Clinical Review
sNDA 20-038

Drug Name	**Fludarabine Phosphate**
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Documents reviewed	**13 volume sponsor submission**

Clinical Review for NDA 20-038s

1. Executive Summary

The intent of this sNDA is to provide information from clinical trials of fludarabine phosphate (Fludara®) in pediatric cancer patients to fulfill the requirements outlined in the FDA Written Request for obtaining pediatric exclusivity.

Fludarabine phosphate was approved in 1991 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. Its patent expires on February 23, 2003.

As CLL does not occur in children, the proposed pediatric labeling for Fludara® contains information regarding pediatric dosing in relapsed pediatric acute lymphocytic leukemia (ALL) and acute myelocytic leukemia (AML).

The sponsor has submitted clinical data on pediatric dosing and pharmacokinetic studies derived from two studies [CCG-097 and CCG-0895] conducted by the Children's Cancer Group (CCG), presently known as Children's Oncology Group (COG). Data from these two studies have been reported in the following publications:

CCG-097 - Avramis V., Champagne J., Sato J., Krailo M., Ettinger L., Poplack D., Finklestein J., Reaman G., Hammond D., Holcenberg J. Pharmacology of Fludarabine Phosphate After a Phase I/II Trial by a Loading Bolus and Continuous Infusion in Pediatric Patients. Cancer Res. 50: 7226-7231 1990.

CCG-0895 - Avramis V., Wiersma S., Krailo M., Ramilo-Torno L., Sharpe A., Liu-Mares W., Kwock R., Reaman G., Sato J. for the Children's Cancer Group. Pharmacokinetic and Pharmacodynamic Studies of Fludarabine and Cytosine Arabinoside Administered as Loading Boluses followed by Continuous Infusions after a Phase I/II Study in Pediatric Patients With Relapsed Leukemias. Clin Cancer Res 4: 45-52 1998.

The first study, CCG-097, was a Phase I dose finding and PK study of a loading bolus followed by continuous infusion of fludarabine in patients with previously treated advanced acute leukemias or solid tumors. Enrollment included 9 patients with acute nonlymphoblastic leukemia (ANLL), 36 patients with ALL and 17 solid tumor patients. The MTD, defined in the above referenced publication in patients with solid tumors, was a loading bolus of 7 mg/m2 followed by a continuous infusion of 20.0 mg/m2 for 5 days. In patients with acute leukemias, the MTD was not reached. The highest dose administered was a loading bolus of 10.5 mg/m2 followed by a continuous infusion of 30.5 mg/m2 for 5 days (Dose Level 6).

The difference in the MTDs between the leukemia and solid tumor patients appeared to be related to the way dose-limiting toxicities (DLT) were evaluated. In leukemia

patients, hematologic toxicities were not considered in the evaluation of DLTs since marrow ablation was a goal of therapy. CCG decided to cease escalation beyond the planned highest dose level because of concern for potential irreversible CNS toxicity previously reported in adults. In the solid tumor patients, the DLT was myelosuppression.

An independent retrospective analysis of the MTD could not be conducted, primarily due to missing or incomplete case report forms (CRFs).

An independent retrospective analysis of response in this trial could not be conducted, primarily due to missing or incomplete case report forms (CRFs).

The second study, CCG-0895, was a Phase 1/2 dose-finding, PK, and pharmacodynamic (PD) study of a loading bolus followed by continuous infusion of fludarabine followed by a loading bolus and then continuous infusion of ara-C in children with previously treated advanced acute leukemias. As such it provided no information on the efficacy or safety of fludarabine phosphate alone in pediatric acute leukemia.

1.1 Recommendations

1.1.1 Recommendation on Approvability

The low response rate, especially the low complete response rate, and relatively brief duration of response in pediatric refractory ALL and the absence of response in ANLL and solid tumors do not suggest a role for fludarabine phosphate in the treatment of these malignancies. The combined fludarabine/ara-C trial achieved a modest response rate at the cost of considerable toxicity (see section 8.3).

While the fludarabine/ara-C study cannot provide data on the efficacy of fludarabine alone it does provide efficacy and safety data for the combination. As such it is valuable since it is unlikely that physicians would treat relapsed pediatric ALL with a single agent.

Conclusions:

1. There is no reason to modify the label to include the pediatric data that was presented in this sNDA.

2. By conducting the two studies the sponsor met the requirement for pediatric exclusivity.

1.1.2 Recommendation on Phase 4 Studies and/or Risk Management Steps

Not relevant

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