

May 28, 2002

Dockets Management Branch  
Food and Drug Administration  
Department of Health and Human Services  
Room 1061, HFA-305  
5630 Fishers Lane  
Rockville, Maryland 20852

**RE: Fludarabine Phosphate Injection,  
25 mg/mL**

**CITIZEN PETITION**

The undersigned submits this Petition under the provisions of the Federal Food, Drug and Cosmetic Act, Section 505(j)(2)(c) and 21 CFR § 314.93, 10.20 and 10.30 to request the Commissioner of Food and Drugs to allow submission of an abbreviated new drug application (ANDA) for Fludarabine Phosphate Injection, 25 mg/mL, in a ready-to-use solution for injection.

The undersigned also submits this request for a full waiver of pediatric studies for the proposed Fludarabine Phosphate Injection product as a treatment for B-cell chronic lymphocytic leukemia (CLL) under 21 CFR § 314.55(c). This waiver is requested because it is impossible or highly impractical to conduct the necessary studies of this drug in a pediatric population due to the extremely small size of the affected population (i.e., nil occurrence of CLL in the population under 20 years of age).

**A. Action Requested**

The Petitioner requests that the Commissioner of Food and Drugs permits a change in the dosage form to allow for submission of an abbreviated new drug application (ANDA) for Fludarabine Phosphate Injection, 25 mg/mL, with a total drug content of 50 mg/2 mL in a single use vial. The basis of the Petition is the reference listed drug product, Fludara® for Injection, marketed by the innovator, Berlex, which is available in one

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presentation: a single use vial containing 50 mg of lyophilized Fludarabine Phosphate. Berlex received approval of NDA 20-038 on April 18, 1991, for Fludara® for Injection (Fludarabine Phosphate for Injection).

The petition also seeks a full waiver of pediatric studies for this product.

**B. Statement of Grounds**

1. Suitability Petition

The subject of the Petition for Fludarabine Phosphate Injection, 25 mg/mL, is to permit a change in the drug dosage form from a lyophilized powder to a ready-to-use liquid. The reference listed drug product, Fludara®, marketed by the innovator, Berlex, is available only as a lyophilized powder requiring reconstitution.

Gensia Sicor's proposed drug product will be packaged in a single use vial Fludarabine Phosphate Injection, 25 mg/mL, with a total drug content of 50 mg/2 mL, which is the same as the reference listed drug product other than that the reference listed drug is a lyophilized powder – 50 mg per vial.

Item	Gensia Sicor's Fludarabine Phosphate Injection	Berlex's Fludara® Fludarabine Phosphate for Injection
Dosage Form	Sterile Liquid Injection	Sterile Lyophilized Powder
Route of Administration	Intravenous	Intravenous
Fludarabine Phosphate Concentration	25 mg/mL	25 mg/mL when reconstituted
Volume	2 mL	2 mL
Total Drug Content	50 mg per vial	50 mg per vial
How Supplied	50 mg/2 mL in Single Use Vial	50 mg Lyophilized Powder in Single Use Vial

A liquid formulation of Fludarabine Phosphate would make dosage preparation easier and less time consuming for practitioners preparing the drug for administration.

A liquid formulation would be safer for the practitioner to use. Because reconstitution is unnecessary, fewer syringe/needle manipulations and fewer vial entries would be required which reduces the number of needle stick opportunities.

There would also be fewer opportunities to introduce extraneous touch contamination to the product.

The proposed drug may provide a reduction in hazardous waste disposal and cost for the course of therapy because no diluent vial is required.

The subject drug is intended for use only as described in the **Indications**, and **Dosage and Administration** sections of the proposed package insert appended in **Attachment 1**. To support this petition, a Medical Rationale for the proposed product is provided in **Attachment 2**.

Appended in **Attachment 3** is the package insert for Berlex's Fludara<sup>®</sup> (Fludarabine Phosphate for Injection). Gensia Sicor's labeling for the proposed drug is essentially identical to that of Berlex's, Fludara<sup>®</sup> (Fludarabine Phosphate for Injection), but differs only with respect to the description of the product, product name, the how-supplied statement, and the specific manufacturer's information.

## 2. Request for Full Waiver of Pediatric Studies Requirement

FDA regulations require that "each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration" must contain "data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric populations..." 21 CFR § 314.55(a). Since this suitability petition requests permission to submit an ANDA for a new dosage form, this new dosage form may be subject to the pediatric studies requirement. Accordingly, the undersigned hereby requests a full waiver of that requirement for the proposed product under 21 CFR § 314.55(c).

FDA may waive the pediatric study requirements for some or all pediatric age groups if it determines that:

- (i) The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients,
- (ii) Necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed, or
- (iii) There is evidence strongly suggesting that the drug product would be ineffective or unsafe in all pediatric age groups.

The undersigned requests this waiver in accordance with 21 CFR § 314.55(c)(2)(ii) because it is impossible or highly impractical to conduct the necessary studies for

this drug in a pediatric population due to the extremely small size of the affected population (i.e., nil occurrence of CLL in the population under 20 years of age).

According to the National Cancer Institute SEER Cancer Statistics Review 1973-1999 (refer to data provided in **Attachment 4**), about 10,800 Americans will develop lymphocytic leukemia. Our research concluded that approximately 30 percent of CLL cases occur among men and women 65 – 74 and 74 – 84 years of age (representing a combined total of approximately 60 percent of CLL cases). Our research also showed nil occurrence of CLL among men and women under 20 years of age.

### **C. Environmental Impact**

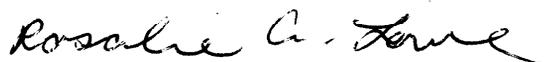
In accordance with 21 CFR § 25.24(c)(1), an Environmental Impact Analysis Statement is not required if there is a determination that Fludarabine Phosphate Injection is suitable for ANDA status.

### **D. Certification**

The undersigned certifies that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the Petitioner which are unfavorable to the Petition.

We trust you will find the information in the Petition to be satisfactory for your review and approval. Should you have any questions or require further clarification, please contact me at (949) 457-2808.

Sincerely,



Rosalie A. Lowe  
Director, Regulatory Affairs

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<b>1</b>	<b>Proposed Package Insert for Gensia Sicor's Fludarabine Phosphate Injection 25 mg/mL</b>
<b>2</b>	<b>Medical Rationale for the Proposed Product Included as Statement of Grounds</b>
<b>3</b>	<b>Berlex Fludara® (Fludarabine Phosphate for Injection) Package Insert</b>
<b>4</b>	<b>National Cancer Institute SEER Cancer Statistics Review 1973 - 1999</b>
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