CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-673

Chemistry Review(s)

NDA 21-673
CLOLAR
(Clofarabine)

Pediatric Primary Relapsed or Refractory Acute Leukemia

Ilex Products, Inc.

Haripada Sarker, Ph.D.
HFD-150 Division of Oncology

Table of Contents

Appears This Way
On Original

Chemistry Review Data Sheet

1. NDA 21-673

2. REVIEW #1:

3. REVIEW DATE: 12-23-2004

4. REVIEWER: Haripada Sarker, Ph.D.

6. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 63,641	November 7, 2001
IND 43,275	September 16, 1993

1. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	February 24, 2004
Amendment (N-000-Bz)	August 5, 2004
Amendment	December 21, 2004
Amendment(e-mail)	December 27, 2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Ilex Products, Inc.
Address:	4545 Horizon Hill Blvd. San Antonio, TX 78229-2263
Representative:	Mike Bernstein
Telephone:	210-949-8285

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Clolar™
b) Non-Proprietary Name (Chemical): 2—chloro-2'-fluoro-deoxy-9-β-D-arabinofuranosyladenine
c) Code Name/#: N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

e) e) Proposed Trade Name: Clolar™

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Pediatric Primary Relapsed or Refractory Acute Leukemia

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 1 mg/mL (20 mL per vial)

13. ROUTE OF ADMINISTRATION: I.V.

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

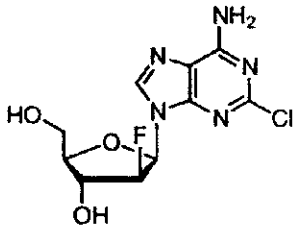
_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Structure:

N21-673 CR#1



Name (drug substance)	Clofarabine (USAN Name)
Chemical Name	2-chloro-2'-fluoro-deoxy-9-beta-D-arabinofuranosyladenine
CAS number	Not provided
Molecular Weight	303.68
Molecular Formula	$C_{10}H_{11}ClFN_5O_3$
Structural formula	As above

17. RELATED/SUPPORTING DOCUMENTS:

A. **DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COM-PLETED	COMMENTS
[redacted]	III	[redacted]	[redacted]	4	N/A	12/15/2004	Not Reviewed
[redacted]	III	[redacted]	[redacted]	4	N/A	12/15/2004	Not Reviewed

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

18. STATUS:

ONDC: To be filled later

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	13-DEC-04	J. D. Ambrogio
Pharm/Tox	Acceptable	16-SEP-04	Anwar Goheer
Biopharm	Acceptable	22-DEC-04	Roshni Ramchandani
DMETS	Acceptable	2-NOV-04	Carol Holquist
Methods Validation	Will be requested post-approval		Haripada Sarker
EA (Categorical Exclusion)	Acceptable	22-MAR-04	Haripada Sarker
Microbiology	Acceptable	29-SEP-04	Brian Riley

The Chemistry Review for NDA 21-649

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for APPROVAL from a chemistry, manufacturing and controls standpoint because:
The applicant addressed all the deficiencies satisfactorily. The applicant has provided a commitment to validate the analytical methods for specified impurities and degradants. The office of compliance has provided an overall acceptable recommendation (see attached). The following comments regarding retest for the drug substance and shelf-life for the drug product should be included in the action letter:

"A retest period of [ ] for the drug substance and a shelf-life of twenty four months for the drug product will be granted based on stability data provided"

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Substance(s) and Drug Product(s

CLOLAR™ (clofarabine) is formulated as a solution (1 mg/mL) and is supplied in a 20 mL, single use vial. The 20 mL vial contains 20 mg of clofarabine formulated in 20 mL unbuffered normal saline. The inactive ingredients are sodium chloride USP and water for injection USP. The drug product is a clear, colorless liquid, free of foreign matter with a pH range of 4.5 to 7.5. The drug product is [ ]. It is stored at 25°C (77°F); excursion permitted to 15°-30°C (59°-86°F). The drug product has to be diluted with 5% dextrose USP or with 0.9% sodium chloride injection USP prior to administration. The stability of clofarabine infusion solution was assessed after mixing in an IV bag and being stored up to three days (at room temperature). A high concentration [ ] and low concentration [ ]) were prepared and tested using saline and 5% dextrose IV solutions. After mixing, samples were tested for baseline values using test method [ ] The infusion solution was tested for assay and impurities. Based on data, the infusion solutions for the drug product are found to be stable up to 24 hours. The applicant proposed [ ] of shelf-life for the drug product. However, based on primary and supportive stability data, an expiration dating period of 24 months may be granted.

Clofarabine drug substance is a modified nucleoside, [

]

Two different HPLC methods, [ ] are utilized for analyzing the impurities in drug substance at release and stability respectively. Method — appears to be capable of analyzing the process impurities, whereas method — capable of analyzing the drug substance degradants. Validations of assay are provided for both the methods, — and — however, only qualitative test data are provided for impurities (process and stability). Based on the profile, method — appears to stability indicating. A third HPLC method, [ ] has been utilized for drug product assay and degradants at release and stability. Based on primary and supportive stability data, a retest period of — may be granted for the drug substance.

B. Description of How the Drug Product is Intended to be Used

The drug product is a single-use vial and contains 20 mL of clofarabine solution at a concentration equivalent to 1 mg/mL of API. CLOLAR™ should be filtered through a sterile 0.2 µm syringe filter and then further diluted with 5% dextrose injection USP or 0.9% sodium chloride injection USP prior to administration.

C. Basis for Approvability Recommendation

This application is recommended for APPROVAL from the stand point of chemistry, manufacturing and controls because all the deficiencies have been satisfactorily addressed and the office of compliance has provided an overall acceptable recommendation (see attached). A commitment to validate the analytical methods for specified impurities and degradants has been provided. The following comments regarding retest for the drug substance and shelf-life for the drug product should be included in the action letter:

"A retest period of [ ] for the drug substance and a shelf-life of twenty four months for the drug product will be granted based on stability data provided"
The overall evaluation for cGMP compliance from the Office of Compliance is acceptable.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Haripada Sarker, Ph.D.
ChemistryTeamLeaderName/Date: Nallaperumal Chidambaram, Ph.D.
ProjectManagerName/Date: Christy Cottrell

C. CC Block

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

(b4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Haripada Sarker
12/27/04 04:58:39 PM
CHEMIST

Nallaperumal Chidambaram
12/27/04 05:07:52 PM
CHEMIST