# CENTER FOR DRUG EVALUATION AND RESEARCH

# Approval Package for:

# APPLICATION NUMBER:

# 76-349

| | |
|---|---|
| Generic Name: | Fludarabine Phosphate for Injection USP 50mg single-dose vials |
| Sponsor: | Sicor Pharmaceuticals, Inc. |
| Approval Date: | August 28, 2003 |

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

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Reviews / Information Included in this ANDA Review.

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

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# APPROVAL LETTER

ANDA 76-349

AUG 28 2003

SICOR Pharmaceuticals, Inc.
Attention: Rosalie A. Lowe
19 Hughes
Irvine, CA 92618-1902

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated January 18, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Fludarabine Phosphate for Injection USP, packaged in 50 mg single-dose vials.

Reference is also made to the tentative approval letter issued by this office on March 12, 2003, and your amendments dated July 31, August 18, and August 20, 2003.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Fludarabine Phosphate for Injection USP, 50 mg/vial to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Fludara® for Injection, 50 mg/vial, of Berlex Laboratories, Inc.).

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

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

We request that you submit, in duplicate, any proposed advertising or promotional copy which 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 final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

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

Sincerely yours,

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

8/28/03

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 76-349

# TENTATIVE APPROVAL LETTER(S)

ANDA 76-349

MAR 12 2003

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

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated January 18, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Fludarabine Phosphate for Injection, 50 mg/single-dose vial.

Reference is also made to your amendments dated August 6, September 26, November 5, and November 19, 2002; and February 24, February 25, February 26, and February 27, 2003.

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

The reference listed drug product (RLD) upon which you have based your application, Fludara® for Injection of Berlex Laboratories, Inc., was subject to a period of patent protection. As noted in the agency's publication entitled with Approved Drug Products Therapeutic Equivalence Evaluations, the "Orange Book", U.S. Patent 4,357,324 (the '324 patent) expired on February 24, 2003. Your application contains a Paragraph III Certification to the '324 patent under Section 505(j)(2)(A)(vii)(III) of the Act stating that you will not market this

drug product prior to the expiration of this patent. However, the expiration of the '324 patent has effectively been extended for a minimum of 60 days of additional marketing exclusivity because the NDA holder, Berlex Laboratories, Inc. has submitted a study requested by the agency to demonstrate the safety and effectiveness of Fludara® for Injection in a pediatric population. This study was submitted under Section 111 of Title I of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act). The Modernization Act created section 505(A) of the Act which permits NDA-holders to obtain up to an additional six months of marketing exclusivity (pediatric exclusivity) if, in accordance with the requirements of the statute, the NDA holder submits pediatric data which is found acceptable by the agency. Berlex submitted the pediatric study data prior to the expiration of the '324 patent. Therefore, final approval of your application may not be made effective pursuant to 21 U.S.C. 355(j)(5)(B)(ii) of the Act until the agency has evaluated the adequacy of the studies submitted by Berlex and made a decision as to whether Berlex should be awarded pediatric exclusivity. The agency will review the adequacy of the studies promptly. If these studies are found to be adequate and acceptable for review, pediatric exclusivity will be granted and your ANDA will be eligible for final approval on August 24, 2003. Alternatively, if the agency were to conclude that the pediatric studies submitted by Berlex are inadequate and would not support labeling intended to address the safety or effectiveness of Fludara® for Injection in a pediatric population, you will be notified that this ANDA is eligible for final approval.

In order to reactivate your application prior to final approval, please submit a MINOR AMENDMENT - FINAL APPROVAL REQUESTED 60 to 90 days prior to the date you believe that your application will be eligible for final approval. This amendment should provide a justification for the reason(s) you believe the ANDA is eligible for final approval, and it should also identify changes, if any, in the conditions under which the product was tentatively approved; i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made.

In addition to the amendment requested above, the agency may request at any time prior to the final date of approval that you submit an additional amendment containing the requested

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

Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to Agency review before final approval of the application will be made. Such changes should be submitted as an amendment to the application and categorized as representing either "major" or "minor" changes. This amendment will be reviewed according to OGD policy in effect at the time of receipt. Your submission of multiple amendments prior to final approval may lead to a delay in the issuance of the final approval letter.

This drug product may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d). Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the "Orange Book".

For further information on the status of this application, or prior to submitting additional amendments, please contact Thuyanh Vu (Ann), R.Ph., Project Manager, at 301-827-5848.

Sincerely yours,

Gary Buehler 3/12/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 76-349

# FINAL PRINTED LABELING

Package Insert

$R_x$ only

GensiaSicor® PHARMACEUTICALS

# Fludarabine Phosphate for Injection, USP

**FOR INTRAVENOUS USE ONLY**

**WARNING**

Fludarabine should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy. Fludarabine can severely suppress bone marrow function. When used at high doses in dose-ranging studies in patients with acute leukemia, fludarabine was associated with severe neurologic effects, including blindness, coma, and death. This severe central nervous system toxicity occurred in 36% of patients treated with doses approximately four times greater (96 mg/m²/day for 5–7 days) than the recommended dose. Similar severe central nervous system toxicity has been rarely (≤0.2%) reported in patients treated at doses in the range of the dose recommended for chronic lymphocytic leukemia.

Instances of life-threatening and sometimes fatal autoimmune hemolytic anemia have been reported to occur after one or more cycles of treatment with fludarabine. Patients undergoing treatment with fludarabine should be evaluated and closely monitored for hemolysis.

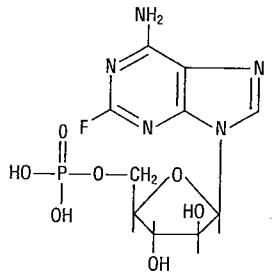
In a clinical investigation using fludarabine in combination with pentostatin (deoxycoformycin) for the treatment of refractory chronic lymphocytic leukemia (CLL), there was an unacceptably high incidence of fatal pulmonary toxicity. Therefore, the use of fludarabine in combination with pentostatin is not recommended.

## DESCRIPTION

Fludarabine phosphate for injection contains fludarabine phosphate, a fluorinated nucleotide analog of the antiviral agent vidarabine, 9-ß-D-arabinofuranosyladenine (ara-A) that is relatively resistant to deamination by adenosine deaminase. Each vial of sterile lyophilized solid cake contains 50 mg of the active ingredient fludarabine phosphate, USP, 50 mg of mannitol, and sodium hydroxide to adjust pH to 7.7. The pH range for the final product is 7.2–8.2. Reconstitution with 2 mL of sterile water for injection USP results in a solution containing 25 mg/mL of fludarabine phosphate intended for intravenous administration.

The chemical name for fludarabine phosphate is 9H-Purin-6-amine, 2-fluoro-9-(5-O-phosphono-ß-D-arabinofuranosyl) (2-fluoro-ara-AMP).

The molecular formula of fludarabine phosphate is $C_{10}H_{13}FN_5O_7P$ (MW 365.2) and the structure is:




## CLINICAL PHARMACOLOGY

Fludarabine phosphate is rapidly dephosphorylated to 2-fluoro-ara-A and then phosphorylated intracellularly by deoxycytidine kinase to the active triphosphate, 2-fluoro-ara-ATP. This metabolite appears to act by inhibiting DNA polymerase alpha, ribonucleotide reductase and DNA primase, thus inhibiting DNA synthesis. The mechanism of action of this antimetabolite is not completely characterized and may be multi-faceted.

Phase I studies in humans have demonstrated that fludarabine phosphate is rapidly converted to the active metabolite, 2-fluoro-ara-A, within minutes after intravenous infusion. Consequently, clinical pharmacology studies have focused on 2-fluoro-ara-A

response rates were obtained using standardized response criteria developed by the National Cancer Institute CLL Working Group and were achieved in heavily pre-treated patients. The ability of fludarabine phosphate for injection to induce a significant rate of response in refractory patients suggests minimal cross-resistance with commonly used anti-CLL agents.

The median time to response in the MDAH and SWOG studies was 7 weeks (range of 1 to 68 weeks) and 21 weeks (range of 1 to 53 weeks) respectively. The median duration of disease control was 91 weeks (MDAH) and 65 weeks (SWOG). The median survival of all refractory CLL patients treated with fludarabine phosphate for injection was 43 weeks and 52 weeks in the MDAH and SWOG studies, respectively.

Rai stage improved to Stage II or better in 7 of 12 MDAH responders (58%) and in 5 of 7 SWOG responders (71%) who were Stage III or IV at baseline. In the combined studies, mean hemoglobin concentration improved from 9.0 g/dL at baseline to 11.8 g/dL at the time of response in a subgroup of anemic patients. Similarly, average platelet count improved from 63,500/mm³ to 103,300/mm³ at the time of response in a subgroup of patients who were thrombocytopenic at baseline.

## INDICATIONS AND USAGE

Fludarabine phosphate for injection is indicated for the treatment of patients with B-cell chronic lymphocytic leukemia (CLL) who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-agent containing regimen. The safety and effectiveness of fludarabine phosphate for injection in previously untreated or non-refractory patients with CLL have not been established.

## CONTRAINDICATIONS

Fludarabine phosphate for injection is contraindicated in those patients who are hypersensitive to this drug or its components.

## WARNINGS (See boxed warning)

There are clear dose dependent toxic effects seen with fludarabine. Dose levels approximately 4 times greater (96 mg/m²/day for 5 to 7 days) than that recommended for CLL (25 mg/m²/day for 5 days) were associated with a syndrome characterized by delayed blindness, coma and death. Symptoms appeared from 21 to 60 days following the last dose. Thirteen of 36 patients (36%) who received fludarabine at high doses (96 mg/m²/day for 5 to 7 days) developed this severe neurotoxicity. This syndrome has been reported rarely in patients treated with doses in the range of the recommended CLL dose of 25 mg/m²/day for 5 days every 28 days. The effect of chronic administration of fludarabine on the central nervous system is unknown; however, patients have received the recommended dose for up to 15 courses of therapy.

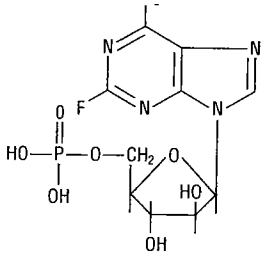
Severe bone marrow suppression, notably anemia, thrombocytopenia and neutropenia, has been reported in patients treated with fludarabine. In a Phase I study in adult solid tumor patients, the median time to nadir counts was 13 days (range, 3–25 days) for granulocytes and 16 days (range, 2–32) for platelets. Most patients had hematologic impairment at baseline either as a result of disease or as a result of prior myelosuppressive therapy. Cumulative myelosuppression may be seen. While chemotherapy-induced myelosuppression is often reversible, administration of fludarabine requires careful hematologic monitoring.

Several instances of trilineage bone marrow hypoplasia or aplasia resulting in pancytopenia, sometimes resulting in death, have been reported in adult patients. The duration of clinically significant cytopenia in the reported cases has ranged from approximately 2 months to approximately 1 year. These episodes have occurred both in previously treated or untreated patients.

Instances of life-threatening and sometimes fatal autoimmune hemolytic anemia have been reported to occur after one or more cycles of treatment with fludarabine in patients with or without a previous history of autoimmune hemolytic anemia or a positive Coombs' test and who may or may not be in remission from their disease. Steroids may or may not be effective in controlling these hemolytic episodes. The majority of patients rechallenged with fludarabine developed a recurrence in the hemolytic process. The mechanism(s) which predispose patients to the development of this complication has not been identified. Patients undergoing treatment with fludarabine should be evaluated and closely monitored for hemolysis.

Transfusion-associated graft-versus-host disease has been observed rarely after transfusion of non-irradiated blood in fludarabine treated patients. Consideration should, therefore, be given to the use of irradiated blood products in those patients requiring transfusions while undergoing treatment with fludarabine.

In a clinical investigation using fludarabine in



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Phase I studies in humans have demonstrated that fludarabine phosphate is rapidly converted to the active metabolite, 2-fluoro-ara-A, within minutes after intravenous infusion. Consequently, clinical pharmacology studies have focused on 2-fluoro-ara-A pharmacokinetics. After the five daily doses of 25 mg 2-fluoro-ara-AMP/m$^2$ to cancer patients infused over 30 minutes, 2-fluoro-ara-A concentrations show a moderate accumulation. During a 5-day treatment schedule, 2-fluoro-ara-A plasma trough levels increased by a factor of about 2. The terminal half-life of 2-fluoro-ara-A was estimated as approximately 20 hours. *In vitro*, plasma protein binding of fludarabine ranged between 19% and 29%.

A correlation was noted between the degree of absolute granulocyte count nadir and increased area under the concentration x time curve (AUC).

### Special Populations

*Pediatric Patients*

Limited pharmacokinetic data for fludarabine phosphate for injection are available from a published study of children (ages 1–21 years) with refractory acute leukemias or solid tumors (Children's Cancer Group Study 097). When fludarabine phosphate for injection was administered as a loading dose over 10 minutes immediately followed by a 5-day continuous infusion, steady-state conditions were reached early.

*Patients with Renal Impairment*

The total body clearance of the principal metabolite 2-fluoro-ara-A correlated with the creatinine clearance, indicating the importance of the renal excretion pathway for the elimination of the drug. Renal clearance represents approximately 40% of the total body clearance. Patients with moderate renal impairment (17–41 mL/min/m$^2$) receiving 20% reduced fludarabine dose had a similar exposure (AUC; 21 versus 20 nM•h/mL) compared to patients with normal renal function receiving the recommended dose. The mean total body clearance was 172 mL/min for normal and 124 mL/min for patients with moderately impaired renal function.

### Clinical Studies

Two single-arm open-label studies of fludarabine phosphate for injection have been conducted in adult patients with CLL refractory to at least one prior standard alkylating-agent containing regimen. In a study conducted by M.D. Anderson Cancer Center (MDAH), 48 patients were treated with a dose of 22–40 mg/m$^2$ daily for 5 days every 28 days. Another study conducted by the Southwest Oncology Group (SWOG) involved 31 patients treated with a dose of 15–25 mg/m$^2$ daily for 5 days every 28 days. The overall objective response rates were 48% and 32% in the MDAH and SWOG studies, respectively. The complete response rate in both studies was 13%; the partial response rate was 35% in the MDAH study and 19% in the SWOG study. These

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In a clinical investigation using fludarabine in combination with pentostatin (deoxycoformycin) for the treatment of refractory chronic lymphocytic leukemia (CLL) in adults, there was an unacceptably high incidence of fatal pulmonary toxicity. Therefore, the use of fludarabine in combination with pentostatin is not recommended.

Of the 133 adult CLL patients in the two trials, there were 29 fatalities during study. Approximately 50% of the fatalities were due to infection and 25% due to progressive disease.

### Pregnancy Category D

Fludarabine may cause fetal harm when administered to a pregnant woman. Fludarabine phosphate was teratogenic in rats and in rabbits. Fludarabine phosphate was administered intravenously at doses of 0, 1, 10 or 30 mg/kg/day to pregnant rats on days 6 to 15 of gestation. At 10 and 30 mg/kg/day in rats, there was an increased incidence of various skeletal malformations. Fludarabine phosphate was administered intravenously at doses of 0, 1, 5 or 8 mg/kg/day to pregnant rabbits on days 6 to 15 of gestation. Dose-related teratogenic effects manifested by external deformities and skeletal malformations were observed in the rabbits at 5 and 8 mg/kg/day. Drug-related deaths or toxic effects on maternal and fetal weights were not observed. There are no adequate and well-controlled studies in pregnant women.

If fludarabine is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

## PRECAUTIONS

### General

Fludarabine is a potent antineoplastic agent with potentially significant toxic side effects. Patients undergoing therapy should be closely observed for signs of hematologic and nonhematologic toxicity. Periodic assessment of peripheral blood counts is recommended to detect the development of anemia, neutropenia and thrombocytopenia.

Tumor lysis syndrome associated with fludarabine treatment has been reported in CLL patients with large tumor burdens. Since fludarabine can induce a response as early as the first week of treatment, precautions should be taken in those patients at risk of developing this complication.

$R_x$ only
Fludarabine Phosphate for Injection, USP
GenisaSicor® PHARMACEUTICALS

$R_x$ only
Fludarabine Phosphate for Injection, USP
GenisaSicor® PHARMACEUTICALS
Y36-000-91A

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## CONTRAINDICATIONS

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## WARNINGS (See boxed warning)

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Transfusion-associated graft-versus-host disease has been observed rarely after transfusion of non-irradiated blood in fludarabine treated patients. Consideration should, therefore, be given to the use of irradiated blood products in those patients requiring transfusions while undergoing treatment with fludarabine.

In a clinical investigation using fludarabine in combination with

There are inadequate data on dosing of patients with renal insufficiency. Fludarabine must be administered cautiously in patients with renal insufficiency. The total body clearance of 2-fluoro-ara-A has been shown to be directly correlated with creatinine clearance. Patients with moderate impairment of renal function (creatinine clearance 30–70 mL/min/1.73 m$^2$) should have their fludarabine dose reduced by 20% and be monitored closely. Fludarabine is not recommended for patients with severely impaired renal function (creatinine clearance less than 30 mL/min/1.73 m$^2$).

### Laboratory Tests

During treatment, the patient's hematologic profile (particularly neutrophils and platelets) should be monitored regularly to determine the degree of hematopoietic suppression.

### Drug Interactions

The use of fludarabine in combination with pentostatin is not recommended due to the risk of severe pulmonary toxicity (see **WARNINGS** section).

### Carcinogenesis

No animal carcinogenicity studies with fludarabine have been conducted.

### Mutagenesis

Fludarabine phosphate was not mutagenic to bacteria (Ames test) or mammalian cells (HGRPT assay in Chinese hamster ovary cells) either in the presence or absence of metabolic activation. Fludarabine phosphate was clastogenic *in vitro* to Chinese hamster ovary cells (chromosome aberrations in the presence of metabolic activation) and induced sister chromatid exchanges both with and without metabolic activation. In addition, fludarabine phosphate was clastogenic *in vivo* (mouse micronucleus assay) but was not mutagenic to germ cells (dominant lethal test in male mice).

### Impairment of Fertility

Studies in mice, rats and dogs have demonstrated dose-related adverse effects on the male reproductive system. Observations consisted of a decrease in mean testicular weights in mice and rats with a trend toward decreased testicular weights in dogs and degeneration and necrosis of spermatogenic epithelium of the testes in mice, rats and dogs. The possible adverse effects on fertility in humans have not been adequately evaluated.

### Pregnancy

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

### 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 in nursing infants from fludarabine, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug for the mother.

### Pediatric Use

Data submitted to the FDA was insufficient to establish efficacy in any childhood malignancy. Fludarabine was evaluated in 62 pediatric patients (median age 10, range 1–21) with refractory acute leukemia (45 patients) or solid tumors (17 patients). The fludarabine regimen tested for pediatric acute lymphocytic leukemia (ALL) patients was a loading bolus of 10.5 mg/m$^2$/day followed by a continuous infusion of 30.5 mg/m$^2$/day for 5 days. In 12 pediatric patients with solid tumors, dose-limiting myelosuppression was observed with a loading dose of 8 mg/m$^2$/day followed by a continuous infusion of 23.5 mg/m$^2$/day for 5 days. The maximum tolerated dose was a loading dose of 7 mg/m$^2$/day followed by a continuous infusion of 20 mg/m$^2$/day for 5 days. Treatment toxicity included bone marrow suppression. Platelet counts appeared to be more sensitive to the effects of fludarabine than hemoglobin and white blood cell counts. Other adverse events included fever, chills, asthenia, rash, nausea, vomiting, diarrhea, and infection. There were no reported occurrences of peripheral neuropathy or pulmonary hypersensitivity reaction.

## ADVERSE REACTIONS

The most common adverse events include myelosuppression (neutropenia, thrombocytopenia and anemia), fever and chills, infection, and nausea and vomiting. Other commonly reported events include malaise, fatigue, anorexia, and weakness. Serious opportunistic infections have occurred in CLL patients treated with fludarabine. The most frequently reported adverse events and those reactions which are more clearly related to the drug are arranged below according to body system.

### Hematopoietic Systems

Hematologic events (neutropenia, thrombocytopenia, and/or anemia) were reported in the majority of CLL patients treated with fludarabine. During fludarabine treatment of 133 patients with CLL, the absolute

requires careful hematologic monitoring.

Several instances of trilineage bone marrow hypoplasia or aplasia resulting in pancytopenia, sometimes resulting in death, have been reported in adult patients. The duration of clinically significant cytopenia in the reported cases has ranged from approximately 2 months to approximately 1 year. These episodes have occurred both in previously treated or untreated patients.

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Of the 133 adult CLL patients in the two trials, there were 29 fatalities during study. Approximately 50% of the fatalities were due to infection and 25% due to progressive disease.

***Pregnancy Category D**

Fludarabine may cause fetal harm when administered to a pregnant woman. Fludarabine phosphate was teratogenic in rats and in rabbits. Fludarabine phosphate was administered intravenously at doses of 0, 1, 10 or 30 mg/kg/day to pregnant rats on days 6 to 15 of gestation. At 10 and 30 mg/kg/day in rats, there was an increased incidence of various skeletal malformations. Fludarabine phosphate was administered intravenously at doses of 0, 1, 5 or 8 mg/kg/day to pregnant rabbits on days 6 to 15 of gestation. Dose-related teratogenic effects manifested by external deformities and skeletal malformations were observed in the rabbits at 5 and 8 mg/kg/day. Drug-related deaths or toxic effects on maternal and fetal weights were not observed. There are no adequate and well-controlled studies in pregnant women.

If fludarabine is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

## PRECAUTIONS

### General

Fludarabine is a potent antineoplastic agent with potentially significant toxic side effects. Patients undergoing therapy should be closely observed for signs of hematologic and nonhematologic toxicity. Periodic assessment of peripheral blood counts is recommended to detect the development of anemia, neutropenia and thrombocytopenia.

Tumor lysis syndrome associated with fludarabine treatment has been reported in CLL patients with large tumor burdens. Since fludarabine can induce a response as early as the first week of treatment, precautions should be taken in those patients at risk of developing this complication.

loading bolus of 15.6 mg/m²/day followed by a continuous infusion of 30.5 mg/m²/day for 5 days. In 12 pediatric patients with solid tumors, dose-limiting myelosuppression was observed with a loading dose of 8 mg/m²/day followed by a continuous infusion of 23.5 mg/m²/day for 5 days. The maximum tolerated dose was a loading dose of 7 mg/m²/day followed by a continuous infusion of 20 mg/m²/day for 5 days. Treatment toxicity included bone marrow suppression. Platelet counts appeared to be more sensitive to the effects of fludarabine than hemoglobin and white blood cell counts. Other adverse events included fever, chills, asthenia, rash, nausea, vomiting, diarrhea, and infection. There were no reported occurrences of peripheral neuropathy or pulmonary hypersensitivity reaction.

## ADVERSE REACTIONS

The most common adverse events include myelosuppression (neutropenia, thrombocytopenia and anemia), fever and chills, infection, and nausea and vomiting. Other commonly reported events include malaise, fatigue, anorexia, and weakness. Serious opportunistic infections have occurred in CLL patients treated with fludarabine. The most frequently reported adverse events and those reactions which are more clearly related to the drug are arranged below according to body system.

### Hematopoietic Systems

Hematologic events (neutropenia, thrombocytopenia, and/or anemia) were reported in the majority of CLL patients treated with fludarabine. During fludarabine treatment of 133 patients with CLL, the absolute neutrophil count decreased to less than 500/mm³ in 59% of patients, hemoglobin decreased from pretreatment values by at least 2 grams percent in 60%, and platelet count decreased from pretreatment values by at least 50% in 55%. Myelosuppression may be severe, cumulative, and may affect multiple cell lines. Bone marrow fibrosis occurred in one CLL patient treated with fludarabine.

Several instances of trilineage bone marrow hypoplasia or aplasia resulting in pancytopenia, sometimes resulting in death, have been reported in postmarketing surveillance. The duration of clinically significant cytopenia in the reported cases has ranged from approximately 2 months to approximately 1 year. These episodes have occurred both in previously treated or untreated patients.

Life-threatening and sometimes fatal autoimmune hemolytic anemia have been reported to occur in patients receiving fludarabine (see **WARNINGS** section). The majority of patients rechallenged with fludarabine developed a recurrence in the hemolytic process.

### Metabolic

Tumor lysis syndrome has been reported in CLL patients treated with fludarabine. This complication may include hyperuricemia, hyperphosphatemia, hypocalcemia, metabolic acidosis, hyperkalemia, hematuria, urate crystalluria, and renal failure. The onset of this syndrome may be heralded by flank pain and hematuria.

### Nervous System

(See **WARNINGS** section)

Objective weakness, agitation, confusion, visual disturbances, and coma have occurred in CLL patients treated with fludarabine at the recommended dose. Peripheral neuropathy has been observed in patients treated with fludarabine and one case of wrist-drop was reported.

### Pulmonary System

Pneumonia, a frequent manifestation of infection in CLL patients, occurred in 16%, and 22% of those treated with fludarabine in the MDAH and SWOG studies, respectively. Pulmonary hypersensitivity reactions to fludarabine characterized by dyspnea, cough and interstitial pulmonary infiltrate have been observed.

In post-marketing experience, cases of severe pulmonary toxicity have been observed with fludarabine use which resulted in ARDS, respiratory distress, pulmonary hemorrhage, pulmonary fibrosis, and respiratory failure. After an infectious origin has been excluded, some

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Y36-000-51B

patients experienced symptom improvement with corticosteroids.

**Gastrointestinal System**

Gastrointestinal disturbances such as nausea and vomiting, anorexia, diarrhea, stomatitis, and gastrointestinal bleeding have been reported in patients treated with fludarabine.

**Cardiovascular**

Edema has been frequently reported. One patient developed a pericardial effusion possibly related to treatment with fludarabine. No other severe cardiovascular events were considered to be drug related.

**Genitourinary System**

Rare cases of hemorrhagic cystitis have been reported in patients treated with fludarabine.

**Skin**

Skin toxicity, consisting primarily of skin rashes, has been reported in patients treated with fludarabine.

Data in the following table are derived from the 133 patients with CLL who received fludarabine in the MDAH and SWOG studies.

**PERCENT OF CLL PATIENTS REPORTING NON-HEMATOLOGIC ADVERSE EVENTS**

| ADVERSE EVENTS | MDAH (N=101) | SWOG (N=32) |
|---|---|---|
| ANY ADVERSE EVENT | 88% | 91% |
| BODY AS A WHOLE | 72 | 84 |
| FEVER | 60 | 69 |
| CHILLS | 11 | 19 |
| FATIGUE | 10 | 38 |
| INFECTION | 33 | 44 |
| PAIN | 20 | 22 |
| MALAISE | 8 | 6 |
| DIAPHORESIS | 1 | 13 |
| ALOPECIA | 0 | 3 |
| ANAPHYLAXIS | 1 | 0 |
| HEMORRHAGE | 1 | 0 |
| HYPERGLYCEMIA | 1 | 6 |
| DEHYDRATION | 1 | 0 |
| NEUROLOGICAL | 21 | 69 |
| WEAKNESS | 9 | 65 |
| PARESTHESIA | 4 | 12 |
| HEADACHE | 3 | 0 |
| VISUAL DISTURBANCE | 3 | 15 |
| HEARING LOSS | 2 | 6 |
| SLEEP DISORDER | 1 | 3 |
| DEPRESSION | 1 | 0 |
| CEREBELLAR SYNDROME | 1 | 0 |
| IMPAIRED MENTATION | 1 | 0 |
| PULMONARY | 35 | 69 |
| COUGH | 10 | 44 |
| PNEUMONIA | 16 | 22 |
| DYSPNEA | 9 | 22 |
| SINUSITIS | 5 | 0 |
| PHARYNGITIS | 0 | 9 |
| UPPER RESPIRATORY INFECTION | 2 | 16 |
| ALLERGIC PNEUMONITIS | 0 | 6 |
| EPISTAXIS | 1 | 0 |
| HEMOPTYSIS | 1 | 6 |
| BRONCHITIS | 1 | 0 |
| HYPOXIA | 1 | 0 |
| GASTROINTESTINAL | 46 | 63 |
| NAUSEA/VOMITING | 36 | 31 |
| DIARRHEA | 15 | 13 |
| ANOREXIA | 7 | 34 |
| STOMATITIS | 9 | 0 |
| GI BLEEDING | 3 | 13 |
| ESOPHAGITIS | 3 | 0 |
| MUCOSITIS | 2 | 0 |
| LIVER FAILURE | 1 | 0 |
| ABNORMAL LIVER FUNCTION TEST | 1 | 3 |
| CHOLELITHIASIS | 0 | 3 |
| CONSTIPATION | 1 | 3 |
| DYSPHAGIA | 1 | 0 |
| CUTANEOUS | 17 | 18 |
| RASH | 15 | 15 |
| PRURITUS | 1 | 3 |
| SEBORRHEA | 1 | 0 |
| GENITOURINARY | 12 | 22 |
| DYSURIA | 4 | 3 |
| URINARY INFECTION | 2 | 15 |
| HEMATURIA | 2 | 3 |
| RENAL FAILURE | 1 | 0 |

## OVERDOSAGE

High doses of fludarabine phosphate for injection (see **WARNINGS** section) have been associated with an irreversible central nervous system toxicity characterized by delayed blindness, coma, and death. High doses are also associated with severe thrombocytopenia and neutropenia due to bone marrow suppression. There is no known specific antidote for fludarabine phosphate for injection overdosage. Treatment consists of drug discontinuation and supportive therapy.

## DOSAGE AND ADMINISTRATION

**Usual Dose**

The recommended adult dose of fludarabine phosphate for injection is 25 mg/m$^2$ administered intravenously over a period of approximately 30 minutes daily for five consecutive days. Each 5 day course of treatment should commence every 28 days. Dosage may be decreased or delayed based on evidence of hematologic or nonhematologic toxicity. Physicians should consider delaying or discontinuing the drug if neurotoxicity occurs.

A number of clinical settings may predispose to increased toxicity from fludarabine phosphate for injection. These include advanced age, renal insufficiency, and bone marrow impairment. Such patients should be monitored closely for excessive toxicity and the dose modified accordingly.

The optimal duration of treatment has not been clearly established. It is recommended that three additional cycles of fludarabine phosphate for injection be administered following the achievement of a maximal response and then the drug should be discontinued.

**Renal Insufficiency**

Adult patients with moderate impairment of renal function (creatinine clearance 30–70 mL/min/1.73 m$^2$) should have a 20% dose reduction of fludarabine phosphate for injection. Fludarabine phosphate for injection should not be administered to patients with severely impaired renal function (creatinine clearance less than 30 mL/min/1.73 m$^2$).

**Preparation of Solutions**

Fludarabine phosphate for injection should be prepared for parenteral use by aseptically adding sterile water for injection USP. When reconstituted with 2 mL of sterile water for injection, USP, the solid cake should fully dissolve in 15 seconds or less; each mL of the resulting solution will contain 25 mg of fludarabine phosphate, USP, 25 mg of mannitol, and sodium hydroxide to adjust the pH to 7.7. The pH range for the final product is 7.2–8.2. In clinical studies, the product has been diluted in 100 cc or 125 cc of 5% dextrose injection USP or 0.9% sodium chloride USP.

Reconstituted fludarabine phosphate for injection contains no antimicrobial preservative and thus should be used within 8 hours of reconstitution. Care must be taken to assure the sterility of prepared solutions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

**Handling and Disposal**

Procedures for proper handling and disposal should be considered. Consideration should be given to handling and disposal according to guidelines issued for cytotoxic drugs. Several guidelines on this subject have been published.[1–8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Caution should be exercised in the handling and preparation of fludarabine phosphate for injection solution. The use of latex gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage. If the solution contacts the skin or mucous membranes, wash thoroughly with soap and water; rinse eyes thoroughly with plain water. Avoid exposure by inhalation or by direct contact of the skin or mucous membranes.

## HOW SUPPLIED

Fludarabine phosphate for injection, USP is supplied as a white, lyophilized solid cake. Each vial contains 50 mg of fludarabine phosphate, USP, 50 mg of mannitol, and sodium hydroxide to adjust pH to 7.7. The pH range for the final product is 7.2–8.2. Store under refrigeration, between 2°–8°C (36°–46°F).

Fludarabine phosphate for injection, USP is supplied in a clear glass single dose vial (6 mL capacity) and packaged in a single dose vial carton in a shelf pack of five.

| NDC Number | Fludarabine Phosphate for Injection, USP |
|---|---|
| 0703-**5854-01** | 50 mg single dose vial packaged individualy |

## REFERENCES


1. ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and Recommendations for Practice. Pittsburgh, Pa: Oncology

| | | |
|---|---|---|
| RATORY INFECTION | 2 | 16 |
| NEUMONITIS | 0 | 6 |
| | 1 | 0 |
| S | 1 | 6 |
| | 1 | 0 |
| | 1 | 0 |
| NAL | 46 | 63 |
| MITING | 36 | 31 |
| | 15 | 13 |
| | 7 | 34 |
| | 9 | 0 |
| | 3 | 13 |
| S | 3 | 0 |
| | 2 | 0 |
| RE | 1 | 0 |
| LIVER FUNCTION TEST | 1 | 3 |
| ASIS | 0 | 3 |
| ON | 1 | 3 |
| | 1 | 0 |
| | 17 | 18 |
| | 15 | 15 |
| | 1 | 3 |
| | 1 | 0 |
| Y | 12 | 22 |
| | 4 | 3 |
| FECTION | 2 | 15 |
| | 2 | 3 |
| URE | 1 | 0 |
| RENAL FUNCTION TEST | 1 | 0 |
| A | 1 | 0 |
| | 0 | 3 |
| AR | 12 | 38 |
| | 8 | 19 |
| | 0 | 6 |
| E HEART FAILURE | 0 | 3 |
| A | 0 | 3 |
| RICULAR TACHYCARDIA | 0 | 3 |
| L INFARCTION | 0 | 3 |
| US THROMBOSIS | 1 | 3 |
| | 1 | 3 |
| ISCHEMIC ATTACK | 1 | 0 |
| | 1 | 0 |
| SCULAR ACCIDENT | 0 | 3 |
| ETAL | 7 | 16 |
| | 4 | 16 |
| ISIS | 2 | 0 |
| A | 1 | 0 |
| YNDROME | 1 | 0 |

adult patients received fludarabine in studies of other homas, and other solid tumors. The spectrum of eported in these studies was consistent with the data

appropriate.

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|---|---|
| 0703-**5854-01** | 50 mg single dose vial packaged individualy |

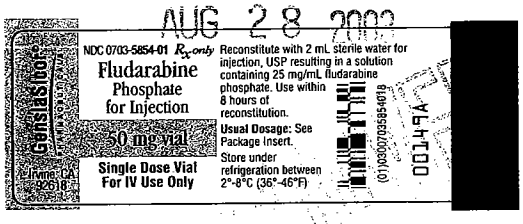
## REFERENCES


1. ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and Recommendations for Practice. Pittsburgh, Pa: Oncology Nursing Society. 1999:32–41.
2. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. Washington, DC; Division of Safety, Clinical Center Pharmacy Department and Cancer Nursing Services, National Institute of Health; 1992. US Department of Health and Human Services, Public Health Service Publication NIH 92-2621.
3. AMA Council on Scientific Affairs. Guidelines for Handling Parenteral Antineoplastics. *JAMA*. 1985;253:1590–1591.
4. National Study Commission on Cytotoxic Exposure — Recommendations for Handling Cytotoxic Agents. 1987. Available from Louis P. Jeffrey, Sc.D., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115.
5. Clinical Oncological Society of Australia: Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Med J Australia*. 1983;1:426–428.
6. Jones, R.B, Frank R, Mass T. Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. *CA Cancer J Clin*. 1983; 33:258–263.
7. American Society of Hospital Pharmacists. ASHP Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm*. 1990; 47:1033–1049.
8. Controlling Occupational Exposure to Hazardous Drugs (OSHA Work-Practice Guidelines). *Am J Health-Syst Pharm*. 1996;53:1669–1685.

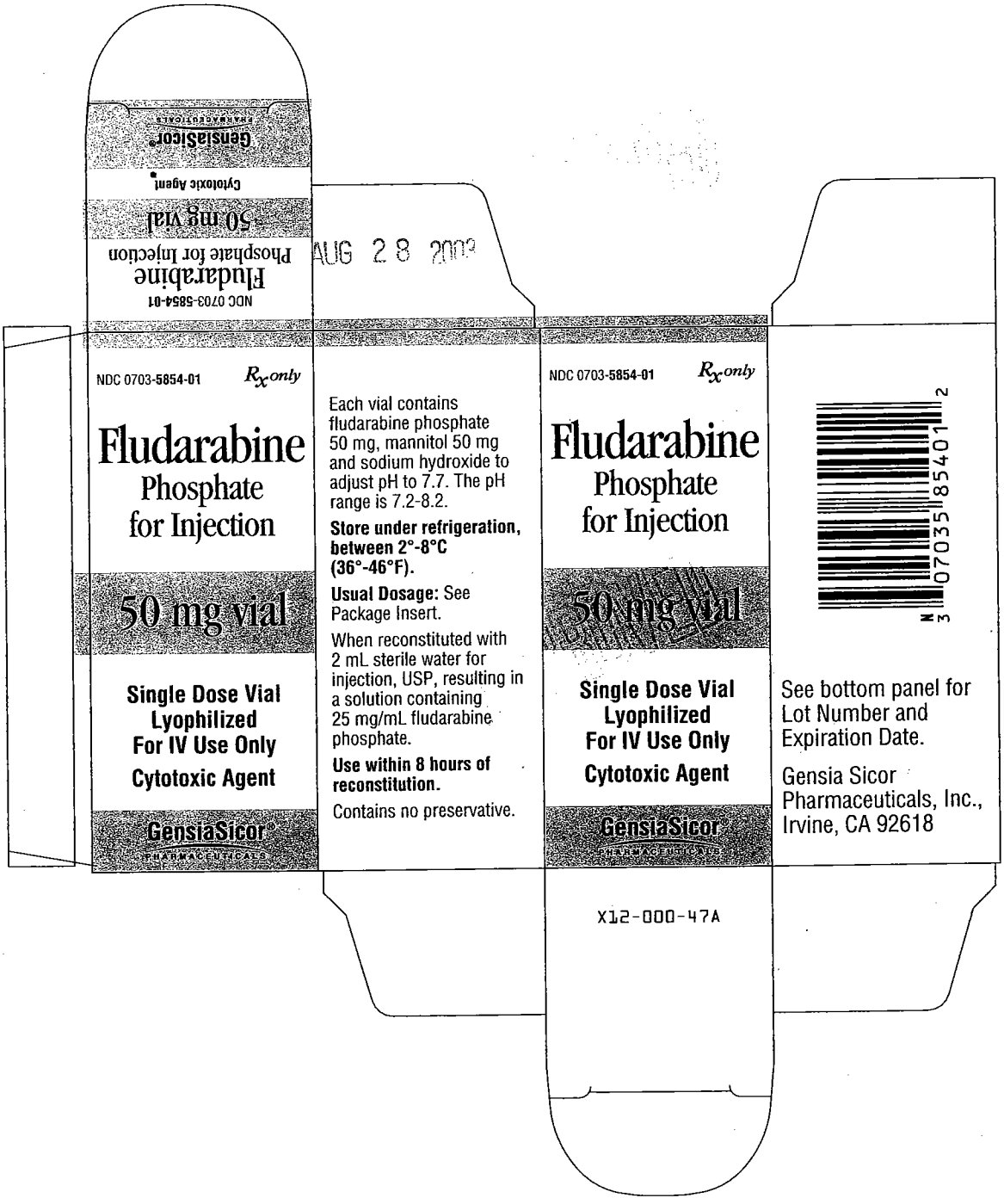


Issued: August 2003
Gensia Sicor Pharmaceuticals, Inc.
Irvine, CA 92618

# 50 mg VIAL LABEL
# Part #Y29-001-49A



# 50 mg CARTON
# Part #X12-000-47A



# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 76-349

# CSO LABELING REVIEW(S)

APPROVAL SUMMARY (First Generic)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH
Supercedes the August 2002 Approval Summary

| | |
|---|---|
| **ANDA Number** | 76-349 |
| **Date of Submission** | August 18, 2003 |
| **Applicant** | Gensia Sicor Pharmaceuticals |
| **Drug Name** | Fludarabine Phosphate for Injection, |
| **Strength(s)** | 50 mg vial (lyophilized) |

| FPL Approval Summary | | Submitted |
|---|---|---|
| **Container Labels** | | |
| | 50 mg vial | Aug 6, 2002 vol. 2.1 A&B FPL |
| **Carton labeling** | 1's | Aug 6, 2002 vol. 2.1A&B FPL |
| **Package Insert Labeling** | #Y36-00051B Rev. 8/ 2003 | Aug 18, 2003 vol. 2.1A FPL |

**BASIS OF APPROVAL:**

**Patent Data For NDA 20-038**

| Patent No | Patent Expiration | Use Code | Description | How Filed | Labeling Impact |
|---|---|---|---|---|---|
| 4357324 | 2/24/03 | None | - | PIII | Same As |

**Exclusivity Data For NDA 20-038**

| Code/sup | Expiration | Description | *Labeling impact* |
|---|---|---|---|
| None | | None | |

**Reference Listed Drug**

| | |
|---|---|
| RLD on the 356(h) form | Fludara |
| NDA Number | 20-038 |
| RLD established name | Fludarabine Phosphate for Injection |
| Firm | Ben Venue Lab |
| Currently approved PI | S/028 pediatric |
| AP Date | 8/01/03 |

Note. The RLD did not get the 3 year W/H.

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING CHECKLIST

| Applicant's 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.<br>**USP 24** | | 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* -See applicant's packaging configuration in FTR | | | |
| Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? 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. [see FTR] | | 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 | |
| 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 (p. #) 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 p. # 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?[see FTR] | | X | |
| Does USP have labeling recommendations? If any, does ANDA meet them? | | X | |
| Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container? | X | | |
| Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. | | X | |
| **Bioequivalence Issues:** (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable) | | | |
| Insert labeling references a food effect or a no-effect? If so, was a food study done? | | X | |
| Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why. | | X | |
| **Patent/Exclusivity Issues:** FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. | X | | |

FOR THE RECORD:

1. MODEL LABELING

   This review was based on the labeling for Fludara® Fludara (Ben Venue Lab; NDA 20-038S/028; Approved 8/01/03;). W/H was not granted because the RLD has only pk data.

2. PATENTS/EXCLUSIVITIES [Vol. A1.1 pg. 1012]. See table above.

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

   GensiaSicor ; 19 Hughes St, Irvine Ca [Vol. B1.1 pg. 1093]

4. CONTAINER/CLOSURE

   6 ml vial, with — glass tubing '— stopper is gray with flip off cap and aluminum seal. [Vol. B1.1

pg. 1251]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. B1.1 pg. 1038]

6. PACKAGING CONFIGURATIONS

RLD: Clear glass SDV, 6 mL capacity; packaged in shelf cartons of 5s.
ANDA: Same as RLD. However individually packaged

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: None.
RLD: Store under refrigeration 2 - 8C (36-46F).
ANDA: Same as RLD.

8. DISPENSING STATEMENTS COMPARISON

USP: None
RLD: Handle according to the handling of cytoxotic agents.
ANDA: Same as

9. BIOAVAILABILITY/BIOEQUIVALENCE:

Firm's request for a waiver of *in vivo* bioequivalence study requirements.

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Date of Review: 8/19/03 Date of Submission: 8/18/03

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cc:

ANDA: 76-349
DUP/DIVISION FILE
HFD-613/aPayne/JGrace (no cc)
v:\firmsam\gensia\ltrs&rev\76349ap2.lab
Review

Angela 8/19/03

Angela Payne for J. Grace 8/20/03

-10, Shift
6 SEP 2.1

APPROVAL SUMMARY (First Generic) minor
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

| | |
|---|---|
| **ANDA Number** | 76-349 |
| **Date of Submission** | August 6, 2002 |
| **Applicant** | Gensia Sicor Pharmaceuticals |
| **Drug Name** | Fludarabine Phosphate for Injection, |
| **Strength(s)** | 50 mg vial (lyophilized) |

| FPL Approval Summary | | Submitted |
|---|---|---|
| **Container Labels** | | |
| | 50 mg vial | August 6, 2002 vol. 2.1B **FPL** |
| **Carton labeling** | 1's | August 6, 2002 vol. 2.1B FPL |
| **Package Insert Labeling** | #Y36-00051A Rev. Jul 2002 | August 6, 2002 vol. 2.1B **FPL** |

**BASIS OF APPROVAL:**

**Patent Data For NDA 20-038**

| Patent No | Patent Expiration | Use Code | Description | How Filed | Labeling Impact |
|---|---|---|---|---|---|
| 4357324 | 2/24/03 | None | | PIII | Same As |

**Exclusivity Data For NDA 20-038**

| Code/sup | Expiration | Description | *Labeling impact* |
|---|---|---|---|
| None | | None | |

**Reference Listed Drug**

| | |
|---|---|
| RLD on the 356(h) form | Fludara |
| NDA Number | 20-038 |
| RLD established name | Fludarabine Phosphate for Injection |
| Firm | Ben Venue Lab |
| Currently approved PI | S/019 |
| AP Date | 12/03/01 Revised 12/01 |

12/03/02

Note.

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING CHECKLIST

| Applicant's 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 24** | | 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* -See applicant's packaging configuration in FTR | | | |
| Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? 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. [see FTR] | | 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 | |
| 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 (p. #) 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 p. # 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?[see FTR] | | X | |
| Does USP have labeling recommendations? If any, does ANDA meet them? | | X | |
| Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container? | X | | |
| Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. | | X | |
| **Bioequivalence Issues:** (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable) | | | |
| Insert labeling references a food effect or a no-effect? If so, was a food study done? | | X | |
| Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why. | | X | |
| **Patent/Exclusivity Issues:** FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. | X | | |

**FOR THE RECORD:**

1. MODEL LABELING

   This review was based on the labeling for Fludara® Fludara (Ben Venue Lab; NDA 20-038S/019; Approved 12/01/01; Revised 12/01).

2. PATENTS/EXCLUSIVITIES [Vol. A1.1 pg. 1012]. See table above.

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

   GensiaSicor ; 19 Hughes St, Irvine Ca [Vol. B1.1 pg. 1093]

4. CONTAINER/CLOSURE

   6 ml vial, with — glass tubing —— stopper is gray with flip off cap and aluminum seal. [Vol. B1.1 pg. 1251]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. B1.1 pg. 1038]

6. PACKAGING CONFIGURATIO.NS

RLD: Clear glass SDV, 6 mL capacity; packaged in shelf cartons of 5s.
ANDA: Same as RLD. However individually packaged

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: None.
RLD: Store under refrigeration 2 - 8C (36-46F).
ANDA: Same as RLD.

8. DISPENSING STATEMENTS COMPARISON

USP: None
RLD: Handle according to the handling of cytoxotic agents.
ANDA: Same as

9. BIOAVAILABILITY/BIOEQUIVALENCE:

Firm's request for a waiver of *in vivo* bioequivalence study requirements.

---

Date of Review: 8/14/02 Date of Submission: 8/6/02

---

cc:

ANDA: 76-349
DUP/DIVISION FILE
HFD-613/aPayne/JGrace (no cc)
v:\firmsam\gensia\ltrs&rev\76349ap.lab
Review

aPayne 8/14/02
aPayne for JGrace 8/20/02

APPEARS THIS WAY
ON ORIGINAL

**First Generic**
**REVIEW OF PROFESSIONAL LABELING #1**
**DIVISION OF LABELING AND PROGRAM SUPPORT**
**LABELING REVIEW BRANCH**

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| | |
|---|---|
| ANDA Number: | 76-349 |
| Dates of Submission: | January 18, 2002 (original) |
| Applicant's Name: | Gensia Sicor Pharmaceuticals |
| Established Name: | Fludarabine Phosphate for Injection, 50 mg vial (lyophilized) |

---

Labeling Deficiencies:

1. **CONTAINER:** 50 mg vial
   a. Your statement of strength should read 50 mg vial.
   b. Delete "6 mL".

2. **CARTON:** 50 mg vial
   a. See comments under CONTAINER.
   b. Cite "(lyophilized)" on the labeling.
   c. We encourage you to cite in red print "cytoxotic agent" on the main panel.

3. **INSERT:**

   a. GENERAL COMMENT

      i. Please revise your labeling so that it is in accord with the latest approved labeling for Fludara (Ben Venue Lab; NDA 20-038; S/019; Approved 12/03/01; Revised 12/01). We have enclosed a copy for your convenience.

      ii. We encourage you to cite fludarabine" rather than " throughout the adverse reactions, precautions, and warning sections.

   b. HOW SUPPLIED- Replace " —." with "50 mg vial".

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

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

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

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

**Attachment: Fludara insert labeling**

## REVIEW OF PROFESSIONAL LABELING CHECKLIST

| Applicant's 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 24** | | 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* -See applicant's packaging configuration in FTR | | | |
| Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? 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. [see FTR] | | 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 | |
| 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 | |

| | | | |
|---|---|---|---|
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| Has the firm failed to describe the scoring in the HOW SUPPLIED section? | | | x |
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| 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?[see FTR] | | X | |
| Does USP have labeling recommendations? If any, does ANDA meet them? | | X | |
| Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container? | X | | |
| Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. | | X | |
| **Bioequivalence Issues:** (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable) | | | |
| Insert labeling references a food effect or a no-effect? If so, was a food study done? | | X | |
| Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why. | | X | |
| **Patent/Exclusivity Issues:** FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. | X | | |

## FOR THE RECORD:

1. MODEL LABELING

   This review was based on the labeling for Fludara® Fludara (Ben Venue Lab; NDA 20-038S/019; Approved 12/01/01; Revised 12/01).

2. PATENTS/EXCLUSIVITIES

**Patent Data – NDA 20-038**

| Patent No. | Patent Expiration | Use Code | Description | How Filed | Labeling Impact |
|---|---|---|---|---|---|
| 4357324 | 2/24/03 | None | | PIII | Same As |

**Exclusivity Data– NDA 20-038**

| Code | Reference | Expiration | Labeling Impact |
|---|---|---|---|
| None | There is no unexpired exclusivity for this product in the Orange Book Database. | N/A | None |

[Vol. A1.1 pg. 1012]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

   GensiaSicor ; 19 Hughes St, Irvine Ca [Vol. B1.1 pg. 1093]

4. CONTAINER/CLOSURE

   6 ml vial, with ~~ glass tubing ~~ stopper is gray with flip off cap and aluminum seal. [Vol. B1.1 pg. 1251]

5. INACTIVE INGREDIENTS

   The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. B1.1 pg. 1038]

6. PACKAGING CONFIGURATIONS

   RLD: Clear glass SDV, 6 mL capacity; packaged in shelf cartons of 5s.
   ANDA: Same as RLD. However individually packaged

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   USP: None.
   RLD: Store under refrigeration 2 - 8C (36-46F).
   ANDA: Same as RLD.

8. DISPENSING STATEMENTS COMPARISON

   USP: None
   RLD: Handle according to the handling of cytoxotic agents.
   ANDA: Same as

9. BIOAVAILABILITY/BIOEQUIVALENCE:

   Firm's request for a waiver of *in vivo* bioequivalence study requirements.

---

Date of Review: 4/29/02 Date of Submission: 1/18/02

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cc:

ANDA: 76-349
DUP/DIVISION FILE
HFD-613/aPayne/JGrace (no cc)
v:\firmsam\gensia\ltrs&rev\76349NA1.L.doc
Review

9/30/02

5/7/2002

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 76-349

# CHEMISTRY REVIEW(S)

# ANDA 76-349

## Fludarabine Phosphate for Injection
## 50 mg/vial (Lyophilized)

## Gensia Sicor Pharmaceuticals, Inc.

**Nashed E. Nashed, Ph.D.**

**Division of Chemistry I**

# Table of Contents

# Chemistry Review Data Sheet

1. ANDA 76-349

2. REVIEW #: 1

3. REVIEW DATE: 5/20/02

4. REVIEWER: Nashed E. Nashed, Ph.D.

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| N/A | N/A |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Original | 1/18/02 |

7. NAME & ADDRESS OF APPLICANT:

Name: Gensia Sicor Pharmaceuticals, Inc.

Address: 19 Hughes, Irvine, CA 92618

Representative: Rosalie A. Lowe

Telephone: 949-457-2808

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Fludarabine Phosphate

9. LEGAL BASIS FOR SUBMISSION:

The firm certifies that in their opinion and to the best of their knowledge, U.S. Patent 4,357,324 will expire on 2/24/03. The firm does not intend to market the drug product until after the patent expires.
The firm indicated that there is no marketing exclusivities exist for Berlex Laboratories' Fludara® NDA 20-038

10. PHARMACOL. CATEGORY: For the treatment of patients with B-cell chronic lymphocytic leukemia.

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 50 mg/vial

13. ROUTE OF ADMINISTRATION: Intravenous Injection

14. Rx/OTC DISPENSED: _X__Rx ___OTC

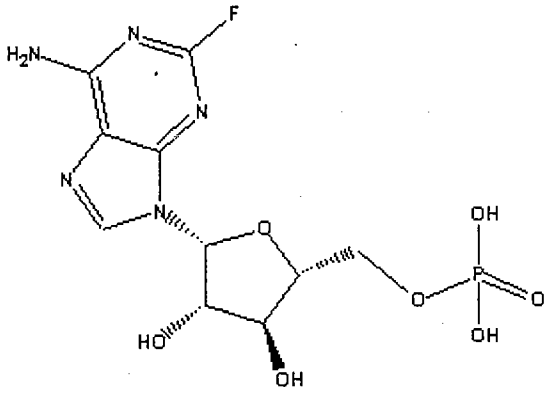
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

9H-Purin-6-amine, 2-fluoro-9-(5-O-phosphono-β-D-arabinofuranosyl)



$C_{10}H_{13}FN_5O_7P$ Molecular Weight 365.21

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| [redacted] | II | [redacted] | [redacted] | 1 | Sat. | 5/23/02 | |
| [redacted] | III | [redacted] | [redacted] | 4 | | | |

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents: N/A**

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| | | |
| | | |
| | | |
| | | |



## 18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Microbiology | Pending | | |
| EES | Pending | | |
| Methods Validation | Submitted | 5/17/02 | |
| Labeling | Deficient | 5/7/02 | A. Payne |
| Bioequivalence | Bio waiver is granted | 5/3/02 | H. Nguyen |
| EA | Categorical exclusion requested | | |
| Radiopharmaceutical | N/A | | |

## 19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes _xx___ No If no, explain reason(s) below:

Transferred from Team 2

APPEARS THIS WAY
ON ORIGINAL

# The Chemistry Review for ANDA 76-349

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

Not approvable due to minor deficiencies.

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

## II. Summary of Chemistry Assessments

### A. Description of the Drug Product(s) and Drug Substance(s)

The drug product Fludarabine Phosphate is packaged in 6 mL vial, — glass tubing USP —————— . Stopper ———————— gray. Aluminum seal filp-off cap 20 mm finish.

The reference listed drug for this application is Fludara® manufactured by Ben Venue Laboratories and marketed by Berlex Laboratories.

The drug substance Fludarabine Phosphate is white to almost-white crystalline powder with molecular formula $C_{10}H_{13}FN_5O_7P$ and molecular weight 365.21.

In terms of chemistry there are no difference between Fludara® and Fludarabine Phosphate. Both products are injection.

Fludarabine Phosphate drug products contain sodium hydroxide, mannitol, and water.
The manufacturing process of the drug product involves ————

The firm has provided blank batch record for intended production ———
The firm has submitted a copy of the executed batch record lot #X01K610 for —
— The manufacturing process is the same.

In-process controls limited to description, osmolality, pH, assay and microbial bioburden.

All analytical methods submitted by the firm were reviewed and found to be satisfactory. The drug substance and drug product are not USP compendial items. Therefore, analytical method validation package for the drug product and drug substance will be submitted to the FDA district laboratory for validation purposes.

**B. Description of How the Drug Product is Intended to be Used**

Fludarabine Phosphate is approved for intravenous injection for treatment of patients with B-cell chronic lymphocytic leukemia. The recommended storage condition is refrigeration, between 2° -8°C (36° -46°F).

**C. Basis for Approvability or Not-Approval Recommendation**

This application is not approvable due to minor deficiencies.

## III. Administrative

**A. Reviewer's Signature**

N. Nashed

**Nashed E. Nashed, Ph.D.** 7/22/02

**B. Endorsement Block**

James M. Fan/7/1/02 7/22/02

APPEARS THIS WAY
ON ORIGINAL

**Redacted** 10

**Page(s) of trade secret and /or confidential commercial information**

APPROVAL PACKAGE SUMMARY FOR 76-349

ANDA: 76-349

FIRM: Gensia Sicor Pharmaceuticals, Inc.

DRUG: Fludarabine Phospate

DOSAGE: Injection

STRENGTH: 50 mg/vial

CGMP STATEMENT/EIR UPDATE STATUS: EER is acceptable 9/16/02

BIO STUDY/BIOEQUIVALENCE: Bio is satisfactory 5/3/02

METHOD VALIDATION: MV is pending.

STABILITY: The firm has provided satisfactory 3 months accelerated stability data at 25±2°C/60±5%RH and 9 months stability data at 5±3°C/ambient humidity. The stability samples will be stored in both upright and inverted positions.

LABELING REVIEW STATUS: Labeling is acceptable 8/20/02

STERILIZATION VALIDATION: Microbiology is acceptable 11/26/02.

BATCH SIZES: The firm has provided master batch record for intended production ——. Also a copy of the executed batch record lot #X01K610 for ——, was included.
The firm will be using the same drug substance manufacturer, same equipment and same process.

COMMENTS: The application is approvable – Pending, MV,

REVIEWER: N. Nashed Nashed E. Nashed, Ph.D. DATE: 12/3/02 12/11/02 NN 2/28/03

SUPERVISOR: James M. Fan 12/12/02 2/28/03

# ANDA 76-349

## Fludarabine Phosphate for Injection
## 50 mg/vial (Lyophilized)

## Gensia Sicor Pharmaceuticals, Inc.

Nashed E. Nashed, Ph.D.

Division of Chemistry I

# Table of Contents

# Chemistry Review Data Sheet

1. ANDA 76-349 (First Generic)

2. REVIEW #: 2

3. REVIEW DATE: 8/19/02

4. REVIEWER: Nashed E. Nashed, Ph.D.

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| N/A | N/A |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Original | 1/18/02 |
| Amendment | 8/6/02 |
| Amendment (Micro) | 9/26/02 |
| Amendment (Micro) | 11/5/02 |
| Amendment (Micro) | 11/19/02 |
| Amendment | 2/24/03 |
| Amendment | 2/25/03 |
| Amendment | 2/26/03 |
| Amendment | 2/27/03 |

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name: Gensia Sicor Pharmaceuticals, Inc.

Address: 19 Hughes, Irvine, CA 92618

Representative: Rosalie A. Lowe

Telephone: 949-457-2808

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Fludarabine Phosphate

9. LEGAL BASIS FOR SUBMISSION:

The firm certifies that in their opinion and to the best of their knowledge, U.S. Patent 4,357,324 will expire on 2/24/03. The firm does not intend to market the drug product until after the patent expires.
The firm indicated that there is no marketing exclusivities exist for Berlex Laboratories' Fludara® NDA 20-038

10. PHARMACOL. CATEGORY: For the treatment of patients with B-cell chronic lymphocytic leukemia.

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 50 mg/vial

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14. Rx/OTC DISPENSED: _X__Rx ___OTC

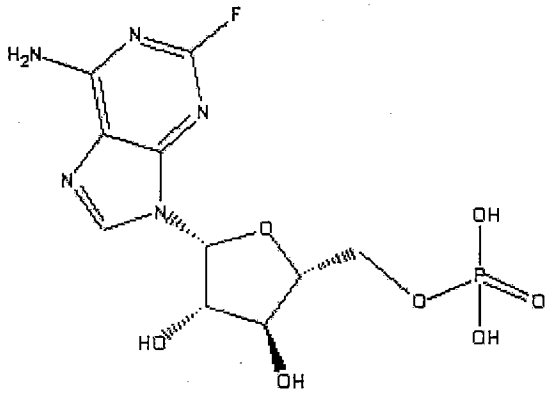
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

9H-Purin-6-amine, 2-fluoro-9-(5-O-phosphono-β-D-arabinofuranosyl)




$C_{10}H_{13}FN_5O_7P$ Molecular Weight 365.21

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| [redacted] | II | [redacted] | [redacted] | 3 | Sat. | 2/26/03 | |
| [redacted] | III | [redacted] | [redacted] | 4 | | | |

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review

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5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents: N/A**

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| | | |
| | | |
| | | |
| | | |

18. STATUS:

APPEARS THIS WAY
ON ORIGINAL

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Microbiology | Acceptable | 11/26/02 | M. Stevens-Riley |
| EES | Acceptable | 9/16/02 | |
| Methods Validation | Submitted | 5/17/02 | |
| Labeling amendment | Acceptable | 8/20/02 | A. Payne |
| Bioequivalence | Bio waiver is granted | 5/3/02 | H. Nguyen |
| EA | Categorical exclusion requested | | |
| Radiopharmaceutical | N/A | | |

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes _xx___ No If no, explain reason(s) below:

The application is MINOR

APPEARS THIS WAY
ON ORIGINAL

# The Chemistry Review for ANDA 76-349

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

The application is approvable (Tentative) pending MV.

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

## II. Summary of Chemistry Assessments

### A. Description of the Drug Product(s) and Drug Substance(s)

The drug product Fludarabine Phosphate is packaged in 6 mL vial, — glass tubing USP — Stopper. — gray. Aluminum seal filp-off cap 20 mm finish.

The reference listed drug for this application is Fludara® manufactured by Ben Venue Laboratories and marketed by Berlex Laboratories.

The drug substance Fludarabine Phosphate is white to almost-white crystalline powder with molecular formula $C_{10}H_{13}FN_5O_7P$ and molecular weight 365.21.

In terms of chemistry there is no difference between Fludara® and Fludarabine Phosphate. Both products are injection.

Fludarabine Phosphate drug products contain sodium hydroxide, mannitol, and water.
The manufacturing process of the drug product involves —

The firm has provided blank batch record for intended production of —
The firm has submitted a copy of the executed batch record lot #X01K610 for —. The manufacturing process is the same.

In-process controls are limited to description, osmolality, pH, assay and microbial bioburden.

All analytical methods submitted by the firm were reviewed and found to be satisfactory. The drug substance and drug product are not USP compendial items. An analytical method validation package for the drug product and drug substance was submitted to the FDA district laboratory on 5/17/02 for validation.

**B. Description of How the Drug Product is Intended to be Used**

Fludarabine Phosphate is approved for intravenous injection for treatment of patients with B-cell chronic lymphocytic leukemia. The recommended storage condition is refrigeration, between 2° -8°C (36° -46°F).

**C. Basis for Approvability or Not-Approval Recommendation**

This application is approvable .

## III. Administrative

**A. Reviewer's Signature**

N. Nashed 2/28/03

**Nashed E. Nashed, Ph.D.**

**B. Endorsement Block**

James M. Fan 2/28/03

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ON ORIGINAL

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**Page(s) of trade secret and /or confidential commercial information**

# ANDA 76-349

## Fludarabine Phosphate for Injection 50 mg/vial (Lyophilized)

## Gensia Sicor Pharmaceuticals, Inc.

**Nashed E. Nashed, Ph.D.**

**Division of Chemistry I**

# Table of Contents



APPEARS THIS WAY
ON ORIGINAL

# Chemistry Review Data Sheet

1. ANDA 76-349 (First Generic)

2. REVIEW #: 3

3. REVIEW DATE: 8/21/03

4. REVIEWER: Nashed E. Nashed, Ph.D.

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| N/A | N/A |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Original | 1/18/02 |
| Amendment | 8/6/02 |
| Amendment (Micro) | 9/26/02 |
| Amendment (Micro) | 11/5/02 |
| Amendment (Micro) | 11/19/02 |
| Amendment | 2/24/03 |
| Amendment | 2/25/03 |
| Amendment | 2/26/03 |
| Amendment | 2/27/03 |
| Correspondence | 3/24/03 |
| Amendment | 7/31/03 |
| Amendment | 8/18/03 |
| Amendment | 8/20/03 |

7. NAME & ADDRESS OF APPLICANT:

Name: Gensia Sicor Pharmaceuticals, Inc.

Address: 19 Hughes, Irvine, CA 92618

Representative: Rosalie A. Lowe

Telephone: 949-457-2808

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Fludarabine Phosphate

9. LEGAL BASIS FOR SUBMISSION:

The firm certifies that in their opinion and to the best of their knowledge, U.S. Patent 4,357,324 will expire on 8/24/03. The firm does not intend to market the drug product until after the patent expires.
The firm indicated that there is no marketing exclusivities exist for Berlex Laboratories' Fludara® NDA 20-038

10. PHARMACOL. CATEGORY: For the treatment of patients with B-cell chronic lymphocytic leukemia.

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 50 mg/vial

13. ROUTE OF ADMINISTRATION: Intravenous Injection

14. Rx/OTC DISPENSED: _X__Rx ___OTC

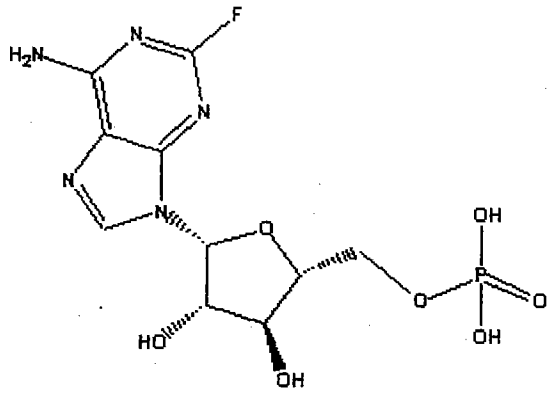
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

9H-Purin-6-amine, 2-fluoro-9-(5-O-phosphono-β-D-arabinofuranosyl)




$C_{10}H_{13}FN_5O_7P$ Molecular Weight 365.21

17. RELATED/SUPPORTING DOCUMENTS:

APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| [redacted] | II | [redacted] | [redacted] | 3 | Sat. | 2/26/03 | |
| [redacted] | III | [redacted] | [redacted] | 4 | | | |

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents: N/A**

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| | | |
| | | |
| | | |
| | | |

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ON ORIGINAL

18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Microbiology | Acceptable | 11/26/02 | M. Stevens-Riley |
| EES | Acceptable | 9/16/02 | |
| Methods Validation | Submitted | 5/17/02 | |
| Labeling amendment | Satisfactory | 8/20/03 | A.Payne |
| Bioequivalence | Bio waiver is granted | 5/3/02 | H. Nguyen |
| EA | Satisfactory | | |
| Radiopharmaceutical | N/A | | |

APPEARS THIS WAY
ON ORIGINAL

## 19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes _xx___ No If no, explain reason(s) below:

The application is MINOR

APPEARS THIS WAY
ON ORIGINAL

# The Chemistry Review for ANDA 76-349

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

The application is approvable - pending MV.

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

## II. Summary of Chemistry Assessments

### A. Description of the Drug Product(s) and Drug Substance(s)

The drug product Fludarabine Phosphate is packaged in 6 mL vial, — glass tubing USP ~~~~~ Stopper ~~~~~ gray. Aluminum seal filp-off cap 20 mm finish.

The reference listed drug for this application is Fludara® manufactured by Ben Venue Laboratories and marketed by Berlex Laboratories.

The drug substance Fludarabine Phosphate is white to almost-white crystalline powder with molecular formula $C_{10}H_{13}FN_5O_7P$ and molecular weight 365.21.

In terms of chemistry there is no difference between Fludara® and Fludarabine Phosphate. Both products are injection.

Fludarabine Phosphate drug products contain sodium hydroxide, mannitol, and water.
The manufacturing process of the drug product involves ~~~~~

The firm has provided blank batch record for intended production of ~~~~~
The firm has submitted a copy of the executed batch record lot #X01K610 for ~~~~~ The manufacturing process is the same.

In-process controls are limited to description, osmolality, pH, assay and microbial bioburden.

All analytical methods submitted by the firm were reviewed and found to be satisfactory. The drug substance and drug product are not USP compendial items. An analytical method validation package for the drug product and drug substance was submitted to the FDA district laboratory on 5/17/02 for validation.

**B. Description of How the Drug Product is Intended to be Used**

Fludarabine Phosphate is approved for intravenous injection for treatment of patients with B-cell chronic lymphocytic leukemia. The recommended storage condition is refrigeration, between 2° -8°C (36° -46°F).

**C. Basis for Approvability or Not-Approval Recommendation**

This application is approvable – pending MV.

## III. Administrative

**A. Reviewer's Signature**

N. Nashed 8/21/03

**Nashed E. Nashed, Ph.D.**

**B. Endorsement Block**

James M. Fan For, GK 8/21/03

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**Page(s) of trade secret and /or confidential commercial information**

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 76-349

# MICROBIOLOGY REVIEW

# Product Quality Microbiology Review
## Review for HFD-620

**24 September 2002**

**ANDA: 76-349**

**Drug Product Name**
**Proprietary:** Fludara®
**Non-proprietary:** Fludarabine Phosphate for Injection
**Drug Product Classification:** N/A

**Review Number:** 1

**Subject of this Review**
**Submission Date:** January 18, 2002 and September 26, 2002 (telephone amendment)
**Receipt Date:** January 22, 2002 and September 27, 2002
**Consult Date:** N/A
**Date Assigned for Review:** September 11, 2002

**Submission History (for amendments only)**
**Date(s) of Previous Submission(s):**
**Date(s) of Previous Micro Review(s):**

**Applicant/Sponsor**
**Name:** Gensia Sicor
**Address:** 19 Hughes
Irvine, CA 92618-1902
**Representative:** Rosalie A. Lowe
**Telephone:** 949-457-2808

**Name of Reviewer:** Marla Stevens-Riley

**Conclusion:** Not recommended for approval on the basis of sterility assurance.

# Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUPPLEMENT:** N/A

2. **SUPPLEMENT PROVIDES FOR:** N/A

3. **MANUFACTURING SITE:** Gensia Sicor
21 Hughes
Irvine, CA 92618-1902

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 50 mg/ 6 mL vial (25 mg/mL), lyophilized, intravenous

5. **METHOD(S) OF STERILIZATION:** [redacted]

6. **PHARMACOLOGICAL CATEGORY:** For treatment of patients with B-cell lymphocytic leukemia who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-agnt containing regimen.

B. **SUPPORTING/RELATED DOCUMENTS:** none

C. **REMARKS:** A telephone amendment dated September 26, 2002 in response to the September 25, 2002 Teleconference is also reviewed.

**filename:** v:microrev\76-349.doc

APPEARS THIS WAY
ON ORIGINAL

# Executive Summary

**I. Recommendations**

**A. Recommendation on Approvability - Not recommended** for approval based on sterility assurance.

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

**II. Summary of Microbiology Assessments**

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

**B. Brief Description of Microbiology Deficiencies** - Incomplete in-process and process validation studies.

**C. Assessment of Risk Due to Microbiology Deficiencies** -The safety risk associated with these deficiencies is minimal.

**III. Administrative**

**A. Reviewer's Signature** Maria Stevens-Riley

**B. Endorsement Block**

M. Stevens-Riley, Ph.D. 10/29/02
N. Sweeney, Ph.D.
10/29/02

**C. CC Block**

cc:
Original ANDA 76-349
Division File
Field copy

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**Page(s) of trade secret and /or confidential commercial information**

# Product Quality Microbiology Review
## Review for HFD-620

**22 November 2002**

**ANDA: 76-349**

**Drug Product Name**
**Proprietary:** Fludara®
**Non-proprietary:** Fludarabine Phosphate for Injection
**Drug Product Classification:** N/A

**Review Number:** 2

**Subject of this Review**
**Submission Date:** November 5, 2002 and November 19, 2002 (telephone amendment)
**Receipt Date:** November 6, 2002 and November 21, 2002
**Consult Date:** N/A
**Date Assigned for Review:** November 12, 2002

**Submission History (for amendments only)**
**Date(s) of Previous Submission(s):** January 18, 2002 and September 26, 2002
**Date(s) of Previous Micro Review(s):** September 24, 2002

**Applicant/Sponsor**
**Name:** Gensia Sicor
**Address:** 19 Hughes
Irvine, CA 92618-1902
**Representative:** Rosalie A. Lowe
**Telephone:** 949-457-2808

**Name of Reviewer:** Marla Stevens-Riley

**Conclusion:** Recommended for approval on the basis of sterility assurance.

# Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUPPLEMENT:** N/A

2. **SUPPLEMENT PROVIDES FOR:** N/A

3. **MANUFACTURING SITE:** Gensia Sicor
21 Hughes
Irvine, CA 92618-1902

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 50 mg/ 6 mL vial (25 mg/mL), lyophilized, intravenous

5. **METHOD(S) OF STERILIZATION:** [redacted]

6. **PHARMACOLOGICAL CATEGORY:** For treatment of patients with B-cell lymphocytic leukemia who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-agent containing regimen.

B. **SUPPORTING/RELATED DOCUMENTS:** none

C. **REMARKS:** The November 5, 2002 subject amendment provides for a response to the Microbiology deficiencies in the letter dated October 29, 2002. In addition, information in the November 19, 2002 telephone amendment will be reviewed.

**filename:** v:microrev\76-349a1.doc

APPEARS THIS WAY
ON ORIGINAL

# Executive Summary

**I. Recommendations**

**A. Recommendation on Approvability - Recommended** for approval based on sterility assurance.

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

**II. Summary of Microbiology Assessments**

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

**B. Brief Description of Microbiology Deficiencies** - There are no deficiencies.

**C. Assessment of Risk Due to Microbiology Deficiencies** -There are no deficiencies for this application. The safety risk associated with this drug product is minimal.

**III. Administrative**

**A. Reviewer's Signature** Maila Stevens-Riley

**B. Endorsement Block**

M. Stevens-Riley, Ph.D. 11/26/02
N. Sweeney, Ph.D. Neal J. Sweeney 11/26/02

**C. CC Block**

cc:
Original ANDA 76-349
Division File
Field copy

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# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 76-349

# BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY COMMENTS

ANDA: 76-349 APPLICANT:Gensia Sicor Pharmaceuticals

DRUG PRODUCT: Fludarabine Phosphate for Injection, 50 mg/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,

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

APPEARS THIS WAY
ON ORIGINAL

Fludarabine Phosphate for Injection
50 mg/vial
ANDA # 76-349
Reviewer: Hoainhon Nguyen
W # 76349w0102.doc

Gensia Sicor Pharmaceuticals
Irvine, CA
Submission Date:
January 18, 2002

Review of a Waiver Request

The firm has requested a waiver from *in vivo* bioavailability requirements for its Fludarabine Phosphate for Injection, 50 mg/vial, in accordance with 21 CFR 320.22 (b) (1).

Comments:

1. The test product is a parenteral drug product intended for intravenous administration.

2. The formulation of the test product is identical to that of the currently approved Fludara® for Injection (NDA # 20-038), 50 mg/vial, manufactured by Berlex, as shown below:

| Ingredients | Test Formulation (per vial) | Fludara's Formulation (per vial) |
|---|---|---|
| Fludarabine Phosphate | 50 mg | 50 mg |
| Mannitol, USP | 50 mg | 50 mg |
| Sodium Hydroxide, NF | to adjust pH | to adjust pH |
| Water for Injection | q.s. | q.s. |

Recommendations:

The Division of Bioequivalence agrees that the information submitted by Gensia Sicor Pharmaceuticals demonstrates that its Fludarabine Phosphate for Injection USP, 50 mg/vial, falls under 21 CFR 320.22 (b) (1) of the Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of *in vivo* bioavailability study be granted. The test product, Fludarabine Phosphate for Injection, 50 mg/vial, is deemed bioequivalent to the currently approved Fludara® for

Injection, 50 mg/vial, manufactured by Berlex.

Hóainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 4/5/2002

Concur: _____ Date: 5/3/2002

for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 76-349 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File

Hnguyen/04-02-02/W #76349w0102.doc
Also under v:\firmsam\gensia\ltrs&rev\76349w0102.doc

Attachments: None

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA 76-349
ANDA DUPLICATE
DIVISION FILE
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen

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Printed in final on / /00

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ YHuang 5/3/2002
HFD-617/K. Scardina 5/3/02
HFD-650/ D. Conner for 5/3/2002

BIOEQUIVALENCY - ACCEPTABLE Submission Date: 01-18-02

**WAIVER** (WAI) oic

Strengths: 50 mg/vial
**Outcome: AC**

Outcome Decisions:
**AC** - Acceptable

WINBIO COMMENTS:

**APPEARS THIS WAY ON ORIGINAL**

# OFFICE OF GENERIC DRUGS
# DIVISION OF BIOEQUIVALENCE

ANDA # : 76-349 SPONSOR : Gensia Sicor Pharmaceuticals
DRUG AND DOSAGE FORM : Fludarabine Phosphate for Injection
STRENGTH(S) : 50 mg/vial
TYPES OF STUDIES : N/A
CINICAL STUDY SITE(S) : N/A
ANALYTICAL SITE(S) : N/A

STUDY SUMMARY : N/A
DISSOLUTION : N/A.
WAIVER REQUEST: Acceptable

**DSI INSPECTION STATUS**

| Inspection needed: NO | Inspection status: | Inspection results: |
|---|---|---|
| First Generic YES | Inspection requested: (date) | |
| New facility _____ | Inspection completed: (date) | |
| For cause _____ | | |
| Other _____ | | |

PRIMARY REVIEWER : Hoainhon Nguyen BRANCH : I
INITIAL : HNC DATE : 4/5/02

TEAM LEADER : Yih-Chain Huang BRANCH : I
INITIAL : YCH DATE : 4/5/2002

for DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.
INITIAL : N Gabrielsson DATE : 5/3/2002

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 : February 22, 2002

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615) 20-FEB-2002

SUBJECT: Examination of the bioequivalence request for waiver submitted with an ANDA for Fludarabine Phosphate for Injection, 50 mg/vial to determine if the application is substantially complete for filing.

Gensia Sicor Pharmaceuticals, Inc. has submitted ANDA 76-349 for Fludarabine Phosphate for Injection, 50 mg/vial. The ANDA contains a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence request for waiver is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for waiver submitted by Gensia Sicor on January 18, 2002 for its Fludarabine Phosphate product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design

   (a) Appropriate number of subjects
   (b) Description of methodology

2. Study results

   (a) Individual and mean data is provided
   (b) Individual demographic data
   (c) Clinical summary

The issue raised in the current situation revolves around whether the study 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.

---

DIVISION OF BIOEQUIVALENCE:

concur:
Barbara M. Davit
TL Branch III
2/21/02

_____ Study meets statutory requirements

_____ Study does **NOT** meet statutory requirements

Reason:

✓ Waiver meets statutory requirements

_____ Waiver does **NOT** meet statutory requirements

Reason:

Director, Division of Bioequivalence

2/22/02
Date

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 76-349

# ADMINISTRATIVE DOCUMENTS

# RECORD OF TELEPHONE CONVERSATION

Telephone conference is in reference to call made by Agency on 2/24/03 to Sonya Hernandez. Agency had questions about two substances: [redacted]
Don't know where the impurities come from?
Why are the stability specifications for drug product release and shelf life different than the drug substance?

The firm responded via Telephone Amendment dated 2/24/2003. The Agency needed further clarification.

Firm: [redacted] are process impurities and are not degradation products. We are uncomfortable with tightening the specs further due to the analytical variability because of the high response factor. The impurities have response factors of [redacted] Therefore, very small peaks would represent approximately [redacted] times the integrated value.

Agency: We still have problem with your spec. If [redacted] are not degradation products, then the amount should not rise from the drug substance, to the release, to the shelf life. The response factor should be same throughout your calculations and thus can not be a reason for the difference in spec limits.

Firm: We have reference from the PF (Pharmacopeia Forum) Nov and Dec 2002, Volume 28/ #6 that gave Fludarabine spec limits even higher than ours. *Paul wanted the firm to fax the reference to him today. Firm agreed to fax reference today.* We have a question about rounding up. For example, if the [redacted] from the drug substance is [redacted] I would round that number to [redacted] and we would be okay; if the [redacted] is [redacted], then we would be over the limit. How could we get around that since the difference could be attributed to analytical variability?

Firm: *After private discussion with the team.* We proposed that the spec limits of [redacted] be the same in release and shelf life ([redacted] and spec limits of [redacted] be the same in release and shelf life [redacted] *However, the proposed specs would be [redacted] higher than the drug substance.* Could you approve the application with our proposal?

Agency: We need to discuss this further, with Frank Holcombe if necessary. We need you to fax the PF.

Orig: ANDA

| |
|---|
| DATE: 2/25/03 |
| ANDA NUMBER 76-349 |
| TELECON INITIATED BY SPONSOR |
| PRODUCT NAME: Fludarabine Injection |
| FIRM NAME: Gensia |
| FIRM REPRESENTATIVES: Rosalie Lowe, Chuan Chen, Allyn Becker |
| TELEPHONE NUMBER: 949-457-2808 |
| FDA REPRESENTATIVES Paul Schwartz, Jim Fan, Nashed Nashed, Ann Vu |
| SIGNATURES: Paul Schwartz PS 2/26/03<br>Jim Fan 2/26/03<br>Nashed Nashed NN 2/26/03<br>Ann Vu |

RECORD OF TELEPHONE CONVERSATION

Called firm about their Micro submission of Nov. 5, 2002.

Dr. Stevens-Riley asked about the answers to deficiency question 4a. which asked: which [redacted] runs included a [redacted] step? The firm's response was [redacted] The data can be found in the original submission, however, the [redacted] were performed with the [redacted] Dr. Stevens-Riley said that she had looked at that data but only [redacted] included a [redacted] step. Ms. Hernandez stated that the information in the [redacted] table was incorrect. Both runs [redacted] and [redacted] should have been foot-noted stating they included a [redacted] step. Run [redacted] was incorrect as submitted. The firm will resubmit the corrected table (4.27).

Dr. Stevens-Riley asked if the [redacted] were run annually or biannually. The SOP on page 3088 of the original submission stated biannually. The firm will check on this and submit the information.

Dr. Stevens-Riley stated that she would need to see data for a [redacted] carried out with the [redacted]. The firm has a [redacted] scheduled for November, but the data will not be ready until December.

The firm said that they have never performed a [redacted] w/ [redacted] step using a [redacted] However, they stated the [redacted] step with the [redacted] is identical to the [redacted] step with the [redacted] Dr. Stevens-Riley asked the firm to submit a description of the equivalency of the [redacted] using the [redacted]. Then she will be able to evaluate if more [redacted] data is needed for review or this application.
Filename:
V:\FIRMSAM\GENSIA\TELECONS\76349MicroNov15-02.doc

**DATE** Nov. 15, 2002

**APPLICATION NUMBER**
76-349

**TELECON**

**INITIATED BY APPLICANT/ FDA**
**Applicant**

**PRODUCT NAME**
Fludarabine Phosphate for Injection, 50 mg/vial

**FIRM NAME**
Gensia Sicor Pharmaceuticals, Inc.

**NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD**
Rosalie Lowe, Regulatory Affairs; Sonya Hernandez, Project Specialist, Reg. Affairs

**TELEPHONE NUMBER**
949-457-2808

**SIGNATURE**
M. Stevens-Riley
M. Stevens-Riley 11/15/02

B. McNeal
B. McNeal 11/15/02

CC: ANDA 76-349 Division File

**Redacted** ____|____

T-Con
9/25/02

**Page(s) of trade secret and /or confidential commercial information**

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: August 27, 2003

FROM: Gregory S. Davis
Deputy Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Gregory S. Davis 28-Aug-2003

Concur Rawlet 8/28/03

SUBJECT: Approval of ANDA 76-349 for Fludarabine Phosphate for Injection USP, 50 mg/vial

TO: The ANDA record for Gensia Sicor, 76-349

This memorandum addresses the approval of a pending ANDA for Fludarabine Phosphate for Injection that references Fludara, a Berlex product. Fludara is a parenteral product intended for the treatment of patients with B-cell chronic lymphocytic leukemia (CLL) who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-agent containing regimen. The ANDA has duplicated the current formulation for Fludara. At the time of submission of the ANDA, there was only one patent protecting the RLD (i.e., U.S. Patent No. 4,357,324) to which Gensia Sicor filed a p III patent certification. This patent had an expiration date of August 24, 2003 and has since expired.

Specifically, this memorandum addresses the concerns raised by Berlex in a letter dated August 11, 2003. The Berlex letter sought to bring to FDA's attention several issues that may affect the agency's determination of the "sameness" of the drug that is the subject of Gensia's abbreviated application and therefore, the ability of the agency to approve their ANDA. The Office of Generic Drugs (OGD) has carefully reviewed the issues brought forward by Berlex and believes that the concerns raised lack merit on their face. Therefore, OGD will proceed with the approval of ANDA 76-349 as planned.

Berlex states that the United States Pharmacopoeia (USP) has recently issued two monographs for fludarabine that became effective on August 1, 2003. Berlex believes that there is a significant likelihood that the Gensia product will not comply with these monographs, thereby rendering the Gensia product

unable to meet the requirement of "same as". Specifically, the first monograph is for the drug substance, fludarabine phosphate. This monograph requires that any product labeled USP must meet a minimum purity standard of 98%. Berlex believes that since the Gensia ANDA has relied on a DMF that was received by the Agency in November 2001, there is a significant likelihood that the Gensia ANDA will not be able to meet this standard. It is unclear to OGD how a conclusion can be drawn regarding the purity of a fludarabine phosphate drug substance based solely on the date of receipt of a DMF. In a minor amendment received by OGD on August 1, 2003, Gensia provided a revised raw material testing specifications and data sheet addressing the new purity standard range of [redacted] Gensia tested their manufacturer's lot number 8376 and found that the purity of their drug substance was [redacted] clearly within the assay limits as determined by USP.

The second monograph is for the drug product, Fludarabine Phosphate for Injection. Berlex believes that ANDA 76-349 is a solution form of fludarabine phosphate injection based on the approved suitability petition, 02P-0245. Berlex states that because this ANDA is not a lyophilized powder, it could not possibly meet the USP monograph for a "for injection" product and could potentially be misbranded if approved.

This claim is based entirely on incorrect information. While it is true that there is an approved suitability petition allowing for the submission of an ANDA for fludarabine phosphate injection (ready to use solution), the basis for submission for ANDA 76-349 is Fludara, fludarabine phosphate for injection. The Gensia product is a lyophilized powder (a "for injection" product) and meets the USP monograph for the drug product.

**Action:** OGD will process the Gensia ANDA in accordance with our routine approval procedures.

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 76-349

# CORRESPONDENCE

sicor
PHARMACEUTICALS, INC.

SICOR Pharmaceuticals, Inc.
19 Hughes
Irvine, CA 92618
Toll Free: 800.729.9991
Telephone: 949.455.4700
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August 20, 2003

Mr. Gary Buehler
Director
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

NAT R 8/26/03

**RE: Fludarabine Phosphate for Injection, USP**
**50 mg/vial**
**ANDA: 76-349**

**TELEPHONE AMENDMENT**

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application, ANDA 76-349, for Fludarabine Phosphate for Injection, 50 mg/mL, submitted on January 18, 2002. Reference is also made to the telephone conversation of August 20, 2003, in which Ms. Anne Vu, Project Manager, requested submission of the following information to the ANDA for Fludarabine Phosphate for Injection, USP:

1. Clarification that the identity of the Related Compound, [redacted] is [redacted]
2. Clarification that the identity of the Related Compound [redacted] is [redacted]
3. Revision of the Related Compound specification for [redacted] to correlate to the USP monograph for Fludarabine Phosphate for Injection, USP.

In accordance with the provisions of Section 314.96(a)(1) of the *Code of Federal Regulations, Title 21*, we hereby amend our application. The following information to Ms. Vu's comments follow:

- We wish to confirm that the identity of the Related Compound, [redacted] is [redacted]
- We wish to confirm that the identity of the Related Compound, [redacted] is [redacted]
- The specification for Related Compound, [redacted] has been revised to correlate to USP monograph for Fludarabine Phosphate for Injection, USP, as follows:

| Tests | Previous Limits Fludarabine Phosphate for Injection, USP | New Limits Fludarabine Phosphate for Injection, USP |
|---|---|---|
| **Related Compounds, %** [redacted] | Shelf Life: NMT [redacted]<br>Release: NMT [redacted] | NMT [redacted] |

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OGD/CDER

The revised Finished Product Testing Specification and Data Sheet for Fludarabine Phosphate for Injection, USP, is attached.

We trust that the information provided in this amendment is satisfactory for your review and final approval of this ANDA. Should you have any additional questions regarding our amendment, please feel free to contact me at (949) 457-2808 or by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Director, Regulatory Affairs
S:\Fludarabine 76-349\Amends\Amend11.doc

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

APPEARS THIS WAY
ON ORIGINAL

sicor
PHARMACEUTICALS, INC.

SICOR Pharmaceuticals, Inc.
19 Hughes
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August 18, 2003

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

ORIG AMENDMENT
N/AF

**RE: Fludarabine Phosphate for Injection, USP**
**50 mg/vial**
**ANDA: 76-349**

**MINOR AMENDMENT – FINAL APPROVAL REQUESTED**

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application, ANDA 76-349, for Fludarabine Phosphate for Injection, 50 mg/mL, submitted on January 18, 2002. Reference is also made to our amendments dated August 6, September 26, November 5, and November 19, 2002; and February 24, February 25, February 26, February 27, 2003, and July 31, 2003. Further reference is made to the Agency's letter dated March 12, 2003.

In accordance with our commitment stated in our ANDA amendment dated July 31, 2003, we have revised our package insert to incorporate the pediatric language revisions reflected in Berlex's Fludara® package insert as approved in their NDA supplement on August 1, 2003. Included in this amendment are twelve (12) samples of final printed labeling (i.e., revised package insert). Additionally, a side-by-side comparison of our revised labeling along with our previous labeling submission is provided for your review with all revisions annotated and explained. No other changes in the conditions under which the product was tentatively approved have occurred.

We ask that OGD not delay the conversion of our tentative ANDA approval to a full ANDA approval beyond August 24, 2003, the expiration of the pediatric exclusivity period granted to Berlex's Fludara®. Congress did not intend to enable the RLD holder to block generic entry beyond the statutory 6 months of extension of an RLD exclusivity under the Pediatric Rule (Section 505a of the Act). Since we believe that this ANDA provides for the first generic form of Fludarabine for Injection, which is eligible for full

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OGD/CDE

approval, it is in the public health interest to provide this generic product to the market in a most expeditious manner to reduce health care costs. Therefore, we request OGD to hasten the issuance of the ANDA approval letter for this application.

We trust that the information provided in this amendment is satisfactory for your review and final approval of this ANDA. Should you have any additional questions regarding our amendment, please feel free to contact me at (949) 457-2808 or by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Director, Regulatory Affairs
S:\Fludarabine 76-349\Amends\Amend10 final approval.doc
cc: Mr. Alonza Cruse, District Director
FDA, Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

August 11, 1993

BERLEX
making medicine work

Berlex Laboratories

Gary Buehler, Pharm D., R.Ph.
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, Maryland 20855-2773

N/NC

2600 Hilltop Drive
P.O. Box 4099
Richmond, CA 94804-0099
Phone: (510) 262-5000
Fax: (510) 669-4350

**RE: ANDA 76-349 and Docket No. 02P-0245/CP1**

Dear Dr. Buehler:

Reference is made to the tentative approval granted by the Food and Drug Administration (FDA) to GensiaSicor Pharmaceuticals' (GSP's) abbreviated new drug application (ANDA) on March 12, 2003, for a solution form of fludarabine phosphate (fludarabine) i.v. injection. This ANDA is based on Berlex's drug, Fludara®, NDA 20-038, a lyophilized powder, and was submitted after FDA approved the above-referenced suitability petition by GSP requesting that FDA accept for filing an ANDA for a solution dosage form.

We are writing to bring to FDA's attention several issues that may affect the agency's determination of the "sameness" of the drug that is the subject of GSP's ANDA, and, hence, the final approval of the ANDA. In particular, the United States Pharmacopeia (USP) has very recently issued two monographs for fludarabine that became effective on August 1, 2003. (Copies attached.) As discussed below, there is a significant likelihood that the GSP product will not comply with these monographs, thereby rendering the GSP product not "the same as" the listed drug, Fludara. Further, such failure to comply with the monographs has implications for the proper labeling of the GSP product, and may also affect FDA's determination as to the therapeutic equivalence of the GSP product to Fludara. We therefore request that the agency give these issues careful consideration prior to granting final approval of GSP's ANDA.

**1. Requirement for "Sameness"**

Section 505(j)(4) of the Federal Food, Drug, and Cosmetic Act (FDC Act) bars the agency from approving an ANDA unless it finds that the active ingredient that is the subject of the proposed drug product is "the same as" that of the listed drug product. 21 U.S.C. § 355(j)(4)(C).[1] FDA's position is that an active ingredient in a generic drug product is the same as that in the listed drug

[1] Although a suitability petition may seek a change of the active ingredient of a listed drug, such a petition may only be approved if the listed drug is a combination drug product. 21 C.F.R. §§ 314.93(b), 314.93(e)(1)(ii). Any other or remaining active ingredient is still subject to the "sameness" requirement. See id. at § 314.93(e)(1)(iii)(D).

if the ingredients meet the same standards for identity. 59 Fed. Reg. 17,950, 17,959 (Apr. 28, 1992). Moreover, FDA typically regards the applicable standards for identity to be those set forth in the relevant USP monograph. Id.; see also Letter from Dennis Baker, FDA, to Donald Beers et al., Docket Nos. 00P-1550 and 01P-0428 (regarding approval of generic cefuroxime axetil drug product), Feb. 15, 2002, at 5 ("FDA often participates in the USP's decisionmaking process with respect to the development and revision of drug substance and drug product monographs because, among other things, these monographs are relevant to FDA's review of ANDAs for generic drug products"). Although the agency is free to impose additional standards that it deems "material" to the sameness of the ingredients, FDA has made clear that the USP compendial standards are the minimum standards governing the sameness inquiry. 59 Fed. Reg. at 17,959.

The USP monograph for the drug substance fludarabine requires a minimum purity of 98%. There is a question as to whether the GSP product will meet this standard. Given that the drug master file (DMF # ———) for fludarabine was filed with FDA in November 2001, there is a significant likelihood that any product made prior to approval of the ANDA will not comply with the purity standard. Moreover, GSP needs to demonstrate in its application that it can consistently produce an active ingredient that meets this standard. Failure of the GSP active ingredient to meet the purity or other standards in the monograph will result in a drug product that is not "the same as" Fludara, and, consequently, final approval of the ANDA would be barred under the statute.

Similarly, the GSP product, as a solution rather than a powder, will not comply with the drug product monograph for fludarabine. The USP monograph for the drug product pertains to "fludarabine phosphate for injection," not "fludarabine phosphate injection." The GSP product will therefore not comply with the monograph with regard to the description, packaging, or directions for reconstitution.

## 2. Labeling Issues

Moreover, the failure of both the drug substance and drug product to meet USP standards raises the potential for a misbranding violation. Section 502(e) of the FDC Act provides that the labeling of a drug must bear its established name. 21 U.S.C. § 352(e)(1). The "established name" is defined as the official name designated under § 508 of the FDC Act, or, if none, the name designated in an official compendium, such as the USP. 21 C.F.R. § 299.4(b). The relevant names in this case are thus "fludarabine phosphate" for the drug substance and "fludarabine phosphate for injection" for the drug product. However, FDA's regulations further provide that "[t]he name by which a drug is designated shall be clearly distinguishing and differentiating from any name recognized in an official compendium unless such drug complies in identity with the identity prescribed in an official compendium under such recognized name." Id. at § 299.5(a). Thus, the drug substance used by GSP to make its product may not bear the name "fludarabine phosphate" in its labeling if the substance does not meet the specifications of the monograph. Nor can the GSP drug product bear the name "fludarabine phosphate injection"

if, in fact, the drug substance used to make the product is not USP-compliant. Failure to bear the established name, however, is a misbranding violation under § 502(e) of the FDC Act.

As well, use of the label "fludarabine phosphate" for the GSP drug product – or the drug substance used to make the product – would render it adulterated if either failed to comply with the monograph specifications. Section 501(b) of the statute provides that a drug is adulterated "[i]f it purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standards set forth in such compendium." 21 U.S.C. § 351(b). To avoid an adulteration charge, the labels of the drug substance and drug product would have to "plainly" state any "difference in strength, quality, or purity" from the USP compendial standards.

Such a statement in the labeling of the GSP product, however, would render it not "the same as" the labeling of Fludara, in defiance of FDA's regulation, 21 C.F.R. § 314.94(a)(8)(iv). Although that regulation permits certain labeling differences, including differences "approved under a petition filed under § 314.93," such authorized differences notably do not include statements describing deviations from USP compendial standards – nor was such a deviation addressed in the GSP suitability petition or FDA's response thereto.

### 3. Equivalence Rating

Finally, even if FDA ultimately decides that the GSP ANDA warrants final approval, the failure of the GSP product to comply with the relevant monographs calls into question the appropriate equivalence rating for the product. In the Preface to FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange Book), FDA states that "[d]rug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling." Orange Book, 23rd ed. (2003), at viii. Drug products are "pharmaceutical equivalents" if they are "formulated to contain the same amount of active ingredient in the same dosage form and to meet the same or compendial or other applicable standards (i.e., strength, quality, purity, and identity)." Id. at vii. Therefore, if two drug products are not pharmaceutical equivalents, they cannot be therapeutic equivalents.

FDA notes that different forms of injectable products (e.g., dry powders for reconstitution, sterile solutions ready for injection) may be regarded as pharmaceutically and therapeutically equivalent provided that they are "designed to produce the same concentration prior to injection and are similarly labeled." Id. at xvii. However, GSP's fludarabine product may present an exception if, as discussed above, its active ingredient does not meet the compendial standard of 98% purity established by the fludarabine drug substance monograph. Its failure to meet this standard would result in its not being pharmaceutically equivalent, and hence, not therapeutically equivalent, to Fludara.

* * * *

BERLEX
making medicine work

In sum, it is the burden of the ANDA applicant to demonstrate not only that its active ingredient complies with the monograph, and is thus "the same as" that of the reference listed drug, but that the applicant possesses the methods and controls necessary to consistently produce a drug substance and drug product that meets such standards. 21 U.S.C. §§ 355(j)(2)(a)(II)(i), 355(j)(4)(A). Given the standards set forth in the newly issued fludarabine monographs, it is dubious whether GSP can meet this burden. We trust that the agency will take the necessary steps to ensure that the GSP product meets all regulatory and compendial requirements, particularly with regard to labeling, prior to the issuance of a final approval letter for ANDA 76-349.

Sincerely,

Anthony Bourdakis

Anthony Bourdakis
Vice President, Regulatory Affairs

x4469

cc: file NDA 20-038

sicor
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July 31, 2003

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

ORIG AMENDMENT
N/AM

**RE: Fludarabine Phosphate for Injection, USP**
**50 mg/vial**
**ANDA: 76-349**

**MINOR AMENDMENT – FINAL APPROVAL REQUESTED**

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application, ANDA 76-349, for Fludarabine Phosphate for Injection, 50 mg/mL, submitted on January 18, 2002. Reference is also made to our amendments dated August 6, September 26, November 5, and November 19, 2002; and February 24, February 25, February 26, and February 27, 2003. Further reference is made to the Agency's letter dated March 12, 2003.

In accordance with the tentative approval granted for this application, we are amending the application approximately 30 days prior to the date we believe we will be eligible for final approval, August 24, 2003.

Subsequent to the tentative approval granted for this application, revisions to the following documents were made to comply with the USP monographs to be effective August 1, 2003.

- Raw Material Specification and Data Sheet for Fludarabine Phosphate, USP
- Finished Product Testing Specification and Data Sheet for Fludarabine Phosphate for Injection, USP

The executed data sheet for a lot of the drug substance (Lot No. K2302550) demonstrates that our test results comply with the USP monograph for Fludarabine Phosphate, USP and is provided in this amendment. The "Related Compounds" test results for the exhibit lot (Lot No. X01K610) of the drug product are summarized in **Table 1** on the following page to demonstrate that our test results also comply with the USP monograph for Fludarabine Phosphate for Injection, USP.

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**Table 1**
**Summary of Test Results for Fludarabine Phosphate for Injection, USP**

| Test | Specification | SICOR Lot No. X01K610 |
|---|---|---|
| **Related Compounds, % w/w** | | |
| A. [redacted] | NMT [redacted] | Not Detected |
| B. [redacted] | NMT [redacted] | [redacted] |
| C. [redacted] | NMT [redacted] | |
| D. [redacted] | NMT [redacted] | Not Detected |
| E. **Any Other (Test A)** | NMT [redacted] | [redacted] |
| F. **Any Other (Test B)** | NMT [redacted] | [redacted] |
| G. **Total Degradation Products** | NMT [redacted] | [redacted] |

No other changes in the conditions under which the product was tentatively approved have occurred.

We acknowledge the potential for labeling revisions given the situation with the pediatric exclusivity held by Berlex for Fludara®. We request that the Agency not allow the issuance of the expected pediatric labeling revisions for our generic Fludarabine to delay the conversion of the tentative ANDA approval to a full ANDA approval beyond the expiration of the pediatric exclusivity period granted to Berlex's Fludara®.

The reference listed drug (RLD) holder is granted an artificial period of exclusivity beyond the statutory exclusivity, when the labeling issues remain unresolved between OGD and the generic company. We do not believe that it is Congress's intent to enable the RLD holder to block generic entry beyond the statutory 6 months of extension of an RLD exclusivity due to unresolved labeling issues. Therefore, we commit to revise the labeling post approval, so the approval can be issued at the time the pediatric exclusivity expires at the end of August.

We trust that the information provided in this amendment is satisfactory for your review and approval. Should you have any additional questions regarding our amendment, please feel free to contact me at (949) 457-2808 or by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Director, Regulatory Affairs
S:\Fludarabine 76-349\Amends\Amend9 final approval.doc
cc: Mr. Alonza Cruse, District Director
FDA, Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

**GensiaSicor™**
PHARMACEUTICALS
A sicor Inc. Company

March 24, 2003

NEW CORRESP
NC

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

RE: Fludarabine Phosphate for Injection
50 mg/vial
ANDA: 76-349

GENERAL CORRESPONDENCE

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application, ANDA 76-349, for Fludarabine Phosphate for Injection, 50 mg/mL, submitted on January 18, 2002. Reference is also made to the telephone conversation of March 24, 2003, in which Ms. Anne Vu, Project Manager, requested submission of additional information to the ANDA for Fludarabine for Injection. Pursuant to Ms. Vu's request, we hereby provide the facsimile correspondence dated February 25, 2003.

If there are any questions concerning this correspondence, please do not hesitate in contacting me at (949) 457-2808. We can also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

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

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MAR 25 2003
OGD / CDER

**GensiaSicor™**
PHARMACEUTICALS
A sicor Company

March 24, 2003

NEW CORRESP

NC

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

**RE: Fludarabine Phosphate for Injection**
**50 mg/vial**
**ANDA: 76-349**

**GENERAL CORRESPONDENCE**

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application, ANDA 76-349, for Fludarabine Phosphate for Injection, 50 mg/mL, submitted on January 18, 2002. Reference is also made to the telephone conversation of March 24, 2003, in which Ms. Anne Vu, Project Manager, requested submission of additional information to the ANDA for Fludarabine for Injection. Pursuant to Ms. Vu's request, we hereby provide the facsimile correspondence dated February 27, 2003.

If there are any questions concerning this correspondence, please do not hesitate in contacting me at (949) 457-2808. We can also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

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

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MAR 25 2003
OGD / CDER

FILE IN ANDA 76-349 (AM)

NEW CORRESP
NC

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GensiaSicor™
PHARMACEUTICALS
A GensiaSicor Company

GensiaSicor Pharmaceuticals
19 Hughes
Irvine, California 92618-1902

# REGULATORY AFFAIRS FAX COVER SHEET

| | | | |
|---|---|---|---|
| **DATE:** | February 27, 2003 | | |
| **TO:** | Anne Vu | | |
| | FDA, CDER, OGD | **PHONE:** | (301) 827-5754 |
| | | **FAX:** | (301) 594-0180 |
| **FROM:** | Rosalie Lowe | **PHONE:** | (949) 457-2808 |
| | Gensia Sicor Pharmaceuticals, Inc. | **FAX:** | (949) 593-8351 |
| **RE:** | Fludarabine Phosphate for Injection, ANDA 76 - 349 | | |
| | **NUMBER OF PAGES INCLUDING COVER SHEET: 1** | | |

Reference is made to Gensia Sicor's Telephone Amendment to ANDA 76-349 dated February 26, 2003. Reference is also made to your telephone message today requesting clarification of the single limits of NMT — and NMT — listed respectively for impurities FP-2HA and FP-2AA on page 2 of 3 of the revised **Finished Product Test Specifications and Data Sheet**. To clarify this point, the single limit applies to both release and stability shelf life and represents Gensia Sicor's standard convention for expressing the limit when the release and shelf life limit are one in the same.

If you have need for further clarification or any additional questions, I can be reached at (949) 455-2808 or by facsimile at (949) 593-8351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Director, Regulatory Affairs

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GensiaSicor™
PHARMACEUTICALS
A sicor Company

February 26, 2003

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

ORIG AMENDMENT
N/AM

**RE: Fludarabine Phosphate for Injection**
**50 mg/vial**
**ANDA: 76-349**

**TELEPHONE AMENDMENT**

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application, ANDA 76-349, for Fludarabine Phosphate for Injection, 50 mg/mL, submitted on January 18, 2002. Reference is also made to the telephone conversations of February 24, 25, and 26, 2003, between Gensia Sicor and the Agency regarding chemistry issues related to the ANDA.

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

Purusant to the FDA's request, the drug product specification limits has been harmonized with the drug substance specification limits for the impurities, ——— , and . ——— The revised **Finished Product Test Specifications and Data Sheet** is attached for your review. These specification limit changes are summarized as follows.

RECEIVED
FEB 27 2003
OGD / CDER

**Summary of Specification Limit Changes for Fludarabine Phosphate for Injection Finished Product**

| Tests | Previous Limits Fludarabine Phosphate for Injection | New Limits Fludarabine Phosphate for Injection |
|---|---|---|
| **Related Compounds, %** | Shelf Life: NMT [redacted]<br>Release: NMT [redacted] | NMT [redacted] |
| • [redacted] | Shelf Life: NMT [redacted]<br>Release: NMT [redacted] | NMT [redacted] |

[1] NMT = Not More Than

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

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Director, Regulatory Affairs

S:\Fludarabine 76-349\Amends\Amend 6.doc

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

Gensia Sicor™
PHARMACEUTICALS
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February 24, 2003

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

ORIG AMENDMENT
N/A M

**RE: Fludarabine Phosphate for Injection**
**50 mg/vial**
**ANDA: 76-349**

**TELEPHONE AMENDMENT**

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application, ANDA 76-349, for Fludarabine Phosphate for Injection, 50 mg/mL, submitted on January 18, 2002. Reference is also made to the telephone conversation of February 24, 2003 between Gensia Sicor and Ms. Anne Vu, Project Manager, regarding chemistry issues related to the ANDA.

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

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

Sincerely,

for Rosalie A. Lowe
Director, Regulatory Affairs

S:\Fludarabine 76-349\Amends\Amend 5.doc

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

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FEB 25 2003
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*Gensia Sicor Pharmaceuticals, Inc.*
*FLUDARABINE PHOSPHATE FOR INJECTION*
*ANDA 76-349*
***Response to Agency Telephone Call of February 24, 2003***

1. *With regard to the related substance specifications, specifically ' ——— and* ———

*Where are these related substances coming from? If they are process impurities, why is the shelf specification higher than the release specification?*

---

The ——— and ——— are process impurities included in the DMF and vendor's Certificate of Analysis (COA) for Fludarabine Phosphate as ——— and ——— with limits of ——— and ——— respectively.

The stability data obtained, to date, for the drug product shows that ——— and ——— are not degradation products. Therefore, Gensia Sicor has tightened the shelf life limits for Related Compounds ———. and ——— to ———, and ——— respectively. The small difference (i.e., ———) between the release and stability limits is implemented for potential analytical variability. The revised **Finished Product Test Specifications and Data Sheet** immediately follows. The specifications are summarized as follows.

**Summary of Specification Limit Changes for Fludarabine Phosphate for Injection Finished Product**

| Tests | Previous Limits Fludarabine Phosphate for Injection | New Limits Fludarabine Phosphate for Injection |
|---|---|---|
| **Related Compounds, %** | Shelf Life: NMT[1] ———<br>Release: NMT ——— | Shelf Life: NMT ———<br>Release: NMT ——— |
| • ——— | Shelf Life: NMT ———<br>Release: NMT ——— | Shelf Life: NMT ———<br>Release: NMT ——— |

[1] NMT = Not More Than

APPEARS THIS WAY
ON ORIGINAL

GensiaSicor™
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November 19, 2002

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

ORIG AMENDMENT
N/AS

**RE: Fludarabine Phosphate for Injection**
**50 mg/vial**
**ANDA: 76-349**

**MICROBIOLOGY AMENDMENT**

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application, ANDA 76-349, for Fludarabine Phosphate for Injection, 50 mg/mL, submitted on January 18, 2002. Reference is also made to the Agency's deficiency letters dated July 24, 2002 and October 29, 2002. Further reference is made to the telephone conversation between Gensia Sicor and the Office of Generic Drugs on November 15, 2002.

The Agency requested clarification with regard to microbiology information presented in our original ANDA and our deficiency letter response dated October 29, 2002. Ms. Stevens-Riley, microbiology reviewer, referenced our response to Microbiology Deficiency Item #A.4 which stated " lots M00E601 and M01D601 , included the step, the data was previously provided in the original application on page 3091." Ms. Stevens-Riley indicated only lot M00E601 is annotated as a run in the original submission, Table 4.27, page 3091. We wish to clarify lot M01D601 was a run, however, Table 4.7 was not appropriately footnoted. The revised table with the correct footnoting immediately follows.

Ms. Stevens-Riley requested clarification with respect to Gensia Sicor's **SOP QML-1021** referenced in the original submission and the text on page 3088, which specifies with a step are performed on a biannual basis. Ms. Stevens-Riley indicated that if this information in the SOP is correct, the do not comply with this schedule.

**SOP QML-1021** specifies the , is a non-routine intervention that must occur once per calendar year. Therefore, the text on page 3088 with respect to the frequency of the step is incorrect.

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Finally, Ms. Stevens-Riley requested [redacted] data on the [redacted] equipment with the [redacted] or a justification on the use of the existing [redacted] data to support the current [redacted] process. We wish to clarify the [redacted] process and procedures after the filling step are identical whether using the [redacted] machines. Specifically, the [redacted] Again, the product, process and personnel flows, equipment room conditions and classifications remain the same for the [redacted] process. Therefore, the use of the existing data supports the use of the current [redacted].

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 above information.

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

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Director, Regulatory Affairs

S:\Fludarabine 76-349\Amends\Amend 2.doc

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

**Table 4.27**

**Summary of the**

| Media Fill Lot # | Date Filled | Fill Volume/ Size of Unit | (mm) | (units/ min) | (hrs) | Microbial Challenge | # Vials Tested/ # Positive | # of samples / # of excursions | | | Total Particulate min-max |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Surface[1] | Microbial | Personnel Surface [3] | |
| M00C601 | | | | | | Positive | | | | | |
| M00E601[5] | | | | | | Positive | | | | | |
| M00K610 | | | | | | Positive | | | | | |
| M00L610 | | | | | | Positive | | | | | |
| M00S601 | 0 | | | | | Positive | | | | | |
| M01B603 | | | | | | Positive | | | | | |
| M01C606 | | | | | | Positive | | | | | |
| M01D601[5] | | | | | | Positive | | | | | |
| M01J605[7] | | | | | | Positive | | | | | |
| M01J601[7] | | | | | | Positive | | | | | |
| M01J606[7] | | | | | | Positive | | | | | |
| M01N601[7] | | | | | | Positive | | | | | |

1 *The MAL for microorganisms when monitoring surfaces located in the*
2 *The MAL for microorganisms when monitoring the*
3 *The MAL for microorganisms when monitoring personnel surfaces located in the are presented in Table 6.2 of Section 6 in this volume.*
4
5 *Lyophilized*
6
7 *Filled using the*

## Conclusion

The studies validate Gensia Sicor's manufacturing processes on and all other operations used to produce products, including Fludarabine Phosphate for Injection. Additionally, the support the proposed manufacturing criteria for Fludarabine Phosphate for Injection, specifically the maximum duration of The theoretical maximum duration of for Fludarabine Phosphate for Injection, at the minimum suitable

**GensiaSicor™**
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November 5, 2002

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

ORIG AMENDMENT
N/AS

**RE: Fludarabine Phosphate for Injection**
**50 mg/vial**
**ANDA: 76-349**

**MICROBIOLOGY AMENDMENT**

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application, ANDA 76-349, for Fludarabine Phosphate for Injection, 50 mg/vial, submitted on January 18, 2002. Reference is also made to the Agency's deficiencies dated July 24, 2002. Reference is also made to the microbiology deficiencies dated October 29, 2002.

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

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

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Director, Regulatory Affairs

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

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A sicor Company

September 26, 2002

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

ORIG AMENDMENT
N/AM

**RE: Fludarabine Phosphate for Injection**
**50 mg/vial**
**ANDA: 76-349**

**TELEPHONE AMENDMENT**

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application, ANDA 76-349, for Fludarabine Phosphate for Injection, 50 mg/mL, submitted on January 18, 2002. Reference is also made to the Agency's deficiencies dated July 24, 2002. Further reference is made to the telephone conversation between Gensia Sicor and the Office of Generic Drugs on September 25, 2002.

The Agency requested clarification with regard to microbiology information presented in ANDA No. 76-349 for Fludarabine Phosphate for Injection. Specifically, Ms. Marla Stevens-Riley, Microbiology Reviewer, OGD, FDA, indicated that the [redacted] data tables presented in Gensia Sicor's ANDAs for [redacted] for [redacted], are exactly the same as the table presented in Gensia Sicor's ANDA No. 76-349 for Fludarabine Phosphate for Injection which refers to [redacted]. Since the data presented in the tables should represent different [redacted] in different rooms, she asked that the data be explained.

In response to Ms. Stevens-Riley's comment, I informed the Agency that the [redacted] data table presented on page 3091 in ANDA No. 76-349 for Fludarabine Phosphate for Injection reflected the correct [redacted] data for [redacted], and that the information presented in the ANDAs for [redacted] were in error. We committed to revise the tables in the ANDAs for [redacted] which would be submitted under separate cover letters to the respective ANDAs.

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Ms. Stevens-Riley then questioned whether the [redacted] data presented in ANDA No. 76-349 for Fludarabine Phosphate for Injection reflected data for the [redacted] equipment, since she had a similar issue related to her review of ANDA No. [redacted] for [redacted] I informed the Agency that the [redacted] data reflected information from both the [redacted] equipment for [redacted]. Ms. Stevens-Riley requested that Gensia Sicor present "equipment specific" (i.e., [redacted] intended for use to commercially manufacture Fludarabine Phosphate for Injection) data from three (3) consecutive [redacted] in [redacted]. Therefore, Table 4.27 has been revised to reflect data from three (3) consecutive [redacted] generated from *only* the [redacted] equipment in [redacted]. The revised table immediately follows.

Additionally, we wish to correct the typographical error on page 3086 (under the subheading "Scope" to reflect the correct room number to [redacted]. The revised page is provided immediately following the aforementioned revised table.

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 above information.

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

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Director, Regulatory Affairs

S:\Fludarabine 76-349\Amends\Amend 2.doc

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

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August 6, 2002

N/AM

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

ORIG AMENDMENT

**RE: Fludarabine Phosphate for Injection**
**50 mg/vial**
**ANDA: 76-349**

**MINOR AMENDMENT**

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application, ANDA 76-349, for Fludarabine Phosphate for Injection, 50 mg/mL, submitted on January 18, 2002. Reference is also made to the Agency's deficiencies dated July 24, 2002.

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

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

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Director, Regulatory Affairs

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

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ANDA 76-349

MAR 14 2002

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

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: Fludarabine Phosphate for Injection, 50 mg/vial

DATE OF APPLICATION: January 18, 2002

DATE (RECEIVED) ACCEPTABLE FOR FILING: January 22, 2002

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

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

Should you have questions concerning this application, contact:

Michelle Dillahunt
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S. Davis for

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

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505(j)(2)(A) OK
13-MAR-2002
Gregory D. Davis

January 18, 2002

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

**RE: Fludarabine Phosphate for Injection**
**50 mg/vial**
**ANDA: Number to be Assigned**

Dear Mr. Buehler:

In accordance with Section 314.92 of the *Code of Federal Regulations, Title 21*, we hereby submit an Abbreviated New Drug Application for Fludarabine Phosphate for Injection, 50 mg/vial, a parenteral preparation supplied as:

| Strength | Drug Content | How Supplied |
|---|---|---|
| 50 mg/vial | 50 mg per 6 mL vial | 6 mL single dose vial |

Gensia Sicor's proposed drug product is the generic version of Berlex Laboratories' Fludara® (Fludarabine Phosphate for Injection, 50 mg/vial), pursuant to NDA No. 20-038 (001). Berlex Laboratories' drug product appears in the FDA listing titled *Approved Drug Products with Therapeutic Equivalence Evaluation, 21st Edition.* The approved drug product marketed by Berlex Laboratories (manufactured by Ben Venue Laboratories) is available as a 50 mg/vial single dose vial.

Our proposed drug product, Fludarabine Phosphate for Injection, has the same active and inactive ingredients, dosage form, strength, route of administration, and conditions of use as Berlex Laboratories' listed drug product.

CENTER FOR DRUG EVALUATION AND RESEARCH
DCRM
JAN 22 2002
OGD

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

Fludarabine Phosphate for Injection will be packaged in clear glass vials. The vials will be sealed with stoppers from [redacted] composed of [redacted]

One (1) stability lot Fludarabine Phosphate for Injection was manufactured and data are presented in **Section XVII** of this application.

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

The application consists of three (3) volumes and has been formatted in accordance with the Office of Generic Drug's Guidance for Industry, Organization of an ANDA, OGD #1, issued February 1999. Copies are provided as follows:

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

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

Since the stability indicating methods are non-compendial, 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.

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. We can also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Director, Regulatory Affairs

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