

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-673**

**Administrative Reviews**

TIME SENSITIVE PATENT INFORMATION  
PURSUANT TO 21 U.S.C. 355 FOR  
Clofarabine

NDA 21-673

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The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	TBA
Generic Name:	Clofarabine
NDA Number:	21-673
Approval Date:	Pending

---

U.S. Patent No. 4,751,221

Expiration Date:	10/18/2005
Type of Patent:	drug product
Name of Patent Owner:	Sloan-Kettering Institute for Cancer Research
Relationship of Applicant:	ILEX Products, Inc. has a right to an exclusive license to this patent for the subject of the application for which approval is being sought.

---

The undersigned declares that the above referenced U.S. Patent covers the active ingredient of Clofarabine and/or its formulation and use in the treatment of cancer. This product is the subject of the application for which approval is being sought.

  
\_\_\_\_\_  
Al A. Jecminek  
Vice President, Licensing & Intellectual Property  
Date: September 24, 2003

**TIME SENSITIVE PATENT INFORMATION  
PURSUANT TO 21 U.S.C. 355 FOR  
Clofarabine**

**NDA 21-673**

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The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	TBA
Generic Name:	Clofarabine
NDA Number:	21-673
Approval Date:	Pending

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**U.S. Patent No. 4,918,179**

Expiration Date:	06/14/2005
Type of Patent:	drug product
Name of Patent Owner:	Sloan-Kettering Institute for Cancer Research
Relationship of Applicant:	ILEX Products, Inc. has a right to an exclusive license to this patent for the subject of the application for which approval is being sought.

---

The undersigned declares that the above referenced U.S. Patent covers the active ingredient of Clofarabine and/or its formulation and use in the treatment of cancer. This product is the subject of the application for which approval is being sought.

  
\_\_\_\_\_  
Al A. Jecminek  
Vice President, Licensing & Intellectual Property  
Date: September 26, 2003

TIME SENSITIVE PATENT INFORMATION  
PURSUANT TO 21 U.S.C. 355 FOR  
Clofarabine

NDA 21-673

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The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	TBA
Generic Name:	Clofarabine
NDA Number:	21-673
Approval Date:	Pending

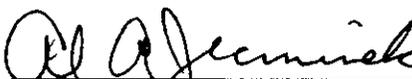
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U.S. Patent No. 5,384,310

Expiration Date:	07/23/2008
Type of Patent:	drug product
Name of Patent Owner:	Southern Research Institute
Relationship of Applicant:	ILEX Products, Inc. has a right to an exclusive license to this patent for the subject of the application for which approval is being sought.

---

The undersigned declares that the above referenced U.S. Patent covers the active ingredient of Clofarabine and/or its formulation and use in the treatment of cancer. This product is the subject of the application for which approval is being sought.



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Al A. Jecmirek  
Vice President, Licensing & Intellectual Property

Date: September 26, 2003

**TIME SENSITIVE PATENT INFORMATION  
PURSUANT TO 21 U.S.C. 355 FOR  
Clofarabine**

**NDA 21-673**

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The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	TBA
Generic Name:	Clofarabine
NDA Number:	21-673
Approval Date:	Pending

---

**U.S. Patent No. 5,661,136**

Expiration Date:	08/26/2014
Type of Patent:	method of use
Name of Patent Owner:	Southern Research Institute
Relationship of Applicant:	ILEX Products, Inc. has a right to an exclusive license to this patent for the subject of the application for which approval is being sought.

---

The undersigned declares that the above referenced U.S. Patent covers the active ingredient of Clofarabine and/or its formulation and use in the treatment of cancer. This product is the subject of the application for which approval is being sought.



Al A. Jecminek  
Vice President, Licensing & Intellectual Property

Date: September 24, 2003

EXCLUSIVITY SUMMARY FOR NDA # 21-673 SUPPL # \_\_\_\_\_

Trade Name Clolar™ Injection Generic Name clofarabine

Applicant Name Genzyme Corporation HFD # 150

Approval Date If Known December 28, 2004

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?  
YES /  / NO /  /

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /  / NO /  /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

\_\_\_\_\_  
\_\_\_\_\_

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

\_\_\_\_\_  
\_\_\_\_\_

d) Did the applicant request exclusivity?

YES /\_\_\_/ NO /\_X\_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

\_\_\_\_\_

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /\_X\_/ NO /\_\_\_/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

\_\_\_\_\_Yes\_\_\_\_\_

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /\_\_\_/ NO /\_\_X\_/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

**PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /\_\_\_/ NO /\_X\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /\_\_\_/ NO /\_X\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any

investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /\_\_\_/ NO /\_\_\_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /\_\_\_/ NO /\_\_\_/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /\_\_\_/ NO /\_\_\_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /\_\_\_/ NO /\_\_\_/

If yes, explain:

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(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /\_\_\_/      NO /\_\_\_/

If yes, explain:

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(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

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Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1                      YES /\_\_\_/                      NO /\_\_\_/

Investigation #2                      YES /\_\_\_/                      NO /\_\_\_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

\_\_\_\_\_  
\_\_\_\_\_

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1                      YES /\_\_\_/                      NO /\_\_\_/

Investigation #2                      YES /\_\_\_/                      NO /\_\_\_/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

\_\_\_\_\_  
\_\_\_\_\_

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

\_\_\_\_\_  
\_\_\_\_\_

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
 IND # \_\_\_\_\_ YES /\_\_\_/ ! NO /\_\_\_/ Explain: \_\_\_\_\_  
 !  
 !

Investigation #2 !  
 IND # \_\_\_\_\_ YES /\_\_\_/ ! NO /\_\_\_/ Explain: \_\_\_\_\_  
 !

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !  
 YES /\_\_\_/ Explain \_\_\_\_\_ ! NO /\_\_\_/ Explain \_\_\_\_\_  
 !  
 \_\_\_\_\_ !  
 \_\_\_\_\_ !

Investigation #2 !  
 YES /\_\_\_/ Explain \_\_\_\_\_ ! NO /\_\_\_/ Explain \_\_\_\_\_  
 !  
 \_\_\_\_\_ !  
 \_\_\_\_\_ !

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /\_\_\_/ NO /\_\_\_/

If yes, explain: \_\_\_\_\_  
 \_\_\_\_\_

Signature  
 Title:

Date

Signature of Office/  
Division Director

Date

Form OGD-011347 Revised 05/10/2004

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

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Christy Cottrell  
12/28/04 03:25:50 PM

Richard Pazdur  
12/28/04 03:30:57 PM

**PEDIATRIC PAGE**

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-673 Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number: \_\_\_\_\_

Stamp Date: March 30, 2004 Action Date: December 30, 2004

HFD-150 Trade and generic names/dosage form: CLOLAR™ (clofarabine) Intravenous

Applicant: Ilex Products, Inc. Therapeutic Class: 1 P V

Indication(s) previously approved: None

**Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.**

Number of indications for this application(s): 1

Indication #1: For the treatment of pediatric patients 1 to 21 years old with refractory or relapsed acute lymphoblastic leukemia after at least two prior regimens.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

Min None kg \_\_\_\_\_ mo. 1 yr. \_\_\_\_\_ Tanner Stage None  
Max None kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 21 Tanner Stage None

Comments:

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

{See appended electronic signature page}

\_\_\_\_\_  
Christy Cottrell  
Consumer Safety Officer

cc: NDA 21-673  
HFD-960/ Grace Carmouze

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.**

(revised 12-22-03)

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/s/

-----  
Christy Cottrell  
12/23/04 12:48:50 PM

**Clofarabine  
NDA 21-673**

**DEBARMENT CERTIFICATION**

In accordance with the certification provision of the Generic Drug Enforcement Act of 1992 as outlined in correspondence dated 29 July 1992, from Daniel L. Michels, Office of Compliance, ILEX Products, Inc. hereby certifies that to the best of its knowledge and belief, it did not and will not use in any capacity the services of any person debarred under section 306 (a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.

*Mike Bernstein*

Mike Bernstein, M.P.H.  
Senior Director, Regulatory Affairs

*26 September 2003*  
Date

# FAX

**FOOD AND DRUG ADMINISTRATION**  
**DIVISION OF ONCOLOGY DRUG PRODUCTS**  
Center for Drug Evaluation and Research, HFD-150  
5600 Fishers Lane, Rockville, MD 20857



---

**To:** Mike Bernstein, Ilex

**From:** Christy Cottrell

---

**Fax:** (210) 949-8282

**Fax:** (301) 594-0499

---

**Phone:** (210) 949-8285

**Phone:** (301) 594-5761

---

**Pages, including cover sheet:** 2

**Date:** 12-28-04

---

**Re:** NDA 21-673 for Clofarabine – General comments

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

---

Mike,

Please refer to your NDA 21-673 for Clofarabine, approved today, December 28, 2004. Included in this fax are general comments regarding your application from the Chemistry and Clinical Pharmacology reviewers for your consideration.

Chemistry

1. We recommend a retest date of [ ] for the drug substance.
2. An expiration dating period of twenty-four months for the drug product will be granted based on stability data provided.

Clinical Pharmacology

1. We recommend that you evaluate the pharmacokinetics of the active metabolite clofarabine triphosphate, both in future studies in adult and pediatric patients to better understand the exposure-response relationship for this drug and to help optimize dosing regimens in the future studies.
2. We recommend that you examine the effect of renal impairment on the safety and pharmacokinetics of clofarabine in patients in future studies.

3. Your studies have shown that clofarabine is not hepatically metabolized and that ~ 60% is renally excreted unchanged. The fate of the remaining 40% is not known. We suggest that you try to explore the fate of the fraction of the clofarabine that is not eliminated by renal or hepatic routes.

If you have any questions, feel free to call me at (301) 594-5761.

Thanks,

Christy Cottrell

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

-----  
Christy Cottrell  
12/28/04 05:04:10 PM  
CSO

genzyme N-000 45

Genzyme Corporation  
4545 Horizon Hill • SAN ANTONIO, TEXAS 78229-2263  
PHONE 210/ 949-8742 • FAX 210/ 949-8282  
INTERNET: TREED@ilexonc.com

RECEIVED

RECEIVED

DEC 28 2004

DDR-150/CDER

**FACSIMILE TRANSMISSION**

**Date:** 28 December 2004

**To:** Christy Cottrell, Consumer Safety Officer  
Center for Drug Evaluation and Research, FDA

**Fax No.:** 301-594-0499

**From:** Tracie Reed, Regulatory Affairs Specialist  
Mike Bernstein, Director, Regulatory Affairs *JS*

**Subject:** NDA 21-673 CLOLAR  
Post-Marketing Commitments

**Pages (including cover page):** - 3 -

**Message:**

**Please find our post-marketing commitments as discussed. This will follow under separate cover as a formal submission.**

**Confidentiality Note:** The documents accompanying this facsimile transmission contain information belonging to ILEX Oncology Inc., which is intended only for the use of the addressee.



Genzyme Corporation  
 4545 Horizon Hill Boulevard  
 San Antonio, TX 78229-2263  
 T 210-949-8200  
 F 210-949-8210

28 December 2004

Christy Cottrell, Consumer Safety Officer  
 Division of Oncology Drug Products  
 Food and Drug Administration  
 CDER, HFD-150  
 1451 Rockville Pike  
 Rockville, MD 20852

**RE: NDA 21-673 CLOLAR™ (clofarabine) Intravenous 52 mg/m<sup>2</sup>/day  
 Post-Marketing Commitments  
 AMENDMENT 18 – Submission #19**

Dear Ms. Cottrell:

Genzyme Corporation commits to the following:

**Commitment #1**

1. Completion of Study CLO-216: This is a Phase 1/2 Dose-Escalation Study of Clofarabine Plus Cytarabine and L-Asparaginase in Pediatric Patients with Refractory or Relapsed Acute Lymphoblastic Leukemia, showing that an acceptable and potentially useful regimen has been developed for study in a Phase 3 study. We expect the Phase 1 part of this study to be completed by March 1, 2006 and the Phase 2 part of the study, assuming a tolerated regimen is found in Phase 1, by October 1, 2006. If either the Phase 1 or 2 components fail to identify a useful and tolerated regimen, you have agreed to promptly develop an alternative plan to verify and describe clinical benefit.

	<u>Phase 1</u>	<u>Phase 2</u>
<b>Protocol Submission:</b>	Done	Done
<b>Study Start:</b>	June 1, 2005	June 1, 2006
<b>Trial Completion:</b>	March 1, 2006	October 1, 2006
<b>Final Report Submission:</b>	June 1, 2006 (Interim)	April 13, 2007

2. Completion of a controlled clinical study to verify and describe the clinical benefit of Clofarabine in pediatric ALL. Your proposed Phase 3 study to be possibly conducted by the COG does not appear to have a realistic chance of showing a clinical benefit of Clofarabine in children with ALL in first relapse. Please submit a new protocol for a study to show Clofarabine clinical benefit in children with All within 2 months of the date of this letter. Timelines for study start, completion and submission of the study report should also be submitted. Please request a meeting to discuss this protocol within 30 days of receipt of this letter, so that a meeting can be scheduled to occur about one month after receipt of the protocol.

C Cottrell  
NDA 21-673  
A-17, Sub 18  
Page 2 of 2

### Commitment #2

1. Genzyme is committed to completing an upgrade to the drug substance test method validation of [ ] This method validation update will include the [ ] specified impurities in the drug substance specification. The preparation, isolation, characterization of [ ] impurities and upgrade of this method validation will be completed by 31 May 2005.
2. Genzyme is committed to completing an upgrade to the drug product and stability indicating test method validation of [ ] This method validation update will include [ ] specified impurities in drug substance and the [ ] degradants listed in the CMC section of the NDA. This effort will require [ ] and the preparation, isolation, characterization of [ ] degradants listed in the CMC section of the NDA. The upgrade of this method validation will be completed by 31 July 2005.

This submission is electronic and it is accompanied by a signed paper 356h form. Please see Attachment "A" concerning size, virus statement and the name, version, and company of the software that was used.

If you have any questions or require additional information for this submission, please direct them to my attention at (210) 949-8285, or to Tracie Reed at (210) 949-8742, or Edda M. Tschirhart at (210) 949-8349, or facsimile (210) 949-8282.

Sincerely,



Mike Bernstein, MPH  
Director, Regulatory Affairs and Safety

**Cottrell, Christy**

---

**From:** Cottrell, Christy  
**ent:** Monday, December 27, 2004 3:16 PM  
**fo:** 'Bernstein, Michael'; 'Reed, Tracie'; 'Tschirhart, Edda'  
**Subject:** Subpart H commitments for Clofarabine

**Importance:** High

Mike,

Below are the Division's draft Subpart H commitments for Clofarabine. Please let us know ASAP if you agree with the wording and timelines for these commitments.

Thanks,  
Christy

1. Completion of study CLO-216: This is a Phase 1/2 Dose-Escalation Study of Clofarabine Plus Cytarabine and L-Asparaginase in Pediatric Patients with Refractory or Relapsed Acute Lymphoblastic Leukemia, showing that an acceptable and potentially useful regimen has been developed for study in a Phase 3 study. We expect the Phase 1 part of this study to be completed by March 1, 2006 and the Phase 2 part of the study, assuming a tolerated regimen is found in Phase 1, by October 1, 2006. If either the Phase 1 or 2 components fail to identify a useful and tolerated regimen, you have agreed to promptly develop an alternative plan to verify and describe clinical benefit.

	<u>Phase 1</u>	<u>Phase 2</u>
Protocol Submission:	Done	Done
Study Start:	June 1, 2005	June 1, 2005
Trial Completion:	March 1, 2006	October 1, 2006
Final Report Submission:	June 1, 2006	April 13, 2007

2. Completion of a controlled clinical study to verify and describe the clinical benefit of clofarabine in pediatric ALL. Your proposed Phase 3 study to be possibly conducted by the COG does not appear to have a realistic chance of showing a clinical benefit of clofarabine in children with ALL in first relapse. Please submit a new protocol for a study to show clofarabine clinical benefit in children with ALL within 2 months of the date of this letter. Timelines for study start, completion and submission of the study report should also be submitted. Please request a meeting to discuss this protocol within 30 days of receipt of this letter, so that a meeting can be scheduled to occur about one month after receipt of the protocol.

*Appears This Way  
On Original*

**ROUTING AND TRANSMITTAL SLIP**

Date 12-22-04

TO:	Initials	Date
1. <u>DPease</u>	<u>JSI</u>	<u>12-23-04</u>
2. <u>AGoheer/JLeighton</u>	<u>JSI</u>	<u>12/22/04 12/22/04</u>
3. <u>HSarker/NChidambaram</u>	<u>JSI</u>	<u>12-23-04 12/23/04</u>
4. <u>RRamchandani/BBooth</u>	<u>JSI</u> 3	<u>12/23/04 12/23/04</u>
5. <u>RSridhara</u>	<u>JSI</u>	<u>12/28/04</u>
6. <u>MCoen/JJohnson</u>	<u>JSI</u>	<u>12-28-04</u>
7. <u>GWilliams/JPazdur</u>	<u>JSI</u>	<u>12-28-04</u>
8. <u>JSimmons/HPatel</u>	<u>JSI</u>	<u>12-28-04 *</u>
9. <u>Dave Green</u>		

- |   |   |
|---|---|
| <input type="checkbox"/> Approval             | <input type="checkbox"/> Note and Return          |
| <input type="checkbox"/> Comment              | <input type="checkbox"/> Per Conversation         |
| <input type="checkbox"/> For Correction       | <input type="checkbox"/> See Me                   |
| <input type="checkbox"/> For Your Information | <input checked="" type="checkbox"/> For Signature |

**ACTION PACKAGE**

NDA 21-673  
**CLOLAR (clofarabine)**  
**Ilex Products, Inc.**

**DUE DATE: DECEMBER 30, 2004**

Contact: Christy Cottrell  
 WOC2 Room 2067  
 (301) 594-5761

\* note changes in labeling (in blue) L 13-14, L 393

**From:** Cottrell, Christy  
**Sent:** Friday, December 17, 2004 4:29 PM  
**To:** 'etschirhart@ilexonc.com'; 'treed@ilexonc.com';  
'mbernstein@ilexonc.com'  
**Subject:** Chemistry deficiencies for Clofarabine  
Tracie/Edda/Mike,

Attached are some deficiencies that have been identified by the Chemistry review team for Clofarabine. Please provide a response to these deficiencies by COB on Tuesday, December 21st.

If you have any questions, please let me know.

Thanks,  
Christy



CMC  
iciencies.doc (31

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/s/

-----  
Christy Cottrell  
12/21/04 08:17:47 AM  
CSO

Sent by email to the sponsor on Friday, 12-17-04.

LIST OF CMC DEFICIENCIES TO BE COMMUNICATED TO THE APPLICANT

Drug Substance

1. Please provide validation report for specified impurities (process impurities and degradants).
2. Please provide release data using HPLC method \_\_\_\_\_
3. Please provide data using HPLC release method \_\_\_\_\_ at initial and at the end of the retest period to show that there is no change in process impurities.
4. Please provide data from photostability studies or provide the location where they are available in the submission.

Drug Product

1. Please clarify whether HPLC method \_\_\_\_\_ is capable of detecting all drug substance process impurities and drug product degradants. Please provide data along with validation report to support your claim.
2. We recommend that the acceptance criteria for total impurities be tightened to 1.0%.
3. Please clarify whether the area percent for known impurities actually reflect the concentration of the impurity in drug product.

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# Memo

**To:** Richard Pazdur, M.D.  
Director, Division of Oncology Drug Products, HFD-150

**From:** Alina R. Mahmud, R.Ph.  
Team Leader, Division of Medication Errors and Technical Support, Office of Drug Safety  
HFD-420

**Through:** Carol Holquist, R.Ph.  
Director, Division of Medication Errors and Technical Support, Office of Drug Safety  
HFD-420

**CC:** Christy Cottrell  
Project Manager, HFD-150

**Date:** December 3, 2004

**Re:** ODS Consult 04-0117-1; Clolar (Clofarabine Injection) 1 mg/mL; NDA 21-673.

---

This memorandum is in response to a request from your Division for a re-review of the proprietary name, Clolar.

Since we conducted our review dated July 21, 2004 (ODS consult 04-0117), DMETS has identified one additional proprietary name, Clobex, as having the potential for look-alike confusion with Clolar. Clobex contains clobetasol and is available as a 0.05% lotion and shampoo. The lotion is indicated for the relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses only in patients 18 years of age or older. The shampoo is indicated for the treatment of scalp psoriasis. Clobex and Clolar begin with the letters "Clo" and end with a similarly scripted ending "bex" vs. "lar" (see writing sample below). The products, however, differ in dosage form, route of administration, dosing regimen, dose and strength. Although the names are similar in script, the product characteristics will minimize the potential for confusion.

Additionally, the proposed labeling in the Electronic Document Room (EDR) dated November 18, 2004 does not address the labeling recommendations cited in DMETS previous consult (ODS consult 04-0117). We refer you to the aforementioned consult for our comments with regard to the labels and labeling. In summary, DMETS has no objections to the proprietary name Clolar. DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review,

the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact Sammie Beam at 301-827-2102.

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/s/

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Alina Mahmud  
12/6/04 03:13:03 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
12/6/04 03:24:27 PM  
DRUG SAFETY OFFICE REVIEWER

## Cottrell, Christy

---

**From:** Gan, David  
**Sent:** Thursday, December 02, 2004 2:05 PM  
**To:** Cohen, Martin H; Cottrell, Christy  
**Cc:** Ball, Leslie; Pazdur, Richard; Williams, Grant A; White Jr, Robert M; Johnson, John R; Li, Ning  
**Subject:** RE: NDA 21673 inspection

Hi, Martin, attached is the draft copy Clinical Inspection Summary for NDA 21673. A official copy will be sent to you once it is ready.



NDA21673Insp  
ionSummaryPre

David

**David Gan, M.D., Dr.P.H., M.P.H.**

**Medical Officer**

DSI, HFD 45, FDA

301 827-0071

-----Original Message-----

**From:** White Jr, Robert M  
**Sent:** Tuesday, September 28, 2004 12:38 PM  
**To:** Johnson, John R; Gan, David  
**Cc:** Ball, Leslie; Cohen, Martin H; Pazdur, Richard; Williams, Grant A  
**Subject:** RE: NDA 21673 inspection

If approved, clofarabine would be the 2nd anticancer drug approved in children before adults--Vumon (teniposide) was the 1st. Another factor should be considered as the driving force for clofarabine's approval.

-----Original Message-----

**From:** Johnson, John R  
**Sent:** Tuesday, September 28, 2004 12:06 PM  
**To:** Gan, David; White Jr, Robert M  
**Cc:** Ball, Leslie; Cohen, Martin H; Pazdur, Richard; Williams, Grant A  
**Subject:** RE: NDA 21673 inspection

This NME is viewed by management as important because it is for children and would be the first anticancer drug ever approved in children before adults. There is relatively little information in the NDA and approvability is uncertain. We need to be confident in the relatively small amount of data we have. [unclear] is one of the two major investigation sites. We believe inspection of this site is essential.

-----Original Message-----

**From:** Gan, David  
**Sent:** Monday, September 27, 2004 3:44 PM  
**To:** White Jr, Robert M  
**Cc:** Ball, Leslie; Cohen, Martin H; Johnson, John R  
**Subject:** RE: NDA 21673 inspection

Thanks!

**David Gan, M.D., Dr.P.H., M.P.H.**

**Medical Officer**

DSI, HFD 45, FDA

301 827-0071

-----Original Message-----

**From:** White Jr, Robert M  
**Sent:** Monday, September 27, 2004 2:00 PM  
**To:** Gan, David  
**Cc:** Ball, Leslie; Cohen, Martin H; Johnson, John R  
**Subject:** RE: NDA 21673 inspection

Dr. Martin Cohen is the medical officer for this NDA. I have cc'ed him this e-mail.

Thanks.

-----Original Message-----

**From:** Gan, David  
**Sent:** Monday, September 27, 2004 12:52 PM  
**To:** White Jr, Robert M  
**Cc:** Ball, Leslie  
**Subject:** NDA 21673 inspection

Hi, Dr. White,

I received one EIR from one of the two sites [redacted] requested for inspection. I contacted the New York District Office inquiring about the status of [redacted] inspection. I was told that the inspection has not been done and will not be done soon. Do you absolutely need an inspection for this site? If you do, I will ask Dr. Leslie Ball, GCP Branch Chief to see what we can do here at DSI to support your NDA decision. Please let me know.

David

**David Gan, M.D., Dr.P.H., M.P.H.**

**Medical Officer**

DSI, HFD 45, FDA

301 827-0071

4 PAGES REMOVED. SEE THE  
ADVISORY COMMITTEE MEETING  
INFORMATION LOCATED ON THE FDA  
WEBSITE BELOW:

<http://www.fda.gov/ohrms/dockets/ac/>

12-1-04





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/s/

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Amy Baird  
9/21/04 02:36:15 PM  
CSO

# Fax



## DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

**To:** Mike Bernstein, MPH

**From:** Amy Baird, CSO

**Fax:** 210-949-8282

**Fax:** 301-827-4590

**Phone:** 210-949-8285

**Phone:** 301-594-5779

**Pages (including cover):** 3

**Date:** September 10, 2004

**Re:** NDA 21-673 Clofarabine.

Urgent     For Review     Please Comment     Please Reply     Please Recycle

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● **Comments:**

Per the request of the clinical team, please review the attached responder summaries for studies CLO 212 and 222 for response duration and TTP. Do you concur? The durations are based on dates of bone marrow examinations recorded in the ASPIRATE data set. For censored patients (indicated by +) the date of the last recorded bone marrow exam was the date used to calculate response duration and TTP. Please call should you have any questions.

Thank you,

Amy Baird

**Table 1: FDA Response Summary CLO-212**

Patient	007-0018	009-0028	014-0030	006-0047	018-0036	009-0045	014-0049	009-0024	012-0014	014-0040	010-0042	004-0025	006-0003	006-0004	014-0007
Time to first relapse (mo)	22	25	86	1	30	53	53	2	31	3	50	11	19	8	28
Time to 2nd relapse (mo)	2	25*	35	3	10	48*	31	4*	1	3	4*	6	1	4*	1
Time to 3 <sup>rd</sup> or later relapse (mo)	1*	-	18*	1, 1*	2, 31*	-	68*	-	1, 1, 2, 1*	1*	-	2, 1*	1, 1*	-	8*
Stem cell transplant (Yes or No)	N	Y	Y (2)	N	Y (2)	N	N	Y	N	N	N	Y	N	Y	Y
Transplant response duration (mo)	-	20	27, 10	-	6, 29	-	-	2	-	-	-	4	-	2	3
Clofarabine response	CR	CRp	CRp	CRp	PR	PR	PR	PR	PR						
Clofar response confirmed (Y or N)	N		Y	N	Y	Y	Y	Y	Y	N	Y	N	N	N	Y
Clofar response duration (days)	43	69	211+	50	82	57+	86+	237	142+	6+	55+	21	16	7	56+
Clofarabine TTP or death (days)	146	88	228+	76	108	82+	110+	296	169+	32+	68+	48	44	21	77+
Post-clofarabine SCT (Y or N)	N	N	N	N	N	Y	N	Y	Y	N	N	N	N	N	Y
Current status (Alive or Dead)	D	A	A	A	A	A	A	A	D	D	A	D	D	D	D
Post-clofarabine OS (w)	58.6	44.0+	32.7+	10.4+	28.3+	17.6+	16.3+	63.1+	42.0	9.1	22.9+	18.1	36.3	7.0	29.7

\* response duration for treatment immediately preceding clofarabine treatment

**Table 2: FDA Responder Summary CLO-222**

Patient	014-0003	006-0013	009-0018	014-0002	014-0019	014-0027	015-0017	006-0036	014-0031
Time to first relapse (mo)	3	2	4*	~24	10*	1	8	14	1
Time to 2nd relapse (mo)	12	1	-	27	-	3*	2*	16	1*
Time to 3 <sup>rd</sup> or later relapse (mo)	3, 9*	2, 1*	-	7,2,9*	-	-	-	1,1*	-
Stem cell transplant (Y or N)	Y	N	N	Y	Y	N	N	Y (2)	N
Stem cell transplant resp dur (mo)	5	-	-	6	6	-	-	12, 4	-
Clofarabine response	CRp	PR							
Clofar response confirmed Y or N	Y	N	N	N	Y	N	N	N	Y
Clofarabine response duration (d)	503+	12	34	33+	44+	14	395+	55+	53+
Clofarabine TTP or death (d)	532+	54	67	54+	78+	49	451+	134+	93+
Post-clofarabine SCT (Y or N)	Y	N	N	Y	Y	Y	Y	Y	Y
Current status (Alive or Dead)	A	D	D	D	D	A	A	A	A
Post-clofarabine OS (w)	93.6+	7.7	24.3	30.3	39.0	29.0+	67.9+	16.4+	24.9+

\* response duration for treatment immediately preceding clofarabine treatment

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/s/

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Amy Baird  
9/10/04 03:43:22 PM  
CSO

# TELECON MINUTES

**TELECON DATE:** Nov. 24, 2004      **TIME:** 4:00      **LOCATION:** B

**NDA:** 21-673

**Submission Receipt Date:** 3-30-04

**Major Amend. Receipt Date:** 8-6-04

**PDUFA Goal Date:** 12-31-04

**DRUG:** Clolar (clofarabine) i.v.      **INDICATION:** pediatric AML/ALL

**SPONSOR:** Ilex      **TYPE of TELECON:** pre-ODAC Meeting

**FDA PARTICIPANTS:** Richard Pazdur, M.D. Dir., DODP

John Johnson, M.D., Medical Team Leader, DODP

Martin Cohen, M.D., Medical Officer, DODP

Johanna Clifford, ACS

Dotti Pease, Project Manager, DODP

**SPONSOR:** Mike Bernstein, Senior Director, Regulatory Affairs  
Steve Whiteman, M.D., Clinical

**MEETING OBJECTIVES:** Discuss general format of ODAC presentations and questions.

**BACKGROUND:** This NDA was submitted as a rolling review, with all parts complete on March 30, 2004. The indications are pediatric AML and ALL and both AML and ALL (not specifically pediatric) were given orphan designation. Sponsor submitted a major amendment August 6, 2004 which extended the PDUFA goal date to December 31, 2004. This NDA is being taken to the Oncologic Drugs Advisory Committee on December 1, 2004. This telecon was arranged to discuss the flow of the meeting.

## DISCUSSION:

Ilex will present first and will have 45 minutes for their presentation, followed by FDA (also 45 minutes), then questions re: either presentation. The schedule is tight as there is another product being discussed in the afternoon session, and all speakers are asked to keep to their time limit.

Ilex inquired as to when they will receive the specific FDA questions for the committee and when the briefing package would become publicly available. The questions will be available the morning of the meeting; the package will be available the day before the meeting. The final list of panel members may not be available until the last moment as they are still being cleared, but there are several pediatric oncologists who have been cleared to participate. Steven Hirschfeld, M.D., the previous clofarabine FDA reviewer will also be seated at the table.

Dr. Pazdur noted that FDA's major focus will be on the use of complete response (CR) as an endpoint and in particular the difficulties in documenting duration because of the confounding factor of transplantation. Ilex would like to use as their primary endpoint the progression of the patients to transplantation.

FDA also noted that our discussion and questions will distinguish between pediatric AML and pediatric ALL.

We also requested Ilex to spend some time in their presentation on confirmatory and ongoing trials that might support accelerated approval. They do not necessarily need to be in the exact same setting or population. Ilex had forwarded information on this issue to the project manager today.

**ACTION ITEMS:**

Mike Bernstein agreed to re-send his e-mail to Dotti re: ongoing trials so that FDA might review it over the weekend (done).

*/s/*

\_\_\_\_\_  
Dotti Pease  
Chief, Project Management Staff

*/s/*

**Concurrence Chair:** \_\_\_\_\_  
Richard Pazdur, M.D.  
Director

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/s/

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Richard Pazdur  
12/3/04 03:56:43 PM

8/24/04

**CONSULTATION RESPONSE**  
**Division of Medication Errors and Technical Support**  
**Office of Drug Safety**  
**(DMETS; HFD-420)**

**DATE RECEIVED:**  
April 26, 2004

**DESIRED COMPLETION DATE:** June 25, 2004  
**PDUFA DATE:** September 30, 2004

**ODS CONSULT #:**  
04-0117

**TO:** Richard Pazdur, M.D.  
Director, Division of Oncology Drug Products  
HFD-150

**THROUGH:** Christy Cottrell  
Project Manager, Division of Oncology Drug Products  
HFD-150

**PRODUCT NAME:**  
Clolar  
(Clofarabine Injection)  
1 mg/mL

**NDA SPONSOR:**  
ILEX™ Products, Inc.

**NDA#:** 21-673  
**(IND#:** 63,641)

**SAFETY EVALUATOR:** Scott Dallas, R.Ph.

**RECOMMENDATIONS:**

1. DMETS has no objections to the use of the proprietary name, "Clolar". This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the labeling revisions outlined in Section III of this review to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name, "Clolar" acceptable from a promotional perspective.

/s/

Carol Holquist, R.Ph.  
Deputy Director  
Division of Medication Errors and Technical Support  
Office of Drug Safety  
Phone: (301) 827-3242 Fax (301) 443-9664

**Division of Medication Errors and Technical Support  
Office of Drug Safety  
HFD-420; Parklawn Building Room 6-34  
Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** July 21, 2004

**NDA NUMBER:** 21-673  
**IND NUMBER:** 63,641

**NAME OF PRODUCT:** Clolar  
(Clofarabine Injection)  
1 mg/mL

**NDA SPONSOR:** Illex™ Products, Inc.

**I. INTRODUCTION:**

This consult was written in response to a request from the Division of Oncology Drug Products for an assessment of the proposed proprietary name, Clolar, regarding potential name confusion with other proprietary or established drug names. Container labels, carton and insert labeling were provided for review and comment.

**PRODUCT INFORMATION**

The sponsor is seeking an indication of use to treat pediatric patients 1 to 21 years of age with refractory or relapsed acute leukemias. The pediatric dose is 52 mg/m<sup>2</sup> administered by intravenous infusion for 5 consecutive days. The treatment cycles can be repeated every 2 to 6 weeks following recovery or return to baseline organ function. Clolar will be available in single use vials with a concentration of 1 mg/mL. The product should be diluted in 5% dextrose injection, USP or 0.9% sodium chloride injection, USP prior to intravenous administration. Undiluted vials should be stored at room temperature.

**II. RISK ASSESSMENT:**

The medication error staff of DMETS conducted a search of several standard published drug product reference texts<sup>1, 2</sup> as well as several FDA databases<sup>3</sup> for existing drug names which sound-alike or look-alike to "Clolar" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online

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<sup>1</sup> MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

<sup>2</sup> Facts and Comparisons, online version, 2004, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> AMF Decision Support System (DSS), the DMETS database of proprietary name consultation requests (ACCESS), New Drug Approvals 98-04, and the online version of the FDA Orange Book.

<sup>4</sup> WWW location <http://www.uspto.gov/main/trademarks.htm>

<sup>5</sup> Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at [www.thomson-thomson.com](http://www.thomson-thomson.com).



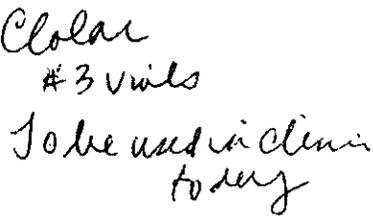
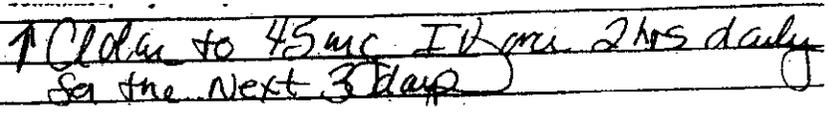
**B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)**

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. The Expert Panel (EPD) discussed all names identified in POCA that were considered to have significant phonetic or orthographic similarities to Clolar.

**C. PRESCRIPTION ANALYSIS STUDIES**

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of "Clolar" with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 124 health care professionals (pharmacists, physicians, and nurses) for each proposed proprietary name. These exercises were conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for "Clolar". These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via email. In addition, outpatient orders were recorded on voice mail and included an order for "Clolar". The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
<p><i>Outpatient:</i></p>  <p>Clolar #3 vials To be used in clinic today</p>	<p><i>Outpatient:</i></p> <p>Clolar 3 vials To be used in the clinic today</p>
<p><i>Inpatient:</i></p>  <p>↑ Clolar to 45mc IV q 2 hrs daily for the next 3 days</p>	

## 2. Results:

One respondent in the inpatient written prescription study interpreted the proposed name as Ceclor. Ceclor is a currently marketed U.S. product that looks similar to the proposed name Clolar. See Attachment A for the complete listing of interpretations from the verbal and written prescription studies.

### D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proposed proprietary name "Clolar", the primary concerns related to look-alike and sound-alike confusion with Acular, Ceclor, Alora, Aldara, and Cholac. No additional names of concern were identified using POCA or through independent review. Upon further review of the names gathered from EPD, the name Alora was not reviewed further due to a lack of convincing look-alike similarities with Clolar in addition to numerous differentiating product characteristics such as the product strength, indication of use, usual dose, frequency of administration, route of administration, and dosage formulation.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that Clolar could be confused with Ceclor. One respondent from the inpatient prescription study misinterpreted the name as Ceclor, an already existing marketed drug product. Although there are limitations to the predictive value of these studies, primarily due to sample size, we have acquired safety concerns due to the positive interpretation with this drug product. A positive finding in a study with a small size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population.

#### Look-alike and Sound-alike Concerns

1. Ceclor was identified to have look-alike similarities to the proposed name, Clolar. This look-alike similarity was confirmed in the prescription studies conducted by DMETS, when one respondent interpreted the scripted inpatient prescription name of Clolar as Ceclor. Ceclor is indicated for the treatment of infections caused by susceptible organisms. Both names consist of six letters, and the first, fourth and sixth letters in each name are the same. When scripted the fifth letter in each name, "o" and "a" can look very similar and cause the last three letters of each name to look similar. Therefore, the second and third letters of each name "ec" vs. "lo" must be clearly scripted to aid in differentiating the names. Despite these similarities the products differ in their strength (250 mg, 500 mg, 125 mg/5mL, 187 mg/5 mL, 250 mg/5 mL, and 375 mg/5mL vs. 1 mg/mL), indication of use (various infections vs. refractory or relapsed acute leukemia), usual pediatric dose (20 to 40 mg/kg/day which converts to 1 or ½ chewable tablet or teaspoonful(s) or mL of an oral suspension vs. 52 mg/m<sup>2</sup>), frequency of administration (every 8 or 12 hours vs. once a day), duration of therapy (7 to 10 days vs. 5 days), route of administration (oral vs. intravenous), and dosage formulation (capsule and oral suspension vs. injection). Although these names possess look-alike similarities, the many aforementioned different product characteristics decrease the likelihood of confusion or medication errors between the two products.

*Clolar*  
*Ceclor*

2. Acular was identified to have look-alike similarities to the proposed name, Clolar. Acular is indicated for the relief of ocular itching caused by seasonal allergic conjunctivitis and for the treatment of postoperative inflammation following cataract extraction. Both names consist of six letters, and the last three letters in each name are the same. Although the first three letters in each name appear different when printed, these same letters can appear similar when scripted and increase the orthographic similarity of the names (refer to the scripted writing sample on page 7). Despite these similarities the products differ in their strength (0.5% and Acular LS 0.4% vs. 1 mg/mL), indication of use (seasonal allergic conjunctivitis and postoperative inflammation vs. refractory or relapsed acute leukemia), usual dose (1 drop vs. 52 mg/m<sup>2</sup>), frequency of administration (four times a day vs. once a day), duration of therapy (as needed or for 14 days following surgery vs. 5 days), route of administration (topical vs. intravenous), and dosage formulation (solution, ophthalmic vs. injection). Although these names possess look-alike similarities, the many aforementioned different product characteristics decrease the likelihood of confusion or medication errors between the two products.

*Acular*  
*Clolar*

3. Aldara was identified to have look-alike similarities to the proposed name, Clolar. Aldara is indicated for the treatment of external genital and perianal warts/condyloma acuminata in individuals 12 years of age and older. When scripted the name Clolar can look similar to the first five letters in Aldara. A scripted capital letter "C" can look similar to a capital letter "A", and also the scripted letters "ol" can look similar to the letter "d". Therefore, the trailing letter "a" in the name Aldara may be the most distinguishing feature differentiating the two names. Despite these similarities the products differ in their strength (5% vs. 1 mg/mL), indication of use (external genital and perianal warts vs. refractory or relapsed acute leukemia), usual dose (apply a thin layer and rub into skin until the cream is no longer visible vs. 52 mg/m<sup>2</sup>), frequency of administration (three times a week vs. once a day), duration of therapy (continuous until warts are cleared or a maximum of 16 weeks vs. 5 days), route of administration (topical vs. intravenous), dosage formulation (cream vs. injection), and package configuration (single use packets vs. 20 mL vials). Although these names possess look-alike similarities, the many aforementioned different product characteristics decrease the likelihood of confusion or medication errors between the two products.

*Clolar*  
*Aldara*

3. Cholac was identified to have look-alike similarities to the proposed name, Clolar. Cholac is a lactulose product that could be used to treat constipation or to prevent and treat portal-systemic encephalopathy (PSE). Both names consist of six letters, and the

first, third, fourth and fifth letters in each name are the same. When scripted the last letter in each name, "c" and "r" can look very similar and increases the orthographic similarity of the last four letters of each name. Therefore, the second letter in each name "h" vs. "l" must be clearly scripted in order to aid in differentiating the names. These products differ in their strength (10 g/15 mL vs. 1 mg/mL), indication of use (constipation or portal-systemic encephalopathy vs. refractory or relapsed acute leukemia), usual pediatric dose (teaspoonful, tablespoonful, grams, or mL vs. 52 mg/m<sup>2</sup>), frequency of administration (3 to 4 divided doses vs. once a day), route of administration (oral vs. intravenous), and dosage formulation (oral solution vs. injection). An inpatient prescription for Clolar should be further differentiated from Cholac, because a physician should specify whether the product should be diluted with 5% dextrose injection or 0.9% sodium chloride injection. Another concern would be if an outpatient prescription scripted as Cholac or Clolar could be confused and result in a medication error. A search conducted by DMETS on July 28, 2004 found that the proprietary name Cholac was not referenced on the following Internet websites, cvs.com, costco.com, rxlist.com, medsfors.com, drugstore.com, and destinationrx.com. This indicates that the proprietary name Cholac may not be widely well known or used by patients or healthcare professionals even though lactulose is a commonly used outpatient product. Although the directions of use on an outpatient Cholac prescription could be scripted as "use as directed", physicians may be more inclined to include specific directions of use, especially because both the dose (teaspoonful(s), tablespoonful(s), grams or mL) and frequency of administration (once, twice, three or four times a day, at bedtime or as needed) for lactulose can vary depending upon the patient's age, the patient's medical history and the indication of use. Also the quantity to be dispensed for an outpatient Cholac prescription would more commonly be scripted as "240 mL" or "8 oz". Whereas, the quantity to be dispensed on an outpatient Clolar prescription should be scripted as "x number of 20 mL vials" or "x number of vials". Although these names possess look-alike similarities, the low usage of the proprietary name Cholac, and the many aforementioned different product characteristics decrease the likelihood of a medication error between these two products.

The image shows two lines of handwritten cursive text. The top line reads "Cholac" and the bottom line reads "Clolar". The letters are fluid and connected, with the 'c' and 'r' in both words being particularly similar in appearance.

### III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container label, carton and insert labeling of Clolar, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

#### A. General Comment:

The presentation of the established name should include the dosage formulation. The established name should be presented as "Clolarabine Injection".

#### B. Container Label:

1. The proprietary and established names are presented in different font styles and colors. While the actual size of the letters for established name might be  $\frac{1}{2}$  the size of the proprietary name, the use of different font styles and colors does not allow for the appropriate prominence of the established name. Ensure the established name appears with at least half the prominence as the proprietary name after accounting for differences with the font style, size, and print color.
2. The last two letters of the proprietary name appear blurry and difficult to read. DMETS recommends that the font size, style and or spacing should be adjusted to clearly present the proprietary name.
3. DMETS suggests that the total drug quantity and the product strength should be presented directly under the established name utilizing two different lines and within a box or border with the same color background. DMETS suggests the total drug quantity be the primary expression of strength followed immediately by the concentration per mL. For example,

<b>20 mg/20 mL</b> 1 mg/mL
-------------------------------

4. The U.S. Pharmacopeia (USP) definition indicates a single-dose container is a single-unit container intended for parenteral administration. However, a single-unit container is designed to hold a quantity of drug product intended for administration as a single dose. Since this vial is not designed to administer a single dose, then DMETS suggest changing the terminology "Single-Dose Vial" to read "Single-Use Vial".
  5. DMETS suggest the phrases "For IV Use Only" and "Dilution Required" should be incorporated to prominently present the information in a single statement (i.e., Must be diluted prior to IV use).
  6. If space permits, DMETS suggests a statement should be included to instruct healthcare professionals to discard any unused medication.
- C. Carton Label (one vial):
1. Refer to comments B1-B4, and B6.
  2. Increase the prominence of the statement, "Must be further diluted prior to IV Infusion."
- D. Carton Labeling (four vials):
1. Refer to comments B1-B4, and B6.
  2. Relocate the net quantity statement away from the product strength and ensure the statement has less prominence than the product strength.

E. Insert Labeling:

1. Relocate the route of administration away from the proprietary name. DMETS suggests inclusion of the word "only".

2. Indications and Usage Section:

Remove any reference to the use of this medication in the adult patient population.

3. Dosage and Administration Section:

- a. The abbreviations "EP" and "IVI" are not commonly used or recognized. Therefore, these abbreviations should not be used.
- b. DMETS recommends that the instructions state the minimum or recommended quantity of 5% dextrose injection, USP or 0.9% sodium chloride injection, USP that should be used to dilute the clofarabine injection.
- c. The statement containing adult dosing information should be removed.

4. Storage and Handling Section:

- a. The second sentence concerning the [ ] " can be removed from this section.
- b. The second paragraph should be relocated to the "Dosage and Administration" section of the labeling.

5. How Supplied Section:

- a. Some of the information presented in this section should be relocated to other sections. For example, information on the pH range of the solution should be included in the Description section. Please review and revise.
- b. This section should indicate that the product is available in cartons containing 1 vial (NDC 68646-1400-1) and also packaged in cartons containing 4 vials (NDC 68646-1400-4).
- c. DMETS recommends that this section indicate [ ] 7

#### IV. RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name "Clolar". This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the labeling revisions outlined in Section III of this review to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name, "Clolar" acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

/s/

---

Scott Dallas, R.Ph.  
Safety Evaluator  
Office of Drug Safety (DMETS)

Concur:

/s/

---

Denise Toyer, Pharm.D.  
Team Leader  
Division of Medication Errors and Technical Support  
Office of Drug Safety

Attachment A:

Prescription Study Results for the proposed name "Clolar"

<b>Outpatient Prescription</b>	<b>Verbal Prescription</b>	<b>Inpatient Prescription</b>
Clolac	Chlolar	Adar
Clolac	Cloar	Ceclor
Clolar	Clolar	Cloban
Clolar	Clolar	Clolac
Clolar	Clolar	Clolai
Clolar	Clolar	Clolar
Clolar	Clo-lar	Clolar
Clolar	Clora	Clolar
Clolar	Klolar	Clolar
Clolar	Klolar	Clolar
Clolar		Clolar
Clolar		Clolar

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/s/  
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Scott Dallas  
8/24/04 03:54:17 PM  
DRUG SAFETY OFFICE REVIEWER

Denise Toyer  
8/24/04 03:58:39 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
8/24/04 04:03:11 PM  
DRUG SAFETY OFFICE REVIEWER

9

                     **Pages Redacted of  
Deliberative Process  
§ 552(b)(5)**

7/27/04

## MEMORANDUM OF TELECON

DATE: July 16, 2004

APPLICATION NUMBER: NDA 21-673 CLOLAR (clofarabine)

BETWEEN:

Name: Mike Bernstein, M.P.H  
Senior Director, Regulatory Affairs  
Phone: 210-949-8285  
Representing: Ilex

AND

Name: Amy Baird, Consumer Safety Officer  
Division of Oncology Drug Products, HFD-150

SUBJECT: Pediatric Exclusivity Meeting

Mr. Bernstein called the Division inquiring as to the status of the exclusivity determination for NDA 21-673 CLOLAR. I told Mr. Bernstein that a Pediatric Exclusivity Board meeting was held July 14, 2004, where the Committee determined that CLOLAR is granted a 6-month exclusivity. The telephone call then ended.



---

Amy Baird  
Consumer Safety Officer

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/s/

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Amy Baird  
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Amy Baird  
7/20/04 05:10:33 PM  
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/s/

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Debbie Avant

7/23/04 01:10:58 PM

## Pediatric Exclusivity Board

July 14, 2004

### Pediatric Exclusivity Board Members Representatives

John Jenkins OND  
Debbie Avant, Peds Team  
Shirley Murphy, Director DPDD  
Sonal Vaid  
Aileen Ciampa, OCC  
Dena Hixon, HFD 600  
Edward Cox HFD 104  
Sonal Vaid  
John Lazor  
Liz Sadove

### Review Division/ Office

Martin H. Cohen, HFD 150  
Amy Baird, HFD 150  
Sheila Ryan, HFD 150  
Roshni Ramchandani, HFD 150  
Steve Hirschfeld, HFD 150  
Suzie McCune Peds Team

### **Pediatric Exclusivity Determination for Clolar (clofarabine) Injectable – Ilex {NDA 21- 673}**

Initial Written Request:	March 7, 2003
Timeframe for submission of studies:	Dec 31, 2005
Date report of studies submitted:	March 30, 2004
Due Date for Pediatric Exclusivity Determination:	June 28, 2004

- The Board and the division discussed the significance of clofarabine, a new molecular entity, being studied in the pediatric population prior to being studied in adults. It was agreed that this is an excellent example of the success of the BPCA legislation.
- The division stated that the clofarabine studies included pediatric patients typically not included in previous clinical trials due to the severity of the condition.
- The sponsor addressed each and every item in the Written Request satisfactorily.
- Division believes sponsor fairly met the terms of the Written Request.

### **Recommendations:**

- Board agreed that the sponsor fairly met all terms in the Written Request.
- Pediatric Exclusivity granted
- Division was instructed to inform the sponsor via telephone that Pediatric Exclusivity was granted. The fact that exclusivity was granted will be posted on the pediatric web site and the exclusivity will be reflected in the next monthly update to the Orange Book.

Prepared by:   
Debbie Avant, R.Ph.

Date: \_\_\_\_\_



Date: \_\_\_\_\_

John Jenkins, M.D.

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Debbie Avant  
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## DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150  
Parklawn Building  
5600 Fishers Lane, Rockville, MD 20857

**To:** Mike Bernstein, MPH

**From:** Amy Baird, CSO

**Fax:** 210-442-8285

**Fax:** 301-827-4590

**Phone:** 210-949-8285

**Phone:** 301-594-5779

**Pages (including cover):** 3

**Date:** June 4, 2004

**Re:** NDA 21-673 Clofarabine. Telephone conference held June 4, 2004, regarding FDA facsimiles dated May 28 and June 2, 2004.

Urgent     For Review     Please Comment     Please Reply     Please Recycle

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● **Comments:**

Ilex asked in our telephone conference about the May 28 FDA facsimile and the fact that some of the tables in that fax were missing lines. On the following pages are the full tables. Please call should you have any questions.

Thank you,

Amy Baird

**CLINICAL REVIEW**

Executive Summary Section

*AML*

FDA Responder Summary

Patient	014-0003	006-0013	009-0018	014-0002	014-0019	014-0027	015-0017
Time to first relapse (mo)	3	2	4*	26	10*	1	8
Time to 2nd relapse (mo)	12	1	-	27	-	3*	2*
Time to 3 <sup>rd</sup> or later relapse (mo)	3, 9*	2, 1*	-	7, 2, 9*	-	-	-
Stem cell transplant (Y or N)	Y	N	N	Y	Y	N	N
Stem cell transplant resp dur (mo)	5	-	-	6	6	-	-
Clofarabine response	CRp	PR	PR	PR	PR	PR	PR
Clofar response confirmed Y or N	Y	N	N	N	N	N	N
Clofarabine response duration (d)	284+	12	34	1+	44+	14	22+
Clofarabine TTP or death (d)	313+	54	67	22+	78+	49	62+
Post-clofarabine SCT (Y or N)	Y	N	N	Y	Y	N	Y
Current status (Alive or Dead)	A	D	D	D	D	A	A
Post-clofarabine OS (w)	68.1+	7.7	24.3	30.3	39.0	7.6+	40.9+

\* response duration for treatment immediately preceding clofarabine treatment

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Patient	007-0018	009-0028	014-0030	018-0036	009-0024	012-0014	014-0040	004-0025	006-0003	006-0004	014-0007
Time to first relapse (mo)	10	25	86	30	2	31	3	11	19	8	28
Time to 2nd relapse (mo)	4	17*	35	11	4*	1	3	6	1	4*	1
Time to 3 <sup>rd</sup> or later relapse (mo)	1*	-	18	2, 31*	-	1, 1, 2, 1*	1*	2, 1*	1, 1*	-	8*
Stem cell transplant (Yes or No)	N	Y	Y (2)	Y (2)	Y	N	N	Y	N	Y	Y
Stem cell transplant resp dur (mo)	-	20	27, 10	6, 29	2	-	-	4	-	2	3
Clofarabine response	CR	CR	CR	CRp	CRp	CRp	CRp	PR	PR	PR	PR
Clofar response confirmed (Y or N)	N	Y	N	Y	Y	Y	N	N	N	N	Y
Clofar response duration (days)	43	69	65+	8+	200	34+	11+	21	16	7	56+
Clofarabine TTP or death (days)	146	97	123+	34+	259	61+	44+	48	44	21	77+
Post-clofarabine SCT (Y or N)	N	N	N	N	Y	Y	N	N	N	N	Y
Current status (Alive or Dead)	A	A	A	A	A	D	A	D	D	D	D
Post-clofarabine OS (w)	46.0+	18.0+	17.6+	4.9+	37+	42.0	6.1+	18.1	36.3	7.0	29.7

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/s/

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Amy Baird  
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## DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

**To:** Mike Bernstein, MPH

**From:** Amy Baird, CSO

**Fax:** 210-442-8285

**Fax:** 301-827-4590

**Phone:** 210-949-8285

**Phone:** 301-594-5779

**Pages (including cover):** 1

**Date:** June 2, 2004

**Re:** NDA 21-673 Clofarabine.

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● **Comments:**

Attached are the DRAFT comments which are proposed to go out in the filing letter. Please call should you have any questions.

1. The ALL and AML protocols state that responses (CR, CRp, PR) have to be confirmed by bone marrow aspiration and/or biopsy done 21 days after the initial response. Please provide patient listings indicating whether bone marrow evaluations were done and what were the results.
2. Regarding patients who went on to transplant please provide patient listings indicating whether a bone marrow aspiration and/or biopsy was performed after transplant and what were the results?

Thank you,

Amy Baird

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/s/

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Amy Baird  
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## DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

**To:** Mike Bernstein, MPH **From:** Amy Baird, CSO

---

**Fax:** 210-442-8285 **Fax:** 301-827-4590

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**Phone:** 210-949-8285 **Phone:** 301-594-5779

---

**Pages (including cover):** 2 **Date:** May 28, 2004

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**Re:** NDA 21-673 Clofarabine.

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• **Comments:**

Per the request of the clinical review team, please review and comment on the following.

Below is the clinical team's analysis of responders in study CLO-220, pediatric AML. The results are based on the Aspirate database. Does ILEX have any comments or questions?

Patient	014-0003	006-0013	009-0018	014-0002	014-0019	014-0027	015-0017
Clofarabine response	CRp	PR	PR	PR	PR	PR	PR
Clofar response confirmed (Yes or No)	Y	N	N	N	N	N	N
Clofarabine response duration (days)	284+	12	34	1+	44+	14	22+
Clofarabine TTP or death (days)	313+	54	67	22+	78+	49	62+

Also, below is the team's analysis of responders in study CLO-212, pediatric ALL. The results are based on the Aspirate database. Does ILEX have any comments or questions?

Patient	007- 0018	009- 0028	014- 0030	018- 0036	009- 002 4	012- 0014	014- 004 0	004- 002 5	006- 000 3	006- 000 4	014- 0007
Clofarabine response	CR	CR	CR	CRp	CRp	CRp	CRp	PR	PR	PR	PR
Clofar response confirmed (Y or N)	N	Y	N	Y	Y	Y	N	N	N	N	Y
Clofar response duration (days)	43	69	65+	8+	200	34+	11+	21	16	7	56+
Clofarabine TTP or death (days)	146	97	123+	34+	259	61+	44+	48	44	21	77+
Post-clofarabine SCT (Y or N)	N	N	N	N	Y	Y	N	N	N	N	Y
Current status (Alive or Dead)	A	A	A	A	A	D	A	D	D	D	D
Post-clofarabine OS (w)	46.0+	18.0+	17.6+	4.9+	37+	42.0	6.1+	18.1	36.3	7.0	29.7

Please call should you have any questions.

Thank you,

Amy Baird

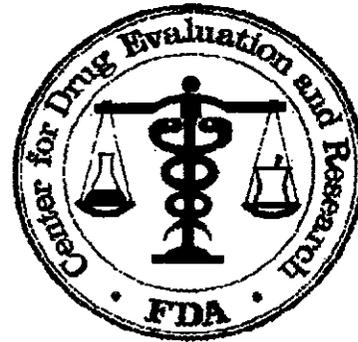
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Amy Baird  
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# FAX

**FOOD AND DRUG ADMINISTRATION**  
**DIVISION OF ONCOLOGY DRUG PRODUCTS**  
Center for Drug Evaluation and Research, HFD-150  
5600 Fishers Lane, Rockville, MD 20857



---

**To:** Mike Bernstein, Ilex

**From:** Christy Cottrell

---

**Fax:** (210) 949-8282

**Fax:** (301) 594-0499

---

**Phone:** (210) 949-8285

**Phone:** (301) 594-5761

---

**Pages, including cover sheet:** 1

**Date:** 4-20-04

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**Re:** NDA 21-673 for Clofarabine

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Mike,

Please refer to your pending NDA 21-673 for Clofarabine. Included in this fax is a request for additional information from the clinical reviewer.

- Please provide the CRFs for all of the PRs, CRs, and CRps for patients in studies 212, 222, and 383.

Please expedite your response to this request. If you have any questions, feel free to call me at (301) 594-5761.

Thanks,

Christy Cottrell

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/s/

-----  
Christy Cottrell  
4/20/04 10:48:37 AM  
CSO

**From:** Cottrell, Christy  
**Sent:** Tuesday, December 30, 2003 9:57 AM  
**To:** 'Bernstein, Michael'  
**Subject:** RE: Item 11 Outline for Clofarabine NDA  
See our answers below in blue.

Christy

-----Original Message-----

**From:** Bernstein, Michael [mailto:mbernstein@ilexonc.com]  
**Sent:** Monday, December 22, 2003 2:36 PM  
**To:** Cottrell, Christy  
**Subject:** FW: Item 11 Outline for Clofarabine NDA

Christy,

In preparation for the Clin/Stat section of the Clofarabine eNDA, we have a few questions that we would like your Stat reviewer to review and get back to us. We can provide additional details or samples if clarification is needed.

-CRTs by domain with applicable documentation for all data collected from pediatric studies ID99-383, CLO-212, and CLO-222, as well as the ISS integrated database will be supplied. The specific data tables requested by the division (FDA response to Question 9, pre-NDA meeting minutes from 13 August, 2003 teleconference) will be part of the CRTs. Currently, we do not plan to create integrated datasets for the ISE, but if they are generated, CRTs for these data will be supplied also. Is this OK?

**FDA stat response: Yes.**

-Note that 1 patient from adult study CLO-221 qualifies as a pediatric patient and will be included in the ISS integrated database. Hence the ISS integrated database will include all patients (up to data cutoff) in ID99-383, CLO-212, CLO-222 and one patient from CLO-221. The patient profile for this patient will be included in the CLO-221 CSR. Is this OK?

**FDA clinical response: Yes.**

-Complete patient profiles are included in the individual study reports and will not be in Item 11. Is this OK?

**FDA clinical response: Yes**

-SAS programs, formats and datasets used to perform the analysis for studies ID99-383, CLO-212, CLO-222, and ISS will be included in Item 11 under its own directory structure. These will stand alone and will allow a SAS user to rerun the tables and other analysis programs used for the clinical study reports and ISS. Is this OK?

**FDA stat response: Yes.**

Thanks and have a happy holiday,

Mike

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/s/

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Christy Cottrell  
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CSO



9/25/03

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-673	Efficacy Supplement Type SE-	Supplement Number
Drug: CLOLAR (clofarabine) Intravenous Infusion		Applicant: Genzyme Corporation
RPM: Christy Cottrell		HFD-150      Phone # (301) 594-5761
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):
❖ Application Classifications:		
• Review priority		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
• Chem class (NDAs only)		1
• Other (e.g., orphan, OTC)		Orphan
❖ User Fee Goal Dates		December 30, 2004 (extended)
❖ Special programs (indicate all that apply)		<input type="checkbox"/> None <input type="checkbox"/> Subpart H <input checked="" type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input checked="" type="checkbox"/> Fast Track <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
• User Fee		<input type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input checked="" type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		N/A
• OC clearance for approval		N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that form FDA-3542a was submitted.		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified

❖ <b>Exclusivity (approvals only)</b>	
• Exclusivity summary	Included
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	( ) Yes, Application # _____ (X) No
❖ <b>Administrative Reviews (Project Manager, ADRA) (indicate date of each review)</b>	N/A
❖ <b>Actions</b>	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ <b>Public communications</b>	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter (X) Burst email
❖ <b>Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))</b>	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	Included
• Most recent applicant-proposed labeling	N/A
• Original applicant-proposed labeling	N/A
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	DDMAC: 7-27-04 ODS: 8-24-04 and 12-6-04 Pharm/Tox: 12-20-04
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ <b>Labels (immediate container &amp; carton labels)</b>	
• Division proposed (only if generated after latest applicant submission)	Included
• Applicant proposed	N/A
• Reviews	N/A
❖ <b>Post-marketing commitments</b>	
• Agency request for post-marketing commitments	Included
• Documentation of discussions and/or agreements relating to post-marketing commitments	Included
❖ <b>Outgoing correspondence (i.e., letters, E-mails, faxes)</b>	Included
❖ <b>Memoranda and Telecons</b>	Included
❖ <b>Minutes of Meetings</b>	
• EOP2 meeting (indicate date)	4-29-02
• Pre-NDA meeting (indicate date)	8-13-03
• Pre-Approval Safety Conference (indicate date; approvals only)	12-22-04 (labeling meeting) 7-14-04: Ped Exc Board Mtg 7-16-04: Guidance telecon 11-24-04: Guidance telecon
• Other	

<ul style="list-style-type: none"> <li>❖ Advisory Committee Meeting</li> </ul>	
<ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li>• Date of Meeting</li> </ul> </li> </ul>	December 1, 2004
<ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li>• 48-hour alert</li> </ul> </li> </ul>	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	Included
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	DD memo: 2-2-05 Pharm/Tox: 12-20-04 Clinical TL: 12-22-04
❖ Clinical review(s) (indicate date for each review)	12-8-04
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	See clinical review
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Included
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	12-22-04
❖ Biopharmaceutical review(s) (indicate date for each review)	12-22-04
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
<ul style="list-style-type: none"> <li>• Clinical studies</li> </ul>	Draft included
<ul style="list-style-type: none"> <li>• Bioequivalence studies</li> </ul>	N/A
❖ CMC review(s) (indicate date for each review)	12-27-04
❖ Environmental Assessment	
<ul style="list-style-type: none"> <li>• Categorical Exclusion (indicate review date)</li> </ul>	See CMC review
<ul style="list-style-type: none"> <li>• Review &amp; FONSI (indicate date of review)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Review &amp; Environmental Impact Statement (indicate date of each review)</li> </ul>	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	9-29-04
❖ Facilities inspection (provide EER report)	Date completed: 12-13-04 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed (X) Requested ( ) Not yet requested
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	9-20-04
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

## MINUTES OF TELECONFERENCE

**DATE:** August 13, 2003    **TIME:** 2:00 pm    **LOCATION:** Conference Room I

**IND/NDA:** IND 63,641

**Meeting Request Submission Date:** 6-3-03

**FDA Response Date:** 6-11-03

**Briefing Document Submission Date:** 7-11-03

**Additional Submission Dates:** N/A

**DRUG:** Clofarabine

**SPONSOR/APPLICANT:** Ilex Products, Inc.

### **TYPE of MEETING:**

1. Pre-NDA meeting
2. Proposed Indication: Pediatric Refractory or Relapsed Acute Lymphoblastic Leukemia

### **FDA PARTICIPANTS:**

Dr. Grant Williams, Deputy Director  
Dr. John Johnson, Clinical Team Leader (Pre-meeting only)  
Dr. Steven Hirschfeld, Clinical Reviewer  
Dr. Kim Benson, Pharm/Tox Reviewer  
Dr. Ning Li, Acting Statistical Team Leader  
Dr. Yong-Cheng Wang, Statistical Reviewer (Industry meeting only)  
Dr. Atiqur Rahman, Biopharmaceutics Team Leader (Pre-meeting only)  
Dr. Anne Zajicek, Biopharmaceutics Reviewer (Industry meeting only)  
Dr. Lilia Talarico, Associate Director (Pre-meeting only)  
Dr. Kevin Ridenhour, Clinical Reviewer  
Dr. Scott Gottlieb, Observer, Office of the Commissioner  
Joann Minor, Associate Director, Cancer Liaison Program, OSHI  
Ruth Hoffman, Patient Representative  
Dr. Gregory Reaman, ODAC Consultant (Pre-meeting only)  
Christy Cottrell, Consumer Safety Officer

### **INDUSTRY PARTICIPANTS:**

Dr. Larry Arthaud, Director, Pharmacology and Toxicology  
Mike Bernstein, Senior Director, Regulatory Affairs  
Dr. Peter Bonate, Director, Pharmacokinetics  
Dr. Adam Craig, Senior Director, Clinical Development  
Dr. Katherine Martinez, Associate Director, Pharmacology  
Kim Norris, Associate Director, Medical Writing  
Bret Wacker, Associate Director, Biostatistics  
Dr. Steve Weitman, Chief Medical Officer  
Jane Weiss, Director, Product Team Leader

**BACKGROUND:**

Clofarabine is a novel, second-generation, halogenated-adenosine analogue. As a pivotal trial, the sponsor proposes a nonrandomized, open-label, Phase 2 study of clofarabine in pediatric patients with refractory or relapsed ALL. Patients must be in second or subsequent relapse or be refractory, i.e., failed to achieve a remission following 2 cycles of the same therapy or 2 different regimens. Forty patients will be enrolled in a Fleming 2-stage sequential study design. The primary endpoint will be overall remission (OR), defined as either complete remission (CR) or complete remission in the absence of total platelet recovery (CRp). Secondary objectives of the study will be to document the rate of CRs, CRp(s), and partial remissions (PRs), as well as to document time-to-event parameters including duration of remission and overall survival (OS). Additionally, the sponsor plans to document the safety profile and tolerability of clofarabine in this population, and to determine the pharmacokinetic profile and intracellular pharmacology and metabolism of clofarabine. The sponsor intends to include supportive data from two additional studies (CLO-222 and ID99-383). CLO-222 is a Phase 2 nonrandomized, open-label, single-arm study of clofarabine in 23 pediatric patients with refractory or relapsed AML. ID99-383 is a Phase 1 study conducted at MD Anderson Cancer Center in 25 pediatric patients with both ALL and AML.

An End-of-Phase 1 meeting was held on April 29, 2002, to discuss both pediatric indications (AML and ALL).

The sponsor requested this meeting to establish agreement with the Division that the clinical and pharmacology/toxicology data are sufficient to support filing an NDA for pediatric ALL. The Division's draft responses were faxed to the sponsor on August 5, 2003.

**QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:**

1. **ILEX contends that completion of the clofarabine nonclinical program as summarized in Section 5 supports filing an eNDA. Does the Division concur?**

**FDA RESPONSE:**

- Yes.

2. **ILEX contends that the design of our Phase II pediatric ALL study (CLO-212) as a single pivotal trial (multicenter) is sufficient for registration approval of clofarabine for treatment of relapsed or refractory pediatric patients with ALL. Does the Division concur?**

**FDA RESPONSE:**

- The design is acceptable for this indication. The number of patients studied is relatively small and the CR rate is relatively low. We encourage you to increase the size of the

study to gain experience. We strongly suggest that you continue to accrue patients regardless of whether you submit the NDA as proposed.

If the proposed NDA is approved, it will likely be accelerated approval under subpart H. This requires confirmatory studies. It must be credible that the confirmatory studies will be completed in an acceptable time frame. This means that the protocols for confirmatory studies should be submitted prior to submission of the NDA. If there is concern that the studies will have difficulty accruing patients or that approval will interfere with completion of the confirmatory studies, the studies should have completed accrual or accrued a substantial portion of the patients, prior to approval under subpart H.

An important issue will be the results achievable in this patient population with other treatments. The NDA should discuss this in detail, supported by submission of photocopies of published articles from the literature.

*Discussion: The sponsor asked whether 40 patients from CLO-212 would be sufficient to file an NDA. The Division stated that a commitment to a specific number of patients generally cannot be made, but encouraged the sponsor to continuing accruing patients.*

*The sponsor asked whether it would be acceptable to submit the data on the first 40 patients, and then submit data on any additional patients at a later date. The Division discouraged this approach and stated that in general, it is acceptable to submit additional safety data (i.e., 120-day safety update), but not efficacy data. The Division explained that in the rolling review process, the sponsor must submit complete sections of the NDA. The sponsor has the option of submitting additional information as an amendment, but if the information is substantial and is submitted within 3 months of the due date, it may extend the review clock by 3 months.*

*The Division further explained that 40 patients may not be enough if the drug has a low response rate, however, 40 patients may be enough if the drug has a high response rate. This will be an ongoing discussion and should be addressed again in the future when more data is available.*

*The sponsor asked whether the Division would accept a post-marketing commitment to conduct a Phase 2 study in a similar population of patients. The Division explained that the type of confirmatory study that may be appropriate has not been assessed at this stage, however, the Division encouraged the sponsor to submit any proposed post-marketing commitment protocols with the NDA for review. The Division reminded the sponsor that the NDA is not restricted to Subpart H accelerated approval, because there may be enough data to receive full approval.*

*The sponsor asked for guidance on how to present the additional AML data they are receiving. The Division stated that the sponsor could pattern the submission of AML data after this NDA for ALL. The sponsor asked whether it would be acceptable to include both AML and ALL in the Integrated Summary of Safety. The Division agreed, as long as they do not represent different findings. The Division further explained that the additional AML data could help with safety assessments, but that efficacy would be reviewed independently.*

- 3. ILEX contends that treatment with a single agent (clofarabine) administered to pediatric patients with relapsed or refractory ALL demonstrating a  $\geq 15\%$  overall response rate (CR + CRp) is clinically significant in this heavily pretreated and refractory population. Does the Division concur?**

**FDA RESPONSE:**

- The Oncology Division does not commit to a particular response rate in advance. This will be a review issue. There are many other factors to consider, such as response duration, toxicity and results that can be achieved with other therapy.
- An important aspect will be the proportion of responding patients that have a successful transplant.

- 4. ILEX contends that the use and definitions of Complete Response (CR), Complete Response without full platelet recovery (CRp), and Partial Response (PR) of the Children's Oncology Group Response Criteria are acceptable for filing an eNDA. Does the Division concur?**

**FDA RESPONSE:**

- The COG response criteria could be acceptable, but were not provided in the Pre-NDA meeting package for our review.

- 5. ILEX contends that a 1 to 3 month remission is considered durable and a clinical benefit in this population of patients (refractory or in second or subsequent relapse). Does the Division concur?**

**FDA RESPONSE:**

- This will be a review issue. See answer to question #3.

6. **ILEX contends that a CR or CRp is a clinical benefit, especially for patients who are enabled to undergo a bone marrow, stem cell, or umbilical cord transplant. Does the Division concur?**

**FDA RESPONSE:**

- Possibly. For transplant patients, it depends on the success of the transplant after treatment with Clofarabine. For non-transplant patients, it depends on response duration, survival, toxicity and results achievable with other therapy.

7. **ILEX contends that a PR (>5% to <25% blasts) is of clinical benefit in this population of children, allowing selected patients to receive a bone marrow, stem cell, or umbilical cord transplant. Does the Division concur?**

**FDA RESPONSE:**

- See answer to question #6.

8. **ILEX contends that the ID99-383 pediatric ALL efficacy data will be supportive of the registration application by demonstrating additional clinical activity in pediatric leukemia. Does the Division concur?**

**FDA RESPONSE:**

- Possibly. This will be a review issue. We note that only 9 patients were treated with the regimen proposed for marketing and none of these had a CR. In patients treated at other doses, there was disagreement between the independent review board and the investigator regarding CR status.

9. **ILEX contends that the proposed analysis of pivotal trial data (CLO-212) and proposed presentation of data support filing an eNDA (see Appendices B and C). Does the Division concur?**

**FDA RESPONSE:**

- A filing decision is not made until after the NDA is received. There is no mention of an electronic database. We strongly encourage the submission of an electronic database. This is standard for 21<sup>st</sup> century NDAs. This would greatly facilitate review of the NDA.

Documentation of Refractory/Relapse history should be provided for each patient. Please submit for each patient the prior treatment regimens received (including dates) and the response and response duration status after each regimen. The date of most recent relapse or documentation of refractoriness should be provided for each patient.

For transplanted patients the date of transplant and results of transplant should be submitted.

- Please send the datasets from the existing tables as SAS transport files and send the following additional tables:

**Table 1:**

Pt ID/ht/wt/BSA/age/dx/sex/daily dose (mg/m<sup>2</sup>)/daily dose (mg)/total dose in cycle (mg/m<sup>2</sup>)/total dose (mg)

**Table 2:**

Pt ID/time (from start of infusion)/plasma concentration (ng/ml) of clofarabine/intracellular clofarabine triphosphate concentration

**Table 3:**

Pt ID/ Day#/Dose (mg)/Dose (mg/m<sup>2</sup>)/ wt (kg)/BSA(m<sup>2</sup>)/Cl (L/h)/Vd (L)/t<sub>1/2</sub> (hr)

**Table 4:**

Pt ID/BUN/cr/GGT/ALT/AST/bili/albumin/nadir WBC

**Table 5:**

Pt ID/Dose #/ urine collection interval/urine volume during interval/urine concentration/amount of drug excreted during interval

*Discussion: The sponsor asked whether a SAS data set was acceptable. The Division said yes and noted that data submitted in anything except SAS is not acceptable.*

*The sponsor asked what the age cut-off was for pediatric studies and gave the following scenario: Suppose a patient is diagnosed at age 17, then relapses at age 18 or 19. Would that patient be treated on the adult protocol and can the data from this patient be included in the pediatric patient dataset? The Division said that this is a review issue and would have to be addressed on a case-by-case basis. The Division referred the sponsor to minutes from the April 2001 advisory committee meeting concerning criteria for linking adult and pediatric hematologic malignancies.*

- 10. ILEX contends that the proposed patient populations for the ISS and ISE are acceptable to support filing an eNDA (see Tables 10-1 and 10-2). Does the Division concur?**

**FDA RESPONSE:**

- See answer to question #9.

- 11. ILEX contends that Case Report Forms for only those patients who died or discontinued from the study be supplied. Does the Division concur?**

**FDA RESPONSE:**

- This would be acceptable, if a complete electronic database on all patients is submitted. Otherwise, CRFs on all patients should be submitted. We need complete information on each patient. There are relatively few patients in this NDA.

- 12. ILEX contends that the bioanalytical assays for clofarabine and clofarabine triphosphate are acceptable and that the results from a population analysis of such data support filing an eNDA. Does the Division concur?**

**FDA RESPONSE:**

- The assay validation report is under review. If the assay validation was performed according to FDA guidance (<http://www.fda.gov/cder/guidance/4252fnl.pdf>) and the results are acceptable, then the clofarabine concentrations should provide useful information.

*Discussion: The sponsor noted that the clofarabine triphosphate assay was not conducted under GLP conditions. The Division stated that was acceptable, but the sponsor should still submit the data for review.*

- 13. ILEX contends that merging pharmacokinetic and pharmacodynamic data across the three studies, ID99-383, CLO-212, and CLO-222, is acceptable for the population pharmacokinetic/ pharmacodynamic analysis necessary to support filing an eNDA. Does the Division concur?**

**FDA RESPONSE:**

- Providing that the patient populations are similar in terms of clinical status (e.g. renal and hepatic function), merging of the three data sets appears reasonable. Please clarify

the number of datasets that contain dense and sparse data; there is a discrepancy between Table 8-1, page 99 and Appendix A, III, page 7.

- 14. ILEX contends that the proposed population pharmacokinetic/ pharmacodynamic data analysis plan is acceptable to support filing an eNDA (see Appendix A). Does the Division concur?**

**FDA RESPONSE:**

- Your analysis plan appears to be acceptable. Interpretation of the pediatric data may be problematic if all pediatric data is sparse, and adult priors are used in the population pharmacokinetic analysis.

- 15. Will the Division allow a “rolling eNDA submission strategy” of specific sections of the eNDA based on the proposed schedule of completion in Section 11?**

**FDA RESPONSE:**

- This is acceptable. Labeling should be submitted with the clinical submission.

**OTHER COMMENTS**

**NDA/sNDA Presentations to CDER’s Division of Oncology**

The Center for Drug Evaluation and Research’s Division of Oncology Drug Products implemented an initiative in which we request an NDA/sNDA applicant to present their NDA/sNDA to Division personnel shortly after NDA/sNDA submission and before the expected NDA/sNDA filing date. This initiative allows the applicant to present an overview of the entire NDA/sNDA to the review team and interested Division personnel.

These presentations are generally expected to last one hour followed by a half-hour question and answer session. The applicant, not consultants, should present important information on each technical aspect (i.e., clinical, statistical, CMC, pre-clinical pharmacology and toxicology, and clinical pharmacology and biopharmaceutics) of the NDA/sNDA. In addition to providing an overview of the NDA/sNDA, the applicant should present their reasons for why the Division or the Office of Drug Evaluation I should approve their NDA/sNDA.

Please contact your Project Manager shortly after NDA/sNDA submission to schedule a date for your presentation. Alternatively, you may provide available dates in the cover letter of your NDA/sNDA and we will try to accommodate them.

Financial Disclosure Final Rule

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective and any study in which a single investigator makes a significant contribution to demonstration of safety.

Please refer to the March 20, 2001 "Guidance for Industry: Financial Disclosure By Clinical Investigators" (posted on the Internet 3/27/2001) at <http://www.fda.gov/oc/guidance/financialdis.html>.

Demographics

In response to a final rule published 2-11-98, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this analysis. To assist you in this regard, the following table is a suggestion for presentation of the numeric patient demographic information. This data, as well as the pertinent analyses, should be provided in the NDA.

Please provide information for each category listed below from the primary safety database excluding PK studies.

	DRUG	DRUG	DRUG	DRUG	DRUG	DRUG
Gender	Males	All Females	Females >50			
Age:	0-1 Mo.	>1 Mo.-2 Year				
	12-16	17-21	16			
Race:	White	Black	Asian			
	Other					

There were no unresolved issues or action items.

/s/  
Christy Cottrell

Concurrence Chair: /s/  
Steven Hirschfeld, M.D., Ph.D.

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

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Christy Cottrell  
9/15/03 10:27:05 AM

Steven Hirschfeld  
9/23/03 03:42:22 PM

## MEETING MINUTES

**MEETING DATE:** April 29, 2002      **TIME:** 2:00 pm      **LOCATION:** G

**IND/NDA:** IND 63,641

**Meeting Request Submission Date:** 4-2-02  
**Briefing Document Submission Date:** 4-2-02  
**Additional Submission Dates:** N/A

**DRUG:** Clofarex (clofarabine)

**SPONSOR/APPLICANT:** Ilex Products, Inc.

### TYPE OF MEETING:

1. End-of-Phase 1 meeting
2. **Proposed Indication:** Pediatric Acute Lymphoblastic Leukemia  
Pediatric Acute Myelogenous Leukemia

### FDA PARTICIPANTS:

Dr. Richard Pazdur, Division Director  
Dr. Grant Williams, Deputy Director (Pre-meeting only)  
Dr. Lilia Talarico, Associate Director (Pre-meeting only)  
Dr. Donna Griebel, Medical Team Leader  
Dr. Steven Hirschfeld, Medical Officer  
Dr. Peiling Yang, Statistical Reviewer  
Dr. Haripada Sarker, Chemistry Reviewer (Industry meeting only)  
Dr. John Leighton, Pharm/Tox Team Leader (Pre-meeting only)  
Dr. Kimberly Benson, Pharm/Tox Reviewer (Industry meeting only)  
Dr. Atik Rahman, Biopharmaceutics Team Leader (Pre-meeting only)  
Dr. Robert Shore, Biopharmaceutics Reviewer (Industry meeting only)  
Joann Minor, Associate Director, Cancer Liaison Program, OSHI  
Ruth Hoffman, Patient Representative  
Dr. Victor Santana, ODAC consultant (Pre-meeting only)  
Christy Wilson, Consumer Safety Officer

### INDUSTRY PARTICIPANTS:

Mike Bernstein, Senior Director, Regulatory Affairs  
Dr. Adam Craig, Director, Clinical Operations  
Jenny Swalec, Manager, Regulatory Affairs  
Bret Wacker, Associate Director, Biostatistics  
Jane Weiss, Director, Program Management  
Dr. Steve Weitman, VP Global Research  
Dr. Varsha Gandhi, Assistant Professor, Experimental Therapeutics, MD Anderson (Consultant)  
Dr. Sima Jeha, Associate Professor Medicine, MD Anderson (Consultant)

### MEETING OBJECTIVES:

Discuss sponsor's questions in briefing document dated April 2, 2002.

**QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:**

**1. FDA COMMENT SENT IN MARCH 13, 2002 FAX:**

*The protocol should clarify whether the repeat occurrence of non-infectious non-hematologic Grade 3 adverse events need to be the same type of event or if any combination of Grade 3 events will trigger a dose reduction.*

**SPONSOR RESPONSE AND QUESTION:**

**We propose that patients who experience any combination of Grade 3 events (excluding NCI CTC grade 3 transient elevations in liver function tests that occur without clinical significance and nausea/vomiting that can be controlled with antiemetic therapy), either the same event or different in nature, will require a 25% dose reduction. Do you concur?**

**FDA RESPONSE:**

- Yes.
- Grade 3 nonhematological toxicities where the patients don't recover in two weeks and third occurrence of grade 3 toxicity should be added to the list in bullet #2 of Section 4.5 Patient Discontinuation of the protocols to be consistent with the protocols' dose modification table.

**2. FDA COMMENT SENT IN MARCH 13, 2002 FAX:**

*The threshold for dose reduction should be reduced to Grade 2 for cardiac and neurologic events.*

**SPONSOR RESPONSE AND QUESTION:**

**Due to the fact that we have not observed any CLOFAREX-induced CNS toxicity preclinically and have not observed any cardiac clinical toxicity in the ongoing Phase I pediatric study at MDACC, we would like clarification of your concerns regarding CNS and cardiac toxicity. We believe that the Grade 2 threshold for dose reduction is too conservative and may compromise the potential therapeutic benefit of receiving the 52 mg/m<sup>2</sup> dose.**

**FDA RESPONSE:**

- It is not uncommon, particularly in pediatric patients, for Grade 2 neurotoxicity to be considered a dose limiting toxicity, especially when there is a relatively modest amount of clinical data available for the drug and dose. Given the limited data available for clofarabine 52 mg/m<sup>2</sup> in the proposed study population, the study should be considered as much a dose finding study as an efficacy and safety study. Neurotoxicity can have a major impact on patient function and grade 2 severity has been viewed as a clinically relevant level to signal reassessment of further exposure to drug. Grade 2 motor toxicity is defined as having weakness that interferes with function, Grade 2 sensory toxicity is objective sensory loss or paresthesia (including tingling), interfering with function, and Grade 2 cranial toxicity is defined as having cranial nerve involvement, though not interfering with daily living. Grade 2 cognitive toxicity is defined as cognitive disability; interfering with

work/school performance; decline of 1 SD (Standard Deviation) or loss of developmental milestones.

- Based on a signal from the pre-clinical data, we are concerned about the potential for cardiotoxicity. Grade 2 cardiac toxicity is defined as symptomatic.

*Comment: After discussion, the following bullet was added:*

- *At Grade 2 toxicity, dose re-evaluation will be done.*

**3. FDA COMMENT SENT IN MARCH 13, 2002 FAX:**

*There are no criteria in the protocol that define the indications for cardiac assessments during the study. Are cardiac assessments intended for every patient or only those with an abnormality on the baseline scan or clinical symptoms? Given the limited data in children, and the animal data and adult deaths, it is recommended to collect cardiac function assessment data such as echocardiogram or MUGA scan on the first 20 patients at baseline and then following induction either at the start of maintenance or upon study withdrawal for those patients that do not continue on a maintenance phase and then reassess the need for further repeat cardiac studies after baseline assessment.*

**SPONSOR RESPONSE AND QUESTION:**

**We concur. This deficiency has been addressed in the enclosed protocol amendments CLO-212-A2 and CLO-222-A2.**

**FDA RESPONSE:**

- Upon review of the revised protocol, we recommend cardiac assessments every 4 cycles.

**4. FDA COMMENT SENT IN MARCH 13, 2002 FAX:**

*Remission rates should be calculated on the basis of intent to treat.*

**SPONSOR RESPONSE AND QUESTION:**

**Can the Division clarify if their definition of "intent to treat" includes all patients enrolled in the study, regardless of whether or not they actually received a dose of CLOFAREX.**

**In the Phase II pediatric protocols, CLO-212 and CLO-222, the overall response rate will be estimated by the sum of the number of patients with either a CR or CRp divided by the total number of eligible patients who receive CLOFAREX. ILEX believes this population satisfies the intention-to-treat principle for evaluation of efficacy and will provide the most accurate estimate of response rate. Do you concur?**

**FDA RESPONSE:**

- Yes, the proposed plan is acceptable for a single arm open label study. All patients who received at least one dose should be included in the calculation of response rate. See answer to # 7 below for our comments on inclusion of CRp in the definition of overall response rate.

**5. FDA COMMENT SENT IN MARCH 13, 2002 FAX:**

*The protocol should clarify how many patients and by what criteria such as age or gender, PK analysis will be performed.*

**SPONSOR RESPONSE AND QUESTION:**

**While participation in the PK portion of these studies is voluntary, ILEX will encourage all patients to participate, regardless of age or sex. In an effort to ensure an adequate number of patients to draw meaningful conclusions, we have included in the enclosed amendments a statement requiring a minimum of 12 patients per protocol to participate in the PK study.**

**FDA RESPONSE:**

- A minimum of 12 patients per protocol is adequate. Since you are taking sparse sampling approach, you should be able to obtain plasma samples from all the patients in the trials (at least 20 patients per protocol from Stage 1). You need to submit a justification of the population pharmacokinetics sampling scheme. For example, were optimal sampling times calculated? Is there a previous model that you can rely on for designing your sampling scheme? If you can incorporate dense sampling (traditional PK sampling) along with sparse sampling, that might produce more reliable pharmacokinetic parameter estimates. The sparse sampling with no *a priori* knowledge may not result in reliable pharmacokinetic parameter estimates.
- We strongly recommend that you assess relationship between plasma concentration and response rate in the Phase 2 trials.

**6. ILEX contends that the patient selection criteria as described in Section 4.2 of protocols CLO-212 and CLO-222 defines a group of patients with a clear unmet medical need. Do you concur?**

**FDA RESPONSE:**

- Possibly. Although there are available treatments, a marked improvement over existing therapy would address an unmet medical need.
- See answer to Question #8.

*Comment: After discussion, the following bullet was added:*

- *The FDA views the planned Phase 2 study as exploratory. Plans for a randomized Phase 3 trial should be made. Please be advised that the Agency strongly recommends two Phase 3 trials to support an application. (2 pediatric or 1 adult/1 pediatric, all in leukemia).*

**7. ILEX contends that a combination safety database consisting of data collected from the Phase II pediatric ALL study (CLO-212), the Phase II pediatric AML study (CLO-222), and the Phase II adult acute leukemia studies are mutually supportive and will support registration approval. Do you concur?**

**FDA RESPONSE:**

- Yes, the adult and pediatric safety data could potentially support each other. If the toxicities are sufficiently similar, the size of the database may be adequate. If there are differences, additional data may be needed.

- 8. ILEX contends that treatment with a single agent (CLOFAREX) administered to pediatric patients with refractory/relapsed ALL and AML and demonstrating a  $\geq 30\%$  overall response rate is clinically significant in this refractory patient population. Do you concur?**

**FDA RESPONSE:**

- No, not if you are asking whether this endpoint and magnitude demonstrated in the proposed single arm trials would be adequate for registration. Although Phase 2 trials may be the next step in the development of this drug, and an overwhelmingly positive result (extremely high rate of durable complete response) in single arm trials might be considered for registration in these diseases, randomized controlled studies are generally required for approval because the clinical relevance of the observed magnitude of response and duration is best evaluated in the presence of a comparator arm. Historical comparisons are fraught with difficulty and conclusions drawn from such comparisons are not generally valid.

- 9. ILEX believes that a 1-3 month remission is considered durable, allowing patients to receive bone marrow transplant. Do you concur?**

**FDA RESPONSE:**

- No. Inclusion of a comparator arm in the study would allow an interpretable analysis of time to disease recurrence in both patients who do and don't go on to subsequent bone marrow transplantation. Outside a controlled trial setting, where remission duration can be adequately assessed and interpreted, a 3-month duration of remission seems a low goal. Patients that go on to bone marrow transplant should be documented to survive engraftment, which is also best assessed in the setting of a comparator arm.

- 10. Do you concur that the study design of our Phase II pediatric ALL (CLO-212) and/or AML pediatric (CLO-222) protocol as a single pivotal trial (multi-center) would be sufficient for registration approval of CLOFAREX for treatment of pediatric salvage ALL?**

**FDA RESPONSE:**

- No. (See answers to #7 and #8 above.) Complete response rate observed in a properly designed randomized trial might be accepted as the basis for accelerated approval. The biological rationale to support the clinical significance of a CRp associated with the proposed chemotherapy combination is not evident, and it would not be considered a valid component of the CR-endpoint. (See Oncologic Drug Advisory Committee discussion of the Mylotarg NDA- March 17, 2000)

*Comment: After discussion, the following bullet was added:*

- *Two randomized trials in leukemia are strongly recommended.*

#### **ADDITIONAL COMMENTS**

##### **Statistical Comments:**

- The proposed two-stage design is acceptable in principle. However, the type-I error rate for a one-sided test (i.e., false positive rate) should be controlled at 0.025, not 0.04, level.
- Please clarify how the 95% CI for the primary endpoint will be derived.

##### **Pharmacology/Toxicology Comment:**

- Regarding further development of clofarabine, please recall that you were informed at both the Pre-IND meeting and with the IND review, that genetic toxicity studies are required for further Phase II development. Please update the Division on the status of these studies.

*Comment: The sponsor confirmed that genetic toxicology studies are ongoing.*

##### **Patient Representative Comments:**

- See ATTACHMENT A for a Sample Assent for Children 7-12 Years Old
- See ATTACHMENT B for comments on the Informed Consent Document

##### **Regulatory Comments:**

#### **Final Protocols**

- Please refer to the December 1999 DRAFT "Guidance for Industry - Special Protocol Assessment" (posted on the Internet 2/8/2000) and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT (SPA)** in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical) and include a reference to this EOP2 meeting. 10 desk copies of this SPA should be submitted directly to the project manager. Since we would like to use our ODAC consultant for this protocol review, and their clearance takes several weeks, we would appreciate any lead-in time you could give us as to when the SPA will be submitted.

#### **Submission Of Clinical Trials To NIH Public Access Data Base**

- Section 113 of the Food and Drug Modernization Act (Modernization Act) amends 42 U.S.C. 282 and requires the establishment of a public resource for information on studies of drugs for serious or life-threatening diseases conducted under FDA's Investigational New Drug (IND) regulations (21 CFR part 312). The National Institutes of Health (NIH) through its National Library of Medicine (NLM), and with input from the FDA and others, developed the Clinical Trials Data Bank, as required by the Modernization Act.

FDA has made available a final guidance to implement Section 113 of the Modernization Act. The guidance describes the type of information to submit and how to submit information to the Clinical Trials Data Bank. The guidance entitled "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions" was made available on March 18, 2002. It is accessible through the Internet at <http://www.fda.gov/cder/guidance/4856fnl.htm>

The clinical trial information for the Clinical Trials Data Bank should include the purpose of the trial, the patient eligibility criteria, the location of the trial sites and, a contact for patients wanting to enroll in the trial. The data fields and their definitions are available in the Protocol Registration System at <http://prsinfo.clinicaltrials.gov/>. Protocols listed in this system by will be made available to the public on the Internet at <http://clinicaltrials.gov>.

If you have any questions, contact Theresa Toigo at (301) 827-4460 or [113trials@oc.fda.gov](mailto:113trials@oc.fda.gov).

#### **Financial Disclosure Final Rule**

- We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective and any study in which a single investigator makes a significant contribution to demonstration of safety.

Please refer to the March 20, 2001 "*Guidance for Industry: Financial Disclosure By Clinical Investigators*" (posted on the Internet 3/27/2001) at <http://www.fda.gov/oc/guidance/financialdis.html>.

#### **Pediatric Exclusivity**

- Under the Food and Drug Administration Modernization Act, you have the opportunity for an exclusivity extension since Clofarabine is appropriate for an indication in pediatrics. If you choose to pursue pediatric exclusivity, your plans for a pediatric drug development, in the form of a Proposed Pediatric Study Request (PPSR), should be submitted so that we can consider issuing a Written Request.

Please refer to the "*Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505 A of the Federal Food, Drug and Cosmetic Act*" at Drug Information Branch (301) 827-4573 or <http://www.fda.gov/cder/guidance/index.htm>. You should also refer to our division's specific guidance on pediatric oncology Written Requests which is at <http://www.fda.gov/cder/guidance/3756dft.htm>.

3 Page(s) Withheld

       § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

       § 552(b)(5) Draft Labeling

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J

...In general, keep one thought per sentence. Sentences tend to be too long with multiple thoughts.  
Be specific about:

1. Types and purpose of imaging tests and purpose for them
2. Amount of blood being drawn each time
3. Order of information that is being given. (For example – in the Possible Risks/Discomforts section – re-order the possible side effects in terms of known human, followed by animal study results)

4. **Bullet, chart information when possible. I would suggest putting the known human Risks/Discomfort section into a chart format, then add a written section on the rat study and cardiotoxicity seen**

**Question:**

Is it really necessary to conduct a BMA/LP prior to each cycle of the drug? As a parent representative, I think this is a bit much. These are highly invasive procedures and in my opinion, not necessary to be done with each cycle in order to complete the study objectives.

**ACTION ITEMS:**

- Sponsor to submit copies of slides shown during the meeting. **DONE- JSWALEC- 4/30/02.**
- Sponsor to request a separate CMC End-of-Phase 2 meeting when appropriate.

The meeting concluded at 3:30 pm.

*/S/*

\_\_\_\_\_  
Christy Wilson  
Consumer Safety Officer

*/S/*

Concurrence Chair:

\_\_\_\_\_  
Steven Hirschfeld, M.D., Ph.D.  
Medical Officer

**ADDENDUM**

In a submission to the Division dated May 6, 2002, the sponsor requested that the following comments be included as part of the official meeting minutes. Although these additional comments will not officially be part of the meeting minutes since they were not captured during the meeting on April 29, 2002, they have been included as an addendum.

- In response to the Division's preference for 2 randomized Phase 3 trials to support registration of Clofarex in the pediatric population, with either 2 pediatric trials OR one trial in adults and the second trial in children, ILEX contends that it will be difficult to enroll patients due to the limited number of patients available for the AML and ALL indications.
- As presented by ILEX, we anticipate great difficulty in gaining consensus from the medical community as to an agreement  pediatric study with Clofarex and to complete these trials in a reasonable time frame. <sup>7</sup>
- The Division gave ILEX approval to initiate the Phase 2 pediatric protocols.

/s/

/s/

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Christy Wilson  
Consumer Safety Officer

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Steven Hirschfeld, M.D., Ph.D.  
Medical Officer

2 Pages Redacted of  
Deliberative Process  
§ 552(b)(5)

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/s/

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Christy Wilson  
6/28/02 03:44:19 PM

Steven Hirschfeld  
7/10/02 10:41:30 AM

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-673**

**Correspondence**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

8/24/04

NDA 21-673

ILEX Products, Inc.  
Attention: Mike Bernstein, MPH  
Sr. Director, Regulatory Affairs  
4545 Horizon Hill Blvd.  
San Antonio, Texas 78229-2263

Dear Mr. Bernstein:

Please refer to your March 29, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CLOLAR<sup>®</sup> (clofarabine) Intravenous 52mg/m<sup>2</sup>/day.

On August 6, 2004, we received your August 5, 2004, major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is December 31, 2004.

If you have any questions, call Amy Baird, Consumer Safety Officer, at (301) 594-5779.

Sincerely,

  
{See appended electronic signature page}

Dotti Pease  
Chief, Project Management Staff  
Division of Oncology Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Amy Baird  
8/24/04 08:47:18 AM  
for Dotti Pease

6/8/04



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-673

ILEX Products, Inc.  
Attention: Mike Bernstein, MPH  
Sr. Director, Regulatory Affairs  
4545 Horizon Hill Blvd.  
San Antonio, Texas 78229-2263

Dear Mr. Bernstein:

Please refer to your March 29, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CLOLAR® (clofarabine) Intravenous 52mg/m<sup>2</sup> per day.

We also refer to your submission dated April 22, 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on May 29, 2004 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. The ALL and AML protocols state that responses (CR, CRp, PR) have to be confirmed by bone marrow aspiration and/or biopsy 21 days after the initial response. An additional bone marrow aspiration and/or biopsy is required 3 months after first documentation of response. Please provide patient listings indicating whether bone marrow evaluations were done and what were the results.
2. Regarding patients who went on to transplant, please provide patient listings indicating whether a bone marrow aspiration and/or biopsy was performed after transplant and what were the results?

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

NDA 21-673

Page 2

If you have any questions, call Amy Baird, Consumer Safety Officer, at (301) 594-5779.

Sincerely,

*{See  appended electronic signature page}*

Richard Pazdur, M.D.  
Director  
Division of Oncology Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Richard Pazdur  
6/8/04 05:25:59 PM

10/17/03



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-673

Ilex Products, Inc.  
4545 Horizon Hill Blvd.  
San Antonio, TX 78229-2263

Attention: Mike Bernstein, MPH  
Senior Director, Regulatory Affairs

Dear Mr. Bernstein:

We have received the first section of your New Drug Application (NDA) under the program for step-wise submission of sections of an NDA (section 506 of the Federal Food, Drug, and Cosmetic Act) for the following:

Name of Drug Product: Clofarabine Intravenous  
52 mg/m<sup>2</sup>/day

Date of Submission: September 26, 2003

Date of Receipt: September 29, 2003

Our Reference Number: NDA 21-673

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete. Please cite the NDA number assigned to this application at the top of the first page of every communication concerning this application.

Address all additional presubmissions as follows:

U.S. Postal Service:  
Center for Drug Evaluation and Research  
Division of Oncology Drug Products, HFD-150  
Attention: Division Document Room  
5600 Fishers Lane  
Rockville, Maryland 20857

NDA 21-673

Page 2

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Division of Oncology Drug Products, HFD-150  
Attention: Document Room  
1451 Rockville Pike  
Rockville, Maryland 20854

Send the submission that completes this application and is intended to start the review clock to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room  
12229 Wilkins Ave.  
Rockville, Maryland 20852-1833

If you have any questions, call Christy Cottrell, Consumer Safety Officer, at (301) 594-5761.

Sincerely,

 {See appended electronic signature page}

Dotti Pease  
Chief, Project Management Staff  
Division of Oncology Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Christy Cottrell  
10/17/03 03:46:30 PM  
Signing for Dotti Pease

5/28/04



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

NDA 21-673

ILEX Products, Inc.  
Attention: Mike Bernstein, MPH  
Sr. Director, Regulatory Affairs  
4545 Horizon Hill Blvd.  
San Antonio, Texas 78229-2263

Dear Mr. Bernstein:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: CLOLAR• (clofarabine) Intravenous 52mg/m<sup>2</sup> day

Review Priority Classification: Priority (P)

Date of Application: March 29, 2004

Date of Receipt: March 30, 2004

Our Reference Number: NDA 21-673

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 29, 2004, in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be September 30, 2004.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

NDA 21-673

Page 2

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:

Center for Drug Evaluation and Research  
Division of Oncology Drug Products  
Attention: Division Document Room, HFD-150  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Oncology Drug Products, HFD-150  
Attention: Document Room 3067  
1451 Rockville Pike  
Rockville, Maryland 20876

If you have any questions, call Amy Baird, Consumer Safety Officer, at (301) 594-5779.

Sincerely,

  
{See appended electronic signature page}

Dotti Pease  
Chief, Project Management Staff  
Division of Oncology Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Amy Baird  
5/28/04 11:03:38 AM  
for Dotti Pease

3/3/04



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

NDA 21-673

Ilex Products, Inc.  
4545 Horizon Hill Blvd.  
San Antonio, TX 78229-2263

Attention: Mike Bernstein, MPH  
Senior Director, Regulatory Affairs

Dear Mr. Bernstein:

We have received the second section of your New Drug Application (NDA) under the program for step-wise submission of sections of an NDA (section 506 of the Federal Food, Drug, and Cosmetic Act) for the following:

Name of Drug Product: Clofarabine Intravenous  
52 mg/m<sup>2</sup>/day  
Date of Submission: February 24, 2004  
Date of Receipt: February 25, 2004  
Our Reference Number: NDA 21-673

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete. Please cite the NDA number assigned to this application at the top of the first page of every communication concerning this application.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you will submit pediatric studies with this application. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

NDA 21-673

Page 2

Address all additional presubmissions as follows:

U.S. Postal Service:

Center for Drug Evaluation and Research  
Division of Oncology Drug Products, HFD-150  
Attention: Division Document Room  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Oncology Drug Products, HFD-150  
Attention: Document Room  
1451 Rockville Pike  
Rockville, Maryland 20854

Send the submission that completes this application and is intended to start the review clock to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room  
12229 Wilkins Ave.  
Rockville, Maryland 20852-1833

If you have any questions, call Christy Cottrell, Consumer Safety Officer, at (301) 594-5761.

Sincerely,

  
{See appended electronic signature page}

Dotti Pease  
Chief, Project Management Staff  
Division of Oncology Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Christy Cottrell  
3/3/04 01:05:24 PM  
Signing for Dotti Pease



DEPARTMENT OF HEALTH & HUMAN SERVICES

10/14/03  
Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 63,641

ILEX Products, Inc.  
4545 Horizon Hill Blvd.  
San Antonio, TX 78229-2263

Attention: Mike Bernstein, MPH  
Senior Director, Regulatory Affairs

Dear Mr. Bernstein:

Please refer to your correspondence dated May 23, 2003, requesting changes to FDA's March 7, 2003, Written Request for pediatric studies for Clofarabine.

We reviewed your proposed changes and are amending the Written Request. For convenience, the full text of the Written Request, as amended, follows. This Written Request supercedes the Written Request dated March 7, 2003.

To obtain needed pediatric information on clofarabine, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the trials in pediatric patients described below. These studies investigate the potential use of clofarabine in the treatment of children with hematological malignancies and solid tumors.

**Background:**

The development of pediatric oncology drugs merits special consideration. Compared to adult malignancies, pediatric cancers afflict small numbers of patients. Because the majority of pediatric patients receive their cancer therapy as participants in clinical research protocols, participation in Phase 3 oncology trials has become the *standard of care* in pediatric oncology. Children with cancer are usually treated at specialized centers by pediatric oncologists who are members of a national pediatric cooperative group. One of the highest priorities of these groups is to develop improved novel therapies. Early access to new drugs is one mechanism to achieve this goal. Known and potential differences in the biology of pediatric and adult tumors usually will not permit the extrapolation of clinical activity from adults to children. Therefore, it is usually impossible to rely on pharmacokinetic and safety data alone to guide the use of these drugs in children. It is imperative that we evaluate the effectiveness and safety of new drugs in pediatric populations. In most cases, in the absence of available therapies to treat refractory stages of most pediatric cancers, the FDA expects to be able to use flexible regulatory approaches in developing and approving drugs for pediatric tumors, e.g., basing approval on an effect on tumor size or other surrogate marker likely to predict clinical benefit (Subpart H), and/or based on safety in smaller numbers of patients (Subpart E).

Please submit information from the following types of studies:

- *Type of studies:*

Phase 1 study in hematologic malignancies: A dose finding study, including pharmacokinetics, with doses determined for all appropriate age groups in pediatric hematologic malignancies. The number of patients entered must be sufficient to achieve Phase 1 objectives. Historically, this has been accomplished with the range of 18-25 patients for other drugs.

Phase 2 study in hematologic malignancies: Enrollment of at least 14 pediatric patients with the same tumor type per trial, in refractory or relapsed hematologic malignancies. Studies should be performed at facilities that have the experience, support, and expertise to care for children with cancer.

- *Indications to be studied:*

Refractory or relapsed pediatric hematologic malignancies

- *Age group in which studies will be performed:*

Infants > 1 month of age to adolescents up to 18 years of age with a distribution of patients that reflects the demographics of the diseases under study

- *Study endpoints*

The Phase 1 study should use maximum tolerated dose (MTD) and must have standard pharmacokinetic (PK) parameters such as half-life of the parent drug and major metabolites, maximum concentration, clearance and area under the curve as endpoints. A traditional or sparse sampling technique may be used to estimate the PK parameters and develop pharmacokinetic-pharmacodynamic relationship.

The Phase 2 study must have complete response (durable remission) as the primary endpoint.

- *Drug information*

- *dosage form:* Age appropriate formulation
- *route of administration:* Intravenous
- *regimen:* As determined by Phase 1 study

- *Drug specific safety concerns:*

Neutropenia, thrombocytopenia, bleeding, infections, anemia, death, hypotension, vascular leak

- *Statistical information, including power of study and statistical assessments:*

Statistical analysis appropriate to the phase of the study including descriptive statistics for the Phase 2 studies must be submitted.

- *Labeling that may result from the study(ies):*

Appropriate sections of the label may be changed to incorporate the findings of the studies.

- *Format of reports to be submitted:*

Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation and all raw data for pharmacokinetic analysis must be submitted. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities.

- *Timeframe for submitting reports of the study(ies):*

Reports of the above studies must be submitted to the Agency on or before December 31, 2005. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a new drug application (NDA) or as a supplement to an approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

IND 63,641

Page 4

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call Christy Cottrell, Consumer Safety Officer, at (301) 594-5761.

Sincerely,

*/s/*  
{See appended electronic signature page}

Rachel E. Behrman, M.D., M.P.H.  
Deputy Director  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Rachel Behrman  
10/14/03 03:44:33 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

7/8/03  
Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 63,641

ILEX Products, Inc.  
4545 Horizon Hill Blvd.  
San Antonio, TX 78229-2263

Attention: Mike Bernstein, MPH  
Senior Director, Regulatory Affairs

Dear Mr. Bernstein:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the Act) for Clofarabine.

We also refer to your May 8, 2003, request for fast track designation and for step-wise submission of sections of a New Drug Application supplemental new drug application under section 506 of the Act.

We have reviewed your request and have concluded that it meets the criteria for fast track designation. Therefore, we are designating Clofarabine for the treatment of pediatric primary refractory or relapsed acute lymphoblastic leukemia (ALL) as a fast track product.

We are granting fast track designation for the following reasons:

1. Relapsed and refractory leukemia are serious life and life threatening diseases.
2. Clofarabine has demonstrated promising activity in patients with relapsed or refractory leukemia. No available treatment will consistently result in remissions in the majority of patients with relapsed or refractory leukemia.

We have also reviewed your request for step-wise submission of sections of an NDA a supplemental new drug application for the indication described above and have concluded that the proposed plan, described in your request, for its step-wise submission is acceptable.

If you pursue a clinical development program that does not support use of Clofarabine for the treatment of pediatric primary refractory or relapsed acute lymphoblastic leukemia (ALL), we will not review the application or accept step-wise submission of sections of an NDA a supplemental new drug application under the fast track program.

IND 63,641

Page 2

If you have any questions, call Christy Cottrell, Consumer Safety Officer, at (301) 594-5761.

Sincerely,

  
{See appended electronic signature page}

Richard Pazdur, M.D.  
Director  
Division of Oncology Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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

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Richard Pazdur  
7/8/03 04:10:20 PM

3/7/03



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 63,641

ILEX Products, Inc.  
4545 Horizon Hill Blvd.  
San Antonio, TX 78229-2263

Attention: Mike Bernstein, MPH  
Senior Director, Regulatory Affairs

Dear Mr. Bernstein:

Reference is made to your Investigational New Drug application (IND) for clofarabine.

To obtain needed pediatric information on clofarabine, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the trials in pediatric patients described below. These studies investigate the potential use of clofarabine in the treatment of children with hematological malignancies and solid tumors.

**Background:**

The development of pediatric oncology drugs merits special consideration. Compared to adult malignancies, pediatric cancers afflict small numbers of patients. Because the majority of pediatric patients receive their cancer therapy as participants in clinical research protocols, participation in Phase 3 oncology trials has become the *standard of care* in pediatric oncology. Children with cancer are usually treated at specialized centers by pediatric oncologists who are members of a national pediatric cooperative group. One of the highest priorities of these groups is to develop improved novel therapies. Early access to new drugs is one mechanism to achieve this goal. Known and potential differences in the biology of pediatric and adult tumors usually will not permit the extrapolation of clinical activity from adults to children. Therefore, it is usually impossible to rely on pharmacokinetic and safety data alone to guide the use of these drugs in children. It is imperative that we evaluate the effectiveness and safety of new drugs in pediatric populations. In most cases, in the absence of available therapies to treat refractory stages of most pediatric cancers, the FDA expects to be able to use flexible regulatory approaches in developing and approving drugs for pediatric tumors, e.g., basing approval on an effect on tumor size or other surrogate marker likely to predict clinical benefit (Subpart H), and/or based on safety in smaller numbers of patients (Subpart E).

Please submit information from the following types of studies:

- *Type of studies:*

Phase 1 study in hematologic malignancies: A dose finding study, including pharmacokinetics, with doses determined for all appropriate age groups in pediatric hematologic malignancies. The number of patients entered must be sufficient to achieve Phase 1 objectives. Historically, this has been accomplished with the range of 18-25 patients for other drugs.

Phase 1 study in solid tumors: A dose finding study, including pharmacokinetics, with doses determined for all appropriate age groups in pediatric solid tumors. The number of patients entered must be sufficient to achieve Phase 1 objectives. Historically, this has been accomplished with the range of 18-25 patients for other drugs.

Phase 2 study in hematologic malignancies: Enrollment of at least 14 pediatric patients with the same tumor type per trial, in refractory or relapsed hematologic malignancies. Studies should be performed at facilities that have the experience, support, and expertise to care for children with cancer.

Phase 2 study in solid tumors: Enrollment of at least 14 pediatric patients with the same tumor type per trial, in refractory or relapsed solid tumors. Studies should be performed at facilities that have the experience, support, and expertise to care for children with cancer.

- *Indications to be studied:*

Refractory or relapsed pediatric hematologic malignancies and solid tumors

- *Age group in which studies will be performed:*

Infants > 1 month of age to adolescents up to 18 years of age with a distribution of patients that reflects the demographics of the diseases under study

- *Study endpoints*

The Phase 1 studies should have maximum tolerated dose (MTD) and must have standard pharmacokinetic (PK) parameters such as half-life of the parent drug and major metabolites, maximum concentration, clearance and area under the curve as endpoints. A traditional or sparse sampling technique may be used to estimate the PK parameters and develop pharmacokinetic-pharmacodynamic relationship.

- *Drug information*

- *dosage form:* Age appropriate formulation
- *route of administration:* Intravenous
- *regimen:* As determined by Phase 1 study

- *Drug specific safety concerns:*

Neutropenia, thrombocytopenia, bleeding, infections, anemia, death

- *Statistical information, including power of study and statistical assessments:*

Statistical analysis appropriate to the phase of the study including descriptive statistics for the Phase 2 studies must be submitted.

- *Labeling that may result from the study(ies):*

Appropriate sections of the label may be changed to incorporate the findings of the studies.

- *Format of reports to be submitted:*

Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation and all raw data for pharmacokinetic analysis must be submitted. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities.

- *Timeframe for submitting reports of the study(ies):*

Reports of the above studies must be submitted to the Agency on or before December 31, 2005. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

- *Response to Written Request:*

As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a new drug application (NDA) or as a supplement to an approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your

IND 63,641

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submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call Christy Cottrell, Consumer Safety Officer, at (301) 594-5761.

Sincerely,

*{see electronic signature page}*

Rachel E. Behrman, M.D., M.P.H.  
Deputy Director  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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

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Rachel Behrman  
3/7/03 11:24:37 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

FILE COPY

Office of Orphan Products Development (HF-35)  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

February 7, 2002

Ilex Products, Incorporated  
4545 Horizon Hill Boulevard  
San Antonio, TX 78229-2263

Attention: Mike Bernstein, MPH

Re: Designation Request 2 3

Dear Mr. Bernstein:

Reference is made to your request for orphan-drug designation dated December 5, 2001, of clofarabine for the treatment of acute lymphoblastic leukemia.

We have completed the review of this request and have determined that clofarabine qualifies for orphan designation for the treatment of acute lymphoblastic leukemia. Please note that it is clofarabine and not its formulation that has received orphan designation. You have notified us that you are currently developing clofarabine under the trade name Clofarex™.

Please be advised that if clofarabine is approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FDCA (21 U.S.C. 360cc). Therefore, prior to final marketing approval, sponsors of designated orphan drugs are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

Finally, please notify this Office within 30 days of submission of a marketing application for the use of clofarabine as designated. Also an annual progress report must be submitted within 14 months after the designation date and annually thereafter until a marketing application is approved (21 CFR 316.30). If you need further assistance in the development of your product for marketing, please feel free to contact John McCormick, MD at (301) 827-3666.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan-drug designation.

Sincerely yours,

A stylized handwritten signature, possibly reading 'M. Haffner', enclosed in a rectangular box.

Marlene E. Haffner, MD, MPH  
Rear Admiral, United States Public Health Service  
Director, Office of Orphan Products Development



Office of Orphan Products Development (HF-35)  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

March 14, 2002

Ilex Products, Inc.  
4545 Horizon Hill Boulevard  
San Antonio, TX 78229-2263

Attention: Mike Bernstein, MPH  
Senior Director, Regulatory Affairs

Re: Designation Request [ 1

Dear Mr. Bernstein:

Reference is made to your request for orphan-drug designation dated January 31, 2002, of clofarabine for the treatment of primary refractory or relapsed acute myelogenous leukemia in pediatric and adult patients. Please also refer to our acknowledgment letter dated February 19, 2002.

We have completed the review of this request and have determined that clofarabine qualifies for orphan-drug designation for the treatment of **acute myelogenous leukemia**. Please note that it is clofarabine and not its formulation that has received orphan-drug designation. You have notified us that you are currently developing clofarabine under the trade name Clofarex™

Please be advised that if clofarabine is approved for an indication broader than the orphan-drug designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FDCA (21 U.S.C. 360cc). Therefore, prior to final marketing approval, we request that you compare the designated orphan indication with the proposed marketing indication, and to submit additional data to amend the orphan-drug designation prior to marketing approval if warranted.

Finally, please notify this Office within 30 days of submission of a marketing application for the use of clofarabine as designated. Also an annual progress report must be submitted within 14 months after the designation date and annually thereafter until a marketing application is approved (21 CFR 316.30). If you need further assistance in the development of your product for marketing, please feel free to contact John McCormick, MD, at (301) 827-3666.

Please refer to this letter as official notification and congratulations on obtaining your orphan-drug designation.

Sincerely yours,

 /S/   
Marlene E. Haffner, MD, MPH   
Rear Admiral, United States Public Health Service  
Director, Office of Orphan Products Development