CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-673
UPDATED

Drug name:	CLOLAR®
Generic name:	Clofarabine
Formulation:	1mg/mL solution for intravenous administration
Pediatric Indication:	Refractory or relapsed acute lymphoblastic leukemia (ALL) and acute myelogenous leukemia (AML) in children.
Current Submission:	NDA-NME
Applicant:	Ilex Products Inc. 4545 Horizon Hill Blvd. San Antonio, Texas 78229-2263
OCPB Division:	Division of Pharmaceutical Evaluation I (HFD-860)
OND Division:	Division of Oncology Drug Products (HFD-150)
Submission Dates:	29-Mar-2004, 2-Aug-2004, 5-Aug-2004, Oct-3-2003
Primary Reviewer:	Roshni Ramchandani, Ph.D.
Pharmacometrics Team Leader:	Joga Gobburu, Ph.D.
Team Leader:	Brian Booth, Ph.D.

I. Executive Summary

Clofarabine is a purine nucleoside analog. The applicant has conducted studies evaluating the use of clofarabine in the treatment of acute lymphoblastic leukemia (ALL) and acute myelogenous leukemia (AML) in pediatric patients. The applicant has conducted 3 clinical studies that form the basis for the NDA application and include a Phase 1 study and 2 phase 2 studies. Study # ID99-383 was a phase 1 open-label, non-randomized, dose escalation study for pediatric patients with hematological malignancies (ALL and AML) who have failed standard therapy or for whom no such therapy existed (n=25). Patients received doses of clofarabine as 1-3 hr IV infusion daily × 5 days, every 2 to 6 weeks for a maximum of 12 cycles. The doses evaluated were 11.25, 15, 30, 40, 52 and 70 mg/m^2/day. The objective of this study was to establish the maximum tolerated dose and obtain pharmacokinetic data in this population. Study # CLO-212 was a phase 2 open-label, non-randomized study in pediatric patients (1-20 yrs) with refractory or relapsed acute lymphoblastic leukemia (ALL) (n=49). Patients received 52 mg/m^2/day of clofarabine as a 2-hr IV infusion daily × 5 days, every 2 to 6 weeks for a maximum of 12 cycles. The objective of this study was to examine the effectiveness of clofarabine in this population as well as to obtain data on the pharmacokinetics (PK) of clofarabine in the pediatric population. Study # CLO-222 was a phase 2 open-label, non-randomized study in pediatric patients (1-20 yrs) with refractory or relapsed acute myelogenous leukemia (AML) (n=35). Patients received 52 mg/m^2/day of clofarabine as a 2-hr IV infusion daily × 5 days, every 2 to 6 weeks for a maximum of 12 cycles. The objective of this study was to examine the effectiveness of clofarabine in this population as well as to obtain data on the PK of clofarabine in the pediatric population.

The population pharmacokinetics of clofarabine were studied in 40 pediatric patients, aged 2 to 19 years (21 males/19 females), from the above studies. Clofarabine pharmacokinetics were best described by a 2-compartment model with first order elimination. Body weight was a significant predictor for all model parameters (CL, Q, V1 and V2). BSA-normalized doses of 52 mg/m^2 produced equivalent exposure across a wide range of BSAs. Based on a non-compartmental analysis, systemic clearance and volume of distribution at steady-state were estimated to be 28.8 $L/h/m^2$ and 172 L/m^2, respectively. The terminal half-life was estimated to be 5.2 hours. The baseline White Blood Cell (WBC) count was found to be a significant predictor of the central compartment volume V1 by the applicant. However, the Agency's analysis determined that WBC counts were not correlated with the central volume estimates and inclusion of WBC in the parameter model did not reduce the population variance for the central volume. Renal excretion of unchanged clofarabine (over a 24-hour interval) accounted for 49-60% of the total clearance. In vitro studies using isolated hepatocytes indicate very limited hepatic metabolism, thus the pathways of non-renal elimination are unknown. No major pharmacokinetic differences were found between ALL and AML patients or between male and female patients. Intra-cellular concentrations of the active metabolite clofarabine triphosphate were also measured in some patients in the phase 1 study, however the data were too sparse for any meaningful evaluation. The inhibition and induction potential of clofarabine for cytochrome p450 enzymes has not been studied. The pharmacokinetics of clofarabine have not been evaluated in patients with renal or

hepatic dysfunction, and use of the drug in these patients should be undertaken with caution.

No significant relationships were found between measures of clofarabine exposure and measures of clofarabine response or toxicity in this population. This may be because the majority of the patients received the 52 mg/m^2 dose and this did not provide an adequate range of exposures to effectively evaluate the exposure-response relationship for clofarabine.

A. Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed the Clinical Pharmacology section of NDA 21-673 and finds it to be acceptable, with some revisions to the applicant's proposed label.

FDA Proposed labeling

1. The following should be inserted under the Human Pharmacokinetics section, under CLINICAL PHARMACOLOGY

The population pharmacokinetics of CLOLAR™ were studied in 40 pediatric patients aged 2 to 19 years (21 males/19 females) with relapsed or refractory ALL or AML. At the given 52 mg/m^2 dose, similar concentrations were obtained over a wide range of BSAs. Clofarabine was 47% bound to plasma proteins, predominantly to albumin. Based on non-compartmental analysis, systemic clearance and volume of distribution at steady-state were estimated to be 28.8 L/h/m^2 and 172 L/m^2, respectively. The terminal half-life was estimated to be 5.2 hours. No apparent difference in pharmacokinetics was observed between patients with ALL and AML or between males and females.

No relationship between clofarabine or clofarabine triphosphate exposure and toxicity or response was found in this population.

Based on 24-hour urine collections in the pediatric studies, 49-60% of the dose is excreted in the urine unchanged. *In vitro* studies using isolated human hepatocytes indicate very limited metabolism (0.2%), therefore the pathways of non-renal elimination remain unknown.

Although no clinical drug-drug interaction studies have been conducted to date, on the basis of the *in vitro* studies, cytochrome p450 inhibitors and inducers are unlikely to affect the metabolism of clofarabine. The effect of clofarabine on the metabolism of cytochrome p450 substrates has not been studied. The pharmacokinetics of clofarabine have not been evaluated in patients with renal or hepatic dysfunction.

2. The following should be inserted under the Drug Interactions section under PRECAUTIONS

Although no clinical drug-drug interaction studies have been conducted to date, on the basis of the *in vitro* studies, cytochrome p450 inhibitors and inducers are unlikely to affect the metabolism of clofarabine. The effect of clofarabine on the metabolism of cytochrome p450 substrates has not been studied.

3. The following should be inserted under the Hepatic and Renal Impairment under WARNING and under the DOSAGE AND ADMINISTRATION section

CLOLAR™ has not been studied in patients with hepatic or renal dysfunction. Its use in such patients should be undertaken only with the greatest caution.

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B. Phase IV Commitments

None.

C. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Clofarabine pharmacokinetics were determined in 40 pediatric patients, ages 2 to 19 years, from 3 studies: a phase 1 dose escalation study and two phase 2 studies in ALL and AML patients. A population pharmacokinetic model was fit to the data from these studies. Clofarabine pharmacokinetics was best described by a 2-compartment model with first order elimination. Body weight was the best predictor in parameter models for all model parameters (CL, Q, V1 and V2). The applicant's model included baseline WBC count as a predictor of the central compartment volume V1. The Agency's analysis determined that WBC counts were not correlated with the central volume estimates and inclusion of WBC in the parameter model did not reduce the population variance for the central volume. Based on a non-compartmental analysis, systemic clearance and volume of distribution at steady-state were estimated to be 28.8 $L/h/m^2$ and 172 L/m^2, respectively. The terminal half-life was estimated to be 5.2 hours. No major pharmacokinetic differences were found between ALL and AML patients or between male and female patients. Intra-cellular concentrations of the active metabolite clofarabine triphosphate were also measured in some patients in the phase 1 study, however the data were too sparse for any meaningful evaluation.

Renal excretion of unchanged clofarabine, measured over a 24-hour period, accounts for 49-60% of the total clearance. *In vitro* studies using isolated hepatocytes indicate very limited hepatic metabolism, thus the pathways of non-renal elimination are unknown. The inhibition and induction potential of clofarabine for cytochrome p450 enzymes has not been studied. The pharmacokinetics of clofarabine has not been evaluated in patients with renal or hepatic dysfunction.

No significant relationships were found between measures of clofarabine exposure and measures of clofarabine response or toxicity. The applicant's analysis only included those patients who had PK measurements. The Agency's re-analysis of this data included estimation of the exposure (AUC) of clofarabine in all the patients in the studies, based on the parameter model for clearance which was a function of body weight. However this did not change the outcome, and there were still no significant associations between AUC and measures of toxicity or response. This may be partly because the majority of the patients received the 52 mg/m^2 dose, which did not provide an adequate range of exposures to effectively evaluate the exposure-response relationship for clofarabine.

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/s/

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