Gensia Sicor
PRODUCT NAME:Vinorelbine Tartrate ANDA 76028
TEL #:9494572808

Notes of Conversation: Elvia Gustafson called on 1/28/03 and indicated that they contacted the USP about the Related Compound A Reference Standard, and was told that RC-A was not available, and may not be available for some time. As a result, they are not able to perform the USP Related Compounds test.

After discussing these developments with Mike Smela, I called Elvia Gustafson to inform her of our recommendations. She was not available, however, I spoke with Sonia Hernandez and informed her that she should do the following:

- Revise their Vinorelbine Tartrate drug substances tests and specifications to include both their in-house Related Substances method/specifications as well as the USP method/specifications for Related Substances.
- Commit to test using both methods at such time as the USP makes the Related Compound A Reference Standard available.
- Provide validation data, when the USP Related Compound A Reference Standard becomes available, to demonstrate that their in-house method can detect and quantitate the related substances identified and quantitated by the USP method.
- Supplement their application at such time as they wish to delete either the in-house method or the USP method (the USP method will still be the regulatory method).

Sonia indicated that she would provide a response to the ANDA and send it in as a Telephone Amendment.

SIGNATURE OF OGD REPRESENTATIVES: *JS*

Location of Electronic Copy: V:\firmsan\gensia\telecons\012903 *1/29/03*

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-028

CORRESPONDENCE

January 29, 2003

ORIG AMENDMENT

NAM

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

**RE: Vinorelbine Tartrate Injection
ANDA 76-028**

TELEPHONE AMENDMENT

Dear Mr. Buehler:

Reference is made to Gensia Sicor's ANDA 76-028 for Vinorelbine Tartrate Injection, 10 mg/mL, which was submitted to the Agency on November 17, 2000. Reference is also made to the telephone conversation today between Kenneth Furnkranz, CDER/FDA, and Ms. Sonia Hernandez, Gensia Sicor.

In accordance with the provisions of Section 314.96(a)(1) of the *Code of Federal Regulations, Title 21*, we hereby amend our application as requested.

Gensia Sicor will incorporate the USP method for related compounds into the raw material release specifications with the understanding that we cannot implement the use of the USP method until the USP Vinorelbine Related Compound A reference standard becomes available. The USP method is included as a release specification in addition to our in-house method, QCP-1327.

Gensia Sicor will run both methods when the USP Vinorelbine Related Compound A reference standard becomes available. Additionally, Gensia Sicor will evaluate our method, QCP-1327, to detect and quantitate Related Compound A and the _____ impurity, and determine equivalency between the methods. We will report any changes to our release test specifications in a supplemental application. The revised Raw Material Testing Specifications and Data Sheet is attached.

We trust that the information provided in this amendment is satisfactory for your review and approval. Should you have any additional questions regarding our application, please feel free to contact me at (949) 457-4724 or by facsimile at (949) 583-7351.

Sincerely,

Rosaline C. Lavine

for Elvia O. Gustavson
Director, Regulatory Affairs

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cc: Mr. Alonza Cruse, District Director
FDA, Los Angeles District
19900 MacArthur Blvd., Suite 300, Irvine, CA 92612

RECEIVED

JAN 30 2003

OGD / CDER

January 14, 2003

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

ORIGINAL
N/AM

**RE: Vinorelbine Tartrate Injection
ANDA 76-028**

TELEPHONE AMENDMENT

Dear Mr. Buehler:

Reference is made to Gensia Sicor's ANDA 76-028 for Vinorelbine Tartrate Injection, 10 mg/mL, which was submitted to the Agency on November 17, 2000. Reference is also made to the telephone conversation with Mr. Mike Smela on January 13, 2003 discussing revisions to the active pharmaceutical ingredient (raw material) specifications.

In accordance with the provisions of Section 314.96(a)(1) of the *Code of Federal Regulations, Title 21*, we hereby amend our application. The following information is included.

- Executed raw material testing specification and data sheet for raw material lot K2902553 which demonstrates conformance with USP 26 specifications for Vinorelbine Tartrate, USP
- Updated blank raw material testing specification and data sheet which demonstrates conformance with USP 26 specifications for Vinorelbine Tartrate, USP
- Acknowledgement that the USP will be considered the regulatory method in cases where the GSPI test methods differ from the USP method.

We trust that the information provided in this amendment is satisfactory for your review and approval. Should you have any additional questions regarding our application, please feel free to contact me at (949) 457-4724 or by facsimile at (949) 583-7351.

Sincerely,

Elvia O. Gustavson
Elvia O. Gustavson
Director, Regulatory Affairs

S:\Vinorelbine76028\Amends\Amend8 Labeling.doc

cc: Mr. Alonza Cruse, District Director
FDA, Los Angeles District
19900 MacArthur Blvd., Suite 300, Irvine, CA 92612

RECEIVED
JAN 15 2003
OGD / CDER

January 9, 2003

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT

N IAF

FPL

**RE: Vinorelbine Tartrate Injection
ANDA 76-028**

LABELING AMENDMENT

Dear Mr. Buehler:

Reference is made to Gensia Sicor's ANDA 76-028 for Vinorelbine Tartrate Injection, 10 mg/mL, which was submitted to the Agency on November 17, 2000. Reference is also made to amendment dated November 13, 2002.

In accordance with the provisions of Section 314.96(a)(1) of the *Code of Federal Regulations, Title 21*, we hereby amend our application to provide additional **labeling** revisions. The package insert was revised based on the changes to the reference listed drug, Navelbine®, posted on the FDA website on November 8, 2002.

Twelve (12) samples of the final printed package insert are provided in this amendment. Additionally, a side-by-side comparison of our proposed labeling with our previous submission with all differences annotated and explained is provided for your review.

We trust that the information provided in this amendment is satisfactory for your review and approval. Should you have any additional questions regarding our application, please feel free to contact me at (949) 457-4724 or by facsimile at (949) 583-7351.

Sincerely,

Elvia O. Gustavson

Elvia O. Gustavson
Director, Regulatory Affairs

S:\Vinorelbine76028\Amends\Amend10 Labeling.doc

cc: Mr. Alonza Cruse, District Director
FDA, Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

RECEIVED

JAN 10 2003

OGD / CDER

November 13, 2002

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT

N/AM

FPL

RE: Vinorelbine Tartrate Injection, 10 mg/mL
ANDA 76-028

MINOR AMENDMENT – FINAL APPROVAL REQUESTED

Dear Mr. Buehler:

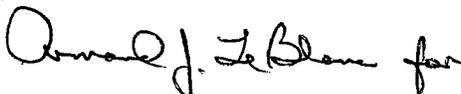
Reference is made to Gensia Sicor's ANDA 76-028 for Vinorelbine Tartrate Injection, 10 mg/mL, which was submitted to the Agency on November 17, 2000. Reference is also made to our amendment dated September 16, 2002. Further reference is made to the Agency's letter dated September 17, 2002.

In accordance with the tentative approval granted for this application, we are amending the application approximately 60 days prior to the date we believe we will be eligible for final approval, January 8, 2003.

In accordance with our commitment to change the "How Supplied" section of the package insert to reflect the total contents per vial and eliminate the column indicating the product size, included in this amendment is twelve (12) samples of final printed revised package insert labeling. Additionally, a side-by-side comparison of our revised labeling along with our previous labeling submission is provided for your review with all differences annotated and explained. No other changes in the conditions under which the product was tentatively approved have occurred.

We trust that the information provided in this amendment is satisfactory for your review and approval. Should you have any additional questions regarding our application, please feel free to contact me at (949) 457-4724 or by facsimile at (949) 583-7351.

Sincerely,



Elvia O. Gustavson
Director, Regulatory Affairs

S:\Vinorelbine76028\Amends\Amend9 final approval.doc
cc: Mr. Alonza Cruse, District Director
FDA, Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

RECEIVED

NOV 14 2002

OGD / CDER

11-25-02
ML



GlaxoSmithKline

October 9, 2002

Gary J. Buehler, Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
United States Food and Drug Administration
Metro Park North 2 (Room 286)
7500 Standish Place
Rockville MD 20855

GlaxoSmithKline

1250 South Collegeville Road
PO Box 5089
Collegeville, PA
19426-0989

Tel. 610 917 7000
Fax. 610 917 7707
www.gsk.com

NEW CORRESP

NO

Re: ANDA # 76-028, referencing NDA # 20-388
Navelbine® (vinorelbine tartrate) Injection

Dear Mr. Buehler:

Under the above-referenced approved New Drug Application, GlaxoSmithKline markets vinorelbine tartrate injection under the trade name Navelbine®. On September 17, 2002, your Office tentatively approved ANDA #76-028, submitted by Gensia Sicor Pharmaceuticals, proposing a generic copy of Navelbine (vinorelbine tartrate) Injection. Other ANDAs proposing generic copies of Navelbine Injection may also be pending in your Office.

The purpose of this letter is to confirm that your reviewers are aware that a USP monograph has been proposed for vinorelbine tartrate, the active ingredient in Navelbine Injection.. The proposed monograph was published in the Sept-Oct 2001 edition of *Pharmacopeial Forum*. A copy of the proposed monograph is attached for your convenience.

As you know, generic and innovator products alike must meet USP monograph standards for strength, quality, and purity to avoid being adulterated under Section 501(b) of the Federal Food, Drug, and Cosmetic Act (unless any discrepancies are plainly stated on their labels, which in the case of generic drugs would violate the Act's "same labeling" requirement). We believe that the proposed monograph reflects current process capability in the manufacture of vinorelbine tartrate and ensures appropriate quality and purity standards in the best interest of patients.

RECEIVED

OCT 11 2002

OGD / CDER

Gary J. Buehler
October 9, 2002
p. 2

We trust your reviewers will follow the progress of the USP monograph and as appropriate will take the USP standards into account in reviewing and monitoring ANDAs for generic vinorelbine tartrate products. Toward that end, we would be grateful if you would forward a copy of this letter to whomever may take part in the decision whether to progress ANDA #76-028 from tentative to final approval, and/or in the review of other ANDAs for generic vinorelbine tartrate products.

If we might be of assistance in furnishing any additional information that you or your staff may require, please feel free to call me at (610) 787-3725 after October 15, 2002.

Sincerely,



Anne-Margaret Martin,
Senior Director
Oncology Regulatory Affairs

enc.

cc w/o enc: Richard Pazdur, MD., Director, Division of Oncology Drug Products

**APPEARS THIS WAY
ON ORIGINAL**

HAF
a/foyle

September 16, 2002

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

NEW CORRESP

NC

**RE: Vinorelbine Tartrate Injection
ANDA 76-028**

TELEPHONE AMENDMENT

Dear Mr. Buehler:

Reference is made to Gensia Sicor's ANDA 76-028 for Vinorelbine Tartrate Injection, 10 mg/mL, which was submitted to the Agency on November 17, 2000. Reference is also made to my telephone conversation today with Ms. Angela Payne, FDA, OGD, DLPS, regarding the "How Supplied" section of the package insert.

In accordance with the provisions of Section 314.96(a)(1) of the *Code of Federal Regulations, Title 21*, we hereby amend our application. Gensia Sicor commits to change the "How Supplied" section of the package insert to reflect the total contents per vial and eliminate the column indicating the product size as follows.

NDC Number	Total Contents	Package
0703-4182-01	10 mg/1 mL	1 Single-Dose Vial per Carton
0703-4183-01	50 mg/5 mL	1 Single-Dose Vial per Carton

We commit to implement this change before introducing the product into commercial distribution.

We trust that the information provided in this amendment is satisfactory for your review and approval. Should you have any additional questions regarding our application, please feel free to contact me at (949) 457-4724 or by facsimile at (949) 583-7351.

Sincerely,

Elvia O. Gustavson

Elvia O. Gustavson
Director, Regulatory Affairs

S:\Winorelbine76028\Amends\Amend8 Labeling.doc

cc: Mr. Alonza Cruse, District Director
FDA, Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

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SEP 17 2002

OGD / CDER

August 27, 2002

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

NEW CORRESP

NC

**RE: Vinorelbine Tartrate Injection, 10 mg/mL
ANDA 76-028**

EXCLUSIVITY AMENDMENT

Dear Mr. Buehler:

Reference is made to Gensia Sicor's ANDA 76-028 for Vinorelbine Tartrate Injection, 10 mg/mL, which was submitted to the Agency on November 17, 2000. Reference is also made to the conversation between Mr. Peter Chen, Project Manager, OGD, FDA, and Ms. Elvia O. Gustavson of Gensia Sicor.

In accordance with the provisions of Section 314.96(a)(1) of the *Code of Federal Regulations, Title 21*, we hereby amend this application to provide the revised Exclusivity Statement as requested.

We trust that the information provided in this amendment is satisfactory for your review and approval. Should you have any additional questions regarding our application, please feel free to contact me at (949) 457-4724 or by facsimile at (949) 583-7351.

Sincerely,

Elvia O. Gustavson
Director, Regulatory Affairs

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cc: Mr. Alonza Cruse
District Director
FDA, Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

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AUG 28 2002

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GensiaSicor™

PHARMACEUTICALS

A sicor Company

July 24, 2002

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT

N/A

**RE: Vinorelbine Tartrate Injection, 10 mg/mL
ANDA 76-028**

**MINOR AMENDMENT
CHEMISTRY DEFICIENCIES**

Dear Mr. Buehler:

Reference is made to Gensia Sicor's ANDA 76-028 for Vinorelbine Tartrate Injection, 10 mg/mL, which was submitted to the Agency on November 17, 2000. Reference is also made to our amendment dated June 27, 2002. Further reference is made to the conversation between Ms. Nancy Sager of the Agency, and Ms. Elvia O. Gustavson of Gensia Sicor.

In accordance with the provisions of Section 314.96(a)(1) of the *Code of Federal Regulations, Title 21*, we hereby amend this application to provide the additional information requested. Specifically, a revised categorical exclusion from performing an Environmental Assessment, including the corrected value of the Maximum Theoretical Introduction Concentration (EIC) of Vinorelbine Tartrate into the Aquatic Environment are provided.

We trust that the information provided in this amendment is satisfactory for your review and approval. Should you have any additional questions regarding our application, please feel free to contact me at (949) 457-4724 or by facsimile at (949) 583-7351.

Sincerely,

Elvia O. Gustavson

Elvia O. Gustavson
Director, Regulatory Affairs

S:\Vinorelbine76028\Amends\Amend6.doc

cc: Mr. Alonza Cruse, District Director
FDA, Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

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JUL 25 2002

OGD / CDER

000003

July 2, 2002

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT

N/A

**RE: Vinorelbine Tartrate Injection, 10 mg/mL
ANDA 76-028**

LABELING AMENDMENT

Dear Mr. Buehler:

Reference is made to Gensia Sicor's ANDA 76-028 for Vinorelbine Tartrate Injection, 10 mg/mL, which was submitted to the Agency on November 17, 2000. Reference is also made to our amendment dated June 27, 2002. Further reference is made to the Agency's labeling website.

In accordance with the provisions of Section 314.96(a)(1) of the *Code of Federal Regulations, Title 21*, we hereby amend our application to revise the package insert labeling. Although we have not received a request from the Agency to revise the package insert, we have noted an updated version of Glaxo Wellcom's insert on the FDA website and have revised our package insert accordingly. Twelve (12) samples of final printed revised package insert are provided. Additionally, a side-by-side comparison of our revised labeling along with the innovator's labeling (Navelbine® (vinorelbine tartrate) Injection – Glaxo Wellcome Inc.; approved on October 2, 2001) is provided for your review with all differences annotated and explained.

We trust that the information provided in this amendment is satisfactory for your review and approval. Should you have any additional questions regarding our application, please feel free to contact me at (949) 457-4724 or by facsimile at (949) 583-7351.

Sincerely,

Elvia O. Gustavson

Elvia O. Gustavson
Director, Regulatory Affairs

RECEIVED

JUL 03 2002

OGD / CDER

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cc: Mr. Alonza Cruse, District Director
FDA, Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

June 27, 2002

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT

N/Am

**RE: Vinorelbine Tartrate Injection, 10 mg/mL
ANDA 76-028**

**MINOR AMENDMENT
CHEMISTRY DEFICIENCIES**

Dear Mr. Buehler:

Reference is made to Gensia Sicor's ANDA 76-028 for Vinorelbine Tartrate Injection, 10 mg/mL, which was submitted to the Agency on November 17, 2000. Reference is also made to our amendments dated July 20, 2001, August 21, 2001, and April 3, 2002. Further reference is made to the Agency's facsimile dated May 7, 2002.

In accordance with the provisions of Section 314.96(a)(1) of the *Code of Federal Regulations, Title 21*, we hereby amend this application to provide the additional **chemistry** information requested.

We trust that the information provided in this amendment is satisfactory for your review and approval. Should you have any additional questions regarding our application, please feel free to contact me at (949) 457-4724 or by facsimile at (949) 583-7351.

Sincerely,

Elvia O. Gustavson

Elvia O. Gustavson
Director, Regulatory Affairs

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cc: Mr. Alonza Cruse, District Director
FDA, Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

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JUN 28 2002
OGD / CDER

April 3, 2002

ORIG AMENDMENT
N/A.M.

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

**RE: Vinorelbine Tartrate Injection, 10 mg/mL
ANDA 76-028**

**MINOR AMENDMENT
CHEMISTRY DEFICIENCIES**

Dear Mr. Buehler:

Reference is made to Gensia Sicor's ANDA 76-028 for Vinorelbine Tartrate Injection, 10 mg/mL, which was submitted to the Agency on November 17, 2000. Reference is also made to our amendments dated July 20 and August 21, 2001. Further reference is made to the Agency's facsimile dated February 12, 2002.

In accordance with the provisions of Section 314.96(a)(1) of the *Code of Federal Regulations, Title 21*, we hereby amend this application to provide the additional **chemistry** information requested.

We trust that the information provided in this amendment is satisfactory for your review and approval. Should you have any additional questions regarding our application, please feel free to contact me at (949) 457-4724 or by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Dowe

for
Elvia O. Gustavson
Director, Regulatory Affairs

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cc: Mr. Alonza Cruse, District Director
FDA, Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

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APR 04 2002

OGD / CDER

*AW
4/5/02*

August 21, 2001

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT

N/AS

**RE: Vinorelbine Tartrate Injection, 10 mg/mL
ANDA 76-028**

AMENDMENT

Dear Mr. Buehler:

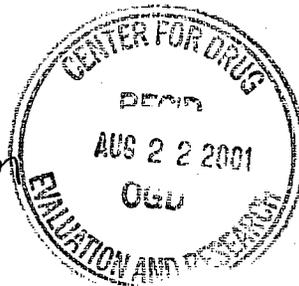
Reference is made to Gensia Sicor's ANDA 76-028 for Vinorelbine Tartrate Injection, 10 mg/mL, which was submitted to the Agency on November 17, 2000. Reference is also made to the Agency's facsimile dated August 21, 2001.

In accordance with the provisions of Section 314.96(a)(1) of the *Code of Federal Regulations, Title 21*, we hereby amend this application to provide the additional **microbiology** information requested.

We trust that the information provided in this amendment is satisfactory for your review and approval. Should you have any additional questions regarding our application, please feel free to contact me at (949) 457-4724 or by facsimile at (949) 583-7351.

Sincerely,

Elvia O. Gustavson
Elvia O. Gustavson
Director, Regulatory Affairs



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cc: Mr. Alonza Cruse
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

July 20, 2001

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

DR Label
ORIG AMENDMENT
Ac

**RE: Vinorelbine Tartrate Injection, 10 mg/mL
ANDA 76-028**

MAJOR AMENDMENT

Dear Mr. Buehler:

Reference is made to Gensia Sicor's ANDA 76-028 for Vinorelbine Tartrate Injection, 10 mg/mL, which was submitted to the Agency on November 17, 2000. Reference is also made to the Agency's facsimile dated May 10, 2001.

In accordance with the provisions of Section 314.96(a)(1) of the *Code of Federal Regulations, Title 21*, we hereby amend this application to provide the additional **chemistry and labeling** information requested.

We trust that the information provided in this amendment is satisfactory for your review and approval. Should you have any additional questions regarding our application, please feel free to contact me at (949) 457-4724 or by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Love

for Elvia O. Gustavson
Director, Regulatory Affairs

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cc: Mr. Alonza Cruse
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612



000003



NDA 20-388/S-012

Glaxo Wellcome Inc.
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

Attention: Marna Doucette
Product Director, Regulatory Affairs

Dear Ms. Doucette:

Please refer to your supplemental new drug application dated November 3, 2000, received November 6, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Navelbine (vinorelbine tartrate) Injection.

This "Changes Being Effected in 30 days" supplemental new drug application provides for addition of pancreatitis to the ADVERSE REACTIONS section of the label.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the November 3, 20000 final printed labeling. Accordingly, the supplemental application is approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, 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 the requirements for an approved NDA set forth under 21CFR 314.80 and 314.81.

NDA 20-388

Page 2

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

Sincerely,

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

Attachment: Labeling

**APPEARS THIS WAY
ON ORIGINAL**

ANDA 76-028

Gensia Sicor Pharmaceuticals, Inc.
Attention: Elvia Gustavson
19 Hughes
Irvine, California 92618-1902
|||||

DEC 13 2000

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Vinorelbine Tartrate Injection, 10 mg (base)/mL,
1 mL and 5 mL vials

DATE OF APPLICATION: November 17, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: November 20, 2000

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Michelle Dillahunt
Project Manager
(301) 827-5848

Sincerely yours,

for *ISI*
Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research