CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-673

Statistical Review(s)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

ADDENDUM 1

NDA /Serial Number:	21-673 /N000
Drug Name:	Clolar (Clofarabine i.v.; Cl-F-Ara-A)
Applicant:	ILEX™ Products, Inc.
Indication(s):	Acute Pediatric Leukemias
Date(s):	Submission Date: March 30, 2004
	PDUFA Date: December 31, 2004
	Review Date: December 21, 2004
Review Priority:	Priority
Biometrics Division:	Division of Biometrics I (HFD-710)
Statistical Reviewers:	Rajeshwari Sridhara, Ph.D.
Concurring Reviewer:	Kooros Mahjoob, Ph.D., Acting Director
Medical Division:	Oncology Drug Products (HFD-150)
Clinical Team:	Martin Cohen, M.D. & John Johnson, M.D.
Project Manager:	Ms. Christy Cottrell
Keywords:	Single arm study, Response Rate

This NDA was reviewed as a joint Clinical and Statistical review. Please refer to the Clinical Review for a detailed review of this NDA.

In this application data from two phase II, single arm studies, Study CLO-212 and Study CLO-222, conducted in ALL (49 patients) and AML (65 patients) pediatric patients, respectively, were submitted in support of the claim that clofarabine is indicated for the treatment of pediatric patients 1 to 21 years old with refractory or relapsed acute leukemias. In similar patient population, complete response (CR) rate with adequate response duration has been accepted as evidence of clinical benefit. Clofarabine effect on response duration could not be evaluated in these two studies, as some of the responders were transplanted before disease progression.

In the CLO-212 trial conducted in ALL patients, 6/49 (12.2%; 95% CI: 4.6% – 24.8%) had complete remission (CR), 4/49 (8.2%; 95% CI: 2.3% – 19.6%) had complete remission without total platelet recovery (CRp), and 5/49 (10.2%: 95% CI: 3.4% - 22.2%) had partial remission. In the CLO-222 trial conducted in AML patients, 0/35 (0%) had CR, 1/35 (2.9%) had CRp and 8/35 (22.9%) had PR.

This reviewer differs from the recommendation of the clinical reviewer regarding the following 2 issues:

1. Because of the open labeled, uncontrolled, non-randomized nature of the phase II trials presented in this NDA, no formal statistical testing or comparisons or evaluation of time to event endpoints could be conducted. Therefore statements such as 'prolonged time to progression (TTP)' based on comparison of a patient's TTP prior to clofarabine vs. TTP after clofarabine, are not supported by valid statistical analysis, are not comparable patient population, and should be interpreted cautiously.

2. Because there were no CRs observed in the AML study, only 1 patient had CRp, and duration of response could not be assessed in the partial responders, in this reviewer's opinion the data presented from a single non-comparative phase II study, is not adequate to support the claimed efficacy in the AML patient population.

This application was discussed at the ODAC meeting held on December 1, 2004. The committee opined that CR's are reasonably likely to predict clinical benefit and further recommended (9 to 6 vote) to consider accelerated approval for ALL patients and non-approval (14 to 1 vote) for AML patients.

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/s/

Rajeshwari Sridhara
12/22/04 12:03:44 PM
BIOMETRICS

Kooros Mahjoob
12/22/04 05:23:09 PM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-673

Microbiology Review(s)

Product Quality Microbiology Review
Review for HFD-150

24 SEPTEMBER 2004

NDA: 21-673

Drug Product Name
Proprietary: Clolar
Non-proprietary: clofarabine
Drug Product Priority Classification: P

Review Number: 1

Subject of this Review
Submission Date: 24 February 2004
Receipt Date: 25 February 2004
Consult Date: 8 June 2004
Date Assigned for Review: 3 July 2004

Submission History (for amendments only)
Date(s) of Previous Submission(s): N/A
Date(s) of Previous Micro Review(s): N/A

Applicant/Sponsor
Name: ILEX Products
Address: 4545 Horizon Hill Blvd, San Antonio, TX 78229
Representative: Mike Bernstein
Telephone: 210-949-8285

Name of Reviewer: Bryan S. Riley, Ph.D.

Conclusion: Recommend Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUPPLEMENT: N/A

2. SUPPLEMENT PROVIDES FOR: N/A

3. MANUFACTURING SITE: AAI Development Services
4221 Faber Place Drive
Charleston, SC 29405-8510
Reg. # 1055790

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile aqueous solution for intravenous infusion in a 20 mL glass vial, 20 mm rubber stopper, [redacted] flip-off cap. 1 mg/mL, 20 mL/vial

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

6. PHARMACOLOGICAL CATEGORY: treatment of pediatric refractory or relapsed acute leukemia.

B. SUPPORTING/RELATED DOCUMENTS: N/A

C. REMARKS: This was an electronic submission (not in CTD).

filename: 21673.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – This submission is recommended for approval on the basis of product quality microbiology.

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 – The drug product is filtered [ ] filled into sterile vials, sealed [ ]

B. Brief Description of Microbiology Deficiencies – N/A

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature /S/

B. Endorsement Block
Bryan S. Riley, Ph.D. (Microbiology Reviewer)
Microbiology Supervisor

C. CC Block
N/A

Withheld

5

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

(b4)

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/s/

Bryan Riley
9/29/04 04:00:18 PM
MICROBIOLOGIST

David Hussong
9/29/04 04:25:37 PM
MICROBIOLOGIST