

Attachment 2

Medical Rationale for the Proposed Product Included as Statement of Grounds

Medical Rationale

Fludarabine Phosphate Injection

25 mg/mL, Single Use Vial

PHARMACOLOGY:

Fludarabine is a fluorinated nucleotide analog of the antiviral agent vidarabine.

Fludarabine 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.

INDICATIONS FOR USE:

Chronic lymphocytic leukemia (CLL): Treatment of patients with B-cell CLL who have not responded to or have progressed during treatment with at least one standard alkylating agent-containing regimen.

DOSAGE:

The recommended dose of fludarabine phosphate is 25 mg/m² administered intravenously over a period of approximately 30 minutes daily for five (5) consecutive days. Each 5-day course of therapy should commence every twenty eight (28) days.

Dosage may be decreased or delayed based on evidence of hematologic or nonhematologic toxicity.

RATIONALE:

The currently marketed product, Fludara[®] (Fludarabine Phosphate for Injection) is available in one size: a single use vial containing 50 mg of Fludarabine Phosphate in lyophilized form requiring reconstitution.

The proposed product contains Fludarabine Phosphate Injection, 25 mg/mL, with a total drug content of 50 mg/2 mL, in an aqueous ready-to-use formulation.

A liquid formulation of Fludarabine Phosphate would make dosage preparation easier and less time consuming for practitioners tasked with 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 would reduce the number of needle stick opportunities. There would also be fewer opportunities to introduce extraneous touch contamination to the product.

Market research indicates that liquid ready-to-use products are highly preferred by practitioners.

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 proposed product, Fludarabine Phosphate Injection, 25 mg/mL, with a total drug content of 50 mg/2 mL, in a single use vial does not pose a question of safety or effectiveness because the uses, doses, and route of administration of the proposed product are the same as those of the listed drug.

SUMMARY:

In summary, the availability of Fludarabine Phosphate Injection, 25 mg/mL, with a total drug content of 50 mg/2 mL, in a single use vial will save time, offer convenience, enhance practitioner safety and deliver cost saving advantages over Fludara[®], which is currently available in a vial requiring reconstitution containing 50 mg of lyophilized Fludarabine Phosphate.

The proposed drug product is intended for use only as described in the **Indications and Usage** and **Dosage and Administration** sections of Gensia Sicor's draft package insert, provided in **Attachment 1**.

We believe that the information presented in this correspondence for Fludarabine Phosphate Injection supports our claim that the product dosage form is suitable for an abbreviated new drug application.

REFERENCES:

1. Package insert for Fludara[®] (Fludarabine Phosphate for Injection). Revised December, 2001.
2. National Cancer Institute SEER Cancer Statistics Review 1973-1999.