CENTER FOR DRUG EVALUATION AND RESEARCH

75-493

APPLICATION NUMBER:

APPROVAL LETTER

ANDA 75-493

SEP 1 1999

Gensia Sicor Pharmaceuticals, Inc.
Attention: Rosalie A. Lowe
17 Hughes
Irvine, CA 92618-1902

Dear Madam:

This is in reference to your abbreviated new drug application dated October 30, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Vincristine Sulfate Injection USP, 1 mg/mL, packaged in 1 mg/1 mL and 2 mg/2 mL vials, (Preservative-Free).

Reference is also made to your amendments dated December 8, 1998; and February 8, June 7 and August 10, 1999.

The reference listed drug (RLD) cited in your application is subject to a period of patent protection which expires on October 28, 2003 (U.S. Patent No. 4,619,935, the '935 patent). Your application contains a patent certification under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of this drug product will not infringe on the '935 patent. Section 505(j)(5)(B)(iii) of the Act provides that approval of your application shall be made effective immediately, unless an action is brought for infringement of the patent which is the subject of the certification before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(i) is received. You have notified FDA that Gensia Sicor Pharmaceuticals, Inc. has complied with the requirements of Section 505(j)(2)(B) of the Act and that no action for patent infringement was brought against Gensia Sicor Pharmaceuticals, Inc. within the statutory forty-five day period.

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 Vincristine Sulfate Injection USP, 1 mg/mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Oncovin® Injection, 1 mg/mL of Eli Lilly and Company).

Under 21 CFR 314.70, 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 FD-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 FD-2253 at the time of their initial use.

Sincerely yours,

D. L. Spoon 9/1/99

Douglas L. Spoon
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

75-493

APPLICATION NUMBER:

APPROVED DRAFT LABELING

Y36-511-411
Package Insert

$R_x only$

Gensia Sicor™ PHARMACEUTICALS

Vincristine Sulfate Injection, USP

Preservative Free Solution

WARNINGS

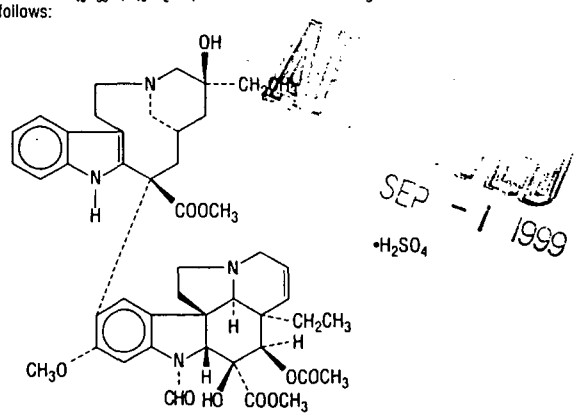
Caution—This preparation should be administered by individuals experienced in the administration of Vincristine Sulfate Injection, USP. It is extremely important that the intravenous needle or catheter be properly positioned before any vincristine is injected. Leakage into surrounding tissue during intravenous administration of Vincristine Sulfate Injection, USP may cause considerable irritation. If extravasation occurs, the injection should be discontinued immediately, and any remaining portion of the dose should then be introduced into another vein. Local injection of hyaluronidase and the application of moderate heat to the area of leakage help disperse the drug and are thought to minimize discomfort and the possibility of cellulitis.

FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY.

See **WARNINGS** *section for the treatment of patients given intrathecal Vincristine Sulfate Injection, USP.*

DESCRIPTION

Vincristine Sulfate Injection, USP is vincaleukoblastine, 22-oxo-, sulfate (1:1) (salt). It is the salt of an alkaloid obtained from a common flowering herb, the periwinkle plant (*Vinca rosea* Linn). Originally known as leurocristine, it has also been referred to as LCR and VCR. The molecular formula for vincristine sulfate is $C_{46}H_{56}N_4O_{10}•H_2SO_4$. It has a molecular weight of 923.06. The structural formula is as follows:



SEP - 1 1999

Vincristine sulfate is a white to off-white powder. It is soluble in methanol, freely soluble in water, but only slightly soluble in 95% ethanol. In 98% ethanol, vincristine sulfate has an ultraviolet spectrum with maxima at 221 nm (ε+47,000).

Each mL contains vincristine sulfate, 1 mg (1.08 µmol); mannitol, 100 mg; and water for injection, qs. Acetic acid and sodium acetate have been added for pH control. The pH of Vincristine Sulfate Injection, USP ranges from 3.5 to 5.5. This product is a sterile solution for cancer/oncolytic use.

CLINICAL PHARMACOLOGY

The mechanisms of action of vincristine sulfate remain under investigation. The mechanism of action of vincristine sulfate has been related to the inhibition of microtubule formation in the mitotic spindle, resulting in an arrest of dividing cells at the metaphase stage.

Central nervous system leukemia has been reported in patients undergoing otherwise successful therapy with vincristine sulfate. This suggests that vincristine sulfate does not penetrate well into the cerebrospinal fluid.

Pharmacokinetic studies in patients with cancer have shown a triphasic serum decay pattern following rapid intravenous injection. The initial, middle, and terminal half-lives are 5 minutes, 2.3 hours, and 85 hours respectively; however, the range of the terminal half-life in humans is from 19 to 155 hours. The liver is the major excretory organ in humans and animals; about 80% of an injected dose of vincristine sulfate appears in the feces and 10% to 20% can be found in the urine. Within 15 to 30 minutes after injection, over 90% of the drug is distributed from the blood into tissue, where it remains tightly, but not irreversibly bound.

Current principles of cancer chemotherapy involve the simultaneous use of several agents. Generally, each agent used has a unique toxicity and mechanism of action so that therapeutic enhancement occurs without additive toxicity. It is rarely possible to achieve equally good results with single-agent methods of treatment. Thus, vincristine sulfate is often chosen as part of polychemotherapy because of lack of significant bone-marrow suppression (at recommended doses) and of unique clinical toxicity (neuropathy). See **DOSAGE AND ADMINISTRATION** for possible increased toxicity when used in combination therapy.

INDICATIONS AND USAGE

Vincristine sulfate is indicated in acute leukemia.

Vincristine sulfate has also been shown to be useful in combination with other oncolytic agents in Hodgkin's disease, non-Hodgkin's malignant lymphomas (lymphocytic, mixed-cell, histiocytic, undifferentiated, nodular, and diffuse types), rhabdomyosarcoma, neuroblastoma, and Wilms' tumor.

CONTRAINDICATIONS

Patients with the demyelinating form of Charcot-Marie-Tooth syndrome should not be given vincristine sulfate. Careful attention should be given to those conditions listed under **WARNINGS** And **PRECAUTIONS**.

WARNINGS

This preparation is for intravenous use only. It should be administered by individuals experienced in the administration of vincristine sulfate injection. The intrathecal administration of vincristine sulfate usually results in death. Syringes containing this product should be labeled using the auxiliary sticker provided, to state "FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY".

Extemporaneously prepared syringes containing this product must be packaged in an overwrap which is labeled "DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION. FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY."

Treatment of patients following intrathecal administration of vincristine sulfate has included immediate removal of spinal fluid and flushing with Lactated Ringer's, as well as other solutions and has not prevented ascending paralysis and death. In one case, progressive paralysis in an adult was arrested by the following treatment **initiated immediately after the intrathecal injection:**

1. As much spinal fluid was removed as could be safely done through lumbar access.
2. The subarachnoid space was flushed with Lactated Ringer's solution infused continuously through a catheter in a cerebral lateral ventricle at the rate of 150 mL/h. The fluid was removed through a lumbar access.
3. As soon as fresh frozen plasma became available, the fresh frozen plasma, 25 mL, diluted in 1 L of Lactated Ringer's solution was infused through the cerebral ventricular catheter at the rate of 75 mL/h with removal through the lumbar access. The rate of infusion was adjusted to maintain a protein level in the spinal fluid of 150 mg/dL.
4. Glutamic acid, 10 g, was given intravenously over 24 hours followed by 500 mg 3 times daily by mouth for 1 month or until neurological dysfunction stabilized. The role of glutamic acid in this treatment is not certain and may not be essential.

Pregnancy Category D—Vincristine sulfate can cause fetal harm when administered to a pregnant woman. When pregnant mice and hamsters were given doses of vincristine sulfate that caused the resorption of 23% to 85% of fetuses, fetal malformations were produced in those that survived. Five monkeys were given single doses of vincristine sulfate between days 27 and 34 of their pregnancies; 3 of the fetuses were normal at term, and 2 viable fetuses had grossly evident malformations at term. In several animal species, vincristine sulfate can induce teratogenesis as well as embryo death at doses that are nontoxic to the pregnant animal. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy or if the patient becomes pregnant while receiving this drug, she should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

General—Acute uric acid nephropathy, which may occur after the administration of oncolytic agents, has also been reported with vincristine sulfate. In the presence of leukopenia or a complicating infection, administration of the next dose of vincristine sulfate warrants careful consideration.

If central nervous system leukemia is diagnosed, additional agents may be required because vincristine sulfate does not appear to cross the blood-brain barrier in adequate amounts.

Particular attention should be given to dosage and neurologic side effects if vincristine sulfate is administered to patients with preexisting neuromuscular disease and when other drugs with neurotoxic potential are also being used.

Acute shortness of breath and severe bronchospasm have been reported following the administration of vinca alkaloids. These reactions have been encountered most frequently when the vinca alkaloid was used in combination with mitomycin C and may require aggressive treatment, particularly when there is preexisting pulmonary dysfunction. The onset of these reactions may occur minutes to several hours after the vinca alkaloid is injected and may occur up to 2 weeks following the dose of mitomycin. Progressive dyspnea requiring chronic therapy may occur. Vincristine sulfate should not be readministered.

Care must be taken to avoid contamination of the eye with concentrations of vincristine sulfate used clinically. If accidental contamination occurs, severe irritation (or, if the drug was delivered under pressure, even corneal ulceration) may result. The eye should be washed immediately and thoroughly.

Laboratory Tests—Because dose-limiting clinical toxicity is manifested as neurotoxicity, clinical evaluation (eg, history, physical examination) is necessary to detect the need for dosage modification. Following administration of vincristine sulfate, some individuals may have a fall in the white-blood-cell count or platelet count, particularly when previous therapy or the disease itself has reduced bone-marrow function. Therefore, a complete blood count should be done before administration of each dose. Acute elevation of serum uric acid may also occur during induction of remission in acute leukemia; thus, such levels should be determined frequently during the first 3 to 4 weeks of treatment or appropriate measures taken to prevent uric acid nephropathy. The laboratory performing these tests should be consulted for its range of normal values.

Drug Interaction—The simultaneous oral or intravenous administration of phenytoin and antineoplastic chemotherapy combinations that included vincristine sulfate has been reported to reduce blood levels of the anticonvulsant and to increase seizure activity. Dosage adjustment should be based on serial blood level monitoring. The contribution of vincristine sulfate to this interaction is not certain. The interaction may result from reduced absorption of phenytoin and an increase in the rate of its metabolism and elimination.

Carcinogenesis, Mutagenesis, Impairment Of Fertility—Neither *in vivo* nor *in vitro* laboratory tests have conclusively demonstrated the mutagenicity of this product. Fertility following treatment with vincristine sulfate alone for malignant disease has not been studied in humans. Clinical reports of both male and female patients who received multiple-agent chemotherapy that included vincristine sulfate indicate that azoospermia and amenorrhea can occur in postpubertal patients. Recovery occurred many months after completion of chemotherapy in some but not all patients. When the same treatment is administered to prepubertal patients, permanent azoospermia and amenorrhea are much less likely.

Patients who received chemotherapy with vincristine sulfate in combination with anticancer drugs known to be carcinogenic have developed second malignancies. The contributing role of vincristine sulfate in this development has not been determined. No evidence of carcinogenicity was found following intraperitoneal administration of vincristine sulfate in rats and mice, although this study was limited.

Usage In Pregnancy—Pregnancy Category D. See **WARNINGS**.

Nursing Mothers—It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions due to vincristine sulfate in nursing infants, a decision should be made either to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use—See **DOSAGE AND ADMINISTRATION** section.

ADVERSE REACTIONS

Prior to the use of this drug, patients and/or their parents/guardian should be advised of the possibility of untoward symptoms.

In general, adverse reactions are reversible and are related to dosage. The most common adverse reaction is hair loss; the most troublesome adverse reactions are neuromuscular in origin.

When single, weekly doses of the drug are employed, the adverse reactions of leukopenia, neuritic pain, and constipation occur but are usually of short duration (ie, less than 7 days). When the dosage is reduced, these reactions may lessen or disappear. The severity of such reactions seems to increase when the calculated amount of drug is given in divided doses. Other adverse reactions, such as hair loss, sensory loss, paresthesia, difficulty in walking, slapping gait, loss of deep-tendon reflexes, and muscle wasting, may persist for at least as long as therapy is continued. Generalized sensorimotor dysfunction may become progressively more severe with continued treatment. Although most such symptoms usually disappear by about the sixth week after discontinuance of treatment, some neuromuscular difficulties may persist for prolonged periods in some patients. Regrowth of hair may occur while maintenance therapy continues.

The following adverse reactions have been reported:

Hypersensitivity—Rare cases of allergic-type reactions, such as anaphylaxis, rash, and edema, that are temporally related to vincristine therapy have been reported in patients receiving vincristine as a part of multidrug chemotherapy regimens.

Gastrointestinal—Constipation, abdominal cramps, weight loss, nausea, vomiting, oral ulceration, diarrhea, paralytic ileus, intestinal necrosis and/or perforation, and anorexia have occurred. Constipation may take the form of upper-colon impaction, and, on physical examination, the rectum may be empty. Colicky abdominal pain coupled with an empty rectum may mislead the physician. A flat film of the abdomen is useful in demonstrating this condition. All cases have responded to high enemas and laxatives. A routine prophylactic regimen against constipation is recommended for all patients receiving vincristine sulfate.

Paralytic ileus (which mimics the "surgical abdomen") may occur, particularly in young pediatric patients. The ileus will reverse itself with temporary discontinuance of vincristine sulfate and with symptomatic care.

Genitourinary—Polyuria, dysuria, and urinary retention due to bladder atony have occurred. Other drugs known to cause urinary retention (particularly in the elderly) should, if possible, be discontinued for the first few days following administration of vincristine sulfate.

Cardiovascular—Hypertension and hypotension have occurred. Chemotherapy combinations that have included vincristine sulfate, when given to patients previously treated with mediastinal radiation, have been associated with coronary artery disease and myocardial infarction. Causality has not been established.

Neurologic—Frequently, there is a sequence to the development of neuromuscular side effects. Initially, only sensory impairment and paresthesia may be encountered. With continued treatment, neuritic pain and, later, motor difficulties may occur. There have been no reports of any agent that can reverse the neuromuscular manifestations that may accompany therapy with vincristine sulfate.

Loss of deep-tendon reflexes, foot drop, ataxia, and paralysis have been reported with continued administration. Cranial nerve manifestations, such as isolated paresis and/or paralysis of muscles controlled by cranial motor nerves, may occur in the absence of motor impairment elsewhere; extraocular and laryngeal muscles are those most commonly involved. Jaw pain, pharyngeal pain, parotid gland pain, bone pain, back pain, limb pain, and myalgias have been reported; pain in these areas may be severe. Convulsions, frequently with hypertension, have been reported in a few patients receiving vincristine sulfate. Several instances of convulsions followed by coma have been reported in pediatric patients. Transient cortical blindness and optic atrophy with blindness have been reported.

Pulmonary—See **PRECAUTIONS.**

Endocrine—Rare occurrences of a syndrome attributable to inappropriate antidiuretic hormone secretion have been observed in patients treated with vincristine sulfate. This syndrome is characterized by high urinary sodium excretion in the presence of hyponatremia; renal or adrenal disease, hypotension, dehydration, azotemia, and clinical edema are absent. With fluid deprivation, improvement occurs in the hyponatremia and in the renal loss of sodium.

Hematologic—Vincristine sulfate does not appear to have any constant or significant effect on platelets or red blood cells. Serious bone-marrow depression is usually not a major dose-limiting event. However, anemia, leukopenia, and thrombocytopenia have been reported. Thrombocytopenia, if present when therapy with vincristine sulfate is begun, may actually improve before the appearance of marrow remission.

Skin—Alopecia and rash have been reported.

Other—Fever and headache have occurred.

OVERDOSAGE

Side effects following the use of vincristine sulfate are dose related. In pediatric patients under 13 years of age, death has occurred following doses of vincristine sulfate that were 10 times those recommended for therapy. Severe symptoms may occur in this patient group following dosages of 3 to 4 mg/m². Adults can be expected to experience severe symptoms after single doses of 3 mg/m² or more (see **ADVERSE REACTIONS**). Therefore, following administration of doses higher than those recommended, patients can be expected to experience exaggerated side effects. Supportive care should include the following: (1) prevention of side effects resulting from the syndrome of inappropriate antidiuretic hormone secretion (preventive treatment would include restriction of fluid intake and perhaps the administration of a diuretic affecting the function of Henle's loop and the distal tubule); (2) administration of anticonvulsants; (3) use of enemas or cathartics to prevent ileus (in some instances, decompression of the gastrointestinal tract may be necessary); (4) monitoring the cardiovascular system; and (5) determining daily blood counts for guidance in transfusion requirements.

Folinic acid has been observed to have a protective effect in normal mice that were administered lethal doses of vincristine sulfate (*Cancer Res* 1963; 23:1390). Isolated case reports suggest that folinic acid may be helpful in treating humans who have received an overdose of vincristine sulfate. It is suggested that 100 mg of folinic acid be administered intravenously every 3 hours for 24 hours and then every 6 hours for at least 48 hours. Theoretically (based on pharmacokinetic data), tissue levels of vincristine sulfate can be expected to remain significantly elevated for at least 72 hours. Treatment with folinic acid does not eliminate the need for the above-mentioned supportive measures.

Most of an intravenous dose of vincristine sulfate is excreted into the bile after rapid tissue binding (see **CLINICAL PHARMACOLOGY**). Because only very small amounts of the drug appear in dialysate, hemodialysis is not likely to be helpful in cases of overdosage. An increase in the severity of side effects may be experienced by patients with liver disease that is severe enough to decrease biliary excretion.

Enhanced fecal excretion of parenterally administered vincristine has been demonstrated in dogs pretreated with cholestyramine. There are no published clinical data on the use of cholestyramine as an antidote in humans.

There are no published clinical data on the consequences of oral ingestion of vincristine. Shc oral ingestion occur, the stomach should be evacuated. Evacuation should be followed by ι administration of activated charcoal and a cathartic.

DOSAGE AND ADMINISTRATION

This preparation is for intravenous use only (see **WARNINGS***).*

Neurotoxicity appears to be dose related. Extreme care must be used in calculating and administering the dose of vincristine sulfate, since overdosage may have a very serious or fatal outcome.

The concentration of vincristine contained in all vials of Vincristine Sulfate Injection, USP is 1 mg/mL. Do not add extra fluid to the vial prior to removal of the dose. Withdraw the solution of vincristine sulfate into an accurate dry syringe, measuring the dose carefully. Do not add extra fluid to the vial in an attempt to empty it completely.

Caution—It is extremely important that the intravenous needle or catheter be properly positioned before any vincristine sulfate injection, usp is injected. Leakage into surrounding tissue during intravenous administration of vincristine sulfate may cause considerable irritation. If extravasation occurs, the injection should be discontinued immediately, and any remaining portion of the dose should then be introduced into another vein. Local injection of hyaluronidase and the application of moderate heat to the area of leakage will help disperse the drug and may minimize discomfort and the possibility of cellulitis.

Vincristine sulfate must be administered via an intact, free-flowing intravenous needle or catheter. Care should be taken that there is no leakage or swelling occurring during administration (see boxed **WARNINGS**).

The solution may be injected either directly into a vein or into the tubing of a running intravenous infusion (see *Drug Interactions* below). Injection of vincristine sulfate should be accomplished within 1 minute.

The drug is administered intravenously *at weekly intervals.*

The usual dose of vincristine sulfate for pediatric patients is 2 mg/m². For pediatric patients weighing 10 kg or less, the starting dose should be 0.05 mg/kg, administered once a week. The usual dose of vincristine sulfate for adults is 1.4 mg/m². A 50% reduction in the dose of vincristine sulfate is recommended for patients having a direct serum bilirubin value above 3 mg/100 mL.

Vincristine sulfate should not be given to patients while they are receiving radiation therapy through ports that include the liver. When vincristine sulfate is used in combination with L-asparaginase, vincristine sulfate should be given 12 to 24 hours before administration of the enzyme in order to minimize toxicity; administering L-asparaginase before vincristine sulfate may reduce hepatic clearance of vincristine sulfate.

Drug Interactions—Vincristine sulfate should not be diluted in solutions that raise or lower the pH outside the range of 3.5 to 5.5. It should not be mixed with anything other than normal saline or glucose in water.

Whenever solution and container permit, parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Special Dispensing Information—WHEN DISPENSING VINCRISTINE IN OTHER THAN THE ORIGINAL CONTAINER, IT IS IMPERATIVE THAT IT BE PACKAGED IN THE PROVIDED OVERWRAP WHICH BEARS THE FOLLOWING STATEMENT: "DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION. FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY" (see **WARNINGS**). A syringe containing a specific dose must be labeled, using the auxiliary sticker provided, to state: "FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY."

HOW SUPPLIED

Vincristine Sulfate Injection, USP is preservative free and is supplied as follows:

NDC Number	Vincristine Sulfate Injection	Volume
0703-**4402-11**	1 mg/mL	1 mL
0703-**4412-11**	1 mg/mL	2 mL

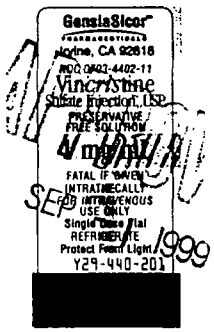
This product should be refrigerated. Protect from light and retain in carton until time of use.

REFERENCES

1. Recommendations for the Safe Handeling of Parenteral Antineoplastic Drugs, NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.
2. AMA Council Report, Guidelines for Handeling Parenteral Antineoplastics, JAMA, 1985; 253 (11): 1590-1592.
3. National Study Commission on Cytotixic Exposure—Recommendations for Handeling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
4. Clinical Oncological Society of Australia, Guidlines and Recommendations for Safe Handeling of Antineoplastic Agents. Med J Australia, 1983; 1: 426-428.
5. Jones RB, et al: Safe Handeling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. CA—A Cancer Journal for Clinicians, 1983; (Sept/Oct) 258-263.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handeling Cytotoxic and Hazardous Drugs. Am J Hosp Pharm, 1990; 47: 1033-1049.
7. OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs. Am J Hosp Pharm, 1986; 43: 1193-1204.

Issued: May 1999
Gensia Sicor Pharmauticals, Inc.
Irvine, CA 92618

Container Label - 1 mL vial
(Part No. Y29-440-201)



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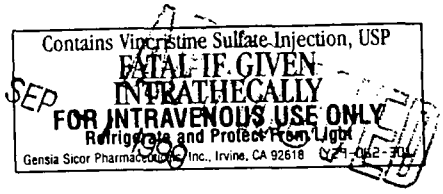

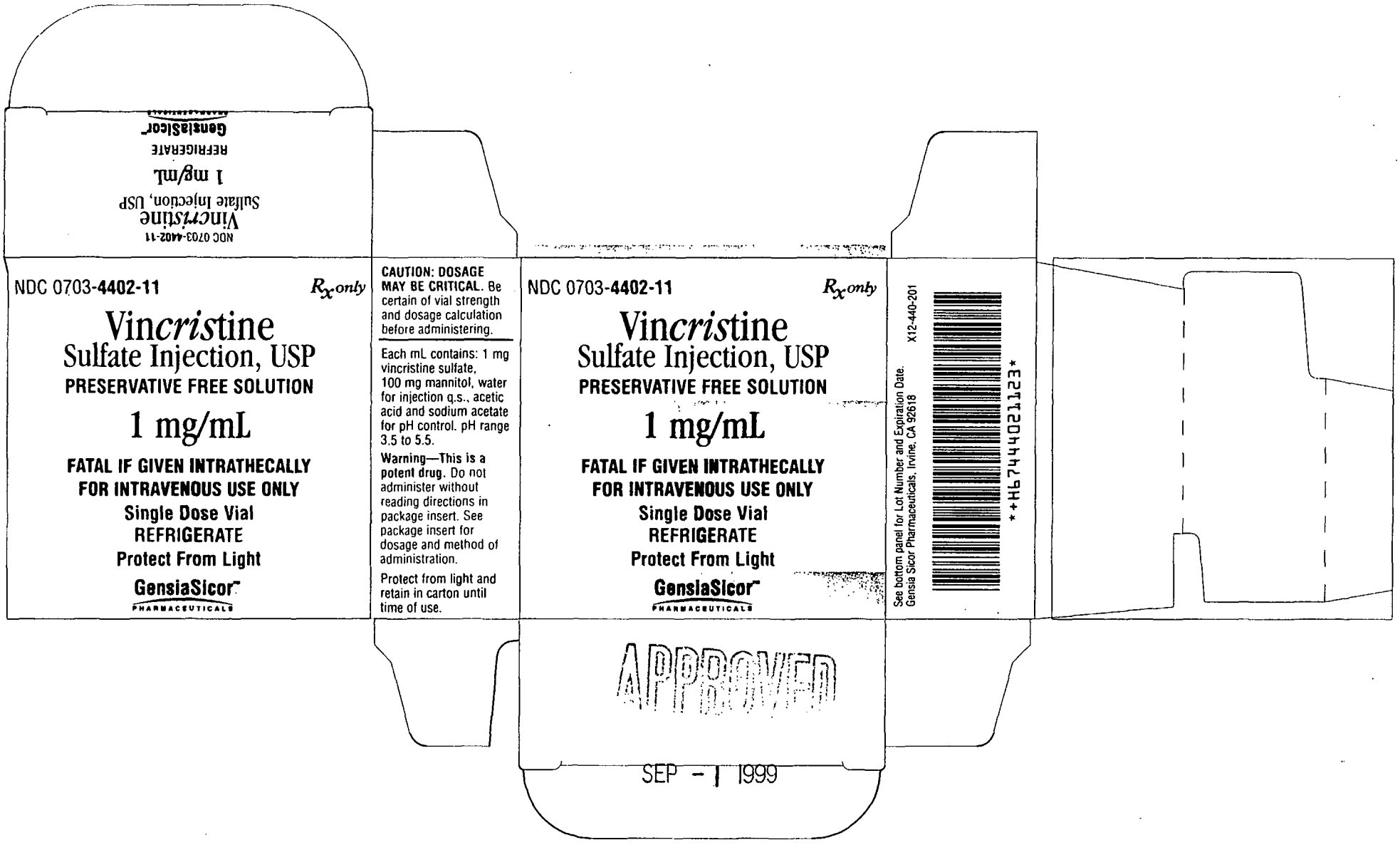
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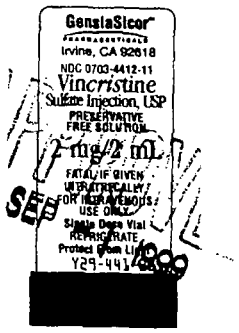
Vincristine
Sulfate Injection, USP
1 mg/mL
REFRIGERATE
GensiaSicor
NDC 0703-4402-11
Rx only
Vincristine
Sulfate Injection, USP
PRESERVATIVE FREE SOLUTION
1 mg/mL
FATAL IF GIVEN INTRATHECALLY
FOR INTRAVENOUS USE ONLY
Single Dose Vial
REFRIGERATE
Protect From Light
GensiaSicor
PHARMACEUTICALS
CAUTION: DOSAGE MAY BE CRITICAL. Be certain of vial strength and dosage calculation before administering.
Each mL contains: 1 mg vincristine sulfate, 100 mg mannitol, water for injection q.s., acetic acid and sodium acetate for pH control. pH range 3.5 to 5.5.
Warning—This is a potent drug. Do not administer without reading directions in package insert. See package insert for dosage and method of administration.
Protect from light and retain in carton until time of use.
NDC 0703-4402-11
Rx only
Vincristine
Sulfate Injection, USP
PRESERVATIVE FREE SOLUTION
1 mg/mL
FATAL IF GIVEN INTRATHECALLY
FOR INTRAVENOUS USE ONLY
Single Dose Vial
REFRIGERATE
Protect From Light
GensiaSicor
PHARMACEUTICALS
See bottom panel for Lot Number and Expiration Date.
Gensia Sicor Pharmaceuticals, Irvine, CA 92618
X12-440-201
+H67440211 23
APPROVED
SEP - 1 1999

Container Label - 1 mL vial
(Part No. Y29-440-201)

Container Label - 2 mL vial
(Part No. Y29-441-201)



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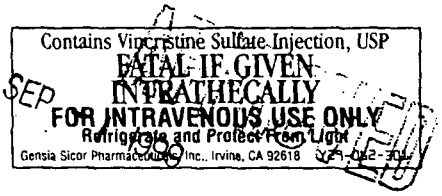

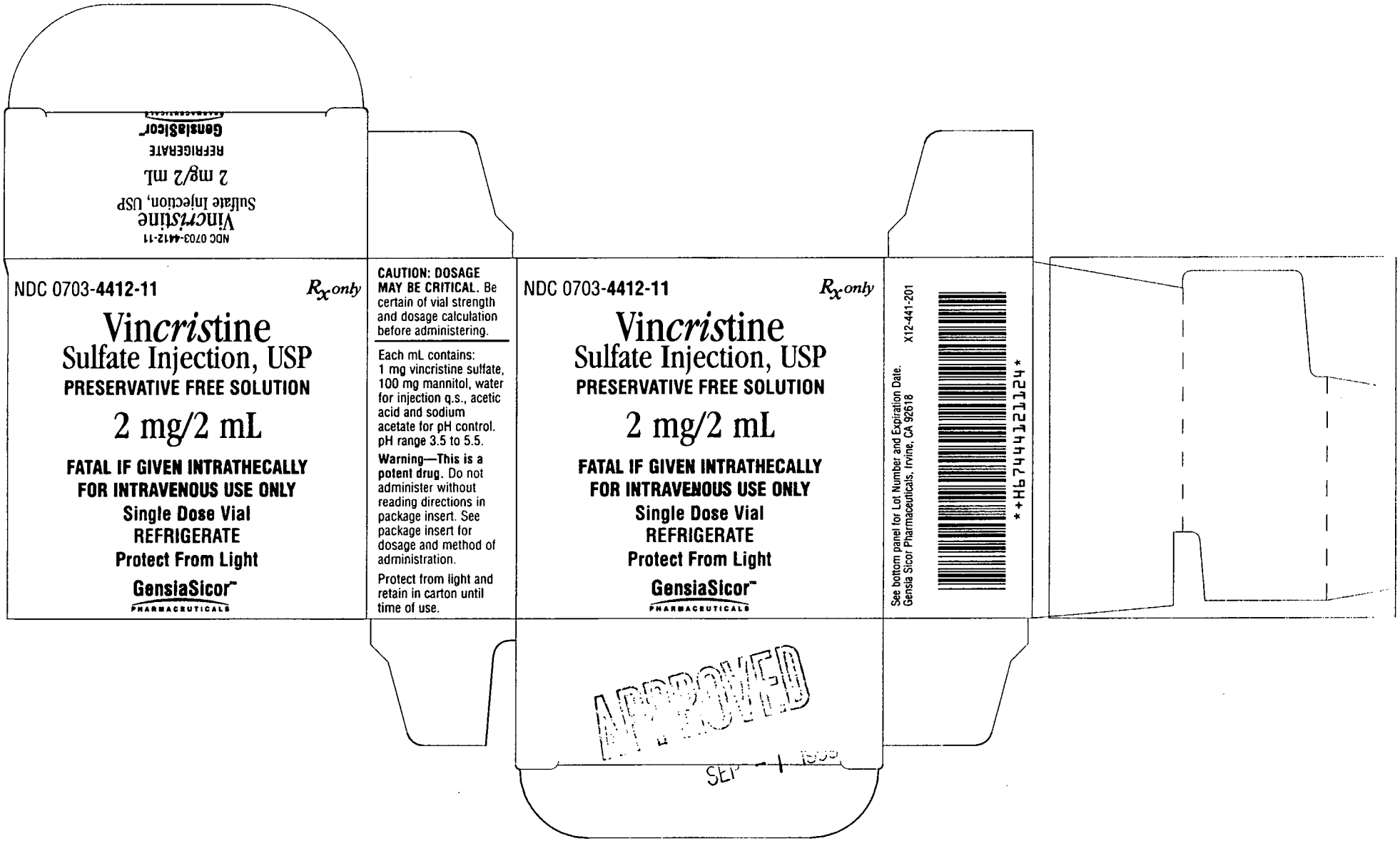
NDC 0703-4412-11
Vincristine
Sulfate Injection, USP
2 mg/2 mL
REFRIGERATE
GensiaSicor
PHARMACEUTICALS
NDC 0703-4412-11
Rx only
Vincristine
Sulfate Injection, USP
PRESERVATIVE FREE SOLUTION
2 mg/2 mL
FATAL IF GIVEN INTRATHECALLY
FOR INTRAVENOUS USE ONLY
Single Dose Vial
REFRIGERATE
Protect From Light
GensiaSicor
PHARMACEUTICALS
CAUTION: DOSAGE MAY BE CRITICAL. Be certain of vial strength and dosage calculation before administering.
Each mL contains:
1 mg vincristine sulfate, 100 mg mannitol, water for injection q.s., acetic acid and sodium acetate for pH control. pH range 3.5 to 5.5.
Warning—This is a potent drug. Do not administer without reading directions in package insert. See package insert for dosage and method of administration.
Protect from light and retain in carton until time of use.
NDC 0703-4412-11
Rx only
Vincristine
Sulfate Injection, USP
PRESERVATIVE FREE SOLUTION
2 mg/2 mL
FATAL IF GIVEN INTRATHECALLY
FOR INTRAVENOUS USE ONLY
Single Dose Vial
REFRIGERATE
Protect From Light
GensiaSicor
PHARMACEUTICALS
See bottom panel for Lot Number and Expiration Date.
Gensia Sicor Pharmaceuticals, Irvine, CA 92618
X12-441-201
+H67441211124
APPROVED
SEP - 1 1995

GensiaSicor™ PHARMACEUTICALS

Contains Vincristine Sulfate Injection, USP

DO NOT REMOVE COVERING UNTIL THE MOMENT OF INJECTION.

FATAL IF GIVEN INTRATHECALLY.

SEP - 1 1995

FOR INTRAVENOUS USE ONLY.

Refrigerate and Protect From Light

Gensia Sicor Pharmaceuticals, Inc., Irvine, CA 92618

Y29-062-401

CENTER FOR DRUG EVALUATION AND RESEARCH

75-493

APPLICATION NUMBER:

CHEMISTRY REVIEW(S)

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO.:** No. 3

2. **ANDA #:** 75-493

3. **NAME AND ADDRESS OF APPLICANT:**
Rosalie A. Lowe
Associate Director, Regulatory Affairs
Gensia Sicor Pharmaceuticals, Inc.
17 Hughes
Irvine, CA 92715

4. **LEGAL BASIS FOR ANDA SUBMISSION:**
21 CFR 314.92

5. **SUPPLEMENTS:** N/A

6. **PROPRIETARY NAME:** N/A

7. **NONPROPRIETARY NAME:** Vincristine Sulfate Injection USP, 1 mg/mL

8. **SUPPLEMENT(S) PROVIDE(S) FOR:**
N/A

9. **AMENDMENTS AND OTHER DATES:**
Gensia:

10/30/98	Original ANDA Submission(received 11/02/98.
12/08/98	New Correspondence: Patent Amendment certification
2/8/99	New Correspondence; Return receipt documentation from Eli Lilly.
5/26/99	Facsimile Amendment
6/7/99	Original New Correspondence
8/10/99	Minor Amendment (response to N/A Minor FAX of 7/23/99)

FDA:

11/20/98	Acknowledgment letter
1/7/99	Bio Review; No questions at this time.
12/4/98	Labeling review completed (N/A).
4/12/99	EER Submitted
5/4/99	N/A Facsimile Amendment (Chemistry Review #1)
6/8/99	Labeling Review Satisfactory
7/23/99	N/A Minor Amendment (Chemistry Review #2)

10. **PHARMACOLOGICAL CATEGORY:**
Treatment of acute leukemia and, in combination with other oncolytic agents, in Hodgkins disease, non-Hodgkins malignant lymphomas, rhabdomycosarcoma, neuroblastoma, and Wilms' tumor.

11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**:
Innovator: Oncovin®, Eli Lilly & Co., Vincristine Sulfate Injection USP, 1 mg/mL, glass vials.

Gensia's 356h contains 4 DMFs.

13. **DOSAGE FORM**: Injection

14. **POTENCY**: 1 mg/mL; 1 and 2 mL vials.

15. **CHEMICAL NAME AND STRUCTURE**:
Vincaleukoblastine 22-oxo-, sulfate (1:1)(salt)

16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS**:
EER has been submitted to OC on November 2, 1998. Goal date is October 2, 1999. EER Update requested 4/12/99. Acceptable 8/13/99.
Labeling is satisfactory as per T. Watkins/J.Grace on 6/8/99.
Method Validation is not necessary.
Bioequivalence Review is satisfactory (no further questions were at this time).
Microbiological review is satisfactory (refer to the review dated 6/21/99.
The drug product differs from the innovator product, in that it is preservative-free, and is packaged in plastic vials.

18. CONCLUSIONS AND RECOMMENDATIONS: Approve.

19. **REVIEWER**: Kenneth J. Furnkranz
DATE COMPLETED: 08/20/99

Page(s) 11

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

Chem Rev 3
8/20/99

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO.:** No. 2

2. **ANDA #:** 75-493

3. **NAME AND ADDRESS OF APPLICANT:**
Rosalie A. Lowe
Associate Director, Regulatory Affairs
Gensia Sicor Pharmaceuticals, Inc.
17 Hughes
Irvine, CA 92715

4. **LEGAL BASIS FOR ANDA SUBMISSION:**
21 CFR 314.92

5. **SUPPLEMENTS:** N/A

6. **PROPRIETARY NAME:** N/A

7. **NONPROPRIETARY NAME:** Vincristine Sulfate Injection USP, 1 mg/mL

8. **SUPPLEMENT(S) PROVIDE(S) FOR:**
N/A

9. **AMENDMENTS AND OTHER DATES:**
Gensia:

10/30/98	Original ANDA Submission(received 11/02/98.
12/08/98	New Correspondence: Patent Amendment certification
2/8/99	New Correspondence; Return receipt documentation from Eli Lilly.
5/26/99	Facsimile Amendment
6/7/99	Original New Correspondence

FDA:

11/20/98	Acknowledgment letter
1/7/99	Bio Review; No questions at this time.
12/4/98	Labeling review completed (N/A).
4/12/99	EER Submitted
6/8/99	Labeling Review Satisfactory

10. **PHARMACOLOGICAL CATEGORY:**
Treatment of acute leukemia and, in combination with other oncolytic agents, in Hodgkins disease, non-Hodgkins malignant lymphomas, rhabdomycosarcoma, neuroblastoma, and Wilms' tumor.

11. **Rx or OTC:** Rx

12. **RELATED IND/NDA/DMF(s):**
Innovator: Oncovin®, Eli Lilly & Co., Vincristine Sulfate Injection USP, 1 mg/mL, glass vials.

Gensia's 356h contains 4 DMFs.

13. **DOSAGE FORM:** Injection

14. **POTENCY:** 1 mg/mL; 1 and 2 mL vials.

15. **CHEMICAL NAME AND STRUCTURE:**
Vincaleukoblastine 22-oxo-, sulfate (1:1)(salt)

16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:**
EER has been submitted to OC on November 2, 1998. Goal date is October 2, 1999. EER Update requested 4/12/99. Results are pending.
Labeling is satisfactory as per T. Watkins/J.Grace on 6/8/99.
Method Validation is not necessary. There is a USP monograph for the Vincristine Sulfate drug substance and Injection drug product.
Bioequivalence Review is satisfactory (no further questions were at this time).
Microbiological review is satisfactory (refer to the review dated 6/21/99.
The drug product differs from the innovator product, in that it is preservative-free, and is packaged in plastic vials.

18. CONCLUSIONS AND RECOMMENDATIONS: Not Approvable (Minor Amendment). USP issue is outside control of applicant.

19. **REVIEWER:** Kenneth J. Furnkranz
DATE COMPLETED: 06/30/99

Page(s) 11

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clem Rev 2

6/30/99

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO.:** No. 1

2. **ANDA #:** 75-493

3. **NAME AND ADDRESS OF APPLICANT:**
Rosalie A. Lowe
Associate Director, Regulatory Affairs
Gensia Sicor Pharmaceuticals, Inc.
17 Hughes
Irvine, CA 92715

4. **LEGAL BASIS FOR ANDA SUBMISSION:**
21 CFR 314.92

6. **PROPRIETARY NAME:**
Oncovin®

7. **NONPROPRIETARY NAME:** Vincristine Sulfate Injection USP, 1 mg/mL

8. **SUPPLEMENT(S) PROVIDE(S) FOR:**
N/A

9. **AMENDMENTS AND OTHER DATES:**

Gensia:

10/30/98	Original ANDA Submission(received 11/02/98.
12/08/98	New Correspondence: Patent Amendment certification
2/8/99	New Correspondence; Return receipt documentation from Eli Lilly.

FDA:

11/20/98	Acknowledgment letter
1/7/99	Bio Review; No questions at this time.
(12/4/98)	Labeling review completed.

10. **PHARMACOLOGICAL CATEGORY:**
Treatment of acute leukemia and, in combination with other oncolytic agents, in Hodgkins disease, non-Hodgkins malignant lymphomas, rhabdomycosarcoma, neuroblastoma, and Wilms' tumor.

11. **Rx or OTC:** Rx

12. **RELATED IND/NDA/DMF(s):**
Innovator: Oncovin®, Eli Lilly & Co., Vincristine Sulfate Injection USP, 1 mg/mL, glass vials.
Gensia's 356h contains 3 DMFs.

13. **DOSAGE FORM**: Injection

14. **POTENCY**: 1 mg/mL; 1 and 2 mL vials.

15. **CHEMICAL NAME AND STRUCTURE**:
Vincaleukoblastine 22-oxo-, sulfate (1:1)(salt)

16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS**:
EER has been submitted to OC on November 2, 1998. Goal date is October 2, 1999. Results are pending.
A labeling review was performed and deficiencies have been noted.
There is a USP monograph for the Vincristine Sulfate drug substance and Injection drug product. Validation of the methods is not necessary. Gensia Sicor has developed a stability-indicating method for determining the assay and impurities in the drug product, however, the USP method will be the regulatory method.
An initial Bio review has been performed, and no further questions were asked at the time.
Microbiological review is not completed at this time. CMC deficiencies will be listed in item 38.
The drug product differs from the innovator product, in that it is preservative-free, and is packaged in plastic vials.

18. CONCLUSIONS AND RECOMMENDATIONS: Not Approvable (Facsimile Amendment).

19. **REVIEWER**: Kenneth J. Furnkranz

DATE COMPLETED: 04/09/99

Page(s) 17

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Chem Rev 1
4/9/99

CENTER FOR DRUG EVALUATION AND RESEARCH

75-493

APPLICATION NUMBER:

MICROBIOLOGY REVIEW

OFFICE OF GENERIC DRUGS, HFD-620

Microbiology Review #1

June 17, 1999

A. 1. **ANDA 75-493**

APPLICANT Gensia Sicor Pharmaceuticals, Inc
17 Hughes
Irvine California 92718-1902

2. PRODUCT NAMES: Vincristine Sulfate Injection USP

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 1 mg/mL, 1 mL and 2 mL Fill in Single Dose 3 mL Polypropylene Vials, Intravenous, Preservative-Free

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Oncolytic/Chemotherapeutic Agent

B. 1. DATE OF INITIAL SUBMISSION: October 30, 1998
Subject of this Review (Received November 2, 1998)

2. DATE OF AMENDMENT: None

3. RELATED DOCUMENTS: None

4. ASSIGNED FOR REVIEW: 6/15/99

C. REMARKS: The subject drug product is filled in Room Filling Line at the Irvine California pharmaceutical facility.

D. CONCLUSIONS: The submission is recommended for approval on the basis of sterility assurance. Specific comments regarding the aseptic filling process are provided in "E. Review Notes".

Andrea S. High, Ph. D. 6/18/99

cc:

crorev\75-493

6/21/99

Page(s) 8

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Micro Rev. 1

6/18/99

CENTER FOR DRUG EVALUATION AND RESEARCH

75-493

APPLICATION NUMBER:

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 75-493

FIRM: GensiaSicor Pharmaceuticals, Inc.

DOSAGE FORM: Injection

STRENGTHS: 1 mg/mL, 1 and 2mL (single dose vials)

DRUG: Vincristine Sulfate Injection

CGMP STATEMENT/EIR UPDATED STATUS: EER status for all facilities listed in Section # 33 of the Chemistry Review #3 is acceptable on 8/13/99.

BIOEQUIVALENCE STATUS: Acceptable. Bioequivalence sign-off occurred on 1/11/99.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): Methods Validation is not required for the drug product.

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 a plastic vial. Acceptable.

LABELING: FPL - acceptable per review completed by T. Watkins/J. Grace on 6/8/99.

STERILIZATION VALIDATION (IF APPLICABLE): Product is filled. Validation of the process was found acceptable as per A. High/M. Fanning on 6-18-99/6-21-99.

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?): Gensia Sicor manufactured a pilot plant scale batch of (Batch #XP8E202 and XP8E202F1) on 5/20/98. Based on the pilot batch, Gensia Sicor's maximum production batch size will be . Gensia Sicor has submitted a blank master batch production record for a batch of a 1 mg/mL strength bulk solution batch and the filling records for the 1 mL and 2 mL drug product.

The Vincristine Sulfate drug substance is manufactured by The DMF was last reviewed on June 30, 1999 as a result of a DMF Update, and was found adequate. No new information has been submitted since this last review (COMIS checked 8/25/99).

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 100 Liters. The exhibit batch was 10 Liters.

cc:

Enc

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **ANDA 75493/000**
Priority:
Org Code: **600**
Stamp: **02-NOV-1998** Regulatory Due:
Action Goal:
District Goal: **02-OCT-1999**
Applicant: **GENSIA SICOR PHARMS**
17 HUGHES
IRVINE, CA 926181902
Brand Name:
Established Name: **VINCRISTINE SULFATE**
Generic Name:
Dosage Form: **INJ (INJECTION)**
Strength: **1 MG/ML**

FDA Contacts: **D. HUIE** **(HFD-615)** **301-827-5862 , Project Manager**
M. SMELA JR **(HFD-625)** **301-827-5848 , Team Leader**

Overall Recommendation:

Establishment
GENSIA INC
19 HUGHES
IRVINE, CA 926181902
DMF No:
AADA No:

Profile: **SVS** OAI Status: **NONE**
Last Milestone: **ASSIGNED INSPECTION TO IB**
Milestone Date: **23-DEC-1998**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment:
DMF
AADA No:
IND
3E

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **09-DEC-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Vincristine Sulfate Injection, USP
1 mg/ml vial
ANDA #75-493
Reviewer: Carol Y. Kim
v:\new\firmsam\Gensia\ltrs&rev\"75493w.o98"

Gensia Sicor Pharmaceuticals, Inc.
Irvine, CA
Submission Date:
October 30, 1998

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, Vincristine Sulfate Injection, 1 mg/ml, single dose vial. The reference listed product is Oncovin[R] (Vincristine Sulfate Injection, USP) Injection, 1 mg/ml vial, by Eli Lilly and Company. Gensia's Vincristine Sulfate Injection is a ready-to-use product solution. The proposed product is a single-use injection which differs from the reference product by the absence of the preservatives, methylparaben and propylparaben.

2. The Vincristine Sulfate Injection is an antimicrotuble antineoplastic agent indicated in acute leukemia. It has also been used in combination with other oncolytic agents in Hodgkin's disease, non-Hodgkin's malignant lymphomas, rhabdomyosarcoma, neuroblastoma, and Wilms' tumor.

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:

Ingredient	Test product (each ml)	Eli Lilly's Onvovin[R] (each ml)
Vincristine Sulfate, USP	1 mg	1 mg
Mannitol,	100 mg	100 mg
Glacial Acetic Acid,	adjust pH	adjust pH
Water for Injection,	QS 1ml	QS 1ml

III. Comments

1. The test product, Vincristine Sulfate Injection, USP, 1 mg/ml, contains active ingredient in the same concentration and dosage form as the reference product, Oncovin[R] (Vincristine Sulfate, USP) Injection, 1 mg/ml.

2. The absence of .1 in test product is in accordance with 21 CFR 314.94 (1) (9) (iii), which allows for change in preservative provided that the change does not affect the safety of the proposed drug product. Pharmacia-Upjohn currently markets a generic formulation of Vincristine Sulfate Injection, USP, 1 mg/ml, which is preservative free, under the trade name Vincasar[R] (ANDA 71426, DBE Review dated 8/3/86).

3. 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 Pharmaceuticals, Inc. on its drug product, Vincristine Sulfate Injection,USP, 1 mg/ml vial, 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, Vincristine Sulfate Injection,USP, 1 mg/ml vial, bioequivalent to the reference product, Oncovin[R] (Vincristine Sulfate,USP) Injection, 1 mg/ml vial, manufactured by Eli Lilly and Company.

The firm should be informed of the recommendation.

Carol Y. Kim, Pharm.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BY BDAVIT brw 1/8/99
FT INITIALLED BY BDAVIT Barbara M Davit Date: 1/9/99

Concur: Dale P. Conner Date: 1/11/99
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : November 5, 1998

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615) 11/5/98

SUBJECT: Examination of the bioequivalence waiver submitted with an ANDA for Vincristine Sulfate Injection USP, 1 mg/ml to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to USC 355(4)(B)(iv).

Gensia Sicor Pharmaceuticals, Inc. has submitted ANDA 75-493 for Vincristine Sulfate Injection USP,1 mg/ml. The ANDA contains a certification pursuant to 21 USC 355(j)(2)(A)(vii)(iv) stating that a patent expiring October 28, 2003 will not be infringed by the manufacture or sale of the proposed product. In order to accept an ANDA for filing that contains such a patent certification, the Agency must formally make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence Waiver is complete, and could establish that the product is bioequivalent.

Please evaluate whether the bioequivalence waiver submitted by Gensia Sicor on October 30, 1998 for its Vincristine Sulfate Injection USP, 1 mg,ml product satisfies the statutory requirements of "completeness" so that the ANDA may be filed and that a period of six months of market exclusivity can be granted to the applicant who submitted the first substantially complete ANDA under 21 USC 355(j)(4)(B)(iv).

The issue raised in the current situation revolves around whether the waiver can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

75-493
Gensia Sicor
Vincristine Sulfate Injection USP, 1 mg/ml

DIVISION OF BIOEQUIVALENCE:

__✓__ Waiver meets statutory requirements 11/9/98

_____ Waiver does **NOT** meet statutory requirements

Reason:

11/17/98

Dale P. Conner
~~Acting~~ Director, Division of Bioequivalence

11/17/98
Date

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **ANDA 75493/000**
Priority:
Org Code: **600**
Stamp: **02-NOV-1998** Regulatory Due:
Action Goal:
District Goal: **02-OCT-1999**
Applicant: **GENSIA SICOR PHARMS**
17 HUGHES
IRVINE, CA 926181902
Brand Name:
Established Name: **VINCRISTINE SULFATE**
Generic Name:
Dosage Form: **INJ (INJECTION)**
Strength: **1 MG/ML**

FDA Contacts: **D. HUIE** **(HFD-615)** **301-827-5862 , Project Manager**
M. SMELA JR **(HFD-625)** **301-827-5848 , Team Leader**

Overall Recommendation:

Establishment:
GENSIA INC
19 HUGHES
IRVINE, CA 926181902
DMF No:
AADA No:

Profile: **SVS** OAI Status: **NONE**
Last Milestone: **ASSIGNED INSPECTION TO IB**
Milestone Date: **23-DEC-1998**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment
DMF No:
AADA No:
IND

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **09-DEC-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

A 2.1

Bags?

~~TENTATIVE~~ APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-493 **Date of Submission: May 26, 1999**

Applicant's Name: GensiaSicor Pharmaceuticals

Established Name: Vincristine Sulfate Injection USP, 1 mg/mL

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: (1 mL and 2 mL) Satisfactory as of May 26, 1999 submission.

Carton Labeling: (1 x 1 mL and 1 x 2 mL) Satisfactory as of May 26, 1999 submission.

Warning Label: Satisfactory as of May 26, 1999 submission.

Polymer Bag: Satisfactory as of May 26, 1999 submission. (wording to be directly imprinted ~~on~~ on Bag) per Rosalie Dow on 6/7/1999
Professional Package Insert Labeling: Satisfactory as of May 26, 1999 submission.

Revisions needed post-approval:

BASIS OF APPROVAL:
Was this approval based upon a petition? No

What is the RLD on the 356(h) form: ONCOVIN®

NDA Number: 14-103/S-051
NDA Drug Name: Vincristine Sulfate Injection USP
NDA Firm: Lilly

Date of Approval of NDA Insert and supplement #: Dec. 16, 1992
Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.
Basis of Approval for the Carton Labeling: Side-by-side comparison with innovator carton labeling in jacket.

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		
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 ½ 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:

FOR THE RECORD:

1. The reference listed drug for this product is ONCOVIN®(Lilly; NDA#14-103/S-051; Approved December 16, 1992; Revised February 6, 1992).

2. This is a USP item. USP has the following storage and labeling requirements.

   Storage: Preserve in light-resistant, glass containers in a refrigerator.

   Labeling: The labels states "FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY." Where labeled as containing more that 2 mg, it must also be labeled as a *Pharmacy bulk package*. The labeling directs that the be dispensed only in containers enclosed in overwrap labeled as directed below. When packaged in a *Pharmacy bulk package*, it is exempt under (1) Injections, that the closure be penetrated only one time after constitution with a suitable sterile transfer device or dispensing set, when it contains a suitable substance or mixture of substances to prevent the growth of microorganisms.

   When dispensed, the container or syringe(holding the individual dose prepared for administration to the patient)must be enclosed in an overwrap bearing the statement "DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION. FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY."

3. There is one patent in effect for this product.

   4619935 Expires October 28, 2003.

   The applicant has file and paragraph IV certification. See Vol. 1.1, page 13.

4. The product is manufactured by Gensia Sicor Pharmaceuticals, Inc., 17 Hughes, Irvine, CA 92618-1902. See Vol. 1.1, page 126.

5. No outside firms are utilized. See Vol. 1.1, page 130.

6. Container/Closure:

Vials:
Resin:
Fabricator: 3 mL capacity vial 13 mm finish

Stopper: 13 mm

Overseal: 13 mm Aluminum with plastic flip-off cap.

See Vol. 1.1, page 383.

7. Finished Product

white to off-white powder. Soluble in methanol, freely soluble in water, but only slightly soluble in 95% ethanol.

Vol. 1.1, page 36.

8. Product line

1 mg/mL preservative free 1 mL and 2 mL.

See Vol. 1.1, page 37.

9. Components/Composition

Innovator:
Active: Vincristine Sulfate 1 mg/mL
Inactive: mannitol 100 mg/mL

water for injection q.s.
acetic acid pH control
sodium acetate pH control

Applicant:
Active: Vincristine Sulfate 1 mg/mL
Inactive: mannitol 100 mg/mL
glacial acetic acid to adjust pH
sodium acetate(anhydrous) to adjust pH
water for injection q.s.

See Vol. 1.1, page 49.

10. Storage/Dispensing

NDA: This product should be refrigerated.

ANDA: This product should be refrigerated. Protect from light and retain in carton until time of use.

See Vol. 1.1, page 25.

Date of Review: June 3, 1999
Date of Submission: May 26, 1999

Reviewer: J. Watts Date: 6/3/99

Team Leader: John D'Isa Date: 6/8/1999

CC:

L

Concur:
Charlie Clapis

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

ANDA Number: 75493 **Date of Submission: October 30, 1998**

Applicant's Name: GensiaSicor Pharmaceuticals

Established Name: Vincristine Sulfate Injection USP, 1 mg/mL

Labeling Deficiencies:

1. GENERAL COMMENTS:

   Please note that certain items appear in red on the labels and labeling for the reference listed drug. For your convenience we have enclosed a color copy of the reference listed drug's container and carton labeling. Please revise your container labels and carton labeling to be in accord.

2. CONTAINER (1 mL and 2 mL)

   See GENERAL COMMENTS-

   Revise "Refrigerate" to appear in red print.

3. CARTON (1 x 1 mL and 1 x 2 mL)

   See GENERAL COMMENTS-

   a. Revise "WARNING FATAL..." to appear in **BOLD**, red print.

   b. Revise "WARNING-This is a potent..." to appear in red.

   c. Revise "CAUTION: DOSAGE MAY..." to appear in red and relocate it to a more conspicuous position on the carton.

4. WARNING LABEL

   Satisfactory in draft.

5. POLYMER BAG

Satisfactory in draft.

6. INSERT

a. TITLE

i. We encourage the inclusion of "℞ only" in this section.

b. DESCRIPTION

i. Revise "empirical" to read "molecular" in the third sentence of the first paragraph of this section.

ii. Revise the molecular weight to read "923.06" rather than "923.04".

iii. Include the following to appear as sentence two of paragraph two of this section.

In 98% ethanol, vincristine sulfate has an ultraviolet spectrum with maxima at 221 nm (ε+47,000).

c. CLINICAL PHARMACOLOGY

Revise the third sentence of paragraph three to the end of this paragraph to read as follows:

...animals; about 80% of an injected dose of vincristine sulfate appears in the feces and 10% to 20% can be found in the urine. Within 15 to 30 minutes after injection, over 90% of the drug is distributed from the blood into tissue, where it remains tightly, but not irreversibly bound.

d. PRECAUTIONS (Drug Interactions)

Delete the second paragraph of this subsection.

e. ADVERSE REACTIONS(Neurologic)

i. Delete the following from sentence two of paragraph two of this subsection:

...including potentially life-threatening bilateral vocal cord paralysis...

ii. Delete sentence seven through the end of paragraph two of this subsection.

f. DOSAGE AND ADMINISTRATION

i. Relocate paragraph three of this section to appear as the last paragraph of this section.

ii. Revise "Incompatibilities" to read "Interactions" in sentence one of paragraph seven of this section.

iii. Delete "1.5-" from sentence one of paragraph nine of this section.

iv. Drug Incompatibilities

Revise this subsection title to read "Drug Interactions".

g. REFERENCES

Delete references 1 through 21. Renumber the remaining references (22-28) to be references 1 through 7 and revise the insert text to be in accord.

Please revise your container labels and carton, warning label, polymer bag, and insert labeling, as instructed above, and submit 12 copies of final printed container labels, along with 12 copies each of final printed carton, warning label, polymer bag, and insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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 your last submission with all differences annotated and explained.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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: (1 mL and 2 mL)

Carton Labeling: (1 x 1 mL and 1 x 2 mL)

Warning Label:

Polymer Bag:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes No

What is the RLD on the 356(h) form: ONCOVIN®

NDA Number: 14-103/S-051

NDA Drug Name: Vincristine Sulfate Injection USP

NDA Firm: Lilly

Date of Approval of NDA Insert and supplement #: December 16, 1992/S-051
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: Side-by-side comparison with innovator labels in jacket.
Basis of Approval for the Carton Labeling: Side-by-side comparison with innovator carton labeling in jacket.

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		
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 ½ 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:

FOR THE RECORD:

1. The reference listed drug for this product is ONCOVIN®(Lilly; NDA#14-103/S-051; Approved December 16, 1992; Revised February 6, 1992).

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   Storage: Preserve in light-resistant, glass containers in a refrigerator.

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   When dispensed, the container or syringe(holding the individual dose prepared for administration to the patient)must be enclosed in an overwrap bearing the statement "DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION. FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY."

3. There is one patent in effect for this product.

   4619935 Expires October 28, 2003.

   The applicant has file and paragraph IV certification. See Vol. 1.1, page 13.

4. The product is manufactured by Gensia Sicor Pharmaceuticals, Inc., 17 Hughes, Irvine, CA 92618-1902. See Vol. 1.1, page 126.

5. No outside firms are utilized. See Vol. 1.1, page 130.

6. Container/Closure:

Vials:
Resin:
Fabricator: 3 mL capacity vial 13 mm finish

Stopper: 13 mm

Overseal: 13 mm Aluminum with plastic flip-off cap.

See Vol. 1.1, page 383.

7. Finished Product

white to off-white powder. Soluble in methanol, freely soluble in water, but only slightly soluble in 95% ethanol.

Vol. 1.1, page 36.

8. Product line

1 mg/mL preservative free 1 mL and 2 mL.

See Vol. 1.1, page 37.

9. Components/Composition

Innovator:
Active: Vincristine Sulfate 1 mg/mL
Inactive: mannitol 100 mg/mL
water for injection q.s.
acetic acid pH control
sodium acetate pH control

Applicant:
Active: Vincristine Sulfate 1 mg/mL
Inactive: mannitol 100 mg/mL
glacial acetic acid to adjust pH
sodium acetate(anhydrous) to adjust pH
water for injection q.s.

See Vol. 1.1, page 49.

10. Storage/Dispensing

NDA: This product should be refrigerated.

ANDA: This product should be refrigerated. Protect from light and retain in carton until time of use.

See Vol. 1.1, page 25.

Date of Review: December 4, 1998
Date of Submission: October 30, 1998

Reviewer: J. Nath Date: 2/4/99

Team Leader: John D. Graham Date: 2/10/99

cc:

CENTER FOR DRUG EVALUATION AND RESEARCH

75-493

APPLICATION NUMBER:

CORRESPONDENCE

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 75-493 APPLICANT: Gensia Sicor Pharmaceuticals, Inc.

DRUG PRODUCT: Vincristine Sulfate Injection USP 1mg/mL; 1 and 2 mL vials

A. Deficiencies: There are no deficiencies at this time.

cc:

8/30/99

8/30/99

GensiaSicor™
PHARMACEUTICALS
A GensiaSicor Company

August 10, 1999

Mr. Douglas Sporn
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

NDA ORIG AMENDMENT
N/Am

RE: Vincristine Sulfate Injection
1 mg/mL
ANDA 75-493

MINOR AMENDMENT

Dear Mr. Sporn:

Reference is made to Gensia Sicor's ANDA 75-493 for Vincristine Sulfate Injection, 1 mg/mL, which was submitted to the Agency on October 30, 1998. Reference is also made to the Agency's facsimile dated July 23, 1999. In accordance with the provisions of Section 314.96(a)(3) of the *Code of Federal Regulations, Title 21*, we hereby amend our application to provide the additional information requested by the Agency.

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) 457-2808 or Mr. Dwain Allen, Regulatory Affairs Project Specialist, at (949) 457-2861. We can also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

H:\DATA\IRG\Vin75493\Amends\Amend3.doc

cc: Mr. Thomas Savage
Acting District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Boulevard, Suite 300
Irvine, CA 92715

N 8-13-99

GensiaSicor™
PHARMACEUTICALS
A GensiaSicor Company

June 7, 1999

Mr. Douglas Sporn
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: Vincristine Sulfate Injection
ANDA 75-493

GENERAL CORRESPONDENCE

Dear Mr. Sporn:

Reference is made to Gensia Sicor's ANDA 75-493 for Vincristine Sulfate Injection, 1 mg/mL, which was submitted to the Agency on October 30, 1998. Reference is also made to today's teleconference with Ms. Teresa Watkins, Labeling Reviewer, OGD, in which she requested clarification as to how the text would be applied to the polymer overwrap bag. I informed Ms. Watkins that the text would be imprinted directly onto the polymer overwrap bag. An adhesive label would not be used to label this component.

We trust that the information provided in this general correspondence is satisfactory. Should you have any additional questions regarding our application, please feel free to contact me at (949) 457-2808 or Mr. Dwain Allen, Regulatory Affairs Project Specialist, at (949) 457-2861. We can also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

H:\DATA\IRG\Vin75493\CORRESPD\6-7-99 Gen Corrspd.doc

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Boulevard, Suite 300
Irvine, CA 92715

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUN 0 8 1999
OGD

JUL 23 1999

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 75-493 APPLICANT: Gensia Sicor Pharmaceuticals, Inc.

DRUG PRODUCT: Vincristine Sulfate Injection USP 1mg/mL; 1 and 2 mL vials

The deficiencies presented below represent MINOR deficiencies:

A. Deficiencies:

1. The Vincristine Sulfate Injection drug product is proposed in plastic vials. Please contact the USP and obtain a letter of intent from them to change the monograph to allow for a plastic container as the current monograph does not.

2. We recommend that either a sterility test, or, preferably, a container closure integrity test be performed on upright and inverted vials at yearly intervals during the stability study to assess the integrity of the container/closure barrier.

   It is still unclear whether Gensia Sicor is doing any container/closure integrity testing other than that performed on vials in the inverted configuration at the end of the stability study (refer to Attachment #5 pp. 41-46 of the 5/26/99 ANDA Amendment). This is in conflict with the Stability Testing Schedule (which indicates that container/closure integrity testing is performed at each station in the inverted position only [see p. 26 of the 5/26/99 ANDA Amendment]).

3. The stability specifications established for Individual Related Compounds in the drug product appears high and should be substantiated by demonstrating that the innovator's marketed drug product (Oncovin®, Eli Lilly & Co.) have comparable levels of Related Compounds. The RLD product should be tested within expiry as received from commercial sources.

4. The target fill volume for the 1 mL and 2 mL vial significant exceeds the recommended overfill in USP <1151>. Please justify.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide any additional stability data accrued to date in the long term stability studies.

2. The CGMP status of the firms referenced in the ANDA will be evaluated by our Office of Compliance. Firms referenced in this ANDA must be in compliance with Current Good Manufacturing Practices at the time of approval.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 75-493 APPLICANT: Gensia Sicor Pharmaceuticals, Inc.

DRUG PRODUCT: Vincristine Sulfate Injection USP 1mg/mL; 1 and 2 mL vials

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4. The target fill volume for the 1 mL and 2 mL vial significant exceeds the recommended overfill in USP <1151>. Please justify.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide any additional stability data accrued to date in the long term stability studies.

2. The CGMP status of the firms referenced in the ANDA will be evaluated by our Office of Compliance. Firms referenced in this ANDA must be in compliance with Current Good Manufacturing Practices at the time of approval.

Sincerely yours,

9/14/99

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

GensiaSicor™
PHARMACEUTICALS
A GensiaSicor Company

FPL
ORIG AMENDMENT
FA

May 26, 1999

Mr. Douglas Sporn
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: Vincristine Sulfate Injection
1 mg/mL
ANDA 75-493

FACSIMILE AMENDMENT

Dear Mr. Sporn:

Reference is made to Gensia Sicor's ANDA 75-493 for Vincristine Sulfate Injection, 1 mg/mL, which was submitted to the Agency on October 30, 1998. Reference is also made to the Agency's facsimile dated May 4, 1999. Further reference is made to the teleconferences of May 10, 1999 with Ms. Teresa Watkins, Labeling Reviewer, OGD, and, also of May 12, 1999, with Mr. Ken Furnkrantz, Chemistry Reviewer, OGD.

In accordance with the provisions of Section 314.96(a)(3) of the *Code of Federal Regulations, Title 21*, we hereby amend our application to provide the additional information requested by the Agency.

In addition to our response to the deficiency letter, we wish to revise our proposed release and stability specifications for [redacted] ased upon an assessment of our stability lot and an evaluation of the ΔE value for a clear or colorless solution, we propose to increase the [redacted] specification from [redacted] The revised specification represents the upper limit of ΔE for solutions described as "clear, colorless solution." A copy of the revised **Finished Product Specifications and Data Sheet** is presented in **Attachment 1.**

Gensia Sicor Pharmaceuticals, Inc. • 19 Hughes • Irvine CA • 92618-1902 • USA
Phone (949) 455-4700, (800) 729-9991 • Fax (949) 855-8210 • http://www.gensiasicor.com

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) 457-2808 or Mr. Dwain Allen, Regulatory Affairs Project Specialist, at (949) 457-2861. We can also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

H:\DATA\IRG\Vin75493\Amends\Amend3.doc

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Boulevard, Suite 300
Irvine, CA 92715

MAY 4 1999

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 75-493 APPLICANT: Gensia Sicor Pharmaceuticals, Inc.

DRUG PRODUCT: Vincristine Sulfate Injection USP 1mg/mL; 1 and 2 mL vials

The deficiencies presented below represent FACSIMILE deficiencies.

A. Deficiencies:

1. Testing performed as per the Finished Product and Stability report (pp. 200412 and 200423 are not consistent with the stability testing table presented on page 200396.

   a. Test stations are different between the tables. Please reconcile.

   b. Please indicate which tests are performed during the stability testing of the drug product, and which test stations will be followed.

2. Gensia Sicor should perform an admixture compatibility study to substantiate the compatibility of the drug product when administered in the diluents referred to in the package insert labeling (p. 100037):

   a. glucose injection

   b. 0.9% sodium chloride injection.

3. The Vincristine Sulfate Injection monograph in the USP indicates that the drug product is to be packaged in glass vials. Your drug product is packaged in plastic vials.

   Please provide appropriate certification that the plastic vials used for the referenced drug product has been previously approved for use for injectable drug products. Alternatively, please provide a safety package which demonstrates that the plastic utilized for the package is safe for use for injectable products. The Office of Generic Drugs will need to consult the safety data package to the Assistant Director (Pharmacology), Office of New Drug Chemistry II, HFD-502 for acceptance of the new packaging.

Once it has been determined that the plastic vials are safe for use, you will be asked to obtain a letter of intent from USP to change the mongraph to allow the plastic container after approval of the ANDA.

4. It is also necessary that you demonstrate that the plastic vials meet the requirements for light resistance as defined in USP 23.

5. Please include the additional USP Identification test for Vincristine which is currently in the USP monograph for the drug product.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide any additional stability data accrued to date in their long term stability studies.

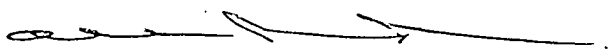
2. The CGMP status of the firms referenced in the ANDA will be evaluated by our Office of Compliance. Firms referenced in this ANDA must be in compliance with Current Good Manufacturing Practices at the time of approval.

3. The USP analytical methods, as written, are considered regulatory for this product. Results from those methods shall prevail in the event of a dispute.

4. Your sterility assurance information is pending review.

5. Your response must also address the labeling deficiencies.

Sincerely yours,



Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #75493 APPLICANT: Gensia Sicor Pharmaceuticals

DRUG PRODUCT: Vincristine Sulfate Injection,USP, 1 mg/ml vial

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

GensiaSicor™
PHARMACEUTICALS
A GensiaSicor Company

February 8, 1999

Mr. Douglas Sporn
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 CORRES

RE: Vincristine Sulfate Injection, 1 mg/mL
ANDA 75-493

PATENT AMENDMENT

Dear Mr. Sporn:

Reference is made to Gensia Sicor's ANDA 75-493 for Vincristine Sulfate Injection, 1 mg/mL, which was submitted to the Agency on October 30, 1998. Reference is also made to the amendment dated December 8, 1998, in which we certified that notice of our Paragraph IV filing was provided to Eli Lilly and Company at the same time of that amendment.

In accordance with Sections CFR 314.95(b) and 314.107 (f)(2) of the *Code of Federal Regulations, Title 21,* we hereby amend this application.

As required under CFR 314.95(b), we wish to provide the Return Receipt documentation requested of the U.S. Postal Service (USPS) for the Patent Certification notice sent to Eli Lilly and Company on December 8, 1998. A copy of the Return Receipt is attached.

In addition, as required under CFR 314.107 (f)(2), we wish to inform the Agency that neither Gensia Sicor nor its legal representatives have been served with a legal complaint that has been precipitated by our Notice of Certification received by Eli Lilly. To the best of our knowledge, we are not aware of any legal action taken within the requisite 45 days that expired on January 22, 1999.

Gensia Sicor Pharmaceuticals, Inc. • 19 Hughes • Irvine CA • 92618-1902 • USA
Phone (949) 455-4700, (800) 729-9991 • Fax (949) 855-8210 • http://www.gensiasicor.com

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) 457-2808 or Mr. Dwain Allen, Regulatory Affairs Project Specialist, at (949) 457-2861. We can also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Boulevard, Suite 300
Irvine, CA 92715

2/1/99
I Consult Dwain Allen
From the documentation provided there is no way to confirm the exact receipt date of the notice by Lilly. We can confirm General Receipt by the signed return-receipt form on 1/4/99. Thus we agreed that the 45-day period would begin on the 4th. No Secretin that Genta/Scarlas not been sued to date by Lilly.
Robert Hurst

GensiaSicor™
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NEW CORRESP
NC

December 8, 1998

Mr. Douglas Sporn
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: Vincristine Sulfate Injection, 1 mg/mL
ANDA 75-493

PATENT AMENDMENT

Dear Mr. Sporn:

Reference is made to Gensia Sicor's ANDA 75-493 for Vincristine Sulfate Injection, 1 mg/mL, which was submitted to the Agency on October 30, 1998.

In accordance with Section 505(j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.95(b), we hereby amend this application.

As required, the Patent Amendment certifies that notice of our Paragraph IV filing has been provided to Eli Lilly and Company, the holders of the approved application for Oncovin® and the owner of the U.S. Patent No. 4619935, at the same time this amendment was submitted to the application. The notice met the content requirements of 21 CFR 314.95(c) and was sent by certified/registered mail, return receipt requested.

[illegible] RECEIVED
DEC 09 1998
[illegible]

Gensia Sicor Pharmaceuticals, Inc. • 19 Hughes • Irvine CA • 92618-1902 • USA
Phone (949) 455-4700, (800) 729-9991 • Fax (949) 855-8210 • http://www.gensiasicor.com

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) 457-2808 or Mr. Dwain Allen, Regulatory Affairs Project Specialist at (949) 457-2861. We can also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Boulevard, Suite 300
Irvine, CA 92715

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 75-493 APPLICANT: Gensia Sicor Pharmaceuticals, Inc.

DRUG PRODUCT: Vincristine Sulfate Injection USP 1mg/mL; 1 and 2 mL vials

The deficiencies presented below represent FACSIMILE deficiencies.

A. Deficiencies:

1. Testing performed as per the Finished Product and Stability report (pp. 200412 and 200423 are not consistent with the stability testing table presented on page 200396.

   a. Test stations are different between the tables. Please reconcile.

   b. Please indicate which tests are performed during the stability testing of the drug product, and which test stations will be followed.

2. Gensia Sicor should perform an admixture compatibility study to substantiate the compatibility of the drug product when administered in the diluents referred to in the package insert labeling (p. 100037):

   a. glucose injection

   b. 0.9% sodium chloride injection.

3. The Vincristine Sulfate Injection monograph in the USP indicates that the drug product is to be packaged in glass vials. Your drug product is packaged in plastic vials.

   Please provide appropriate certification that the plastic vials used for the referenced drug product has been previously approved for use for injectable drug products. Alternatively, please provide a safety package which demonstrates that the plastic utilized for the package is safe for use for injectable products. The Office of Generic Drugs will need to consult the safety data package to the Assistant Director (Pharmacology), Office of New Drug Chemistry II, HFD-502 for acceptance of the new packaging.

Once it has been determined that the plastic vials are safe for use, you will be asked to obtain a letter of intent from USP to change the mongraph to allow the plastic container after approval of the ANDA.

4. It is also necessary that you demonstrate that the plastic vials meet the requirements for light resistance as defined in USP 23.

5. Please include the additional USP Identification test for Vincristine which is currently in the USP monograph for the drug product.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide any additional stability data accrued to date in their long term stability studies.

2. The CGMP status of the firms referenced in the ANDA will be evaluated by our Office of Compliance. Firms referenced in this ANDA must be in compliance with Current Good Manufacturing Practices at the time of approval.

3. The USP analytical methods, as written, are considered regulatory for this product. Results from those methods shall prevail in the event of a dispute.

4. Your sterility assurance information is pending review.

5. Your response must also address the labeling deficiencies.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Grace, S
1/1

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #75493 APPLICANT: Gensia Sicor Pharmaceuticals

DRUG PRODUCT: Vincristine Sulfate Injection,USP, 1 mg/ml vial

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

ANDA 75-493

Gensia Sicor Pharmaceuticals, Inc.
Attention: Rosalie A. Lowe
17 Hughes
Irvine, CA 92618

NOV 20 1998

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: Vincristine Sulfate Injection USP, 1 mg/mL

DATE OF APPLICATION: October 30, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: November 2, 1998

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

  2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b),provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a final order or judgement from which no appeal may be taken (which might not be the one from the District Court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Peter Rickman, Chief, Regulatory Support Branch, at (301)827-5862.

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:

Denise Huie
Project Manager
(301) 827-5848

Sincerely yours,

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

GensiaSicor™
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June 7, 1999

Mr. Douglas Sporn
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

NDA CORRESP
NC

RE: Vincristine Sulfate Injection
ANDA 75-493

GENERAL CORRESPONDENCE

Dear Mr. Sporn:

Reference is made to Gensia Sicor's ANDA 75-493 for Vincristine Sulfate Injection, 1 mg/mL, which was submitted to the Agency on October 30, 1998. Reference is also made to today's teleconference with Ms. Teresa Watkins, Labeling Reviewer, OGD, in which she requested clarification as to how the text would be applied to the polymer overwrap bag. I informed Ms. Watkins that the text would be imprinted directly onto the polymer overwrap bag. An adhesive label would not be used to label this component.

We trust that the information provided in this general correspondence is satisfactory. Should you have any additional questions regarding our application, please feel free to contact me at (949) 457-2808 or Mr. Dwain Allen, Regulatory Affairs Project Specialist, at (949) 457-2861. We can also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

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cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Boulevard, Suite 300
Irvine, CA 92715

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUN 0 8 1999
OGD

Gensia Sicor Pharmaceuticals, Inc. • 19 Hughes • Irvine CA • 92618-1902 • USA
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ack for filing
3. Mitchell
11/6/98

October 30, 1998

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

RE: Vincristine Sulfate Injection, USP, 1 mg/mL
ANDA: Number to be Assigned

Dear Mr. Sporn:

In accordance with Section 314.92 of the *Code of Federal Regulations, Title 21*, we hereby submit an Abbreviated New Drug Application for Vincristine Sulfate Injection, USP, a parenteral preparation supplied as:

Strength	Drug Content	How Supplied
1 mg/mL	1 mg Vincristine Sulfate per vial	1 mL Single Dose Vial
1 mg/mL	2 mg Vincristine Sulfate per vial	2 mL Single Dose Vial

Oncovin® (Vincristine Sulfate Injection, USP), 1 mg/mL, is held under NDA 14-103, Supplement 003, by Eli Lilly and Company as listed in the *Approved Drug Products with Therapeutic Equivalence Evaluation, 18th Edition.*

Our drug product has the same active ingredient, dosage form, strength, and route of administration as the reference listed drug, Eli Lilly's Oncovin®. The inactive ingredients differ only in that Gensia Sicor's formulation is preservative-free, i.e.; it contains no

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The absence of preservatives, in Gensia Sicor's formulation is in accordance with 21 CFR §314.94(a)(9)(iii), which allows for a change in preservative provided that the change does not affect the safety of the proposed drug product.

The safety of the change (i.e., the elimination of the preservatives) for Gensia Sicor's proposed drug product is based upon the following:

1. Pharmacia and UpJohn currently markets a generic formulation of Vincristine Sulfate Injection, USP, 1 mg/mL, which is preservative-free (ANDA 71-426), under the trade name Vincasar®. The presence of an approved preservative-free formulation of Vincristine Sulfate Injection, USP, supports the safety of Gensia Sicor's preservative-free formulation.

2. Gensia Sicor will adhere to the USP monographs for Vincristine Sulfate drug substance and drug product. Therefore, the Gensia Sicor's preservative-free formulation will meet the established standards for a safe product.

Four (4) copies of the proposed labeling have also been provided in **Section V** of the application in both the archival and review copies.

Two (2) stability lots were manufactured and data are presented in **Section XVII** of this application.

The application consists of three (3) volumes and has been formatted in accordance with the Office of Generic Drug's Policy and Procedure Guide #30-91 issued April 10, 1991; and, as modified by FDA's October 14, 1994 letter to all NDA, ANDA, and AADA applicants. Copies are provided as follows:

1) One (1) Archival Copy bound in Blue Jackets
2) One (1) Review Copy bound in Red Jackets

Since the method for assay and related substances is a modification of the USP method, three (3) additional methods validation packages have been included in this application and are marked "Analytical Methods." These three additional copies are identical to **Section XVI** as presented in the archival and review copies, and have been separately bound in Black Jackets.

A true copy of this application, which was bound in Burgundy Jackets, has been submitted to the U.S. Food and Drug Administration of Irvine, California, Los Angeles District Office.

Please note that Gensia Laboratories, Ltd., is in the process of changing our company name to Gensia Sicor Pharmaceuticals, Inc., therefore documents presented in this application may have either name listed.

We trust you will find the information in this application satisfactory for your review and approval. If there are any questions concerning this application, please do not hesitate in contacting me at (949) 457-2808, or by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulator Affairs

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715