



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 5,661,136 **Attorney Docket No.:** 10103-028-999
Issued: August 26, 1997 **CAM:** 052922-999025
Inventors: Montgomery and Secrist
For: 2-Halo-2'-Fluoro Ara
Adenosines as Antineoplastic
Agents

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BOX PATENT EXTENSION
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

FEE TRANSMITTAL LETTER
FOR AN APPLICATION FOR EXTENSION UNDER 35 U.S.C. § 156

Sir or Madame:

Transmitted herewith is an Application for Extension of Patent Term Under 35 U.S.C. §156 for U.S. Patent No. 5,661,136, accompanied by two additional copies. The undersigned attorney for Applicant hereby states that these copies are certified to be duplicates of the original. Each copy contains the following exhibits:

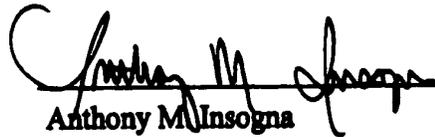
Exhibit A	Assignment
Exhibit B	FDA Approval Letter and Label
Exhibit C	U.S. Patent No. 5,661,136
Exhibit D	Maintenance Fee Payment Record
Exhibit E	Compendium of Significant Regulatory Activities in Connection with CLOLAR™

Further submitted herewith is an Associate Power of Attorney in connection with the above-identified patent appointing Anthony M. Insogna and Michael J. Bruner as associate attorney and associate agent, respectively, to make alterations and amendments therein, and to transact all business in the United States Patent and Trademark Office in connection therewith.

Please charge the \$1,120.00 fee estimated to be due in connection with this Application to Jones Day Deposit Account No. 50-3013. The Director is hereby authorized to charge any additional fees, which may be required, or credit any overpayment to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date: February 25, 2005

 35,203
Anthony M. Insogna (Reg. No.)

JONES DAY
222 East 41st Street
New York, New York 10017
(858) 314-1130

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 5,661,136 **Attorney Docket No.:** 10103-028-999
Issued: August 26, 1997 **CAM:** 052922-999025
Inventors: Montgomery and Secrist
For: 2-Halo-2'-Fluoro Ara
Adenosines as Antineoplastic
Agents

BOX PATENT EXTENSION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION OF PATENT TERM
UNDER 35 U.S.C. §156

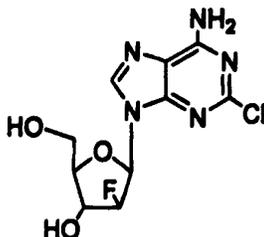
Sir or Madame:

Applicant, Southern Research Institute, hereby requests an extension under 35 U.S.C. §156 of the term of U.S. Patent No. 5,661,136 (the " '136 patent"). Southern Research Institute is the owner of record of the '136 patent by virtue of the assignment recorded at Reel 005776 / Frame 0115.¹ (Exhibit A). The '136 patent is exclusively licensed to Bioenvision, Inc. and sublicensed to Genzyme Corporation. Genzyme Corporation markets the product, CLOLAR™ brand clofarabine, which is covered by the '136 patent and was the subject of regulatory review.

The following information is submitted in accordance with 35 U.S.C. §156(d) and 37 C.F.R. §1.740:

¹ It is noted that the '136 patent is a continuation application of U.S. Patent Application Serial No. 693,646, filed May 10, 1991, which issued to U.S. Patent No. 5,384,310. The attached assignment indicates that Southern Research Institute holds the entire right, title and interest in the 693,646 application, as well as in, *inter alia*, any continuing applications thereof.

(1) The approved product is CLOLAR™, which is a pharmaceutical composition comprising clofarabine. The active ingredient of CLOLAR™ is a small molecule having a chemical name 2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-9H-purin-6-amine and the following chemical structure:



(hereinafter referred to as “clofarabine”). The molecular formula of clofarabine is $C_{10}H_{11}ClFN_5O_3$ with a molecular weight of 303.68.

CLOLAR™ has been approved for treatment of pediatric patients ages 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior treatment regimens. The approved product is marketed in the form of a 20 mL single-use vial containing 20 mg clofarabine in 20 mL unbuffered normal saline. (See package inserts at Exhibit B for further product information). Clofarabine acts by inhibiting DNA synthesis by decreasing cellular deoxynucleotide triphosphate pools through an inhibitory action on ribonucleotide reductase, and by terminating DNA chain elongation and inhibiting DNA repair by competitive inhibition of DNA polymerases.

(2) CLOLAR™ was subject to regulatory review under section 505(b) of the Federal Food, Drug and Cosmetic Act (“FFDCA”).

(3) CLOLAR™ received permission for commercial marketing or use by the Food and Drug Administration (“FDA”) pursuant to section 505(b) of the FFDCA on December 28, 2004. A copy of the FDA approval letter and package inserts are attached as Exhibit B.

(4) The active ingredient in CLOLAR™ is clofarabine. Clofarabine has not been previously approved for commercial marketing or use under the FFDCA, the Public Health Service Act or the Virus-Serum-Toxin Act.

(5) This application is being submitted within the sixty day period permitted for submission pursuant to 37 C.F.R. §1.720(f), the last day for said submission being February 28, 2005 (February 26, 2005 is a Saturday).

(6) The complete identification of the patent for which extension is sought is as follows:

Inventors:	John A. Montgomery and John A. Secrist, III
Patent No.:	5,661,136
Issue Date:	August 26, 1997
Expiration Date:	August 26, 2014

Applicants note that because the patent application from which the '136 patent issued was filed before June 8, 1995, the effective date of provisions of the Uruguay Round Agreements Act relating to patent term, the '136 patent is entitled to a patent term that is the greater of twenty (20) years from the earliest priority date (*i.e.*, May 23, 2009) or seventeen (17) years from the patent issue date (*i.e.*, August 26, 2014). Thus, absent an extension, the '136 patent expires on August 26, 2014.

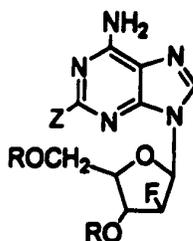
(7) A copy of U.S. Patent No. 5,661,136 for which this extension is sought is attached hereto as Exhibit C.

(8) There are no certificates of correction, disclaimers or reexamination certificates for the '136 patent. A copy of the eighth year maintenance fee receipt is enclosed as Exhibit D; thus, no maintenance fee is currently due.

(9) The '136 patent claims, *inter alia*, a method of using the approved product, CLOLAR™ or its active ingredient. At least claims 1, 3-5, 6, 8, 9, 11 and 12 of the '136 patent read on a method of using the approved product or active ingredient, as described below:

Claim 1

1. A method for bringing about a cytotoxic effect in a mammalian cancerous cell which comprises contacting said cancerous cell with an effective amount of a cytotoxic compound having the formula



wherein R, each which may be the same or different, is hydrogen or a protecting group; wherein Z is selected from the group consisting of F, Cl, and Br; and pharmaceutically acceptable salts thereof.

Claim 1 recites a method for bringing about a cytotoxic effect in a mammalian cancerous cell by contacting such a cell with an effective amount of, *inter alia*, clofarabine (*i.e.*, when R is hydrogen and Z is Cl). The approved labeling for the drug product states that, "Clofarabine is cytotoxic to rapidly proliferating and quiescent cancer cell types *in vitro*." The approved labeling further states that CLOLAR™ is indicated for the treatment of patients with relapsed or refractory acute lymphoblastic leukemia, based upon clinical data showing the induction of complete responses. Complete responses during chemotherapeutic treatment for acute lymphoblastic leukemia arise from a cytotoxic effect of the active ingredient upon such leukemia cells. Accordingly, a method for bringing about a cytotoxic effect in a mammalian cancerous cell reads on the approved use of treating patients with relapsed or refractory acute lymphoblastic leukemia.

Claim 3

3. A method according to claim 1 which comprises contacting said cancerous cell with the compound wherein R is hydrogen.

Claim 3 depends from claim 1 and reads on a method of using the approved product or its active ingredient when Z is Cl.

Claim 4

4. A method according to claim 1 which comprises contacting said cancerous cell with the compound wherein Z is Cl.

Claim 4 depends from claim 1 and reads on a method of using the approved product or its active ingredient when R is hydrogen.

Claim 5

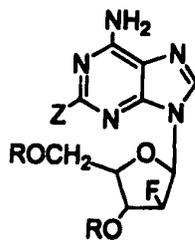
5. A method according to claim 1 which comprises contacting said cancerous cell with the compound wherein the compound is 2-Chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-9H-purin-6-amine.

Claim 5 depends from claim 1 and reads on a method of using clofarabine.

Thus, claims 1 and 3-5 read on the approved use of CLOLAR™.

Claim 6

6. A method for inhibiting ribonucleotide reductase and DNA polymerase α in a mammalian cell which comprises contacting said mammalian cell with of a cytotoxic compound having the formula



wherein R, each which may be the same or different, is hydrogen or a protecting group; wherein Z is a halogen selected from the group consisting of F, Cl, and Br; and pharmaceutically acceptable salts thereof.

Claim 6 recites a method for inhibiting ribonucleotide reductase and DNA polymerase α in a mammalian cell by contacting such a cell with, *inter alia*, clofarabine (*i.e.*, when R is hydrogen and Z is Cl). The approved labeling states in the Mechanisms of Action section that clofarabine has an inhibitory action on ribonucleotide reductase and DNA polymerases.

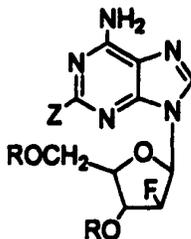
Claim 8

8. A method according to claim 6 wherein R of said compound is hydrogen.

Claim 8 depends from claim 6 and reads on a method of using the approved product or its active ingredient when Z is Cl.

Claim 9

9. A method for inhibiting ribonucleotide reductase and DNA polymerase α in a mammalian cell which comprises contacting said mammalian cell with of a cytotoxic compound having the formula



wherein R, each which may be the same or different, is hydrogen or a protecting group; wherein Z is a halogen selected from the group consisting of F, Cl, and Br; and the pharmaceutically acceptable salts thereof.

Claim 9 recites a method for inhibiting ribonucleotide reductase and DNA polymerase α in a mammalian cell by contacting such a cell with, *inter alia*, clofarabine (*i.e.*, when R is hydrogen and Z is Cl). The approved labeling states in the Mechanisms of Action section that clofarabine has an inhibitory action on ribonucleotide reductase and DNA polymerases.

Claim 11

11. A method according to claim 9 wherein R of said compound is hydrogen.

Claim 11 depends from claim 9 and reads on a method of using the approved product or its active ingredient when Z is Cl.

Claim 12

12. A method according to claim 9 wherein said compound is 2-Chloro-9-(2-deoxy-2-fluoro- β -D-arabinofuranosyl)-9H-purin-6-amine.

Claim 12 depends from claim 9 and reads on a method of using clofarabine.

Thus, claims 6, 8, 9, 11 and 12 read on the approved use of CLOLAR™.

(10) The relevant dates and information pursuant to 35 U.S.C. §156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period for CLOLAR™, a human drug, are as follows:

(a) Investigational new drug (“IND”) application number 43,275 was submitted to the FDA on August 23, 1993, by the University of Texas M.D. Anderson Cancer Center. This IND was placed on “Clinical Hold” status by the FDA on or about September 29, 1993, and subsequently became effective upon the withdrawal of “Clinical Hold” status on or about February 10, 1999. IND number 63,641 was filed by Ilex Oncology on November 7, 2001, and became effective on December 7, 2001. On April 10, 2002, the contents of IND number 43,275 were transferred to the file for IND number 63,641, whereupon IND number 43,275 was withdrawn. Accordingly, the “date an exemption under subsection (i) of section 505 . . . of the Federal Food, Drug, and Cosmetic Act became effective for the approved product” is determined to be **February 10, 1999**.

(b) The new drug application (“NDA”) for CLOLAR™ was submitted under the FDA’s “fast track” provisions over the course of approximately six months. The first such portion was initially submitted on **September 26, 2003**. The NDA was later assigned NDA number 21-673. (Exhibit B).

(c) NDA No. 21-673 was approved by the FDA on **December 28, 2004**. (Exhibit B).

(11) Exhibit E is attached hereto to briefly describe significant activities undertaken with respect to CLOLAR™ during the applicable regulatory review period and the dates applicable to such activities.

(12) Applicant is of the opinion that the '136 patent is eligible for an extension of **1303 days**.

A. **Eligibility:**

(a) Pursuant to 35 U.S.C. §156(a), the '136 patent claims, *inter alia*, a method of using the approved product;

(b) Pursuant to 35 U.S.C. §156(a)(1), the term of the '136 patent has not expired before submission of this application for extension;

(c) Pursuant to 35 U.S.C. §156(a)(2), the term of the '136 patent has never been extended;

(d) Pursuant to 35 U.S.C. §156(a)(3), the application for extension is submitted by the owner of record of the '136 patent;

(e) Pursuant to 35 U.S.C. §156(a)(4), the product, CLOLAR™, has been subject to a regulatory review period before its commercial marketing or use;

(f) Pursuant to 35 U.S.C. §156(a)(5), the permission for the commercial marketing or use of CLOLAR™ after the regulatory review period is the first permitted commercial marketing or use of the product;

(g) Pursuant to 35 U.S.C. §156(c)(4), no other patent has been extended for the same regulatory review period for the product CLOLAR™.

B. **Regulatory Review Period:**

(a) Pursuant to 37 C.F.R. §1.775(c)(1), the period from February 10, 1999 (the date IND application number 43,274 became effective) to September 26, 2003 (the date the NDA was initially submitted) is 1689 days. Accordingly, Applicant calculates the "Testing Phase" as 1689 days.

(b) Pursuant to 37 C.F.R. §1.775(c)(2), the period from September 26, 2003 (the date the NDA was initially submitted) to December 28, 2004 (the date of NDA approval) is 459 days. Accordingly, Applicant calculates the "Approval Phase" as 459 days.

C. Extended Patent Term:

$$\begin{aligned}\text{Period of Extension} &= \frac{1}{2} (\text{Adjusted Testing Phase}) + \text{Approval} \\ &\quad \text{Phase} \\ &= \frac{1}{2} (1689) + 459 \\ &= \mathbf{1303 \text{ days}}\end{aligned}$$

(a) The number of days in the regulatory review period which were on and before August 26, 1997, the date on which the '136 patent issued, is 0 days.

Accordingly, 0 days are subtracted from the regulatory review pursuant to 37 C.F.R. §1.775(d)(1)(i).

(b) As demonstrated in Exhibit E, the Applicant acted with due diligence during the regulatory review period. Accordingly, zero (0) days are subtracted from the regulatory review period pursuant to 37 C.F.R. §1.775(d)(1)(ii).

(c) One half of the number of days remaining in the Testing Phase after the above reductions is 844 days. Accordingly, 844 days are subtracted from the regulatory review period pursuant to 37 C.F.R. §1.775(d)(1)(iii).

(d) The period remaining in the term of the patent (originally set to expire August 26, 2014) measured from the date of approval of CLOLAR™ (December 28, 2004) (3528 days) when added to the period of extension (1303 days) is 4831 days, which is less than fourteen (14) years. Accordingly, the fourteen (14) year limitation set forth in 37 C.F.R. §1.775(d)(2)-(4) does not operate to further reduce the regulatory review period.

(e) The period of extension (1303 days) is less than five (5) years. Accordingly, the five (5) year limitation set forth in 37 C.F.R. §1.775(d)(5)(i)(ii) does not operate to further reduce the regulatory review period.

(13) Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought pursuant to 37 C.F.R. §1.765.

(14) The prescribed fee for receiving and acting upon this application is \$1,120.00 pursuant to 37 C.F.R. §1.20(j). The Director is authorized to charge this fee and any additional fees, or credit any overpayment, to Jones Day Deposit Account No. 50-3013.

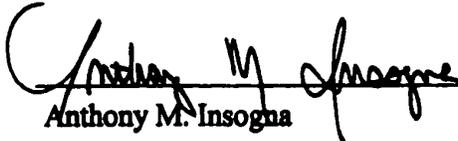
(15) Please direct all inquiries and correspondence relating to this application to:

Anthony M. Insogna
JONES DAY
222 East 41st Street
New York, New York 10017
(858) 314-1130

(16) This Application is accompanied by two additional copies of such application for a total of three copies.

Respectfully submitted,

Date: February 25, 2005

 35,203
Anthony M. Insogna (Reg. No.)
JONES DAY
222 East 41st Street
New York, New York 10017
(858) 314-1130

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Art Unit: 1083
Examiner: Crane, L.
Applicant: Montgomery *et al.*
Patent No.: 5,661,136
Issued: August 26, 1997
For: 2-HALO-2'FLUORO ARA ADENOSINES AS ANTINEOPLASTIC AGENTS

ASSOCIATE POWER OF ATTORNEY

Sir:

The undersigned attorney of record in U.S. Patent No. 5,661,136, issued August 26, 1997, hereby appoints:

Anthony M. Insigna, Registration No. 35,203; and
Michael J. Bruner, Registration No. 47,458,

each of whom can be reached at:

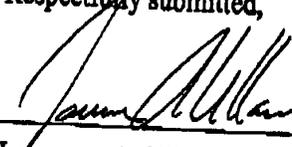
Jones Day
222 East 41st Street
New York, New York 10017
(212) 326-3939

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as associate attorney and associate agent, respectively, in the above-identified patent, to make alterations and amendments therein, and to transact all business in the United States Patent and Trademark Office in connection therewith.

Respectfully submitted,

Date: February 25, 2005



Lawrence A. Villanueva (Reg. No.) 43,968

Needle & Rosenberg, P.C.
Suite 1000
999 Peachtree Street
Atlanta, Georgia 30309-3915

EXHIBIT A

ASSIGNMENT

IN CONSIDERATION of the sum of one dollar (\$1.00) and other good and valuable considerations, the receipt and sufficiency of which are hereby acknowledged, the undersigned JOHN A. MONTGOMERY and JOHN A. SECRIST III hereby sell, assign and transfer to SOUTHERN RESEARCH INSTITUTE, having a place of business at 2000 Ninth Avenue, Birmingham, Alabama 35255, its successors, assigns and legal representatives, the entire right title and interest for the United States and all countries foreign thereto, in and to any and all improvements disclosed in my application for United States Letters Patent (United States Patent Application 07/693,646) entitled PURINE NUCLEOSIDES and which was filed in the United States Patent and Trademark Office on May 10th 1991, and in and to said application and all divisional, continuing, renewal, reissue, continuation-in-part and all other applications for Letters Patent which shall be filed in the United States and all countries foreign thereto on any of said improvements, including all Letters Patent which shall issue on said improvements; and

The undersigned further agree that said Assignee may apply for and receive Letters Patent for said improvements in its own name or any other name it deems fit; and

The undersigned further agree, when requested, without charge to, but at the expense of said Assignee, its successors, assigns and legal representatives, to carry out in good faith the intent and purpose of this assignment; to execute all divisional continuing, continuation-in-part, renewal, reissue and all other patent applications on any and all said improvements, to execute all rightful oaths, assignments, powers of attorney and other papers; to communicate to said Assignee, its successors, assigns and legal representatives, all facts known relating to said improvements and the history thereof; and to do generally everything possible which said Assignee, its successors, assigns and representatives shall consider desirable for aiding in securing and maintaining proper patent protection for said improvements and for vesting title to said improvements and all applications for patent in said Assignee, its successors, assigns and legal representatives; and

The undersigned hereby covenant with said Assignee, its successors, assigns and legal representatives that no assignment, grant, mortgage, license or other agreement affecting the rights and property herein conveyed has been made to others by the undersigned; that full right to convey the same as herein expressed is possessed by the undersigned; and that the foregoing provisions shall be binding upon the heirs, legal representatives, administrators and assigns of the undersigned.

date 6/18/91 John A. Montgomery (Seal)

date 6/19/91 John A. Secrist III (Seal)

RECORDED
PATENT & TRADE MARK OFFICE

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REF 5776 FRAME 117

EXHIBIT B





NDA 21-673

Genzyme Corporation
4545 Horizon Hill Blvd.
San Antonio, TX 78229-2263

Attention: Mike Bernstein, MPH
Senior Director, Regulatory Affairs

Dear Mr. Bernstein:

Please refer to your new drug application (NDA) dated March 29, 2004, received March 30, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CLOLAR™ (clofarabine) Intravenous Infusion.

We acknowledge receipt of your submissions dated April 22, July 7, August 2 and 5, September 15, October 6, November 18, and December 15, 21, and 28, 2004.

This new drug application provides for the use of CLOLAR™ (clofarabine) Intravenous Infusion for the treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens. This use is based on the induction of complete responses. Randomized trials demonstrating increased survival or other clinical benefit have not been conducted.

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.510), effective on the date of this letter, for use as recommended in the enclosed labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "FPL for approved NDA 21-673." Approval of this submission by FDA is not required before the labeling is used.

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your post marketing study commitments specified in your facsimile submission dated December 28, 2004. These commitments, along with any completion dates agreed upon, are listed below.

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, 2006
Trial Completion:	March 1, 2006	October 1, 2006
Final Report Submission:	June 1, 2006 (interim report)	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 will 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.

The Division will monitor your progress closely with regard to these post marketing commitments to ensure due diligence.

Submit final study reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to these postmarketing study commitments must be clearly designated "**Subpart H Postmarketing Study Commitments.**"

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 have fulfilled the pediatric study requirement for this application.

Immediately submit all promotional materials (both promotional labeling and advertisements) to be used within the first 120 days after approval. Send one copy to this Division and two copies of the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville MD 20857

In addition, as required by 21 CFR 314.550, submit all subsequent promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement. Send two copies of the promotional materials and the package insert to the address above.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

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

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

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

/s/

Robert Temple
12/28/04 04:48:55 PM

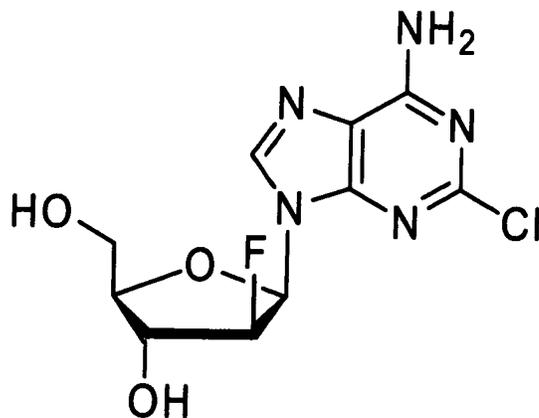
1 CLOLAR™ FOR INTRAVENOUS INFUSION**2 (clofarabine)****3 DESCRIPTION**

4 CLOLAR™ For Intravenous Infusion (CLOLAR™; clofarabine) contains clofarabine, a
5 purine nucleoside anti-metabolite. CLOLAR™ (1 mg/mL) is supplied in a 20 mL, single-use
6 vial. The 20 mL vial contains 20 mg clofarabine formulated in 20 mL unbuffered normal
7 saline (comprised of Water for Injection, USP, and Sodium Chloride USP). The pH range of
8 the solution is 4.5 to 7.5. The solution is clear and practically colorless, and free from
9 foreign matter.

10

11 The chemical structure of clofarabine is 2-chloro-9-(2-deoxy-2-fluoro-β-D-
12 arabinofuranosyl)-9H-purin-6-amine. The molecular formula of clofarabine is
13 C₁₀H₁₁ClFN₅O₃ with a molecular weight of 303.68.

14



Clofarabine

15

16

17

18 **CLINICAL PHARMACOLOGY**

19 **Mechanism of Action:** Clofarabine is sequentially metabolized intracellularly to the 5'-
20 monophosphate metabolite by deoxycytidine kinase and mono- and di-phosphokinases to the
21 active 5'-triphosphate metabolite. Clofarabine has high affinity for the activating
22 phosphorylating enzyme, deoxycytidine kinase, equal to or greater than that of the natural
23 substrate, deoxycytidine. Clofarabine inhibits DNA synthesis by decreasing cellular
24 deoxynucleotide triphosphate pools through an inhibitory action on ribonucleotide reductase,
25 and by terminating DNA chain elongation and inhibiting repair through incorporation into
26 the DNA chain by competitive inhibition of DNA polymerases. The affinity of clofarabine
27 triphosphate for these enzymes is similar to or greater than that of deoxyadenosine
28 triphosphate. In preclinical models, clofarabine has demonstrated the ability to inhibit DNA
29 repair by incorporation into the DNA chain during the repair process. Clofarabine 5'-
30 triphosphate also disrupts the integrity of mitochondrial membrane, leading to the release of
31 the pro-apoptotic mitochondrial proteins, cytochrome C and apoptosis-inducing factor,
32 leading to programmed cell death.

33

34 Clofarabine is cytotoxic to rapidly proliferating and quiescent cancer cell types *in vitro*.

35

36 *Human Pharmacokinetics:* The population pharmacokinetics of CLOLAR™ were studied in
37 40 pediatric patients aged 2 to 19 years (21 males/19 females) with relapsed or refractory
38 ALL or AML. At the given 52 mg/m² dose, similar concentrations were obtained over a
39 wide range of BSAs. Clofarabine was 47% bound to plasma proteins, predominantly to
40 albumin. Based on non-compartmental analysis, systemic clearance and volume of
41 distribution at steady-state were estimated to be 28.8 L/h/m² and 172 L/m², respectively. The
42 terminal half-life was estimated to be 5.2 hours. No apparent difference in pharmacokinetics
43 was observed between patients with ALL and AML or between males and females.

44

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

47

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

51

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

57

58 CLINICAL STUDIES

59 Sixty-six (66) pediatric ALL patients were exposed to CLOLAR™. Fifty-eight (58) of the
60 patients received the recommended pediatric dose of CLOLAR™ 52 mg/m² daily × 5 as an
61 intravenous infusion (IVI).

62

63 The safety and efficacy of CLOLAR™ were evaluated in pediatric patients with refractory or
64 relapsed hematologic malignancies in an open-label, dose-escalation, noncomparative study.
65 The starting dose of CLOLAR™ was 11.25 mg/m²/day IVI daily × 5 and escalated to 70
66 mg/m²/day IVI daily × 5. This dosing schedule was repeated every 2 to 6 weeks depending
67 on toxicity and response. Nine of 17 ALL patients were treated with CLOLAR™ 52 mg/m²
68 daily × 5. In the 17 ALL patients there were 2 complete remissions (12.5%) and 2 partial
69 remissions (12.5%) at varying doses. Dose-limiting toxicities (DLTs) in this study were

70 reversible hyperbilirubinemia and elevated transaminase levels and skin rash, experienced at
71 70 mg/m². As a result of this study, the recommended dose for subsequent study in pediatric
72 patients was determined to be 52 mg/m²/day for 5 days.

73

74 **Single Arm Study in Pediatric ALL**

75 A single arm study was conducted in relapsed/refractory pediatric patients with ALL at a
76 single dose. All patients had disease that had relapsed after and/or was refractory to two or
77 more prior therapies. Most patients, 46/49 (93.8%), had received 2 to 4 prior regimens and
78 15/49 (30.6%) of the patients had undergone at least 1 prior transplant. The median age of
79 the treated patients was 12 years. There were more males, 29/49 (59.2%), than females,
80 20/49 (40.8%). Most of the patients were either Caucasian (n=20, 40.8%) or Hispanic (n=20,
81 40.8%), with 12.2% African-American (n=6), and 6.1% Other race (n=3). All patients
82 received a dose of 52 mg/m² daily × 5 IVI. There was no dose modification during the
83 remission induction phase of treatment (maximum of 2 cycles). Doses could be modified
84 (reduced/delayed) during the post-induction phase. There was no dose escalation. The
85 planned study endpoint was the rate of Complete Remission (CR), defined as no evidence of
86 circulating blasts or extramedullary disease, an M1 bone marrow (<5% blasts), and recovery
87 of peripheral counts (platelets > 100 × 10⁹ L and absolute neutrophil count (ANC) > 1.0 ×
88 10⁹ L) and Complete Remission in the Absence of Total Platelet Recovery (CRp), defined as
89 meeting all criteria for CR except for recovery of platelet counts to > 100 × 10⁹ L. Partial
90 Response (PR) was also determined, defined as complete disappearance of circulating blasts,
91 an M2 bone marrow (> 5% and < 25% blasts), and appearance of normal progenitor cells or
92 an M1 marrow that did not qualify for CR or CRp. Transplantation rate was not a study
93 endpoint.

94

95 Response rates for these studies were determined by an unblinded Independent Response
96 Review Panel (IRRP).

97

98 Table 1 summarizes results for the pediatric ALL study. Responses were seen in both pre-B
99 and T-cell immunophenotypes of ALL. The median cumulative dose was 540 mg (range 29-
100 1905 mg) in 1 (42.9%), 2 (38.8%) or 3 or more (18.4%) cycles.

101

102

Table 1: Results in Pediatric ALL Study

n=49			
Responses	n	%	95% CI
CR	6	12.2	4.6 to 24.8
CRp	4	8.2	2.3 to 19.6
PR	5	10.2	3.4 to 22.2

103

104 Of the 15 responding pediatric ALL patients, 6 had post-clofarabine bone marrow
105 transplantation, so that duration of response could not be determined. In the 9 responding
106 patients who were not transplanted, the response durations for CR were 43, 50, 82, 93+, and
107 160+ days; for CRp the response duration was 32 days; and for PR the response durations
108 were 7, 16, and 21 days.

109

110 INDICATIONS AND USAGE

111 CLOLAR™ is indicated for the treatment of pediatric patients 1 to 21 years old with relapsed
112 or refractory acute lymphoblastic leukemia after at least two prior regimens. This use is
113 based on the induction of complete responses. Randomized trials demonstrating increased
114 survival or other clinical benefit have not been conducted.

115

116 **CONTRAINDICATIONS**

117 None

118

119 **WARNINGS**

120 CLOLAR™ should be administered under the supervision of a qualified physician
121 experienced in the use of antineoplastic therapy. Suppression of bone marrow function
122 should be anticipated. This is usually reversible and appears to be dose dependent. The use
123 of CLOLAR™ is likely to increase the risk of infection, including severe sepsis, as a result of
124 bone marrow suppression. Administration of CLOLAR™ results in a rapid reduction in
125 peripheral leukemia cells. For this reason, patients undergoing treatment with CLOLAR™
126 should be evaluated and monitored for signs and symptoms of tumor lysis syndrome, as well
127 as signs and symptoms of cytokine release (eg, tachypnea, tachycardia, hypotension,
128 pulmonary edema) that could develop into systemic inflammatory response syndrome
129 (SIRS)/capillary leak syndrome, and organ dysfunction. Physicians are encouraged to give
130 continuous IV fluids throughout the five days of CLOLAR™ administration to reduce the
131 effects of tumor lysis and other adverse events. Allopurinol should be administered if
132 hyperuricemia is expected. CLOLAR™ should be discontinued immediately in the event of
133 clinically significant signs or symptoms of SIRS or capillary leak syndrome, either of which
134 can be fatal, and use of steroids, diuretics, and albumin considered. CLOLAR™ can be re-
135 instituted when the patient is stable, generally at a lower dose.

136

137 Severe bone marrow suppression, including neutropenia, anemia, and thrombocytopenia, has
138 been observed in patients treated with CLOLAR™. At initiation of treatment, most patients
139 in the clinical studies had hematological impairment as a manifestation of leukemia. Because
140 of the pre-existing immunocompromised condition of these patients and prolonged
141 neutropenia that can result from treatment with CLOLAR™, patients are at increased risk for

142 severe opportunistic infections. Careful hematological monitoring during therapy is
143 important, and hepatic and renal function should be assessed prior to and during treatment
144 with CLOLAR™ because of CLOLAR™'s predominantly renal excretion and because the
145 liver is a target organ for CLOLAR™ toxicity. The respiratory status and blood pressure
146 should be closely monitored during infusion of CLOLAR™.

147

148 **Hepatic and Renal Impairment**

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

151

152 **Pregnancy – Teratogenic Effects: Pregnancy Category D**

153 CLOLAR™ (clofarabine) may cause fetal harm when administered to a pregnant woman.
154 Clofarabine was teratogenic in rats and rabbits. Developmental toxicity (reduced fetal body
155 weight and increased post-implantation loss) and increased incidences of malformations and
156 variations (gross external, soft tissue, skeletal and retarded ossification) were observed in rats
157 receiving 54 mg/m²/day (approximately equivalent to the recommended clinical dose on a
158 mg/m² basis), and in rabbits receiving 12 mg/m²/day (approximately 23% of the
159 recommended clinical dose on a mg/m² basis).

160

161 There are no adequate and well-controlled studies in pregnant women using clofarabine. If
162 this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug,
163 the patient should be apprised of the potential hazard to the fetus.

164

165 Women of childbearing potential should be advised to avoid becoming pregnant while
166 receiving treatment with clofarabine.

167

168 **PRECAUTIONS**169 **Information for Patients and Caregivers**

170 Physicians are advised to discuss the following with patients to whom CLOLAR™ will be
171 administered and patient caregivers, as appropriate.

172

173 ***Dehydration/Hypotension***

174 Patients receiving CLOLAR™ may experience vomiting and diarrhea; they should therefore
175 be advised regarding appropriate measures to avoid dehydration. Patients should be
176 instructed to seek medical advice if they experience symptoms of dizziness, lightheadedness,
177 fainting spells, or decreased urine output. CLOLAR™ administration should be stopped if
178 the patient develops hypotension for any reason during the 5 days of administration. If
179 hypotension is transient and resolves without pharmacological intervention, CLOLAR™
180 treatment can be re-instituted, generally at a lower dose.

181

182 ***Concomitant Medications***

183 Since CLOLAR™ is excreted primarily by the kidneys, drugs with known renal toxicity
184 should be avoided during the 5 days of CLOLAR™ administration. In addition, since the
185 liver is a known target organ for CLOLAR™ toxicity, concomitant use of medications known
186 to induce hepatic toxicity should also be avoided. Patients taking medications known to
187 affect blood pressure or cardiac function should be closely monitored during administration
188 of CLOLAR™.

189

190 **Pregnancy/Nursing**

191 All patients should be advised to use effective contraceptive measures to prevent pregnancy.

192 Female patients should be advised to avoid breast feeding during treatment with CLOLAR™.

193

194 **Laboratory Tests**

195 Complete blood counts and platelet counts should be obtained at regular intervals during

196 CLOLAR™ therapy, and more frequently in patients who develop cytopenias. In addition

197 liver and kidney function should be monitored frequently during the 5 days of CLOLAR™

198 administration.

199

200 **Drug Interactions**

201 Although no clinical drug-drug interaction studies have been conducted to date, on the basis

202 of the *in vitro* studies, cytochrome p450 inhibitors and inducers are unlikely to affect the

203 metabolism of clofarabine. The effect of clofarabine on the metabolism of cytochrome p450

204 substrates has not been studied.

205

206 **Drug/Laboratory Tests Interactions**

207 There are no known clinically significant interactions of CLOLAR™ with other medications

208 or laboratory tests. No formal drug/laboratory test interaction studies have been conducted

209 with CLOLAR™.

210

211 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

212 **Carcinogenesis**

213 Clofarabine has not been tested for carcinogenic potential.

214

215 **Mutagenesis**

216 Clofarabine showed clastogenic activity in the *in vitro* mammalian cell chromosome
217 aberration assay (CHO cells) and in the *in vivo* rat micronucleus assay. It did not show
218 evidence of mutagenic activity in the bacterial mutation assay (Ames test).

219

220 **Impairment of Fertility**

221 Studies in mice, rats, and dogs have demonstrated dose-related adverse effects on male
222 reproductive organs. Seminiferous tubule and testicular degeneration and atrophy were
223 reported in male mice receiving IP doses of 3 mg/kg/day (9 mg/m²/day, approximately 17%
224 of clinical recommended dose on a mg/m² basis). The testes of rats receiving 25 mg/kg/day
225 (150 mg/m²/day, approximately 3 times the recommended clinical dose on a mg/m² basis) in
226 a 6-month IV study had bilateral degeneration of the seminiferous epithelium with retained
227 spermatids and atrophy of interstitial cells. In a 6-month IV dog study, cell degeneration of
228 the epididymis and degeneration of the seminiferous epithelium in the testes were observed
229 in dogs receiving 0.375 mg/kg/day (7.5 mg/m²/day, approximately 14% of the clinical
230 recommended dose on a mg/m² basis). Ovarian atrophy or degeneration and uterine mucosal
231 apoptosis were observed in female mice at 75 mg/kg/day (225 mg/m²/day, approximately
232 4 fold of recommended human dose on a mg/m² basis), the only dose administered to female
233 mice. The effect on human fertility is unknown.

234

235 **Pregnancy**

236 **Teratogenic Effects: Pregnancy Category D**

237 See **WARNINGS**.

238

239 **Nursing Mothers**

240 It is not known whether clofarabine or its metabolites are excreted in human milk. Because
241 of the potential for tumorigenicity shown for clofarabine in animal studies and the potential
242 for serious adverse reactions, women treated with clofarabine should not nurse.

243

244 **Other Special Population: Adults**

245 Safety and efficacy have not been established in adults. One study was performed in highly
246 refractory and/or relapsed adult patients with hematologic malignancies. The Phase 2 dose of
247 CLOLAR™ was determined to be 40 mg/m²/day administered as a 1- to 2-hour IVI daily × 5
248 every 28 days.

249

250 **ADVERSE REACTIONS**

251 One hundred thirteen (113) pediatric patients with ALL (67) or AML (46) were exposed to
252 CLOLAR™. Ninety six (96) of the pediatric patients treated in clinical trials received the
253 recommended dose of CLOLAR™ 52 mg/m² daily × 5.

254

255 The most common adverse effects after CLOLAR™ treatment, regardless of causality, were
256 gastrointestinal tract symptoms, including vomiting, nausea, and diarrhea; hematologic

257 effects, including anemia, leukopenia, thrombocytopenia, neutropenia, and febrile
258 neutropenia; and infection.

259

260 Table 2 lists adverse events by System Organ Class regardless of causality, including severe
261 or life threatening events (NCI CTC grade 3 or grade 4), reported in $\geq 10\%$ of the 96 patients
262 in the 52 mg/m²/day dose group. More detailed information and follow-up of certain events
263 is given below.

264

265

Table 2: Most Commonly Reported ($\geq 10\%$ Overall) Adverse Events by System Organ Class (N=96)						
System Organ Class Adverse Event ¹	52 mg/m ² (N=96)					
	Total		Grade 3		Grade 4	
	N	%	n	%	n	%
Blood and Lymphatic System Disorders						
Febrile neutropenia	55	57	51	53	3	3
Neutropenia	10	10	3	3	7	7
Transfusion reaction	10	10	3	3	.	.
Cardiac Disorders						
Tachycardia NOS	33	34	6	6	.	.
Gastrointestinal Disorders						
Abdominal pain NOS	35	36	7	7	.	.
Constipation	20	21
Diarrhea NOS	51	53	10	10	.	.
Gingival bleeding	14	15	7	7	1	1
Nausea	72	75	14	15	1	1
Sore throat NOS	13	14
Vomiting NOS	80	83	8	8	1	1
General Disorders and Administration Site Conditions						
Edema NOS	19	20	1	1	2	2
Fatigue	35	36	3	3	1	1
Injection site pain	13	14	1	1	.	.
Lethargy	11	11
Mucosal inflammation NOS	17	18	3	3	.	.
Pain NOS	18	19	6	6	1	1
Pyrexia	39	41	15	16	.	.
Rigors	36	38	3	3	.	.
Hepato-Biliary Disorders						
Hepatomegaly	14	15	8	8	.	.
Jaundice NOS	14	15	2	2	.	.
Infections and Infestations						
Bacteremia	10	10	10	10	.	.
Cellulitis	11	11	9	9	.	.
Herpes simplex	11	11	6	6	.	.
Oral candidiasis	12	13	2	2	.	.
Pneumonia NOS	10	10	5	5	2	2
Sepsis NOS	14	15	7	7	7	7
Staphylococcal infection NOS	12	13	10	10	.	.
Investigations						
Weight decreased	10	10	1	1	.	.

System Organ Class Adverse Event ¹	52 mg/m ² (N=96)					
	Total		Grade 3		Grade 4	
	n	%	n	%	n	%
Metabolism and Nutrition Disorders						
Anorexia	30	31	5	5	7	7
Appetite decreased NOS	11	11
Musculoskeletal, Connective Tissue and Bone Disorders						
Arthralgia	11	11	3	3	.	.
Back pain	12	13	3	3	.	.
Myalgia	13	14
Pain in limb	28	29	5	5	.	.
Nervous System Disorders						
Dizziness (exc vertigo)	15	16
Headache NOS	44	46	4	4	.	.
Somnolence	10	10	1	1	.	.
Tremor NEC	10	10
Psychiatric Disorders						
Anxiety NEC	21	22	2	2	.	.
Depression NEC	11	11	1	1	.	.
Irritability	11	11	1	1	.	.
Renal and Urinary Disorders						
Hematuria	16	17	2	2	.	.
Respiratory, Thoracic and Mediastinal Disorders						
Cough	18	19
Dyspnea NOS	12	13	4	4	2	2
Epistaxis	30	31	14	15	.	.
Pleural effusion	10	10	3	3	2	2
Respiratory distress	13	14	6	6	5	5
Skin and Subcutaneous Tissue Disorders						
Contusion	11	11	1	1	.	.
Dermatitis NOS	39	41	7	7	.	.
Dry skin	10	10	1	1	.	.
Erythema NEC	17	18
Palmar-plantar erythrodysesthesia syndrome	12	13	4	4	.	.
Petechiae	28	29	7	7	.	.
Pruritus NOS	45	47	1	1	.	.
Vascular Disorders						
Flushing	17	18
Hypertension NOS	11	11	4	4	.	.
Hypotension NOS	28	29	12	13	7	7

¹ Patients with more than one occurrence of the same preferred term are counted only once.
Grade 4 includes deaths (Grade 5).

267

268 **Cardiovascular**

269 The most frequently reported cardiac disorder was tachycardia (34%), which was however,
270 already present in 27.4% of patients at study entry. Most of the cardiac adverse events were
271 reported in the first 2 cycles.

272

273 Pericardial effusion was a frequent finding in these patients on post-treatment studies, [19/55
274 (35%)]. The effusion was almost always minimal to small and in no cases had hemodynamic
275 significance.

276

277 Left ventricular systolic dysfunction (LVSD) was also noted. Fifteen out of fifty-five
278 patients [15/55 (27%)] had some evidence of LVSD after study entry. In most cases where
279 subsequent follow-up data were available, the LVSD appeared to be transient. The exact
280 etiology for the LVSD is unclear because of previous therapy or serious concurrent illness.

281

282 **Hepatic**

283 Hepato-biliary toxicities were frequently observed in pediatric patients during treatment with
284 CLOLAR™. Grade 3 or 4 elevated AST occurred in 38% of patients and grade 3 or 4
285 elevated ALT occurred in 44% of patients. Grade 3 or 4 elevated bilirubin occurred in 15%
286 of patients, with 2 cases of grade 4 hyperbilirubinemia resulting in treatment discontinuation.

287

288 For patients with follow-up data, elevations in AST and ALT were transient and typically of
289 <2 weeks duration. The majority of AST and ALT elevations occurred within 1 week of
290 CLOLAR™ administration and returned to baseline or ≤ grade 2 within several days.
291 Although less common, elevations in bilirubin appeared to be more persistent. Where

292 follow-up data are available, the median time to recovery from grade 3 and grade 4
293 elevations in bilirubin to \leq grade 2 was 6 days.

294

295 **Infection**

296 At baseline 47% of the patients had 1 or more concurrent infections. A total of 85% of
297 patients experienced at least 1 infection after CLOLAR™ treatment, including fungal, viral
298 and bacterial infections.

299

300 **Renal**

301 The most prevalent renal toxicity was elevated creatinine. Grade 3 or 4 elevated creatinine
302 occurred in 6% of patients. Nephrotoxic medications, tumor lysis, and tumor lysis with
303 hyperuricemia may contribute to renal toxicity.

304

305 **Systemic Inflammatory Response Syndrome (SIRS)/Capillary Leak Syndrome**

306 Capillary leak syndrome or SIRS (signs and symptoms of cytokine release, e.g., tachypnea,
307 tachycardia, hypotension, pulmonary edema) occurred in 4 pediatric patients overall (3 ALL,
308 1 AML). Several patients developed rapid onset of respiratory distress, hypotension,
309 capillary leak (pleural and pericardial effusions), and multi-organ failure. Close monitoring
310 for this syndrome and early intervention are recommended. The use of prophylactic steroids
311 (eg, 100 mg/m² hydrocortisone on Days 1 through 3) may be of benefit in preventing signs or
312 symptoms of SIRS or capillary leak. Physicians should be alert to early indications of this
313 syndrome and should immediately discontinue CLOLAR™ administration if they occur and
314 provide appropriate supportive measures. After the patient is stabilized and organ function
315 has returned to baseline, re-treatment with CLOLAR™ can be considered at a lower dose.

316

317 Overdosage

318 There were no known overdoses of CLOLAR™. The highest daily dose administered to a
319 human to date (on a mg/m² basis) has been 70 mg/m²/day × 5 days (2 pediatric ALL
320 patients). The toxicities included in these 2 patients included grade 4 hyperbilirubinemia,
321 grade 2 and 3 vomiting, and grade 3 maculopapular rash.

322

323 DOSAGE AND ADMINISTRATION**324 Recommended Dose**

325 CLOLAR™ should be diluted per instructions below with 5% dextrose injection, USP or
326 0.9% sodium chloride injection, USP prior to intravenous infusion (IVI).

327

328 The recommended pediatric dose and schedule is 52 mg/m² administered by intravenous
329 infusion (IVI) over 2 hours daily for 5 consecutive days. Treatment cycles are repeated
330 following recovery or return to baseline organ function, approximately every 2 to 6 weeks.
331 The dosage is based on the patient's body surface area (BSA), calculated using the actual
332 height and weight before the start of each cycle. To prevent drug incompatibilities, no other
333 medications should be administered through the same intravenous line.

334

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

337

338 Physicians are encouraged to give continuous IV fluids throughout the 5 days of CLOLAR™
339 administration to reduce the effects of tumor lysis and other adverse events. The use of
340 prophylactic steroids (e.g., 100 mg/m² hydrocortisone on Days 1 through 3) may be of

341 benefit in preventing signs or symptoms of SIRS or capillary leak (e.g., hypotension). If
342 patients show early signs or symptoms of SIRS or capillary leak (e.g., hypotension), the
343 physician should immediately discontinue CLOLAR™ administration and provide
344 appropriate supportive measures. Close monitoring of renal and hepatic function during the
345 5 days of CLOLAR™ administration is advised. If substantial increases in creatinine or
346 bilirubin are noted, physicians should immediately discontinue administration of
347 CLOLAR™. CLOLAR™ should be re-instituted when the patient is stable and organ
348 function has returned to baseline, possibly at a lower dose. If hyperuricemia is anticipated
349 (tumor lysis), patients should prophylactically receive allopurinol.

350

351

352 **STORAGE AND HANDLING**

353 Vials containing undiluted CLOLAR™ should be stored at 25°C (77°F); excursions permitted
354 to 15-30°C (59-86°F).

355

356 CLOLAR™ should be filtered through a sterile 0.2 µm syringe filter and then further diluted
357 with 5% dextrose injection USP or 0.9% sodium chloride injection USP prior to intravenous
358 infusion (IVI). The resulting admixture may be stored at room temperature, but must be used
359 within 24 hours of preparation.

360

361 **HOW SUPPLIED**

362 CLOLAR™ is formulated at a concentration of 1 mg/mL in sodium chloride (9 mg/mL),
363 USP, and water for injection, USP, quantity sufficient (qs) to 1 mL. CLOLAR™ is supplied
364 in 20 mL flint vials in a box of 4 (NDC 58468-0100-2). The 20 mL flint vials contain 20 mL
365 (20 mg) of solution. The pH range of the solution is 4.5 to 7.5. The solution is clear and
366 practically colorless, is preservative free, and is free from foreign matter.

367

368 **Rx only**

369 **U.S. Patents:** 4,751,221; 4, 918,179; 5,384,310; 5,661,136, 6,680,382 B2.

370 Other patents pending.

371

372 **NAME AND ADDRESS OF MANUFACTURER**

373 **Manufactured by:** AAI Development Services

374 Charleston, SC 29405

375 **Manufactured for:** Genzyme Corporation

376 4545 Horizon Hill Blvd

377 San Antonio, TX 78229

378 **Distributed by:** Genzyme Corporation

379 500 Kendall Street

380 Cambridge, MA 02142

381

EXHIBIT C





US005661136A

United States Patent [19]

[11] Patent Number: 5,661,136

Montgomery et al.

[45] Date of Patent: Aug. 26, 1997

[54] 2-HALO-2'-FLUORO ARA ADENOSINES AS ANTINOPLASTIC AGENTS

[75] Inventors: John A. Montgomery; John A. Secrist, III, both of Birmingham, Ala.

[73] Assignee: Southern Research Institute, Birmingham, Ala.

[21] Appl. No.: 320,879

[22] Filed: Sep. 21, 1994

Related U.S. Application Data

[63] Continuation of Ser. No. 693,646, May 10, 1991, Pat. No. 5,384,310, which is a continuation-in-part of Ser. No. 355,358, May 23, 1989, Pat. No. 5,034,518.

[51] Int. Cl.⁶ A61K 31/70

[52] U.S. Cl. 514/46; 536/27.4; 536/27.63

[58] Field of Search 514/46, 27.4; 536/27.63

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Assistant Examiner—L. Eric Crane

Attorney, Agent, or Firm—Yahwak & Associates

[57] ABSTRACT

The present invention is directed to certain 2'-fluoro, 2-substituted purine nucleosides which are toxic to cancerous cell lines.

12 Claims, No Drawings

2-HALO-2'-FLUORO ARA ADENOSINES AS ANTINOPLASTIC AGENTS

The application is a continuation of application Ser. No. 07/693,646, filed May, 10, 1991, now U.S. Pat. No. 5,384,310 which is a continuation-in-part of application Ser. No. 07/355,358, filed May 23, 1989 now U.S. Pat. No. 5,034,518.

The research leading to the discovery of the present invention was funded, in part, by funds from the United States Department of Health and Human Services. Accordingly, the United States government has certain statutory rights to the present invention under 37 USC 200 et seq.

The development of effective anticancer agents is a complex problem for a number of reasons, but primarily because of the lack of an identifiable, exploitable biochemical difference between normal and malignant tumor cells, be they of animal or human origin.

The simplest and most used strategy for the discovery of new anticancer agents is by empirical search, which has been most successful in identifying useful antitumor antibiotics. The search for lead compounds among synthetics is somewhat different, since few clinically useful agents have resulted from strictly random screening, which in fact is not a truly random search since it reflects the status of organic chemistry and, largely, what synthetic chemists have found of interest for whatever reason. In fact, most synthetics found to have clinical activity were screened for a reason. A prime example is one of the first clinically useful agents, nitrogen mustard, which was tested because of its effects on the blood elements discovered in the chemical warfare program. Regardless of the method of discovery, anticancer agents can be classified in five broad groupings:

A. Antimetabolites

Glutamine antagonists
Inhibitors of dihydrofolic reductase
Purine and pyrimidine analogs
Nucleoside diphosphate inhibitors
B. Nucleic acid complexors

Actinomycins
Anthracyclines
Bleomycins
Mitomycins
Mithramycin
Neocarzinostatin

Anthramycins

C. Chemically reactive compounds

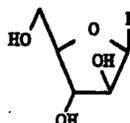
Nitrogen mustards
Aziridines
Sulfonates
Triazenes
Nitrosoureas
Procarbazine
cis-Platinum
D. Mitotic inhibitors
Vinca alkaloids
Podophyllum derivatives

E. Hormones

Estrogens
Androgens
Progestogens
Glucocorticoids
Miscellaneous synthetics

From these groupings, it is clear that anticancer agents with proven utility interfere one way or another with cell division and, since cancer cells must divide or eventually die, they are cytotoxic agents with some degree of specificity for neoplastic cells. Thus it would seem logical that the search for new lead compounds should focus on new structural types that will also interfere with one or another of the processes of cell division. The most approachable of these is the design of enzyme inhibitors. There are at least 85 enzymatic reactions involved in the de novo synthesis of purine and pyrimidine nucleotides, in their interconversion, in their polymerization to nucleic acids, and in the so called salvage pathways. Of these 85 enzymes, approximately 14 are known to be inhibited by metabolic analogs or analogites thereof. These inhibitions are thought to be responsible for, or at least contribute to, the anticancer activity of these compounds.

Two such compounds are the arabinofuranosyl nucleosides, 9- β -D-arabinofuranosyladenine and 1- β -D-arabinofuranosylcytosine, of the formula:



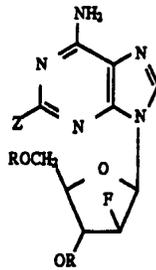
wherein B is adenine or cytosine, have well-known antiviral (B=adenine) and anticancer (B=cytosine) activity. In addition, other arabinofuranosyl nucleosides with 2'-substituents other than hydroxyl have also exhibited useful biological effects. All of these nucleosides require activation (phosphorylation) to be effective, and generally this is accomplished by different enzymes than the corresponding ribofuranosyl nucleosides.

In addition, a number of 2'-substituted-9- β -D-arabinofuranosyl-2-haloadenines [see *J. Med. Chem.* 31:405 (1988), and *J. Med. Chem.* 29:2389 (1986)] have also been developed along this general design. 9- β -D-arabinofuranosyl-2-fluoroadenine monophosphate is, for example, is a drug of choice against chronic lymphocytic leukemia; and 2-chloro-2'-deoxyadenosine has shown some promise in a phase I trial against T-cell neoplasms and in phase II trials against chronic lymphocytic leukemia of B-cell origin that is refractory to conventional therapy, and against hairy-cell leukemia. However, the search for better and more effective, anticancer compounds continues.

Thus, in accordance with the present invention it has now been found that the incorporation of a 2-halo substituent onto the purine ring of these prior compounds significantly alters the metabolism of adenine nucleosides, specifically by reducing the ability of the compound to serve as a substrate for adenosine deaminase; that substituting a fluorine in the arabino configuration at C-2' makes these derivatives highly resistant to phosphorolytic cleavage; and that the combination of these two changes in the same molecule provide enhanced biological and anti cancer activity of the resulting compound.

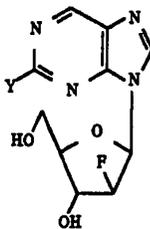
The present invention relates to a family of novel nucleoside compounds, and pharmaceutically acceptable salts thereof, represented by the general formula:

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in which R, which may be the same or different, is a hydrogen or acyl protecting group such as an alkanoyl protecting or blocking group such as benzoyl, and wherein Z is a halogen of the group F, Cl, and Br. In accordance with one aspect of the present invention, where R is acyl, the nucleoside compound acts as a prodrug in prolonging the in vivo life of the compound.

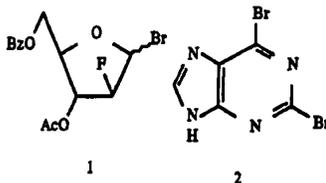
More specifically, the most preferred compounds of the present invention are those of formula:



wherein Y is F, Cl or Br, or the pharmaceutically acceptable salts thereof.

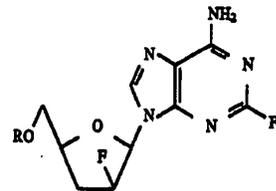
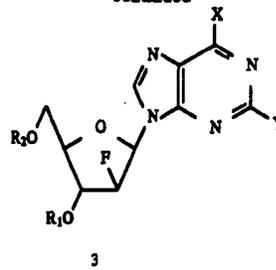
This and other aspects of the present invention will become clearer in the following discussion and description, both provided for purposes of clarification and not limitation as to the scope of the present invention.

In its broadest description, 2'-substituted purine arabinonucleosides are prepared from 2-haloadenosines via their 3',5'-O-(tetraisopropylidisiloxane-2'-O-triflate derivatives according to the process discussed in J. Med. Chem. 31:405 (1988). Since this prior approaches failed to provide the 2'-fluoroarabinonucleosides in reasonable yields, these compounds had to be prepared by reaction of the appropriately blocked 2'-fluoro sugar (compound 1) with 2,6-dichloropurine followed by modification of the purine [see J. Med. Chem. 29:2389 (1986)].



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-continued



- a) X = Y = Br, R₁ = Ac, R₂ = Bz a) R = Bz
 b) X = NH₂, Y = Br, R₁ = R₂ = H b) R = H
 c) X = Y = Cl, R₁ = Ac, R₂ = Bz
 d) X = NH₂, Y = Cl, R₁ = R₂ = H
 e) X = Y = NH₂, R₁ = Ac, R₂ = Bz
 f) X = NH₂, Y = F, R₁ = Ac, R₂ = Bz
 g) X = NH₂, Y = F, R₁ = R₂ = H
 h) X = NH₂, Y = F, R₁ = H, R₂ = Bz

The same sequence was also applied to 2,6-dibromopurine (compound 2) for the preparation of the 2-bromoadenine nucleoside. The blocked 2'-fluoro sugar was condensed with 2,6-dibromopurine in refluxing 1,2-dichloroethane in the presence of 4A molecular sieves. The anomeric configuration and substitution positions for compound 3a were confirmed by ¹H NMR comparisons with compound 3c. Animation and deprotection of compound 3a or 3c done in ethanolic ammonia yielded a mixture of the desired product and the 5'-benzoyl protected compound. This residual blocking group may be removed if desired by treating the mixture with LiOH in MeCN-H₂O to give either compound 3b or 3d.

Non-aqueous diazotization of compound 3e with tert-butyl nitrite in 60% hydrogen fluoride/pyridine at -20° C. produced the 2-fluoro compound 3f. Deacylation of compound 3f was accomplished with LiOH in MeCN-H₂O, allowing a reasonable yield of compound 3g, free of any side products.

In order to prepare the dideoxy compound 4b, the 3'-acetyl of compound 3f was first selectively removed with NaHCO₃ in MeOH. The resulting product, compound 3h, was then treated with thiocarbonyldiimidazole followed by reduction with tri-n-butyltin hydride to give compound 4a. The 5'-benzoyl protecting group of compound 4a was then removed with LiOH to produce compound 4b.

The following examples, given for purposes of clarity in more fully demonstrating the methods by which the compounds of the present invention may be prepared, are provided. However, these examples are not meant to be limiting in any manner, and modifications and adaptations may be made to provide other routes, which are to be considered to be within the scope of the present invention, for the synthesis of the desired compounds.

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EXAMPLE I

2,6-Dibromo-9-(3-O-acetyl-5-O-benzoyl-2-deoxy-2-fluoro- β -D-arabinofuranosyl)-9H-purine

(compound 3a)

A solution of 3-acetyl-5-benzoyl-2-deoxy-2-fluoroarabinofuranosylbromide (33.2 mmol) in 400 mL of dry dichloroethane was stirred for 10 min with 4A molecular sieves (250 mL) before the addition of (9.3 g, 33.5 mmol) 2,6-dibromopurine. The mixture was vigorously stirred with an overhead stirrer and placed in a preheated 100° C. oil bath. Heating was continued for 32 h until all the bromo-sugar was consumed. (TLC 2:1 cyclohexane-ethyl acetate, using 4-(4-nitrobenzyl) pyridine spray for detection.) After the mixture had cooled to room temperature, it was filtered through Celite. The solids were washed with dichloroethane, and the combined filtrates were evaporated to dryness in vacuo. The residue (16.5 g) was a mixture of three nucleosides which were separated by flash chromatography on 150 g of silica gel (230-400 mesh) using 2:1 cyclohexane-ethyl acetate as the eluting solvent. By combining pure fractions, the desired compound was obtained as a glass 3.64 g (19.7%) which was chromatographically homogeneous but would not crystallize. A second column run on impure fractions gave 2.21 g (11.9%) more pure product for a total yield of 31.6%.

EXAMPLE II

2-Bromo-9-(2-deoxy-2-fluoro- β -D-arabinofuranosyl)-9H-purin-6-amine

(compound 3b)

A solution of the example I product (5.84 g, 10.5 mmol) in 400 mL of ethanolic ammonia (saturated at 0° C.) was sealed in a glass-lined stainless steel bomb and left at room temperature for 3 days. The solution was evaporated to dryness and evaporated with ethanol to remove ammonia. The residue, containing the desired product and 5'-benzoyl compound, was dissolved in 440 mL of acetonitrile and 120 mL of water. Lithium hydroxide monohydrate (881 mg, 21 mmol) was added, and the solution was stirred for 16 h at room temperature. Thin-layer chromatography (5:1 CHCl₃-MeOH) indicated complete reaction. The chilled solution was carefully neutralized with glacial acetic acid and evaporated to dryness. The white solid residue was recrystallized from water. The product was dried in vacuo at room temperature at 100° C. for 2 h: 2.15 g (59.2%); Mp 209-210° C.

EXAMPLE III

2-Chloro-9-(2-deoxy-2-fluoro- β -D-arabinofuranosyl)-2,0 9H-purin-6-amine

(compound 3d)

A solution of the compound 3c [see J. Med. Chem. 29:2389 (1986)] (5.1 g, 10.9 mmol) in ethanol saturated (0° C.) with anhydrous ammonia (100 mL) was placed in a glass-lined stainless steel bomb and left at room temperature for three days. Thin layer chromatography (2:1 cyclohexane-ethyl acetate and 5:1 CHCl₃-MeOH) indicated the absence of starting material. However, two major products were present: the desired compound and its 5'-benzoyl analog. The solution was evaporated to dryness

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and co-evaporated with acetonitrile. The residue was dissolved in acetonitrile (100 mL) and diluted with water (60 mL) before the addition of lithium hydroxide monohydrate (915 mg, 21.8 mmol). The solution was stirred at room temperature for 3 h, at which time thin layer chromatography (5:1 CHCl₃-MeOH) indicated the reaction had gone to completion. The solution was cooled, neutralized with acetic acid, and evaporated to dryness. Three recrystallizations from water gave the pure compound: 1.4 g (42.3%); Mp 225°-226° C.

EXAMPLE IV

2-Fluoro-9-(3-O-acetyl-5-O-benzoyl-2-deoxy-2-fluoro- β -arabinofuranosyl)-9H-purin-6-amine

(compound 3f)

Diamino compound 3e [see J. Med. Chem. 29:2389 (1986)] (700 mg, 1.63 mmol) was dissolved in 3:2 HF-pyridine (15 mL) at -25° C. and treated with tert-butyl nitrite (271 μ L, 2.28 mmol). After 1 h at -20° C., the reaction was incomplete as indicated by thin layer chromatography. Additional tert-butyl nitrite (70 μ L, 0.59 mmol) was added, and the reaction was held at -20° C. for an additional 2 h. The cold reaction solution was added dropwise to saturated aqueous NaHCO₃ (1 L) containing ice. The foaming mixture was stirred vigorously for 20 min, then diluted with CHCl₃ (300 mL). The solution was allowed to layer, and the layers were separated, and the aqueous layer was extracted with additional CHCl₃ (2 \times 175 mL). The combined organic extracts were washed with water (3 \times 175 mL), dried (over MgSO₄), and evaporated to dryness. The resulting residue, in CHCl₃, was applied to a flash column containing 50 g of silica gel (230-400 mesh) with CHCl₃ as eluant. Fractions were combined to give essentially pure product (500 mg, 70%). Crystallization of a small sample from EtOH gave pure product: Mp 208°-209° C.

EXAMPLE V

2-Fluoro-9-(2-deoxy-2-fluoro- β -D-arabinofuranosyl)-9H-purin-6-amine

(compound 3g)

A suspension of the example IV product (430 mg, 0.99 mmol) in 1:1 MeCN-H₂O (40 mL) was treated in one portion with solid lithium hydroxide monohydrate (125 mg, 2.97 mmol). The reaction became a clear solution after being stirred at room temperature for 20 min. A 3 h thin layer chromatography aliquot showed the deblocking to be complete. Glacial acetic acid (57 μ L) was added, and the solution was evaporated until a white solid was deposited. After being chilled, the solid was collected, washed with cold water, and dried in vacuo at room temperature to give a crude solid (252 mg). This solid was dissolved in 40 mL of water and applied to a water-equilibrated SM-4 Bio-Bead column (1.5 \times 32 cm). After initial elution with water, the product was eluted with a step-wise gradient, 5% \rightarrow 20% EtOH in water. The residue from the combined evaporated column fractions was crystallized from 25 mL of boiling water with charcoal treatment, and dried in vacuo at 56° C. for 16 h to yield a pure product: 178 mg (59%); Mp 207-209° C.

EXAMPLE VI

2-Fluoro-9-(5-O-benzoyl-2-deoxy-2-fluoro- β -D-arabinofuranosyl)-9H-purin-6-amine

(compound 3h)

A suspension of the example IV product (312 mg, 0.72 mmol) in MeOH (25 mL) at 10° C. was treated with solid

NaHCO₃ (181 mg, 2.16 mmol). After being stirred at room temperature for 2.5 h, the reaction was quenched by the addition of glacial acetic acid (170 μ L) and evaporated to dryness. This residue in hot EtOH was applied to two silica gel thick plates (Analtech, GF, 2000 μ m) and subsequently developed in 9:1 CHCl₃—MeOH. The product was extracted with hot EtOH and evaporated to dryness to give essentially pure product: 208 mg (74%).

EXAMPLE VII

2-Fluoro-9-(5-O-benzoyl-2,3-dideoxy-2-fluoro-8- β -arabinofuranosyl)-9H-purin-6-amine

(compound 4a)

191 mg (0.49 mmol) of the compound made in accordance with example VI was dissolved in dry acetonitrile (20 mL) at 45° C., and then treated with 1,1'-thiocarbonyldiimidazole (339 mg, 1.7 mmol). The resulting cloudy yellow solution was stirred under N₂ at 45° C. for 24 h at which time thin layer chromatography analysis (EtOAc) showed one major product. The reaction was evaporated to dryness, and the residue was dissolved in dry toluene (15 mL). Treatment with AIBN (13.7 mg, 0.08 mmol) and tri-n-butyltin hydride (1.3 mL, 4.7 mmol) produced a yellow mixture that was placed directly in a 120° C. bath. A clear solution was observed after a 5 min reflux, and at 1 h the reaction was complete as indicated by thin layer chromatography. The solvent was then removed in vacuo, and the resulting syrup was coevaporated once with EtOH. Trituration of this residue with petroleum ether (50 mL) produced a white solid that was collected and washed with fresh solvent to give 214 mg of crude solid. This material in hot EtOH was applied to two Analtech (GF, 2000 μ m) layer plates. After three developments in 9:1 CHCl₃—MeOH, the product band was extracted with boiling EtOH. The residue from evaporation of the combined extracts was crystallized from boiling EtOH to yield sufficiently pure product 160 mg (87%); Mp 215°–217° C. Without any further purification, this material was used in the deprotection step of example VIII.

Example VIII

2-Fluoro-9-(2,3-dideoxy-2-fluoro- β -D-arabinofuranosyl)-9H-purin-6-amine

(compound 4b)

A suspension of the example VII compound (135 mg, 0.36 mmol) in 3:1 MeCN—H₂O was treated in one portion at room temperature with solid LiOH·H₂O (38 mg, 0.9 mmol). The stirred mixture became a clear solution after 1/2 h. At 7 h an aliquot examined by TLC (5:1 CHCl₃—MeOH) showed the absence of the example VII compound. Glacial acetic acid (35 μ L) was added, and the reaction was evaporated to dryness. This residue in hot acetonitrile was applied to one silica gel thick plate (Analtech, GF, 2000 μ m). After the plate was developed three times in 5:1 CHCl₃—MeOH, the product band was extracted with boiling MeCN. Evaporation of this extract gave slightly impure material that was chromatographed as above on three prep plates (Analtech, GF, 1000 μ m). The resulting residue was crystallized from boiling H₂O (25 mL) containing EtOH (0.5 mL). After being chilled, the white solid was collected, washed with cold H₂O and dried in vacuo at 56° C. for 16 h to give pure product, 71 mg (73%); Mp 249°–250° C.

In contrast to the previously reported 2'-substituted 9- β -D-arabinofuranosyl-2-haloadenines, the 2'-fluoro com-

pounds were quite cytotoxic to three human cell lines, H.Ep.-2, CCRF-CEM, and K562, and the murine leukemia line, L1210. They, in fact, are significantly more cytotoxic than the corresponding 9- β -D-arabinofuranosyl-2-haloadenines, resembling more closely the 2'-deoxy-2-haloadenosines (see Table I).

Obviously, to be useful as anticancer agents, the nucleosides of the present invention must show the ability to kill cells in vitro. The results in Table I, indicating the concentration required to inhibit cell proliferation to 50% of untreated controls, show that these nucleosides can, at reasonable concentrations, kill cells. One cell line (L1210) is a murine leukemia, whereas the other three are human neoplasms. Based on many years of experience, we believe that compounds that do not require activation by the liver must have an IC₅₀ of about 1–10 μ M or less to show useful activity in the in vivo animal models—and in man. Many people today emphasize the importance of toxicity to human cell lines.

TABLE I

Cytotoxicity [as IC₅₀ (μ M)] of 2-Haloadenine Nucleosides

Compound	H.Ep.-2	L1210	CCRF-CEM	K562
when Y = F				
X = OH	9	3	0.4	0.15
X = H	0.2	0.9	0.2	
X = F	0.34	0.38	0.14	0.3
when Y = Cl				
X = OH	3	<3	10	
X = H	0.03	0.07	0.003	
X = F	0.012	0.23	0.05	0.003
when Y = Br				
X = OH	4	3		
X = H	0.02	0.9	0.02	
X = F	0.22	0.26	0.02	0.05

The data in Table I (given in μ M amounts) clearly establishes the ability of the compounds according to the present invention to kill neoplastic cells.

Subsequently, the phosphorolysis of these compounds were compared by *E. coli* purine nucleoside phosphorylase. The arabino and 2'-deoxyribonucleosides are rapidly cleaved by this enzyme, whereas the arabino nucleosides substituted at 2' by Cl, N₃, or NH₂ are almost completely resistant. The 2'-fluoro compounds are less resistant to cleavage, being cleaved at roughly one-third the rate of the arabino and 2'-deoxynucleosides. This reduction in cleavage rate may be acceptable for pharmaceutical purposes as phosphorylation in mammalian cells is quite rapid.

More specifically, an enzyme reaction mixture consisting of 0.5 mM nucleoside substrate, 50 mM pH 8.0 phosphate buffer and purine nucleoside phosphorylase in a final vol-

ume of 1.0 mL was allowed to incubate for 30, 60, 120, 180 and 240 minutes, and the amounts of nucleoside and substrate remaining were determined by HPLC. The results of this experiment are tabulated in the following Table II.

TABLE II

Phosphorolysis of Nucleosides	
Compound	% Cleavage
3b	45
3d	39
3g	10
2-fluoro-9-β-D-arabinofuranosyladenine	99
2-chloro-2'-deoxyadenosine	>99
2-fluoro-2'-deoxyadenosine	>99

A recent report from our laboratory [see *Cancer Research* 51:2386 (May 1st 1991) which is incorporated in toto herein] indicates that the compound 3d of the present invention inhibits DNA synthesis due to the inhibition of ribonucleotide reductase activity and inhibition of chain elongation by DNA polymerase α . These inhibitions of the ribonucleotide reductase and DNA polymerase α enzymes by compound 3d were important to the development of the cancerous K562 cells. Although this finding is similar to observations with 9-β-D-arabinofuranosyl-2-fluoro-adenine and 2-chloro-2'-deoxyadenosine, the degree of inhibition of these enzymes by the 5'-triphosphate of these nucleoside analogues is quite different. The inhibition of ribonucleoside reductase by 2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)adenine 5'triphosphate was the same as that seen with 2-chloro-2'-deoxyadenosine 5'-triphosphate, and the inhibition of DNA polymerase α by 2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl) adenine 5' triphosphate was similar to that seen with 9-13-D-arabinofuranosyl-2-fluoro-adenine 5'triphosphate. In contrast, 9-β-D-arabinofuranosyl-2-fluoro-adenine 5'triphosphate was a much less potent inhibitor of ribonucleotide reductase than either 2-chloro-2'-deoxyadenosine 5'-triphosphate or 2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)adenine 5'triphosphate, and although all of the 2'-deoxyadenosine nucleotide analogues inhibit the incorporation of 2'-deoxyadenosine 5'triphosphate by DNA polymerase α into the DNA and were more efficient substrates for the polymerase, the incorporation of 2-chloro-2'-deoxyadenosine 5'monophosphate into DNA by DNA polymerase α did not inhibit the further elongation of the DNA chain to the degree that was seen with the incorporation of either 9-β-D-arabinofuranosyl-2-fluoro-adenine 5'monophosphate or 2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl) adenine 5'monophosphate. These results indicated that the 2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)adenine (compound 3d) incorporates properties of both 9-β-D-arabinofuranosyl-2-fluoro-adenine and 2-chloro-2'-deoxyadenosine into one compound. Furthermore, in the cell the inhibition of DNA polymerase α by these nucleoside analogues is a function of the ratio of [analogue nucleoside triphosphate] to [2'-deoxyadenosine 5'triphosphate]. Because 9-β-D-arabinofuranosyl-2-fluoro-adenine 5'triphosphate inhibits ribonucleotide reductase at a 10-fold higher concentration than that required with 2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl) adenine 5' triphosphate, the 2'-deoxyadenosine 5'triphosphate pool should be lower and the inhibition of DNA polymerase α should be greater. In cells treated with 2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl) adenine than in cells treated with equimolar concentrations

of 9-β-D-arabinofuranosyl-2-fluoro-adenine, assuming equal conversion to the triphosphate. These metabolic features may contribute to the potent inhibition of K562 cell growth with compound 3d [2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl) adenine] of the present invention. In addition, the solubility problems associated with the administration of 9-β-D-arabinofuranosyl-2-fluoro-adenine should not occur with this compound because of its greater solubility and high potency.

The reason that the 2'-fluorine atom disrupts chain extension is not obvious because the 2'-carbon is not involved in the reaction and a fluorine has an atomic radius slightly larger than a hydrogen atom. Steric hindrance would be expected to be less than is believed to be in the case of arabinofuranosyl nucleotides. It is possible that the electron-withdrawing properties of fluorine may affect the reactivity of the 3'-hydroxyl and/or the three dimensional structure of the DNA chain such that extension of a DNA chain terminated with a 2'-fluoronucleoside by the polymerase is inhibited.

Studies with the P388 leukemia cell line in mice (see Table III) indicate that the most effective compound of the present invention is the compound according to general formula 3d, that is the 2-chloro-2'-fluoro substituted nucleoside. This, coupled with the lower toxicity of the cleavage product, 2-chloro-adenine, relative to 2-fluoro-adenine, make this compound a preferred compound of the present invention. The following Table III provides a summary of the in vivo activity of the 9-(2-fluoro-2-deoxy-β-D-arabinofuranosyl)-2-halo-adenines vs P388 leukemia cell line in which CD2F1 mice were implanted ip with 10⁶ P388 leukemia cells on day 0 in accordance with the protocol of Waud et al [*Cancer Res.* 50:3232 (1990)].

TABLE III

Compound	Optimal IP Dose	Schedule	Median %		Tumor-free Survivors
			ILS (dying mice only)	Log ₁₀ change	
3d	100	qd 1-5	+38	-0.3	0/5
	200	qd 1-5	+59	-1.6	0/3
	20	q 3 h x 8 (Days 1, 5, 9)	+220	-6.6	1/6
	25	q 3 h x 8 (Days 1, 5, 9)	+118	-2.8	0/5
3g	100	qd 1-5	+63	-1.8	0/3
	25	q 3 h x 8 (Days 1, 5, 9)	+81	-0.1	0/6
3b	30	q 3 h x 8 (Days 1, 5, 9)	+100	-1.0	0/6
	50	q 3 h x 8 (Days 1, 5, 9)	+41	+1.6	0/6
	200	qd 1-5	+33	+0.1	0/6

In the above table, the optimal dose refers to mg/kg/dose (\leq LD₅₀); ILS refers to the increase in life span; and the log change refers to the change in viable tumor cell population at the end of therapy compared to that at the start of therapy, based on the median day of death among the animals that died. The data in this table is presented in accordance with the National Cancer Institute activity criteria for drug testing in which an ILS of 20-74% is considered moderate activity, and an ILS of 75% or more is considered good activity.

In addition to the above, the 2,3-dideoxynucleoside depicted as compound 4b showed slight activity against HIV (strain IIIb) in either CEM or MT cell lines in culture.

In a similar test, compound 3d was administered orally and evaluated for antitumor activity against ip P388 leuko-

mia cells. As the data in Table III indicates, the optimal regimen for the compound, administered ip, is in divided doses five on days 1, 5, and 9, a similar schedule was selected for the oral administration of this compound. In this set of experiments, an oral dosage of 67 mg/kg/dose, given q 6 h x 4 on days 1, 5, and 9, effected a reduction in tumor burden of $1.7 \log_{10}$ units, a figure which is approximately $2.5 \log_{10}$ units less than that obtained in studies using ip drug administration.

The compounds according to the present invention are useful for their cytotoxic effects, and thus are useful as anticancer compounds in the treatment of cancerous cells in mammals when administered in an amount sufficient to bring about their cytotoxic effect to the desired cancerous cell. The compounds may be administered in a wide range of regimens ranging from about 10 mg to about 1000 mg per day. These regimens may be designed to give the compounds as a single dose or as multiple doses over extended periods of time, and the regimen may be adapted to provide the optimum therapeutic response. For example, several divided doses may be administered daily, or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. The compounds according to the present invention may be administered in the form of the free purine nucleoside or as a nontoxic pharmaceutically acceptable salt thereof, and may be administered either alone or in combination with one or more compounds of the present invention or with additional pharmaceutically active compounds.

The active compounds of the present invention may be administered parenterally, e.g. by subcutaneous, intramuscular, or intravenous injection. Solutions or suspensions of the active compound as a pharmaceutically acceptable salt can be prepared in water or saline containing the appropriate buffers and additives for administration. The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability is provided; it must be stable under the conditions of manufacture and storage, and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier may be a solvent or dispersion medium containing, for example, water, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. Compositions suitable for intramuscular or subcutaneous injection may also contain minor amounts of salts, acids, and bases to adjust tonicity and buffer the pH.

The compounds according to the present invention may also be suitable for oral administration, for example with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard or soft shell gelatin capsules, or compressed into tablets. For oral therapeutic administration, the compounds may be incorporated with excipients commonly used in the formulation of oral pharmaceutical preparations as, for example, sweetening agents, and preservatives.

In addition, the compounds of the present invention may be formulated in accordance with acceptable pharmaceutical formulation techniques for administration by other routes such as administration within topical ointments, creams or salves, as suppositories, or as lozenges.

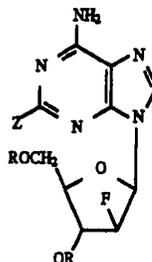
Thus, while we have illustrated and described the preferred embodiment of our invention, it is to be understood

that this invention is capable of variation and modification and we therefore do not wish to be limited to the precise terms set forth, but desire to avail ourselves of such changes and alterations which may be made for adapting the invention to various usages and conditions. Among such variations and modifications are, for example, and without limitation, the use of pharmaceutically acceptable salts of the disclosed purine nucleosides which may be designed for providing the purine nucleosides according to the present invention to a cell susceptible to cytotoxicity, to any minor substitution on the active nucleoside according to the present invention which results in no untoward effects upon the activity of the modified nucleoside from that of the depicted purine nucleosides or which results in the same or substantially the same activity as that found in the purine nucleosides depicted in accordance with the preceding disclosure; changes in formulation made due to the specific route of administration of the nucleosides according to the present invention; and changes made to the nucleoside molecule or composition formulation because of a specific salt form of the nucleoside according to the present invention. Accordingly, such changes, alterations and modifications are properly intended to be within the full range of equivalents, and therefore within the purview of the following claims.

Having thus described our invention and the manner and process of making and using the same in such full, clear, concise, and exact terms so as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same,

We claim:

1. A method for bringing about a cytotoxic effect in a mammalian cancerous cell which comprises contacting said cancerous cell with an effective amount of a cytotoxic compound having the formula



wherein R, each which may be the same or different, is hydrogen or a protecting group; wherein Z is a selected from the group consisting of F, Cl, and Br; and pharmaceutically acceptable salts thereof.

2. A method according to claim 1 which comprises contacting said cancerous cell with a compound wherein R is a protecting group.

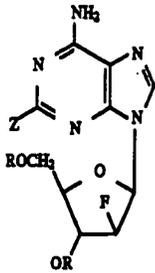
3. A method according to claim 1 which comprises contacting said cancerous cell with compound wherein R is hydrogen.

4. A method according to claim 1 which comprises contacting said cancerous cell with a compound wherein Z is Cl.

5. A method according to claim 1 which comprises contacting said cancerous cell with a compound wherein the compound is 2-Chloro-9-(2-deoxy-2-fluoro- β -D-arabinofuranosyl)-9H-purin-6-amine.

6. A method for inhibiting ribonucleotide reductase and DNA polymerase α in a mammalian cell which comprises contacting said mammalian cell with of a cytotoxic compound having the formula

13



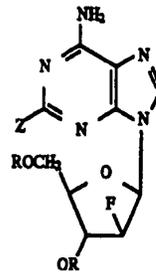
wherein R, each which may be the same or different, is hydrogen or a protecting group; wherein Z is a halogen selected from the group consisting of F, Cl, and Br; and pharmaceutically acceptable salts thereof.

7. A method according to claim 6 wherein R of said compound is a protecting group.

8. A method according to claim 6 wherein R of said a compound is hydrogen.

9. A method for inhibiting ribonucleotide reductase and DNA polymerase α in a mammalian cell which comprises contacting said mammalian cell with of a cytotoxic compound having the formula

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wherein R, each which may be the same or different, is hydrogen or a protecting group; wherein Z is a halogen selected from the group consisting of F, Cl, and Br; and the pharmaceutically acceptable salts thereof.

10. A method according to claim 9 wherein R of said compound is a protecting group.

11. A method according to claim 9 wherein R of said compound is hydrogen.

12. A method according claim 9 wherein said compound is 2-Chloro-9-(2-deoxy-2-fluoro- β -D arabinofuranosyl)-9H-purin-6-amine.

* * * * *

EXHIBIT D



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**United States
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Maintenance Fee Statement

01/25/2005 12:37 PM EST

Patent Number: 5661136

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The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "STAT", below.

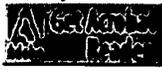
If a maintenance fee payment is defective, the reason is indicated by code in column 10, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for 1 related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

PATENT NUM	FEE CDE	FEE AMT	SUR-CHARGE	APPLICATION NUM	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT	ACTION
5,661,136	1552	\$2,150.00	\$0.00	08/320,879	08/26/97	09/21/94	08	NO	PAID	

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EXHIBIT E



	Internal Memo	Memo from Lawrence Trissel, thru Roger Anderson, to Dr. Michael Keating: Production of Clinical Trial Clofarabine Injection	
	Internal Memo	Memo from Lawrence Trissel to Dr. Michael Keating: Clofarabine Injection IND Filing	18-Feb-93
	Internal Memo	Memo from Lawrence Trissel to Dr. Michael Keating: Clofarabine Injection: Vials of Lot No. 93-I-006; SN: 000 Initial IND submitted by UT MD Anderson: Drug manufactured by UT MD Anderson with no batch records, CoFAs etc.; Pre-Clinical data include - Studies in K562 CML blastle line, Efficacy study in P388 tumor bearing mice, In vitro cytotoxicity in human cell lines, Phase I/II protocol DM 93-036	31-Mar-93
1	Initial IND	Letter from FDA: Receipt of IND acknowledged by FDA and IND number assigned (43,275)	21-Jul-93
1	FDA Corres.	Letter to Paul Zimmerman, CSO at FDA from MD Anderson: C of A provided (copy not attached to memo); still need batch records	23-Aug-93
1	FDA Corres.	Memo from Lawrence Trissel to Betty Shields (both of MD Anderson) C of A & release testing info. for Clofarabine Injection; still waiting on batch records	27-Aug-93
1	Internal Memo	Memo from Betty Shields to Paul Zimmerman/CSO at FDA: Response to Questions from FDA's Chemistry Reviewer (not attached)	14-Sep-01
1	Internal Memo	Memo from Lawrence Trissel to Betty Shields (both of MD Anderson) Clofarabine Questions Regarding Production	15-Sep-93
1	Internal Memo	SN: 001 Clofarabine batch record submitted (1 mg/ml)	16-Sep-93
1	FDA Sub.	FDA Response: IND on Clinical Hold. Deficiencies include: Insufficient Pre-Clinical studies, Protocol Inadequacies	20-Sep-93
1	FDA Corres.	Conference call with FDA to discuss Pre-Clinical program - no minutes or agreements generated	29-Sep-93
1	Tele. Conf.	Memo to Dr. Keating & Kantarjian: IND for Clofarabine on Clinical Hold due to Insufficient Information Supplied....	7-Oct-94
1	Gen Corres.	Letter from Southern Research Institute: Proposal for Preclinical Toxicology Studies under GLP Guidelines includes two letters: Dr. John Montgomery from John Gage (8/17/94) and Dr. Emil Fretlich from John Seibert, III	11-Jun-94
1	Gen Corres.	Letter to Paul Zimmerman/CSO at FDA: Request for Minimal Animal Toxicology Studies (from Dr. Kantarjian)	23-Aug-94
1	FDA Corres.	Letter to Paul Zimmerman/CSO at FDA: Suggested Proposal for Investigating Clofarabine based on FDA response to letter of 9/1/94; one rodent species study; limited phase I study in humans w/pharmacology study	1-Sep-94
1	FDA Corres.	Letter to Paul Zimmerman/CSO at FDA: Following Teleconference of 10/7/94: Suggested Proposal for Investigating Clofarabine GLP study in rats and pharmacology studies in dogs at 2 or 3 dose levels	2-Sep-94
1	FDA Corres.	Memo: Correction to two previous letters to Paul Zimmerman at FDA	10-Oct-94
1	Gen. Corres.	Fax/Letter from John Gage at Southern Research Institute: Costs of Dog Study & Rat Study	12-Oct-94
1	FDA Corres.	Memo to Paul Zimmerman at FDA: Dr. Keating's & Dr. Kantarjian's Proposal to Support Phase I Study - Request for Approval of/Acceptance of Proposal (actual proposal not attached)	6-Jan-95
1	FDA Corres.	Memo to Paul Zimmerman at FDA: Request for Approval to Proceed with Dr. Keating's & Dr. Kantarjian's Proposal to Support Phase I Study	25-Jan-95
1	FDA Corres.		3-Feb-95

2	43,275	FDA Sub.	SN: 021 Safety Report One Patient (No. 396682)	22-Nov-99
2	43,275	FDA Sub.	SN: 022 Follow-Up to Safety Report (Patient No. 396682) (Death)	1-Dec-99
2	43,275	FDA Sub.	SN: 023 CMC Amendment - Supply of Clofarabine from New Supplier - C of A & Synthesis from New Supplier Delmar Chemicals, Inc. Also - Change of Preparation Method by Pharmacist	1-Dec-99
2	43,275	FDA Sub.	SN: 023 Duplicate of Submission sent to FDA on 12/1/99 but not received	11-Jan-00
2	43,275	FDA Sub.	SN: 024 New Protocol ID99-383	8-Mar-00
2	43,275	FDA Sub.	SN: 025 Annual Report Very Little Information (only included objectives & patients enrolled/completed study)	10-Mar-00
2	43,275	FDA Sub.	SN: 026 Response to FDA fax of 3/10/00: No details provided - not a true response (a memo repeating FDA's questions regarding CMC Information)	31-Mar-00
2	43,275	FDA Sub.	SN: 027 Response to FDA fax of 3/10/00: Drug Master File from Delmar Chemicals including GMP compliance statement	3-Apr-00
2	43,275	FDA Sub.	SN: 028 Request to FDA for Scheduling Conference Call to discuss SN 026, SN 027	20-Apr-00
2	43,275	FDA Sub.	SN: 028 (Duplicate Serial No. Used) Safety Report One Patient (No. 356186) under Study ID99-383 - Death, Reported as Progressive Disease	25-Apr-00
2	43,275	FDA Sub.	SN: 029 Safety Report Submitted as SN: 027 on 4/20/00 Acceptable	18-Oct-00
2	43,275	FDA Sub.	SN: 030 Safety Report Two Patients (No. 388664 & 425480)	22-May-00
2	43,275	FDA Sub.	SN: 031 Follow-Up to Safety Report (Patient No. 388664) (Death)	2-Nov-00
2	43,275	FDA Sub.	SN: 032 IND Safety Report Initial Report - Patient No. 416805 F-B, Protocol No. ID99-383 (13 yr old female-hospitalization)	3-Nov-00
2	43,275	FDA Sub.	SN: 033 IND Safety Reports - Follow Up Reports - Patient No. 388664 JS, Protocol No. DM93-036 (21 yr old male - death on study) and Patient No. 453790 AR, Protocol No. DM93-036 (36 yr old female-death on study)	27-Nov-00
2	43,275	FDA Sub.	SN: 034 IND Safety Report - Initial Reports Patient No. 202271 DG, Protocol No. DM93-036 (male - hospitalization) and Patient No. 397304 MTC, Protocol No. DM93-036, (67 yr old female)	2-Feb-01
2	43,275	FDA Sub.	SN: 035 Protocol Amendment - Protocol No. ID99-383 titled "Phase I Study of CL-F-ARA-A (Clofarabine) in Pediatric Patients with Solid and Hematologic Malignancies" (Version 2)	20-Feb-01
2	43,275	FDA Sub.	SN: 036 IND Safety Report - Initial Report - Patient No. 421060 NM, Protocol No. DM93-036, (56 yr old female)	22-Feb-01
2	43,275	FDA Sub.	SN: 037 IND Safety Report - Initial Report - Patient No. 421060 NM, Protocol No. DM93-036 (56 yr old female - death on study)	1-Mar-01
2	43,275	FDA Sub.		13-Mar-01

3	43,275	FDA Sub.	SN: 038 IND Safety Report - Initial Report - Patient No. 319857 SB, Protocol No. DM93-036 (46 yr old male - hospitalization)	22-Mar-01
3	43,275	FDA Sub.	SN: 039 IND Safety Report - Initial Report - Patient No. 428646, Protocol No. ID99-383 (2 yr old male-hospitalization)	26-Mar-01
3	43,275	FDA Sub.	SN: 040 Annual Report for Protocol No. DM99-225 titled "Phase II Study to Assess the Efficacy of 2-Chloro-2-Fluoro-Deoxy-9-B-D-Arabinofuranosyladenine (Cl-F-Ara-A, Clofarabine) in Patients with Chronic Lymphocytic Leukemia Who Are Refractory to Fludarabine and Alkylator Therapy" - only 3 Patients on Study - Actively Recruiting)	5-Apr-01
3	43,275	FDA Sub.	SN: 041 New Protocol - Protocol No. ID00-038 titled "Phase II Study of Clofarabine in Acute Leukemia and Myelodysplastic (MDS) Refractory to Therapy Or In Relapse", submission includes Form FDA 1572 for Dr. Kantarjian, CV for Dr. Kantarjian and IRB Approvals for the Study	16-Apr-01
3	43,275	FDA Sub.	SN: 042 Protocol Amendment - Revised Protocol No. ID00-038 titled "Phase II Study of Clofarabine in Acute Leukemia and Myelodysplastic (MDS) Refractory to Therapy Or In Relapse" (revised to correct the protocol no. in the header on all pages)	18-Apr-01
3	43,275	FDA Sub.	SN: 043 Annual Report for Study ID99-383 titled "Phase I Study of Cl-F-Ara-A (Clofarabine) in Pediatric Patients with Solid and Hematologic Malignancies" (includes list of Aes, grades, dates, outcomes, & relationship to study drug)	30-Apr-01
3	43,275	FDA Sub.	SN: 044 IND Safety Report - Follow Up Patient No. 428646, Protocol No. ID99-383 (2 yr old male-hospitalization, discharged, not study-drug related)	1-May-01
3	43,275	FDA Sub.	SN: 045 Annual Report for Study "Phase I Study of 2-Chloro-2-Fluoro-Deoxy-9-B-D-Arabinofuranosyladenine (Cl-F-Ara-A, Clofarabine) in Solid and Hematologic Malignancies" (closed to patient accrual, patients on therapy continue) includes list of adverse events (dates of events, grades, patient ID nos., event descriptions)	8-May-01
3	43,275	FDA Sub.	SN: 046 Protocol Amendment for Protocol No. DM99-225 titled "Phase II Study to Assess the Efficacy of 2-Chloro-2-Fluoro-Deoxy-9-B-D-Arabinofuranosyladenine (Cl-F-Ara-A, Clofarabine) in Patients with Chronic Lymphocytic Leukemia Who Are Refractory to Fludarabine and Alkylator Therapy" (revision-reduction in dose from 4mg/m2 to 3mg/m2 due to evaluable toxicities)	15-May-01
3	43,275	FDA Sub.	SN: 047 IND Safety Report - Initial Report - Patient No. 476902 A-V, Protocol No. ID99-383, (7 yr old female - prolonged hospitalization)	24-May-01
3	43,275	FDA Sub.	SN: 048 Protocol Amendment for Study ID99-383 titled "Phase I Study of Cl-F-Ara-A (Clofarabine) in Pediatric Patients with Solid and Hematologic Malignancies" (update to response criteria to reflect childrens' therapy & change to reporting requirement for myelosuppression as ADRs in patients with leukemia)	5-Jun-01
3	43,275	FDA Sub.	SN: 049 IND Safety Report - Initial Report - Patient No. 480480 MEG, Protocol No. ID99-383 (12 yr old female - hospitalization)	24-Jul-01
3	43,275	FDA Sub.	SN: 050 IND Safety Report - Initial Report - Patient No. 456363 M-V, Protocol No. ID99-383 (2 yr old male)	31-Jul-01

3	43,275	FDA Corres.	Request for AML Orphan Drug Designation	
3	43,275	FDA Corres.	Fax to Christy Wilson, CSO/FDA: Correction to Serial Numbers for ILEX SN: 060 & ILEX SN: 061 due to duplication of Serial Numbers used by MD Anderson	31-Jan-02
3	43,275	FDA Corres.	Official Acknowledgement of the Change of Sponsorship from MD Anderson to ILEX effective 29 January 2002	4-Feb-02
3	43,275	FDA Corres.	SN: 065 Investigator's Brochure (written by ILEX, originally submitted to new IND 63,641) Official Approval of Orphan Drug Designation for Clorafex in ALL (Acute Lymphoblastic Leukemia)	5-Feb-02 7-Feb-02
3	43,275	FDA Corres.	Fax from FDA: the Finalized Meeting Minutes from the Oncology Division for the Teleconference Held on 14 January 2002: Pharmacology/Toxicology Issues; Pharm/Tox Studies to be Done; Organ Weights, Cardiac Toxicity; Genetic Tox Study; Bridging Study for Oral Dosing	7-Feb-02
3	43,275	FDA Sub.	SN: 068 Informational Amendment CMC: Change in API and DP Manufact/Stability Data	7-Feb-02
3	43,275	FDA Corres.	Fax from FDA: General Comments from the Clinical Reviewer for Improving the Protocol (original Official Acknowledgement of Orphan Drug Application for Clorafex in AML (Acute Myelogenous Leukemia))	8-Feb-02
3	43,275	FDA Corres.	Fax to Christy Wilson, CSO/FDA: Advice requested as to how to file Fast Track Application	12-Feb-02
3	43,275	Internal Memo	Memo to S. Jaha, H. Kantarjian, M. Keating at MDACC RE: CTM Provided by ILEX	19-Feb-02
3	43,275	FDA Sub.	SN: 067 Annual Report for Period Covering 5 April 2001 to 15 January 2002	11-Mar-02
3	43,275	FDA Sub.	SN: 068 IND Safety Report Initial Report, Report No. 12458, Patient No. 001-0016 D-W (6 year old) on Study ID99-383 "Phase I Study of CL-F-ARA-A (clotarex) in Pediatric Patients with Hematologic Malignancies" (includes follow-up details received on 5 April 2002 & 8 April 2002; no autopsy performed per family request, no additional follow up expected)	22-Mar-02 2-Apr-02
3	43,275	FDA Sub.	SN: 069 General Correspondence: Withdrawal of IND - Request to Transfer All Documents to New ILEX IND NO. 63,641	9-Apr-02
4	43,275	Gen. Corres.	Request to Hagop Kantarjian, M.D., University of Texas M.D. Anderson Cancer Center for New Dog Study Reports	10-Apr-02
4	43,275	Memo	Internal Memo from Douglas M. Cromseens, D.V.M. (Chief of Veterinary Medicine) to Hagop Kantarjian, M.D., both of University of Texas M.D. Anderson Cancer Center: Copies of Dog Studies (including pathology)	12-Aug-03
4	43,275	Memo	Internal Memo from Douglas M. Cromseens, D.V.M. (Chief of Veterinary Medicine) to Hagop Kantarjian, M.D., both of University of Texas M.D. Anderson Cancer Center: Mouse Studies (summary provided) and Dog Studies (summary provided)	2-Dec-98
4	43,275	Ref. List	Reference List from Item 5.4 Nonclinical Toxicology Summary Section of NDA 21-673 - for listing of Mouse & Dog Studies submitted to the NDA	16-Apr-98

4	43,275	Report	Clofarabine Dog Study 1, University of Texas MD Anderson Cancer Center, Hagop Kantarjian, M.D., 17 - 21 September 1998 (submitted in clofarabine NDA Item 5.4 Nonclinical Toxicology Summary - Reference No. 11)
4	43,275	Report	Clofarabine Dog Study 2, University of Texas MD Anderson Cancer Center, Hagop Kantarjian, M.D., 24 September 1998 - 3 December 1998 (submitted in clofarabine NDA Item 5.4 Nonclinical Toxicology Summary - Reference No. 11)
4	43,275	Report	Clofarabine Dog Study 1, University of Texas MD Anderson Cancer Center, Hagop Kantarjian, M.D., 17 - 21 September 1998 (submitted in clofarabine NDA Item 5.4 Nonclinical Toxicology Summary - Reference No. 11)
4	43,275	Report	Clofarabine Mouse Study 1, University of Texas MD Anderson Cancer Center, Hagop Kantarjian, M.D., 23 January 1998 (submitted in clofarabine NDA Item 5.4 Nonclinical Toxicology Reference No. 3)
4	43,275	Report	Clofarabine Mouse Study 2, University of Texas MD Anderson Cancer Center, Hagop Kantarjian, M.D., 13 March 1998 & 15 April 1998 (submitted in clofarabine NDA Item 5.4 Nonclinical Toxicology Summary - Reference No. 3)
4	43,275	Report	Clofarabine Mouse Study 3, University of Texas MD Anderson Cancer Center, Hagop Kantarjian, M.D., 28 June 1998 - 26 August 1998, (submitted in clofarabine NDA Item 5.4 Nonclinical Toxicology Summary - Reference No. 3)

BINDER			
1	FDA Sub.	Pre-IND meeting Request for New IND No	17-Jul-01
1	Tel. Contact	Phone Call from Christy Wilson at FDA: pre-IND mtg is scheduled for 9:30am EST (Internal mtg is set for August 28th -FDA will try to get details to ILEX)	23-Jul-01
1	FDA Corres.	Fax from Christy Wilson/FDA: Confirmation of pre-IND Mtg scheduled for 30 August 2001 at 9:30am EST with List of FDA Participants	
1	CTX Applic.	CTX Application	25-Jul-01
1	FDA Sub.	Submission of ILEX's Clofarabine Pre-IND Meeting Minutes from Meeting of 30 August 2001	13-Aug-01
1	FDA Corres.	Receipt of FDA's finalized minutes from Pre-IND Meeting: Meeting of 30 August 2001	20-Sep-01
2	FDA Sub.	Intravenous GLP Toxicity Study of Clofarabine in Male Fisher 344 Rats submitted as Ref. No. 16): This Initial IND application also includes the New Protocol CLO-221 titled: A Phase II, Open Label Clofarabine, Assigned IND No. 63,641 & Request for Additional Desk Copy of Volume 1 - for Pharmacology/Biopharm Reviewer (Vol. 1 & 2 sent same day)	1-Oct-01
2	FDA Corres.		7-Nov-01
2	63,641		
2	FDA Corres.	Official Acknowledgment Letter from FDA: Receipt of Initial IND for Clofarabine & 30-day Review	14-Nov-01
3	FDA Sub.	Clofarax Orphan Drug Application: Clofarax ALL	
3	63,641	Fax from Christy Wilson/FDA: Deficiencies in the CLO-221 Protocol - Specific Changes Required by FDA - ILEX Must Commit to Correct Deficiencies by Close of Day 12/7/01	14-Nov-01
3	FDA Corres.	Fax from Mike Bernstein/ILEX to Christy Wilson/FDA: ILEX Commitment to Correct Six Deficiencies as Requested by FDA	5-Dec-01
3	FDA Corres.	E-mail from Mike Bernstein/ILEX to Christy Wilson/FDA: ILEX Commitment to Correct Six Deficiencies as Requested by FDA and Actual Protocol Pages with Revisions to Inclusion/Exclusion Criteria	7-Dec-01
3	63,641	Fax from Christy Wilson/FDA: Based on ILEX's Commitment to Correct Deficiencies, the Clinical Study CLO-221 May Proceed (effective date of IND)	7-Dec-01
3	FDA Corres.	Clofarax Orphan Drug Application: Clofarax ALL - Corrected Page	
3	FDA Sub.	Fax from Christy Wilson/FDA: Several Comments from the Chemistry Reviewer Regarding Initial IND for Clofarax	7-Dec-01
3	63,641		10-Dec-01
3	FDA Corres.		
3	63,641	Fax from Christy Wilson/FDA: Additional Toxicology & Genetic Toxicology Studies Must be Done: Pre-clinical Studies that have already been done Do Not Support Further Phase II Development SN: 001 Protocol Amendment: CLO-221-A1 "A Phase II, Open Label Study of Clofarax in Adult Patients with Refractory or Relapsed Acute Myelogenous Leukemia". Several Changes Per FDA's Request & Resulting from Two Expert Panel Meetings (Rationale Listed on Pages 2 - 7 in the Protocol Amendment Summary)	14-Dec-01
3	FDA Corres.		
3	63,641	Official Acknowledgment Letter from FDA: Receipt of Orphan Drug Application for Clofarabine for Pediatric and Adult Patients in ALL, Orphan Drug Ref. No. 01-1532	23-Dec-01
3	FDA Sub.	Fax from FDA: Proposed Revisions to Protocol Acceptable & Addresses All Deficiencies/Comments Issued by Reviewers (based on protocol submitted in Initial IND; revisions submitted to FDA via E-mail on 7 December 2001)	27-Dec-01
3	63,641	SN:002 Revised FDA Form 1571 with correct Medical Monitor (Dr. T Rugg)	2-Jan-02
3	FDA Corres.		
3	FDA Sub.		

BINDER			
3	63,641	FDA Corres.	E-mails between Mike Bernstein/ILEX & Christy Wilson/FDA: Request on Status on Proposed CLO221 Protocol Changes & Reply from FDA
4	63,641	FDA Sub.	SN:003 New Protocols: CLO-212 and CLO-222 (Pediatric ALL and Pediatric AML)
4	63,641	FDA Corres.	From Jeff Fritsch (Orphan Drug Division) to Mike Bernstein: Unofficial E-mail indicating that Orphan Drug Status has been approved for Clofarax.
4	63,641	FDA Corres.	Official Letter from Orphan Drug Division: Orphan Drug Approval for ALL (acute lymphoblastic leukemia)
4	63,641	FDA Corres.	Fax from Christy Wilson/FDA: Final Minutes of Pharmacology/Toxicology Teleconference of 14 January 2002 -
4	63,641	FDA Corres.	Fax from FDA: General Comments from the Clinical Reviewer for Improving the Protocol (original protocol filed in the Initial IND) (9 detailed comments)
4	63,641	FDA Corres.	Official Acknowledgment Letter from FDA: Receipt of Orphan Drug Application for Clofarabine for Pediatric and Adult Patients in AML, Orphan Drug Ref. No. 02-1548
4	63,641	FDA Corres.	Official Comments from FDA Review of Initial IND for Clofarax: Includes Chemistry, Pharm/Tox, & Clinical
4	63,641	FDA Corres.	From Christy Wilson (CSO) to Jenny Swalec: Response to request for Division Feedback from 12-Feb 2002.
4	63,641	FDA Corres.	Fax to Christy Wilson, CSO/FDA: Advice requested as to how to file Fast Track Application
4	63,641	Tel. Contact	From Christy Wilson (CSO) to Jenny Swalec: Response to questions regarding filing for fast-track designation for CLOFAREX.
4	63,641	FDA Corres.	Fax from FDA: Comments and Deficiencies: Pediatric Protocols CLO-212 titled "A Phase 2 Open Label Study of Clofarax in Children with Refractory or Relapsed Acute Lymphoblastic Leukemia" and CLO-222 titled "A Phase 2 Open Label Study of Clofarax in Children with Refractory or Relapsed Acute Myelogenous Leukemia" (submitted to FDA as SN: 003, dated 28 January 2002)
4	63,641	FDA Corres.	Official Letter from Orphan Drug Division: Orphan Drug Approval for AML (acute myelogenous leukemia)
4	63,641	FDA Corres.	Internal Distribution of FDA Comments Regarding Clofarax Pediatric Protocols (CLO-212 & CLO-222) and Copy of Fax to FDA Requesting a Teleconference for Discussing the FDA Comments SN:004 Teleconference scheduled for 21 March 2002 to discuss Division comments on ILEX Pediatric Protocols (CLO-212 and CLO-222): ILEX Questions and Current Protocol Amendments (CLO-212-A1 and CLO-222-A1) Included in this Submission
4	63,641	FDA Corres.	Fax to Christy Wilson, CSO/FDA: Details for Discussion During Teleconference of 21 March 2002 (amendments to pediatric protocols due to FDA comments).
4	63,641	FDA Corres.	Janet Woodcock (FDA) to Mike Bernstein: Reference to IND submitted under section 505(i): Information about the Clinical Trials Data Bank
4	63,641	FDA Corres.	To Christy Wilson From Mike Bernstein: Request for a Type A Meeting to discuss the pediatric clinical development and marketing registration of CLOFAREX.
4	63,641	FDA Corres.	To Dr's Jeha, Kantarjian, and Keating at MDACC from Mike Bernstein: Clinical Trial Material Provided by ILEX: Transfer of IND No. 43, 275 from MDACC to ILEX
4	63,641	FDA Corres.	

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4	63,641	Gen. Corres.	Meeting Minutes, Wednesday, 27 Mar 02: Issue: SAEs	27-Mar-02
5	63,641	FDA Corres.	E-mail/Telephone Contact Report between Jenny Swalec & Christy Wilson: Closing IND No. 43,275 and Transferring Active MD Anderson Protocols to ILEX IND No. 63,641 and Official Notification of Transfer: Submitting Active Protocols to IND No. 63,641	1-Apr-02
5	63,641	FDA Corres.	Phase II Meeting at FDA SN:005 Request for End-of-Phase-II Meeting Package: Includes Questions to the Agency and Protocol Amendments CLO-212-A2 and CLO-222-A2 [both Pediatric Protocol Amendments]: also new Med Monitor Dr. Craig	1-Apr-02
5	63,641	FDA Sub.	SN: 006 General Correspondence: Transfer of Documents from MD Anderson IND No. 43,275 to ILEX IND No. 63,641: Includes Copies of MD Anderson Active Protocols ID99-383, ID00-038 & DM99-225 & SN: 067-the Annual Report for 2001 for IND No. 43,275	2-Apr-02
5	63,641	FDA Sub.	SN: 007 Protocol Amendment- New Investigator: Neil Abramson, Baptist Cancer Institute, Jacksonville, FL (dated 3/25/02) for Adult Study CLO-221	10-Apr-02
5	63,641	FDA Sub.	SN: 008 IND Safety Report Initial Report for Patient No. 001-0017 C-E, MedWatch Report No. 12448, Protocol No. ID99-383 (17 yr old female - prolonged hospitalization - seizure)	12-Apr-02
5	63,641	FDA Sub.	SN: 009 IND Safety Report for Patient No. 001-0017 C-E, MedWatch Report No. 12448, Protocol No. ID99-383 (17 yr old female - prolonged hospitalization - seizure) Additional Information received 15 April 2002	12-Apr-02
5	63,641	FDA Sub.	SN: 010 IND Safety Report Follow Up Report, Report No. 12456, Patient No. 001-0016 D-W (5 year old) on Study ID99-383 "Phase I Study of CL-F-ARA-A (Clofarabine) in Pediatric Patients with Hematologic Malignancies" (no additional follow up expected)	15-Apr-02
5	63,641	FDA Corres.	Official FDA Meeting Minutes from End-of-Phase II Meeting held on 4/29/02	26-Apr-02
5	63,641	FDA Corres.	Official FDA Meeting Minutes from pediatric protocol (CLO-212/CLO-222) telecon held on 21 March 02 (received as a facsimile)	29-Apr-02
5	63,641	FDA Corres.	Official Acknowledgment from FDA: Withdrawal of IND No. 43,275 (all active studies transferred to IND No. 63,641 for Clofarabine per SN: 006 under guidance by FDA)	30-Apr-02
5	63,641	FDA Sub.	SN: 011 ILEX Follow-Up to EOP2 042902 Meeting - Pts ILEX wishes to have on Record	30-Apr-02
5	63,641	FDA Sub.	SN: 012 Protocol Amendment - New Investigator: Stewart Goldman, MD, Children's Memorial Hospital, Chicago, IL (dated 3/22/02) CLO-222 Pediatric AML Study	6-May-02
5	63,641	FDA Sub.	SN: 013 Protocol Amendment - New Investigator: Stewart Goldman, MD, Children's Memorial Hospital, Chicago, IL (dated 3/22/02) CLO-212 Pediatric ALL Study	8-May-02
5	63,641	FDA Sub.	SN: 014 Protocol Amendment - New Investigator: Paul Conkling, MD, Virginia Oncology Associates, Norfolk, VA (dated 4/1/02) CLO-221 Adult AML Study	8-May-02
5	63,641	FDA Sub.	SN: 015 Protocol Amendments CLO-212-A3 and CLO-222-A3 [both Pediatric Protocol Amendments] Change in Protocol	8-May-02
6	63,641	FDA Sub.	SN: 016 Protocol Amendment - New Investigator: Sima Jeha, MD, MD Anderson Cancer Center, Houston, Texas (dated 4/23/02) CLO-222 Pediatrics AML Study	9-May-02
6	63,641	FDA Sub.	SN: 017 Protocol Amendment - New Investigator: Sima Jeha, MD, MD Anderson Cancer Center, Houston, Texas (dated 4/23/02) CLO-212 Pediatrics ALL Study	10-May-02
6	63,641	FDA Sub.	Houston, Texas (dated 4/23/02) CLO-212 Pediatrics ALL Study	10-May-02

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6	63,641	FDA Sub.	SN: 018 Protocol Amendment - New Investigator: James Foran, MD, University of Nebraska Medical Center, Omaha, NE (dated 5/9/02) CLO-221 Adult AML Study	17-May-02
6	63,641	FDA Sub.	SN: 019 Protocol Amendment - Change in Protocol: CLO-221-A2 titled "A Phase II, Open Label Study of Clofarabine in Adult Patients with Refractory or Relapsed Acute Myelogenous Leukemia" (Adult AML)	17-May-02
6	63,641	FDA Sub.	SN: 020 IND Safety Report - Initial Report: Report No. 12531, Patient No. 001-0012 (P-L) (19-yr old) on Study ID99-383 "Phase I Study of CL-F-ARA-A (Clofarabine) in Pediatric Patients with Hematologic Malignancies"	24-May-02
6	63,641	FDA Sub.	SN: 021 Protocol Amendment - New Investigator: Arnold Altman, MD, Connecticut Children's Med Ctr. (dated 5/13/02) CLO-212 Pediatric ALL Study	24-May-02
6	63,641	FDA Sub.	SN: 022 Protocol Amendment - New Investigator: Arnold Altman, MD, Connecticut Children's Med Ctr. (dated 5/13/02) CLO-222 Pediatric AML Study	24-May-02
6	63,641	FDA Sub.	SN: 023 Protocol Amendment - New Investigator: Meir Wetzler, MD, Roswell Park Cancer Center, Buffalo, NY, (dated 3/25/02) CLO-221 Adult AML Study	24-May-02
6	63,641	FDA Sub.	SN: 024 OTHER: Updated Investigator's Brochure (Edition No. 2)	24-May-02
7	63,641	FDA Sub.	SN: 025 New Protocol: CLO-151 titled "A Phase II, Open-Label Study of Clofarabine in Adult Patient	30-May-02
7	63,641	FDA Sub.	SN: 026 IND Safety Reports - Follow Up (2 patients): MedWatch Report No. 12531, Patient No. 001-0012 (P-L) (19-yr old) and Patient No. 001-0017 C-E, MedWatch Report No. 12448, both on study No. ID99-383	3-Jun-02
7	63,641	FDA Sub.	SN: 027 Protocol Amendment - New Investigator Dan Douer, MD, USG/ Norris Comprehensive Cancer Center, Los Angeles, CA (dated 6/4/02)	12-Jun-02
7	63,641	FDA Sub.	Incell Report: Effect of Clofarabine and Gemcitabine on Pancreatic Carcinoma Cells (Report No. IL EX11204, Report Date 14 May 2002)	12-Jun-02
7	63,641	Report	USAN Application: Sent to Sophia Fuerst, Director, USAN Secretariat, American Medical Association, Chicago, IL.	
8	63,641	Gen. Corres.		
9	63,641	FDA Sub.	SN: 028 General Correspondence: Request for Division Feedback on CMC Starting Materials	14-Jun-02
9	63,641	FDA Sub.	SN: 029 Protocol Amendment - New Investigator Victor M. Aquino, UT Southwestern Medical Center, Dallas (dated 5/7/02) CLO-212 Pediatric ALL Study	14-Jun-02
9	63,641	FDA Sub.	SN: 030 Protocol Amendment-New Investigator Michael Miilder Swedish Medical Center Cancer Institute CLO-221 (dated 6/17/02)	17-Jun-02
9	63,641	FDA Sub.	Acknowledgement of the Receipt of the USAN Application (14 June 2002) Requesting the Nonproprietary Name of 'Clofarabine' (& receipt of the check for \$8,000) File No. OO-77 Assigned to the Files for the Application	17-Jun-02
9	63,641	FDA Corres.	SN: 031 Protocol Amendment - New Investigator Victor M. Aquino, UT Southwestern Medical Center, Dallas (dated 5/7/02) CLO-222 Pediatric AML Study	21-Jun-02
9	63,641	FDA Sub.	FDA Phone Contact Memo: CLOFAREX Emergency Use Procedures	24-Jun-02
9	63,641	FDA Corres.	SN: 032 Protocol Amendment - New Investigator: Peter Steinhert, MD., Memorial Sloan Kettering Cancer Center, New York (2 Form FDA 1572s - both dated 3/20/02) CLO-212 & CLO-222 Pediatric Studies	25-Jun-02
9	63,641	FDA Sub.		27-Jun-02

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9	63,641	FDA Sub.	SN: 033 Protocol Amendment - New Investigator: Bassem Razzouk, MD, St. Jude's Children's Research Hospital, Memphis, TN (2 Form FDA 1572s) CLO-222/Peds AML (dated 5/21/02) & CLO-212/Peds ALL (dated 3/26/02) Studies	27-Jun-02
9	63,641	FDA Sub.	SN: 034 Protocol Amendment - New Investigator: David A. Rizzieri, MD, Duke University Medical Center, Durham, ND (dated 3/14/02) CLO-221 Adult AML Study	28-Jun-02
9	63,641	FDA Sub.	SN: 035 IND Safety Report - Initial: MedWatch Report No. 12569, Patient No. 0002-0002 (M-M), Pt CLO-212	1-Jul-02
9	63,641	FDA Sub.	SN: 036 New Protocol (CLO-141) Adult Phase III Combo (CLOFAREX + Ara-C)	3-Jul-02
9	63,641	FDA Sub.	SN: 037 Protocol Amendment - New Investigator: Kathleen M. Sakamoto, MD, Mattel's Children's Hospital at UCLA (dated 4/10/02) CLO-212 Peds ALL Study	3-Jul-02
9	63,641	FDA Sub.	SN: 038 Protocol Amendment - New Investigator: Parameswaran VenuGOPal, MD, Chicago, Ill (dated 6/24/02) CLO-221 Adult AML Study	3-Jul-02
9	63,641	FDA Sub.	Facsimile from <u>Christy Wilson/FDA</u> : Comment from Biopharmaceutics Reviewer - Include with all study reports: complete assay description, assay validation, (sensitivity, specificity, recovery, linearity, %accuracy & precision) and stability data from processing samples, storage & during assay procedures	3-Jul-02
9	63,641	FDA Sub.	SN: 039 Protocol Amendment CLO-221-A3 Adult AML Study	9-Jul-02
9	63,641	FDA Sub.	SN: 040 IND Safety Report - Follow Up: Patient No. 001-0017 C-E, MedWatch Report No. 12448, Study No. ID99-383	12-Jul-02
9	63,641	Report	Argus Research Report: The "Intravenous Dosage-Range Developmental Toxicity Study of Clofarabine in Rabbits" (Study No. 0202-02, Report Date 20 June 2002; Protocol No. 1209-002P)(w/diskette). Submitted to IND as SN:072.	12-Jul-02
9	63,641	Report	Argus Research Report: The "Intravenous Dosage-Range Developmental Toxicity Study of Clofarabine in Rats" (Study No. 0202-01, Report Date 11 June 2002; Protocol No. 1209-001P)(w/diskette). Submitted to IND as SN:072	12-Jul-02
10	63,641	FDA Sub.	SN: 041 IND Safety Report - Initial: Patient No. 001-0021 E-W, MedWatch Report No. 12603, Study No. ID99-383	19-Jul-02
10	63,641	FDA Sub.	SN: 042 IND Safety Report - Initial: Patient No. 0004-0010 L-M, MedWatch Report No. 12606, Study No. CLO-221 (Adult AML Study)	19-Jul-02
10	63,641	FDA Sub.	SN: 043 Protocol Amendments CLO-212-A4 and CLO-222-A4 [both Pediatric Protocol Amendments] Change in Protocol	23-Jul-02
10	63,641	FDA Sub.	SN: 044 Protocol Amendment: New Investigators Charles Casey Cunningham, MD, Mary Crowley Med. Research Ctr, Dallas, TX (dated 6/12/02) and Donald Richards, MD, Tyler Cancer Center, Tyler, Texas (dated 5/19/02(?) CLO-151 Adult Solid Tumor Study	25-Jul-02
10	63,641	FDA Sub.	SN: 045 Protocol Amendment: New Investigator - Susan Rhelngold, MD, The Children's Hospital of Philadelphia, PA (dated 6/13/02) CLO-212 Peds ALL Study & CLO-222 Peds AML Study (dated 6/19/02)	25-Jul-02
10	63,641	FDA Sub.	SN: 046 IND Safety Report - Initial: MedWatch Report No. 12602, Patient No. 0010-0007 D-B, 7-Day Expedited Report (faxed) CLO-221 Adult AML Study	25-Jul-02
10	63,641	FDA Sub.	SN: 047 Protocol Amendment: New Investigator - Edythe Albano, MD... The Children's Hospital CLO-222 Peds AML Study and CLO-212 Peds ALL Study	31-Jul-02

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10	63,641	FDA Sub.	SN: 048 Protocol Amendment: New Investigator Paul S. Gaynon, MD, Children's Hospital Los Angeles, Los Angeles, CA (both 1572s dated 7/23/02) CLO-222 Peds AML Study and CLO-212 Peds ALL Study	7-Aug-02
10	63,641	FDA Sub.	SN: 049 Protocol Amendment: New Investigators: Staten H. Faderl, MD, MD Anderson Cancer Center, Houston, TX (dated 7/15/02) CLO-221 Adult AML Study and Donald K. Strickland, MD, The Memphis Cancer Center, Memphis, TN (dated 8/6/02) CLO-221 Adult AML Study SN: 050 Informational Amendment: Pharru Fox Submission of Final Toxicology Study Reports (ILEX Report Nos. 0110-02 and 0111-01, BioReliance Report Nos. AA53PR.503.BTL, AA53PR.331.BTL, AA53PR.125.BTL) E-mail: Response to Jenny Swalec's E-mails of 23 July & 13 Aug: Status on SN: 028 Request for Feedback - CMC	8-Aug-02
10	63,641	FDA Sub.	SN: 051 IND Safety Report - Initial Report: MedWatch Report No. 12621, Patient No. 0006-0009 J.S., 7-day Expedited Report* (*not considered 7-day upon original receipt of reported event- 7-day decision made on 15 August 2002) CLO-221 Adult AML Study	9-Aug-02
10	63,641	FDA Sub.	SN: 052 Protocol Amendment - New Investigator: Blanche Mavromatis, MD., Georgetown University Medical Center, Washington, D.C. (dated 5/6/02) CLO-221 Adult AML Study	15-Aug-02
10	63,641	FDA Sub.	SN: 053 Protocol Amendment - New Investigator: Richard P. Kadota, MD., Children's Hospital & Health Center, San Diego, CA, (dated 5/8/02) for Study CLO-212 Peds ALL and (dated 8/20/02) for Study CLO-222 Peds AML	16-Aug-02
10	63,641	FDA Sub.	SN: 054 Protocol Amendment - New Investigator: John F. Dipersio, MD., Ph.D., Washington University School of Medicine, St. Louis, MO (dated 8/11/02) for CLO-221 Adult AML Study	19-Aug-02
10	63,641	FDA Sub.	SN: 055 Protocol Amendment - New Investigator: Kimo C. Stine, MD., Arkansas Children's Hospital, Little Rock, AR (dated 8/13/02) for CLO-222 Peds AML Study	22-Aug-02
10	63,641	FDA Sub.	SN: 056 IND Safety Report-Initial Report MedWatch Report No. 12656, Patient No. 0013-0013 S-B, 15-day expedited report, for CLO-221 Adult AML Study Official Letter from FDA: Theresa Toigo, RPH, MBA, Director, Office of Special Health Issues, Office of Communications and Consultant Relations, Office of Commissioner (New PRS/Clinical Trials Database Administrator): Reference SN: 036, dated 7/3/02: New Protocol (CLO141): Review for Need to Enter New Protocol into New Clinical Trials Database per new Guidelines "Clinical Trials for Serious or Life-Threatening Diseases"	22-Aug-02
10	63,641	FDA Sub.	SN: 057 IND Safety Report - Follow Up MedWatch Report No. 12602, Patient No. 0010-0007 D-B (Initial report submitted as SN: 046) CLO-221 Adult AML Study	23-Aug-02
10	63,641	FDA Sub.	SN: 058 Protocol Amendment - New Investigator: Lori Luchtmann-Jones, MD, Washington University School of Medicine, St. Louis, MO (2 separate 1572s dated 7/31/02) for two studies CLO-222 & CLO-212	27-Aug-02
10	63,641	FDA Sub.	Telephone Contact Report: Discussion on CLOFAREX Ped Exclusivity, Timing of NDA Submission, etc.	27-Aug-02

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10	63,641	FDA Sub.	SN: 059 Protocol Amendment - New Investigator: Timothy C. Griffin, MD, Cook Children's Hematology/Oncology Center, Fort Worth, TX, (dated 6/28/02) for CLO-212 Peds ALL Study & (dated 6/27/02) for CLO-222 Peds AML Study	28-Aug-02
11	63,641	FDA Sub.	SN: 060 IND Safety Report-Follow Up MedWatch Report No. 12569, Patient No. 0002-0002 M-M (Initial report submitted as SN: 035) CLO-212 Ped ALL Study	
11	63,641	FDA Sub.	SN: 061 IND Safety Report-Follow Up MedWatch Report No. 12606, Patient No. 0004-0010 L-M (Initial report submitted as SN: 042) CLO-221 Adult AML Study	4-Sep-02
11	63,641	FDA Sub.	SN: 062 Protocol Amendment - New Investigator Stefan H. Faderl, M.D., MD Anderson Cancer Center, Houston, TX (dated 7/31/02) CLO-141 In Combination with Ara-C Study	9-Sep-02
11	63,641	FDA Sub.	SN: 063 General Correspondence: Notification to Investigator's from Dr. Adam Craig (renal toxicity)	9-Sep-02
11	63,641	FDA Sub.	SN: 064 IND Safety Report - Follow Up Report: MedWatch Report No. 12656, Patient No. 0013-0013 S-B (Initial report submitted as SN: 056 on 23 August 2002) CLO-221 Adult AML Study	12-Sep-02
11	63,641	FDA Sub.	SN: 065 IND Safety Report-Follow Up MedWatch Report No. 12621, Patient No. 0005-0009 J-S (Initial report submitted as SN: 051) CLO-221 Adult AML Study	17-Sep-02
11	63,641	FDA Sub.	Official Letter from Bioenvision Confirming Tassman Technology Limited as the Agent for Orphan Drug Designation in the Europe and the CTX & Clinical Trials in the UK	17-Sep-02
11	63,641	FDA Sub.	SN: 066 Protocol Amendment - New Investigators: Arthur Kim Ritchey, MD, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania (dated 8/22/02); and Violet Shen, MD, Children's Hospital of Orange County, Orange, California (dated 8/6/02) CLO-222 Pediatric AML Study	20-Sep-02
11	63,641	FDA Sub.	SN: 067 Protocol Amendment - New Investigators: Susan Blaney, MD, Texas Children's Hospital, Houston, Texas (dated 9/12/02); Violet Shen, MD, Children's Hospital of Orange County, Orange, California (dated 8/6/02) and Arthur Kim Ritchey, MD, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania (dated 8/22/02) for CLO-212 Pediatric ALL Study	20-Sep-02
11	63,641	FDA Sub.	Fax from Christy Wilson/FDA: Request for a Reply to 3 Questions Regarding SN: 028 Proposed Starting Materials, drug substance, qualifying vendors for starting materials, & confirmation that commercial sources (Chen YI Pharma Co., Sumica & Ash Stevens) are not performing custom synthesis of proposed starting materials	
11	63,641	FDA Sub.	Response from USAN Council/Stephanie C. Shubat, Associate Secretary, USAN Council: Clofarabine is not an acceptable name with Clofarax - need to submit alternate name	3-Oct-02
11	63,641	FDA Sub.	SN: 068 Protocol Amendment - New Investigator: Susan Blaney, M.D., Texas Children's Hospital, Houston, TX (dated 9/12/02) for CLO-222 Peds AML Study	3-Oct-02
11	63,641	FDA Sub.	SN: 069 IND Safety Report - 2nd Follow Up: MedWatch Report No. 12602, Patient No. 0010-0007 D-B, Additional Information Received 7 Oct 2002 - CLO-221 Adult AML Study	9-Oct-02
11	63,641	Tel. Contact Rep.	Email from Mike Bernstein/LEX to Christy Wilson/FDA: Question Regarding Interim Analysis and Approval to Proceed if 4 CRs are Not Document as Per Protocol CLO-221 (Adult AML Study)	11-Oct-02

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11	63,641	FDA Sub.	SN: 070 Protocol Amendment - New Investigators: Richard K. Shaddock, MD, The Western Pennsylvania Cancer Institute, Pittsburgh, PA (dated 8/5/02) and Clive Zent, MD, University of Arkansas for Medical Sciences, Little Rock, AR (dated 6/18/02) for CLO-221 Adult AML Study	15-Oct-02
11	63,641	FDA Sub.	SN: 071 Protocol Amendment - New Investigator: Kimo C. Stine, MD, Arkansas Children's Hospital, Little Rock, AR (dated 8/13/02) for CLO-212 Peds ALL Study	15-Oct-02
11	63,641	Gen. Corres.	Official Notification from EMEA that the Orphan Drug Sponsorship has been transferred to Bioenvision for clofarabine in the indication of ALL (copy of letter sent to Heather Barker in UK)	15-Oct-02
11	63,641	Tel. Contact Rep.	Additional info. to follow from the European Commission on Acceptance of Transfer E-mail: Reply from Dotti Pease (for Christy Wilson) FDA to Mike Bernstein ILEX: Dr. Hirschfeld Agreed with Study CLO-221 (Adult AML) Proceeding if Interim Analysis Doesn't Show 4 CRs (ILEX to follow up with protocol amendment)	22-Oct-02
12	63,641	FDA Sub.	SN: 072 Information Amendment: Pharm/Tox Submission of Final Toxicology Study Reports (MicroConstant's Report Nos. MC02113, MC02114; Argus Report No. 1209-001P (ILEX Report No. 0202-01); Argus Report No. 1209-002P (ILEX Report No. 0202-02))	22-Oct-02
13	63,641	FDA Sub.	SN: 073 IND Safety Report - Initial: MedWatch Report No. 12741, Patient No. 001-0062 D-L Study ID00-038 (Phase II Acute Leukemia & MDS in Relapse - MD Andersen Study)	22-Oct-02
13	63,641	FDA Sub.	SN: 074 IND Safety Report-Follow Up Report MedWatch Report No. 12656, Patient No. 0013-0013 S B, (additional details of hospitalization & death), for CLO-221 Adult AML Study	23-Oct-02
13	63,641	FDA Sub.	SN: 075 Protocol Amendment: CLO-141-A1 A Phase I/II Study of Clofarabine in Combination with Cytarabine (Ara-C) in Adult Patients in First Relapse of AML or ALL; with High-Risk MDS; or with CML Blast Phase as Front Line Therapy or In First Salvage	23-Oct-02
13	63,641	FDA Sub.	SN: 076 Revised Form FDA 1572s: Kimo C. Stine, MD, Arkansas Children's Hospital, Little Rock (dated 10/15/02) and Susan Blaney, MD, Texas Children's Hospital, Houston, TX (dated 10/3/02) for CLO-212 Peds ALL Study	23-Oct-02
13	63,641	FDA Sub.	SN: 077 Protocol Amendment - New Investigator: Dr. Stephen Johnson, Taunton and Somerset Hospital, Taunton, Somerset (dated 9/13/02) for Study CLO-221 Adult AML Study	25-Oct-02
13	63,641	FDA Sub.	SN: 078 Revised Form FDA 1572: Kimo C. Stine, MD, Arkansas Children's Hospital, Little Rock (dated 10/15/02) for CLO-222 Peds AML Study	25-Oct-02
13	63,641	FDA Sub.	SN: 079 Protocol Amendment - Change in Protocol: CLO-221-A4 Adult AML Study (extending study; no stopping at Interim Analysis)	28-Oct-02
13	63,641	FDA Corres.	Official request (E-mail from Mike Bernstein) to USAN Council (Stephanie Schubat, Assoc. Secretary) to keep Clofarabine - not Clofarabine - after USAN denial for ILEX to use both: see additional correspondence & approval of the name Clofarabine: 3 Oct. 2002, 13 Dec. 2002, 27 Dec. 2002, 29 May 2003 & 23 June 2003	28-Oct-02
13	63,641	FDA Sub.	SN: 080 Revised Form FDA 1562s: Richard P. Kadota, MD, Children's Hospital and Health Center, San Diego, CA (each one dated 10/17/02) for CLO-212 Peds ALL & CLO-222 for Peds AML	1-Nov-02
13	63,641	FDA Sub.	SN: 081 Revised Form FDA 1572: Neil Abramson, MD, Baptist Cancer Institute, Jacksonville, FL, 32207 (dated 8/27/02) CLO-221 Adult AML Study	1-Nov-02

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13	63,641	FDA Sub.	SN: 082 IND Safety Report - Initial Report: MedWatch Report No. 12724, Patient No. 0012-0017 J-K (Expedited 15-Day Report - determined on 1 November 2002) SN: 083 Protocol Amendment - New Investigator: Bruce Gordon, M.D., Pediatric Hematology/Oncology & Bone Marrow Transplantation Program, University of Nebraska Medical Center, 982168 Nebraska Medical Center, Omaha, NE, 68198-2168 (dated 9/30/02) for CLO-222 Adult AML Study and (dated 10/7/02) for CLO-212 Adult ALL Study SN: 084 Informational Amendment: CMC (List New API and DP Manufacturers and also provides UV Data) SN: 085 Revised Form FDA 1572s: James Foran, MD, Univ. of Nebraska Medical Center, Omaha, NE (dated 10/23/02) for CLO-221 Adult AML Study	4-Nov-02
13	63,641	FDA Sub.	SN: 086 Revised Form FDA 1572s: Peter Steinhilber, MD, Memorial Sloan Kettering Cancer Center, New York, NY (both dated 10/17/02) for CLO-212 Peds ALL Study and CLO-222 Peds AML Study SN: 087 Response to FDA Request for Information: Sponsor Response to FDA Request for Additional Information RE: CMC Starting Materials	13-Nov-02
13	63,641	FDA Sub.	SN: 088 Revised Form FDA 1572s: Bassam Razzouk, M.D., St. Jude's Children's Hospital, Memphis, TN (both dated 11/14/02) for CLO-212 Peds ALL Study & CLO-222 Peds AML Study SN: 089 Protocol Amendment: CLO-221A4 Site Specific Addendum (Dr. Wetzel's site to do additional PK sampling) SN: 090 Revised Form FDA 1572s: Dan Douer, M.D., USC/Norris Comprehensive Cancer Center, Los Angeles, CA (dated 7/1/02 and dated 10/23/02) for CLO-221 Adult AML Study SN: 091 Protocol Amendment - New Investigator: Dr. Ann Hunter, Leicester Royal Infirmary, Leicester CLO-221 Adult AML Study (dated 11/09/02) see entry of 16 January 2003: site specific addendum never activated SN: 092 Protocol Amendment - New Investigator: Dr. Michael Potter, Royal Free Hospital, Hampstead, London CLO-221 Adult AML Study (dated 10/22/02) SN: 093 IND Safety Report Follow Up: MedWatch Report No. 12724, Patient No. 0012-0017 J-K (Including details on patient's death) SN: 094 IND Safety Report Follow Up: MedWatch Report No. 12606, Patient No. 0004-0010 L-AM, CLO-221 Adult AML Study (Second Follow Up - Including patients death) Facsimile from Christy Wilson/FDA: Comment from Biopharmaceutics Reviewer - Validate Assay Method prior to use in Trials; PK Sampling is Insufficient - Increase Sampling Points for Characterizing the Disposition of Clofarabine; Need to Conduct In Vitro Cytochrome P450 Screens w/Human Liver Microsomes; Characterize Metabolic Activity & Elimination Pathways SN: 095 Revised Form FDA 1572s: James Foran, MD, (dated 11/4/02) and Neil Abramson, MD (dated 11/7/02) for CLO-221 Adult AML Study	21-Nov-02
13	63,641	FDA Sub.	SN: 096 IND Safety Report - Follow Up Report, MedWatch Report No. 12741, Patient No. 001-0062 D-L on Study ID00-038 "change in causality from drug related to disease related per PI Official Notification from USAN Council: Acceptance of the Name Clofarabine; Request for Check (\$3,000) to the World Health Organization (WHO)	4-Dec-02
13	63,641	FDA Sub.		4-Dec-02
13	63,641	FDA Sub.		13-Dec-02

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13	63,641	FDA Sub.	SN: 097 Protocol Amendment - New Investigator (Replacement PI for Dr. Foran): Stefano Tarantolo, M.D., Univ. of Nebraska Medical Center, Omaha, Nebraska (dated 12/2/02) CLO-221 Adult AML Study	17-Dec-02
13	63,641	FDA Sub.	SN: 098 2002 Annual Report: Report Period Covering 07 Dec 2001 through 01 Nov 2002	18-Dec-02
13	63,641	FDA Corres.	Fax from FDA: Submission No. 089 dated 21 November 2002 - Site Specific Protocol Addendum for PK Sampling - Please Clarify the Dosing vs. Sampling Times as Listed in Chart of Addendum Check for \$3,000 to WHO. Letter sent to American Medical Assoc. for the USAN Council for Processing the Name Clofarabine	24-Dec-02
13	63,641	FDA Sub.	SN: 099 Response to Fax from FDA Biopharmaceutics Reviewer: Clarification of Dosing (X 5 every 28 days) and Table in Site Specific Protocol Addendum for PK & Urine Sampling (Submission SN: 089)	27-Dec-02
13	63,641	FDA Sub.	SN: 100 Revised Form FDA 1572s: John F. Dipersio, M.D., Washington Univ. School of Med., St. Louis, MO, (dated 12/19/02) CLO-221 Adult AML Study	31-Dec-02
13	63,641	FDA Sub.	SN: 101 Protocol Amendment: CLO-141-A2 A Phase III Study of CLOFARABINE in Combination with Cytarabine (Ara-C) in Adult Patients in First Relapse or First Salvage or Primary Refractory AML or ALL (maximum of 2 induction courses); with High-Risk MDS; or with CML Blast Phase as Front Line Therapy or in First Salvage	31-Dec-02
14	63,641	FDA Sub.	SN: 102 Revised Form FDA 1572s: Blanche Mavromatis, MD Lombardi Cancer Center, Washington, DC (dated 12/29/02); and Stefano Tarantolo, MD, Univ. of Nebraska Medical Center, Omaha, Nebraska - 2 qty 1572s (dated 12/6/02 and 1/8/03) for CLO-221 Adult AML Study	6-Jan-03
14	63,641	FDA Sub.	Letter to Meir Wetzler, MD: Withdrawal of Special Addendum to CLO-221 Adult AML Study	13-Jan-03
14	63,641	Gen. Corres.	addendum submitted to FDA as SN: 089 dated 21 November 2002 Never Activated	16-Jan-03
14	63,641	FDA Sub.	SN: 103 Protocol Amendment: CLO-141-A3 A Phase III Study of Clofarabine in Combination with Cytarabine (Ara-C) in Adult Patients in First Relapse or First Salvage of Primary Refractory AML or ALL (maximum of 2 induction courses); with High-Risk MDS; or with CML Blast Phase as Front Line Therapy or in First Salvage	20-Jan-03
14	63,641	FDA Sub.	SN: 104 Revised Form FDA 1572s: David Rizzieri, MD, Duke University Medical Center, Durham, NC (dated 8/28/02); Michael Milder, MD, Swedish Medical Center - Cancer Institute, Seattle, WA (dated 9/3/02) and Meir Wetzler, MD, Roswell Park Cancer Institute, Buffalo, NY (dated 1/3/03) all for CLO 221 Study	20-Jan-03
14	63,641	FDA Sub.	SN: 105 Revised Form FDA 1572: Stefan Faderl, MD, MD Anderson Cancer Center, Houston, TX (dated 1/2/03) CLO-141 Study	20-Jan-03
14	63,641	FDA Sub.	SN: 106 Revised Form FDA 1572s: Edythe Albano, M.D., The Children's Hospital, Denver, CO (dated 1/8/03); Silma S Jeha, M.D., MD Anderson Cancer Center, Houston, Texas (dated 1/8/03); Paul S. Gaynon, M.D., Children's Hospital Los Angeles, Los Angeles, CA (dated 11/6/02); Stewart Goldman, M.D., Children's Memorial Hospital, Chicago, Ill. (dated 4/29/02) all for CLO-212 Peds ALL Study	24-Jan-03

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14	63,641	FDA Sub.	SN: 107 Revised Form FDA 1572s: <u>Edythe Albano, M.D., The Children's Hospital, Denver, CO</u> (dated 1/8/03); <u>Sima S Jeha, M.D., MD Anderson Cancer Center, Houston, Texas</u> (dated 1/8/03); <u>Paul S. Gaynon, M.D., Children's Hospital Los Angeles, Los Angeles, CA</u> (dated 1/6/02); <u>Stewart Goldman, M.D., Children's Memorial Hospital, Chicago, Ill.</u> (dated 4/29/02) all for CLO-222 Peds AML Study	24-Jan-03
14	63,641	FDA Sub.	SN: 108 Revised Form FDA 1572: <u>Stefano Tarantolo, M.D., Univ of Nebraska Medical Center, Omaha, Nebraska</u> (dated 1/17/03) for CLO-221 Adult AML Study	24-Jan-03
14	63,641	FDA Corres.	Official Notification from <u>Michael A. Chappell, District Director/FDA Dallas</u> : Results of GLP Audit Conducted by <u>Iris C. Macines</u> during 9/16/02 through 9/20/02 - Establishment Inspection Report (EIR) (FEI 3003288351)	24-Jan-03
14	63,641	FDA Sub.	SN: 109 IND Safety Report - Initial Report: <u>MedWatch Report No. 12869, Patient No. 0007-0018 (CLO-212 ALL Study)</u>	29-Jan-03
14	63,641	FDA Sub.	SN: 110 IND Safety Report - Initial Report: <u>MedWatch No. 12893, Patient no. 0005-0039 (RLN) (CLO-221 Adult AML Study)</u>	31-Jan-03
14	63,641	FDA Sub.	SN: 111 Revised Form FDA 1572s: <u>Stefano Tarantolo, MD, Univ. of Nebraska Medical Center, Omaha, NE</u> (dated 1/27/03) and <u>Neil Abramson, MD, Baptist Cancer Institute, Jacksonville, FL</u> (dated 1/23/02) for CLO-221 Adult AML Study	4-Feb-03
14	63,641	FDA Corres.	Facsimile for FDA - Biopharmaceutics Reviewer: Sampling Timepoints for the Site Specific Protocol Addendum submitted as Serial No. 089; and Request for Validation Assay (note* the site specific protocol addendum was never implemented - E-mail filed with fax as explanation)	4-Feb-03
15	63,641	FDA Sub.	SN: 112 Information Amendment - <u>Pharmacology/Toxicology</u> : Report No. MC02017 (MicroConstants, Inc., Report Date 17 December 2002) Report No. MC02298 (MicroConstants, Inc., Report Date 17 December 2002); and SLI Study No. 3569.3 (ILEX 0204-05)(Springborn Labs, Report Date 13 January 2003)	5-Feb-03
15	63,641	Report	SLI Study No. 3569.3 "Three Week Oral and Intravenous Dose Bridging Toxicity Study of Clofarabine in Fischer 344 Rats" (Springborn Labs, Report Date 13 January 2003) (ILEX No. 0204-05) Submitted to IND in SN: 112	5-Feb-03
16	63,641	FDA Corres.	Official Acknowledgment of Receipt of \$3,000 Check payable to WHO for Processing the Name 'Clofarabine'	5-Feb-03
16	63,641	FDA Sub.	SN: 113 Response to FDA Request for Information: Sponsor's Response to FDA's 04 February 2003 Facsimile RE: SN:089 Dated 21 November 2002	13-Feb-03
16	63,641	FDA Sub.	SN: 114 Revised Form FDA 1572s: <u>Lori Luchtmann-Jones, M.D., Washington Univ. School of Medicine, St. Louis, MO</u> (dated 1/28/03); <u>Susan Blaney, M.D., Texas Children's Hospital, Houston, Texas</u> (dated 1/09/03) both for CLO-212 Peds ALL Study	14-Feb-03
16	63,641	Gen. Corres.	GLP Inspection Report: Multiple Studies, GLP Inspection of 16 Sept - 20 Sept 2002: Follow Up Visit to 27 July 2002	19-Feb-03
16	63,641	FDA Sub.	SN: 115 Type A Meeting Request and Background Package (Clinical Oral Program)	28-Feb-03
16	63,641	FDA Sub.	SN: 116 Information Amendment - Pharmacology/Toxicology: Argus Report No. 1209-001 (ILEX No. 0204-01), Argus Report No. 1209-002 (ILEX Report No. 0204-02) and MicroConstants Report No. MC02299	28-Feb-03

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16	63,641	Report	Argus Research Report No. 1209-001 (ILEX Report No. 0204-01) titled "Intravenous Developmental Toxicity of Clofarabine in Rats" (report Date 20 December 2002) Submitted to FDA in Serial No. 116 on 28 Feb 2003
16	63,641	Report	Argus Research Report No. 1209-002 (ILEX Report No. 0204-02) titled "Intravenous Developmental Toxicity of Clofarabine in Rabbits" (report Date 18 December 2002) Submitted to FDA in Serial No. 116 on 28 Feb 2003
17	63,641	FDA Sub.	SN: 117 IND Safety Report - Second Follow Up: MedWatch No. 12724, Patient No. 0012-0017 (JK) CLO-221 Adult AML Study
17	63,641	FDA Sub.	SN: 118 IND Safety Report - Follow Up: MedWatch No. 12869, Patient No. 0007-0018 (CMR) CLO-212 Peds ALL Study
17	63,641	FDA Sub.	Official Notification of Formal Written Request for Pediatric Exclusivity (refer to FDA correspondence of 27 August 2002)
17	63,641	FDA Sub.	SN: 119 Revised Form FDA 1572s: Susan Rhelngold, M.D., The Children's Hospital of Philadelphia, Philadelphia, PA (2 qty 1572s, each dated 2/4/03) for Studies CLO-212 Peds ALL and CLO-222 Peds AML+
17	-	FDA Sub.	Orphan Drug Application No. 02-1548 (AML): Annual Progress Report
17	-	FDA Sub.	Orphan Drug Application No. 01-1532 (ALL): Annual Progress Report
17	63,641	FDA Sub.	Facsimile from FDA: Response to SN: 115 Type A Meeting Request (Oral Formulation) - Several Comments Regarding Oral Formulation Package
17	63,641	FDA Sub.	SN: 121 IND Safety Report - Initial Report: MedWatch No. 12777, Patient No. 0005-0025 (DHE) CLO-221 Adult AML Study
17	63,641	FDA Sub.	SN: 122 IND Safety Report - Initial Report: MedWatch No. 12941, Patient No. 0001-0010 (AMO) CLO-141 Combo w/Ara-C Study
17	63,641	FDA Sub.	SN: 123 Cross-Reference Authorization Ltr (Kantarjian/Faderl)
17	63,641	Tel. Contact Rep.	Telephone Contact Between Christy Cottrell/GSO & Jenny Swalec: Non-ILEX Sponsored Clinical Trials (Not Treatment Use - Process for ISTs Investigator Sponsored Trials)
17	63,641	FDA Sub.	SN: 124 Revised Form FDA 1572s - Multiple Investigators, Multiple Protocols: Dan Douer, MD, USC/Norris Comprehensive Cancer Center, Los Angeles, CA (dated 2/27/03) for CLO-221 Adult AML Study; P. Vennugopal, MD, Chicago, Ill (dated 1/17/03) for CLO-221 Adult AML Study; Richard Kadota, MD, Children's Hospital and Health Center, San Diego, CA (dated 10/30/02 and 2nd Form 1572 dated 1/17/03) for CLO-212 Peds ALL Study; Susan Blaney, MD, Texas Children's Hospital, Houston, TX (dated 1/17/03) CLO-222 Peds AML Study
17	63,641	FDA Sub.	SN: 125 Information Amendment - Pharmacology/Toxicology Reports: Report Nos. QKAN-2002-0542-BIO, QKAN-2002-0705-ADM, QKAN-2002-0642-BIO, and QKAN-2002-0763-ADM (original reports filed separately)
17	63,641	FDA Sub.	SN: 126 Protocol Amendment - Change in Protocol: CLO-141-AA "A Phase III Study of Clofarabine in Combination with Cytarabine (Ara-C) in Adult Patients in First Relapse or First Salvage Therapy or Primary Refractory AML or ALL (maximum of two induction courses); with High Risk MDS; or with CML Blast Phase as Front Line Therapy or in First Salvage"

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17	63,641	FDA Sub.	<p>SN: 127 Revised Form FDA 1572s: A. Kim Ritchey, M.D., Pittsburgh, PA (dated 2/21/03) for CLO-212 Study; and Stewart Goldman, M.D., Chicago, ILL (2/ each dated 2/19/02) for CLO-212 & CLO-222 Studies</p>	30-Apr-03
17	63,641	Report	<p>Southern Research Institute (SRI): Results from Clofarabine + Camptosar Efficacy Study: ILEX-25</p>	
18	63,641	FDA Sub.	<p>SN: 120 Information Amendment - Clinical: Final Clinical Study Report for DM93-036 (Volume 1 of 5)</p>	18-Mar-03
19	63,641	Report	<p>SN: 120 Information Amendment - Clinical: Final Clinical Study Report for DM93-036 (Volume 2 of 5)</p>	18-Mar-03
20	63,641	FDA Sub.	<p>SN: 120 Information Amendment - Clinical: Final Clinical Study Report for DM93-036 (Volume 3 of 5)</p>	18-Mar-03
21	63,641	FDA Sub.	<p>SN: 120 Information Amendment - Clinical: Final Clinical Study Report for DM93-036 (Volume 4 & 5 of 5)</p>	18-Mar-03
22	63,641	Tel. Contact Rep.	<p>Telephone Contact Report Between Christy Cottrell/CSO, Mike Bernstein & Jenny Swalec: ILEX called to check the status on the Agency's response to an ILEX facsimile (dated 4/3/03): The Agency's Responses Included: Cross-Reference of Reports Already Submitted is Acceptable for Oral IND Application; Address for Submitting Oral Formulation IND Application and Still Waiting on Agency's Response to Stability Data (developmental or clinical trial material)</p>	1-May-03
22	63,641	Tel. Contact Rep.	<p>Telephone Contact Report Between Christy Cottrell/CSO, Mike Bernstein & Jenny Swalec: Discussion on Timing of NDA Submission for Pediatric ALL, Request/Application for Fast-Track Designation for Pediatric ALL, Pre-NDA Mtg Pkg (submission) & Rolling NDA Submission</p>	1-May-03
22	63,641	FDA Sub.	<p>Pharm/Tox Report QKAN-2002-0783-ADM Original Film Pages of Pictures to Replace Poor Quality Copies in Original Submission</p>	1-May-03
22	63,641	FDA Sub.	<p>SN: 128 Protocol Amendments: Change in Protocols: CLO-212-A5 (Peds ALL) and CLO-222-A5 (Peds AML) Amendments</p>	2-May-03
22	63,641	FDA Sub.	<p>Facsimile from Christy Cottrell/CSO: Response to ILEX's questions - clarification of specific comments regarding the Type A meeting request- prep for Oral Formulation Initial IND</p>	5-May-03
22	63,641	FDA Sub.	<p>See SN: 129 Fast Track Application - Binder 23</p>	8-May-03
22	63,641	FDA Sub.	<p>SN: 130 IND Safety Report - Follow Up Report: MedWatch Report No. 12947, Patient No. 0001-0010 (AMO) for Study CLO-141 (Combo with Ara-C); Initial Report was Submitted as SN: 122 on 28 March 2003</p>	9-May-03
22	63,641	FDA Sub.	<p>SN: 131 IND Safety Report - Follow Up Report: MedWatch Report No. 12893, Patient No. 0005-0039 (RLN) for Study CLO-221, Adult AML Study; Initial Report was Submitted as SN: 110 on 31 Jan 2003</p>	9-May-03
22	63,641	FDA Sub.	<p>Official Acknowledgment of Receipt of Fast Track Application for Pediatric ALL - FDA will Respond within 60 Days</p>	13-May-03

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22	63,641	FDA Sub.	SN: 132 Revised Form FDA 1572s: Arnold Altman, MD, Connecticut Children's Medical Center, Hartford, CT (2 qty - each dated 2/13/03: 1 for CLO-212 Peds ALL Study, one for Peds AML CLO-222 Study; Stefano Taranolo, MD, University of Nebraska Medical Center, Omaha, NE (dated 5/7/03) for the Adult AML CLO-221 Study; and Michael Milder, MD, Swedish Medical Center, Seattle, Washington (dated 3/25/03) for the CLO-221 Adult AML Study Facsimile from Oncology Division/FDA: Meeting Minutes from Type A Meeting - Written Response in Lieu of Face-To-Face Meeting; Includes Addendum to Initial Minutes/Response - Response to ILEX's Request (via Facsimile of 3 April 2003) for Clarification (Oral Indication Needs Separate IND)	14-May-03
22	63,641	FDA Sub.	SN: 133 ILEX's Proposed Changes to Written Request (Dated 07 Mar 03) Issued by FDA	21-May-03
22	63,641	FDA Sub.	SN: 134 Revised Form FDA 1572s: Charles Casey Cunningham, MD, Mary Crowley Medical Research Center, Dallas, Texas (dated 4/24/03) and Donald A. Richards, MD, Tyler Cancer Center, Official Notification from American Medical Association/USAN Council: Clofarabine Adopted (Approved) as the USAN Name	23-May-03
22	63,641	FDA Sub.	Facsimile from Christy Cottrell/FDA: Comments from Chemistry Reviewer Regarding Serial No. 087 of 15 November 2002 and Submission of 7 May 2003: Proposal for Drug Substance Starting	27-May-03
22	63,641	FDA Sub.	SN: 136 Request for Pre-NDA Meeting for Clofarabine in Acute Lymphoblastic Leukemia (ALL); Proposed date of Meeting - First Week in August	28-May-03
22	63,641	FDA Sub.	SN: 137 IND Safety Report - Initial Report: MedWatch Report No. 13026, Patient No. 0010-0022 (D-M), CLO-222 Peds AML Study	29-May-03
22	63,641	FDA Sub.	Facsimile from Christy Cottrell/FDA: Confirmation of Pre-NDA, Scheduled for 13 August 2003 and List of Attendees	3-Jun-03
22	63,641	FDA Sub.	SN: 138 IND Safety Report - Initial Report: MedWatch No. 12777, Patient No. 0005-0025 (DHE) CLO-221 Adult AML Study	10-Jun-03
22	63,641	FDA Sub.	Official E-mail from Mike Bernstein to Christy Cottrell/FDA: Corrections to Serial No. 129 (Fast Track Application, 8 May 2003) Response Definition and Primary/Secondary Objectives	11-Jun-03
22	63,641	FDA Sub.	Response to American Medical Association/USAN Council: Clofarabine Adopted (Approved) as the USAN Name - Changes to the Chemical Name	16-Jun-03
22	63,641	FDA Sub.	SN: 141 Protocol Amendment: Revised Form FDA 1572 - Timothy Griffin, M.D., Cook Children's Hematology/Oncology Ctr (dated 3/31/03) CLO-212 & CLO-222 Studies	20-Jun-03
22	63,641	FDA Sub.	SN: 142 Protocol Amendment: Paul Conkling, M.D., Virginia Oncology Assoc., Mid-Atlantic Consultants, Norfolk, VA (dated 5/19/03) CLO-221 Study	23-Jun-03
22	63,641	FDA Sub.	SN: 129 Request for Fast Track Designation and NDA Rolling Submission Strategy (ALL Indication)	30-Jun-03
24 A	63,641	Report	Bioreliance Report: Bacterial Reverse Mutation Assay (Report No. CLO.00.07.02, Report Date 3 April 2002) Submitted to IND as SN:050	8-May-03
24 A	63,641	Report	Bioreliance Report: In Vitro Mammalian Chromosome Aberration Test (Report No. CLO.00.07.03, Report Date 27 March 2002) Submitted to IND as SN:050	

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24 A	63,641	Report	Report No. QKAN-2002-0542-BIO titled "In Vitro Metabolism of Clotfarabine in Rat, Dog, and Human Cryopreserved Hepatocytes" by Quintilles, Kansas City dated 1 October 2002 (submitted in Serial No. 125 on 10 Apr 03)
24 A	63,641	Report	Report No. QKAN-2002-0705-ADM titled "Radiokinetic and 14C Excretion/Mass Balance Study of 14C-Clotfarabine in Fischer 344 Rats" by Quintilles, Kansas City dated 30 January 2003 (submitted in Serial No. 125 on 10 Apr 03)
24 A	63,641	Report	Report No. QKAN-2002-0642-BIO titled "In Vivo Metabolism of Clotfarabine in Rat Myocardium, Liver, Urine, Feces, and Plasma Samples Collected from Protocol (PK-917)" by Quintilles, Kansas City, dated 5 March 2003 (submitted in Serial No. 125 on 10 Apr 03)
24 A	63,641	Report	Report No. QKAN-2002-0783-ADM titled "Tissue Distribution in Male Fischer 344 Rats Following a Five Day Daily Intravenous Dose Regimen of 14C-Clotfarabine" by Quintilles, Kansas City, dated 20 March 2003 (submitted in Serial No. 125 on 10 Apr 03)
24 B	63,641	Report	BioReliance Report: Mammalian Erythrocyte Micronucleus Test (Report No. AA53PR.125.BTL; CLO.00.48, Report Date 15 July 2002). Submitted to IND as SN:050.
24 B	63,641	Report	Report No. MC02013 titled "MicroConstants Analytical Report: Determination of Clotfarabine Concentrations in Human Plasma for M.D. Anderson Study DM 93-036" (Report Date 29 March 2002) and the revised version of Report No. MC02013 dated 10 July 2002 (submitted to IND in SN: 120 on 18 Mar 2003)
24 B	63,641	Report	Report No. MC02017 titled "MicroConstants Method Validation Report: Validation of a Method for the Determination of Clotfarabine in Human Plasma Using HPLC with Mass Spec Detection" (Report Date 25 April 2002) Submitted to IND in SN: 112
24 B	63,641	Report	Report No. MC02111 - Toxicokinetics Report titled "Clotfarabine: A Multi-cycle (Five Days' Dosing Plus 23 Days Recovery Per Cycle) Intravenous Toxicity and Toxicokinetics Study in Beagle Dogs" by MicroConstants, Inc., dated 23 April 2003 (this report is Appendix VI in the Full Report, ITR Report No. 2758), submitted in SN: 135 on 2 June 2003. This Report MC02111 includes an Appendix A - Bioanalytical Report titled "Determination of Clotfarabine Concentrations in Dogs" (submitted as a stand alone report to the IND in Serial No. 144 on 15 July 2003)
24 B	63,641	Report	Report No. MC02111-A1: Supplemental Toxicokinetics Report titled "Clotfarabine: A Multi-cycle (Five Days' Dosing Plus 23 Days Recovery Per Cycle) Intravenous Toxicity and Toxicokinetics Study in Beagle Dogs" by MicroConstants, Inc., dated 1 July 2003 (submitted to IND in Serial No. 144 on 17 July 2003)
24 B	63,641	Report	Report No. MC02112 - Formulation Analysis Report titled "Determination of Clotfarabine Concentrations in Dosing Formulations: A Multi-cycle (Five Days' Dosing Plus 23 Days Recovery Per Cycle) Intravenous Toxicity and Toxicokinetics Study in Beagle Dogs" by MicroConstants, Inc., dated 21 Feb. 2003 (this report is an Appendix to the Full Report, ITR Report No. 2758 submitted in Serial No. 135 on 2 June 2003)(submitted as a stand alone report to the IND in Serial No. 144 on 15 July 2003)
24 B	63,641	Report	Report No. MC02113 titled "MicroConstants Method Validation Report: Validation of a Method for the Determination of Clotfarabine in Rat Plasma using HPLC with MS/MS Detection" (Report Date 2 July 2002) Submitted to IND as SN:072

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24B	63,641	Report	Report No. MC02114 titled "MicroConstant's Method Validation Report: Validation of a Method for the Determination of Clofarabine in Dog Plasma using HPLC with MS/MS Detection" (Report Date 27 June 2002) Submitted to IND as SN:072
24B	63,641	Report	Report No. MC02115 titled "MicroConstant's Method Validation Report: Validation of a Method for the Determination of Clofarabine in a Formulation using HPLC with MS/MS Detection" (Report Date 8 August 2002)(this is an Appendix to the full Report, No. ITR 5471)(submitted as a stand alone report to the IND in Serial No. 144 on 15 July 2003)
24B	63,641	Report	Report No. MC02116 - Toxicokinetics Report titled "Clofarabine: A Multi-Cycle (Five Days' Dosing Plus 23 Days Recovery Per Cycle) Intravenous Toxicity and Toxicokinetics Study in Fischer 344 Rats" by MicroConstants, Inc., dated 25 May 2003 (this report is an Appendix to the Full Report, ITR Report No. 5471), with an Appendix titled "Determination of Clofarabine Concentrations in Rat Plasma" (submitted as a stand alone report to the IND in Serial No. 144 on 15 July 2003)
24B	63,641	Report	Report No. MC02132 titled "MicroConstant's Analytical Report: Determination of 2-Chloroadenine Concentrations in Human Plasma For MD Anderson Study DM 93-036" (Report Date 29 May 2002)(submitted to IND in SN: 120 on 18 Mar 2003)
24B	63,641	Report	Report No. MC02135 - Formulation Analytical Report: Determination of Clofarabine Formulations in an Intravenous Developmental Toxicity Study of Clofarabine in Rabbits by MicroConstants, Inc. (Report Dated 4 September 2002) (this is an Appendix to Argus Report No. 1209-001) (submitted as a stand alone report to the IND in Serial No. 144 on 15 July 2003)
24B	63,641	Report	Report No. MC02137 - Formulation Analytical Report: Determination of Clofarabine Formulations in an Intravenous Developmental Toxicity Study of Clofarabine in Rats by MicroConstants, Inc. (Report Dated 13 September 2002) (this is an Appendix to Argus Report No. 1209-002) (submitted as a stand alone report to the IND in Serial No. 144 on 15 July 2003)
24B	63,641	Report	Report No. MC02148 - Formulation Analysis Report titled "Determination of Clofarabine Formulations in Clofarabine: A Multi-Cycle (Five Days' Dosing Plus 23 Days Recovery Per Cycle) Intravenous Toxicity and Toxicokinetics Study in Fischer 344 Rats" by MicroConstants, Inc., dated 4 Feb. 2003 (this report is an Appendix to the Full Report, ITR Report No. 5471)(submitted as a stand alone report to the IND in Serial No. 144 on 15 July 2003)
24B	63,641	Report	Report No. MC02013: Bioanalytical Report - "Determination of Clofarabine Concentrations in Human Plasma for M.D. Anderson Study DM 93-036 (Report Dated 8 November 2002)
24B	63,641	Report	Report No. MC02171: Bioanalytical Report - "Determination of Clofarabine Concentrations in Human Plasma for ILEX Oncology Study ID99-383 ("Phase I Study of CL-F-ARA-A (clofarabine) in Pediatric Patients with Hematologic Malignancies") Report Dated 25 March 2003
24B	63,641	Report	Report No. MC02196 Formulation Analysis Report - "Determination of Clofarabine Formulations in Three Weekly Oral and Intravenous Dose Bridging Toxicity Study of Clofarabine in Fischer 344 Rats" by MicroConstants, Inc. (Report Dated 8 November 2002) (Appendix to Springborn Labs Study No. 3569.3)

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24B	63,641	Report	Report No. MC02235 titled "MicroConstant's Stability Report: Evaluation of the Stability of Clofarabine in Liquid Formulations using HPLC with UV Detection" (Report Date 27 August 2002) (this is an Appendix to the Full Report, No. ITR 5471) (submitted as a stand alone report to the IND in Serial No. 144 on 15 July 2003)
24B	63,641	Report	Report No. MC02287: Bioanalytical Report - "Determination of Clofarabine Concentrations in Human Plasma and Urine for a Phase II, Open-Label Study of Clofarabine in Pediatric Patients with Refractory or Relapsed Acute Myelogenous Leukemia" by MicroConstants, Inc. (Report Date 13 January 2004)(in support of Section 6 of eNDA/CLO-222 Study)
24B	63,641	Report	Report No. MC02293 titled "MicroConstant's Qualification Report: Qualification of Minor Modifications to the Method for the Determination of Clofarabine in Human Plasma using HPLC with MS/MS Detection" (Report Date 25 September 2002) (submitted in Serial No. 151 on 8 Aug 2003)
24B	63,641	Report	Report No. MC02298: MicroConstant's Method Validation Report: Validation of a Method for the Determination of Clofarabine in Human Urine Using HPLC with Mass Spec Detection (Report Date 17 December 2002) Submitted to IND in SN: 112
24B	63,641	Report	Report No. MC02299 "Validation of a Method for the Determination of Chloroacetaldehyde in Human Plasma Using HPLC with Mass Spec Detection (MicroConstants, Inc., Report Date 31 January 2003) Submitted to FDA in Serial No. 116 on 28 Feb 2003
24B	63,641	Report	Report No. MC02301 titled: MicroConstant's Non-Interference Report: Evaluation of the Effect of Cytarabine in the Determination of Clofarabine in Human Plasma Containing Heparin using HPLC with MS/MS Detection (Report Date 5 December 2002)
24B	63,641	Report	Report No. MC02307 titled "MicroConstant's Method Validation Report: Extended Stability of Clofarabine in Formulations using HPLC with UV Detection" (Report Date 8 October 2002) (Submitted in Serial No. 151 on 8 Aug 2003)
24B	63,641	Report	Report No. MC02310: Bioanalytical Report - "Determination of Clofarabine Concentrations in Human Plasma and Urine for ILEX Oncology Study CLO-221" by MicroConstants, Inc., Report Dated 10 June 2003 (submitted to IND in Serial No. 144 on 17 July 2003)
24B	63,641	Report	Report No. MC02311: Bioanalytical Report - "Determination of Clofarabine Concentrations in Human Plasma and Urine for ILEX Oncology Study CLO-212" by MicroConstants, Inc., Report Dated 27 May 2003
24B	63,641	Report	Report No. MC02311: Bioanalytical Report - "Determination of Clofarabine Concentrations in Human Plasma and Urine for a Phase II, Open-Label Study of Clofarabine in Pediatric Patients with Refractory or Relapsed Acute Lymphoblastic Leukemia" by MicroConstants, Inc., Report Dated 13 January 2004 (Revision No. 2)(in support of Section 6 of eNDA/CLO-212 Study)
24B	63,641	Report	Report No. MC02410: Pharmacokinetics Report - "Intravenous and Oral Pharmacokinetic Study of Clofarabine in Male CD-1 Mice, Report Dated 8 May 2003 (ILEX Study No. 0212-01 (will be referenced in the Oral Formulation Initial IND and NDA Pkg)(submitted as a stand alone report to the IND in Serial No. 144 on 15 July 2003)
24B	63,641	Report	

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24B	63,641	Report	Report No. MC03045: Bioanalytical Report - "Determination of Clofarabine Concentrations in Human Plasma for ILEX Acute Leukemia Study ID00-038", by MicroConstants, Inc., Report Dated 27 May 2003
24B	63,641	Report	Report No. MC03065 - Qualification Report: Qualification of Minor Modifications to the Method for the Determination of Clofarabine in Human Plasma using High-Performance Liquid Chromatography with Mass Spectrometric (MS/MS) Detection" Report Dated 15 April 2003
24B	63,641	Report	Report No. MC03105 titled Stability Report: "Evaluation of the Frozen Stability of Clofarabine in Human Urine using High-Performance Liquid Chromatography with Mass Spectrometric (MS/MS) Detection" (Report Date 14 July 2003) (this will be submitted in support of Section 6 of the Clinical eNDA)
24B	63,641	Report	Report No. MC03135 - Qualification Report: Qualification of Minor Modifications to the Method for the Determination of Clofarabine in Human Plasma using High-Performance Liquid Chromatography with Mass Spectrometric (MS/MS) Detection" Report Dated 29 June 2003 (submitted to IND in Serial No. 144 on 17 July 2003)
24B	63,641	Report	Report No. MC03153: BioAnalytical Report titled "Determination of Clofarabine Concentrations in Monkey Plasma and CSF for a Study of Clofarabine Delivered Intravenously in Monkeys" (dated 5 March 2004) (this is the original) (will be in support of a both oral and IV formulations of clofarabine; not submitted in Initial eNDA for IV formulation) (not submitted in eNDA; submitted to both clofarabine IND 63,641-IV & 67,954-oral formulation - on 3/23/04)
24B	63,641	Report	Report No. MC03171 titled Stability Report: "Evaluation of the Frozen Stability of Clofarabine in Human Plasma using High-Performance Liquid Chromatography with Mass Spectrometric (MS/MS) Detection" (Report Date 22 August 2003) (this will be submitted in support of Section 6 of the Clinical eNDA)
24B	63,641	Report	Report No. MC03240 titled Stability Report: "Evaluation of the Processed Sample Stability of Clofarabine in Human Plasma and Urine using High-Performance Liquid Chromatography with Mass Spectrometric (MS/MS) Detection" (Report Date 22 October 2003) (this will be submitted in support of Section 6 of the Clinical eNDA)
24B	63,641	Report	Report No. DE1802-02: Clofarabine Dosed PO or IP Against HT29 Human Colorectal Carcinoma Xenograft Model by ILEX Oncology, Inc. (Report Dated 28 August 2003)
24C	63,641	Report	Pharmacology/Toxicology: Clofarabine Used as a Single Agent or in Combination - Data in Support of the In Vivo Efficacy of Clofarabine, Report Nos. ILEX-3, ILEX-4, ILEX-8, ILEX-9, ILEX-11, ILEX-12, ILEX-14, ILEX-16, ILEX-19, ILEX-24, ILEX-25, ILEX-27, 5260-7#138 and NCI Data (submitted in eNDA)
24C	63,641	Report	Report No. ILEX-3: "Response of SC PC-3 Prostate Tumor to Treatment with Taxotere" performed by Southern Research Institute, dated 3-12-2002
24C	63,641	Report	Report No. ILEX-4: "Response of SC HT29 Colon Tumor to Combination Treatment with Clofarabine and Irinotecan" performed by Southern Research Institute, dated 4-1-2002
24C	63,641	Report	Report No. ILEX-8: "Response of SC HT29 Colon Tumor to Combination Treatment with Clofarabine and 5-FU" performed by Southern Research Institute, dated 5-9-2002

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24C	63,641	Report	Report No. ILEX-9: "Response of SC PC-3 Prostate Tumor to Combination Treatment with Clofarabine and Taxotere" performed by Southern Research Institute, dated 5-9-2002	
24C	63,641	Report	Report No. ILEX-11: "Response of SC HT29 Colon Tumor to Treatment with Clofarabine" performed by Southern Research Institute, dated 8-23-2002	
24C	63,641	Report	Report No. ILEX-12: "Response of SC CGRF-CEM Leukemia to Combination Treatment with Clofarabine and ARA-C" performed by Southern Research Institute, dated 2-26-2002	
24C	63,641	Report	Report No. ILEX-14: "Response of SC CCRF-CEM Leukemia to Combination Treatment with ARA-C and Clofarabine" performed by Southern Research Institute, dated 12-12-2002	
24C	63,641	Report	Report No. ILEX-16: "Response of SC NCI-H460 Lung Tumor to Treatment with Clofarabine (Schedule Dependency)" performed by Southern Research Institute, dated 9-18-2002	
24C	63,641	Report	Report No. ILEX-19: "Response of SC HT29 Colon Tumor to Combination Treatment with Clofarabine and Irinotecan" performed by Southern Research Institute, dated 10-23-2002	
24C	63,641	Report	Report No. ILEX-24: "Response of SC HT29 Colon Tumor to Combination Treatment with Oxaliplatin and Clofarabine" performed by Southern Research Institute, dated 3-12-2003	
24C	63,641	Report	Report No. ILEX-25: "Response of SC HT29 Colon Tumor to Combination Treatment with Clofarabine and Camptosar" performed by Southern Research Institute, dated 12-26-2003	
24C	63,641	Report	Report No. ILEX-27: "Response of SC HT29 Colon Tumor to Treatment with Clofarabine or CPT-11" performed by Southern Research Institute, dated 4-17-2003	
24C	63,641	Report	Report No. 3260-7#138: "Response of SC PC-3 Prostate Tumor to Treatment with 2-CL-2-F-ARA-A (NSC 606869) and 2-F-ARA-AMP (NSC 312887)" performed by Southern Research Institute, dated 5-4-98	
24C	63,641	Report	NCI Screening Data: In Vitro Anti-Tumor Screening on 60-Tumor Cell Lines ... Referenced in the IB, Oral IND and IV NDA (Report Date: 16 April 2003; Test Date: 3 March 2003)	
25	63,641	FDA Sub.	SN: 135 Information Amendment - Pharm/Tox: Toxicology Report "Clofarabine: A Multi-cycle (Five Days) Dosing Plus 23 Days Recovery Per Cycle) Intravenous Toxicity and Toxicokinetics Study in Beagle Dogs" (submitted as 3 Volumes) (ITR Study No. 2758 by ITR Laboratories Canada Inc., Report Date 23 May 2003)(ILEX 0203-01)	2-Jun-03
25	63,641	Report	Report No. ITR 2758: Toxicology Report "Clofarabine: A Multi-cycle (Five Days) Dosing Plus 23 Days Recovery Per Cycle) Intravenous Toxicity and Toxicokinetics Study in Beagle Dogs" Volume 1 of 3 (submitted to FDA as SN: 135 Information Amendment - Pharm/Tox: Toxicology Report) . CD-ROM of Report in pdf format also on file (Report Dated 23 May 2003)	
26	63,641	Report	Report No. ITR 2758: Toxicology Report "Clofarabine: A Multi-cycle (Five Days) Dosing Plus 23 Days Recovery Per Cycle) Intravenous Toxicity and Toxicokinetics Study in Beagle Dogs" Volume 2 of 3 (submitted to FDA as SN: 135 Information Amendment - Pharm/Tox: Toxicology Report) (Report Dated 23 May 2003)	
27	63,641	Report	Report No. ITR 2758: Toxicology Report "Clofarabine: A Multi-cycle (Five Days) Dosing Plus 23 Days Recovery Per Cycle) Intravenous Toxicity and Toxicokinetics Study in Beagle Dogs" Volume 3 of 3 (submitted to FDA as SN: 135 Information Amendment - Pharm/Tox: Toxicology Report) (Report Dated 23 May 2003)	

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28	63,641	FDA Sub.	SN: 139 Information Amendment - Pharmacology/Toxicology: Clofarabine Used as a Single Agent or in Combination - Data in Support of the In Vivo Efficacy of Clofarabine, Report Nos. ILEX-4, ILEX-8, ILEX-9, ILEX-12, ILEX-14, ILEX-16, ILEX-19, ILEX-24, ILEX-25, ILEX-27 & ILEX-11	18-Jun-03
29	63,641	FDA Sub.	SN: 140 Information Amendment - Pharmacology/Toxicology: TTR Study No. 54771(ILEX 0204-03) (dated 23 June 2003) Volume 1 of 3	26-Jun-03
30	63,641	FDA Sub.	SN: 140 Information Amendment - Pharmacology/Toxicology: TTR Study No. 54771(ILEX 0204-03) (dated 23 June 2003) Volume 2 of 3	26-Jun-03
31	63,641	FDA Sub.	SN: 140 Information Amendment - Pharmacology/Toxicology: TTR Study No. 54771(ILEX 0204-03) (dated 23 June 2003) Volume 3 of 3 (Includes MicroConstants Reports: Appendix III - MC02116; Appendix IV - MC02148; Appendix V - MC02235; Appendix V - MC02115)	26-Jun-03
32	63,641	FDA Sub.	SN: 143 Pre-NDA Meeting Package (Meeting Scheduled for 13 August 2003)	15-Jul-03
33	63,641	FDA Sub.	SN: 144 Information Amendment: Pharmacology/Toxicology: MicroConstants Reports: MC02111, MC02111-A1, MC02112, MC02115, MC02116, MC02136, MC02137, MC02148, MC02235, MC02310, MC02410, and MC03135	15-Jul-03
34	63,641	FDA Corres.	Fast Track Designation Granted to Clofarabine for Acute Lymphoblastic Leukemia (ALL) Includes: Acceptance of Rolling NDA Submission (now called a 'step-wise' submission)	8-Jul-03
34	63,641	FDA Sub.	SN: 145 Revised Form FDA 1572: Replacement PI: Rytting for Jeha, MD Anderson Cancer Center, Houston, TX, (dated 05/16/03) CLO-221	18-Jul-03
34	63,641	FDA Sub.	SN: 146 Protocol Amendment: New Protocol CLO-152: "Phase I, Dose Escalation and Pharmacokinetic Study of Oral Clofarabine Administered Daily for 5 Days in Adult Patients with Refractory Solid Tumors" (retracted - will be submitted in Initial Oral IND Application)	(see Initial IND for Oral Formulation)
34	63,641	FDA Sub.	SN: 147 Other: Updated Investigator's Brochure, Edition 3 (22 July 2003)	25-Jul-03
34	63,641	FDA Sub.	SN: 148 Protocol Amendment: Revised 1572, Timothy Griffin, MD, Cook Children's Hematology/Oncology Center, Fort Worth, TX (dated 07/11/2003) CLO-222 and CLO-212	31-Jul-03
34	63,641	FDA Sub.	SN: 149 IND Safety Report, Initial Report, Expedited, 7-day, Patient 0001-0031 (K-J), CLO-212, Report No. 13065	01-Aug-03
34	63,641	FDA Sub.	SN: 150 IND Safety Report, Initial Report, Expedited, 7-day, Patient 0004-0024 (S-J), CLO-222, Report No. 13080	05-Aug-03
34	63,641	FDA Corres.	Facsimile from Christy Cottrell/FDA: Comments Regarding the Pre-NDA Package Submitted for Meeting Set for 13 August 2003	05-Aug-03
34	63,641	FDA Corres.	Facsimile from Christy Cottrell/FDA: Pre-NDA Meeting Changed to a Teleconference for 13 August 2003 (in place of face-to-face meeting)	07-Aug-03
34	63,641	FDA Sub.	SN: 151 Information Amendment - Pharmacology/Toxicology: MicroConstants Reports: MC02283 and MC02307	08-Aug-03
34	63,641	Internal Corres	Minutes of Teleconference (in place of Face-To-Face pre-NDA meeting scheduled for 13 Aug 2003) to discuss pre-NDA package: FDA feedback on overall clinical data, the rolling NDA process & timing of CMC submissions....(minutes generated internally by ILEX)	13-Aug-03
34	63,641	FDA Sub.	SN: 152 Information Amendment - Chemistry, Manufacturing and Control, & REQUEST FOR Reinspection, Visual Inspection, Particulates in Drug	21-Aug-03

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34	63,641	FDA Sub.	SN: 153 IND Safety Report - Initial Report: Expediable, 7-Day Facsimile of Control No. 13090, Patient No. 001-0034 (JMA) [death] on Study CLO-212	26-Aug-03
34	63,641	FDA Sub.	SN: 154 IND Safety Report - Initial 15-Day MedWatch Report No. 13090, In Support of SN: 153 (no additional details available; MedWatch and Letters Sent Out to Investigators)	28-Aug-03
34	63,641	FDA Sub.	Facsimile from Christy Cottrell/FDA: Comments Regarding Serial No. 152 CMC - Drug Product Lot No. CO3E015: DO NOT USE - FDA Will Do a 30-Day Review	28-Aug-03
34	63,641	FDA Sub.	SN: 155 IND Safety Report - Follow Up: Follow Up Report to Initial 7-Day Report, (Control No. 13080 Faxed on 5 August 2003); MedWatch No. 13080, Patient No. 0004-0024 (S-J), CLO-222 Study	29-Aug-03
34	63,641	FDA Sub.	SN: 156 Response to FDA Request for Information: CMC - Starting Materials (Response to Facsimile form FDA of 29 May 2003)	04-Sep-03
34	63,641	FDA Sub.	SN: 157 Information Amendment - Chemistry, Manufacturing and Control - Additional Information to SN: 156 (per teleconference of 4 September 2003 with FDA reviewer)	09-Sep-03
34	63,641	FDA Sub.	Facsimile from Christy Wilson/FDA: Follow Up to Teleconference of 4 September 2003, SN: 152 and SN: 157 Regarding the Failed Lot of Clofarabine Drug Product (Lot No. CO3E015)	10-Sep-03
34	63,641	FDA Sub.	SN: 158 Protocol Amendment - New Investigator: Robert J. Arcaci, MD, PhD, Baltimore, MD, for CLO-222 Study (dated 9/10/02) and CLO-212 Study (dated 9/14/02)	11-Sep-03
34	63,641	FDA Sub.	Facsimile from Christy Cottrell/FDA: Comments from Biopharmaceutics Reviewer Regarding SN: 126 (protocol amendment CLO-141) submitted on 17 April 2003; Sampling Strategy - Request An Added Time Point Following Last Dosing & Request for Assay Validation Report	15-Sep-03
34	63,641	FDA Sub.	SN: 159 Responses to FDA Request for Information - FDA Fax of 15 September 2003 Regarding SN: 126 (protocol amendment CLO-141) submitted on 17 April 2003: Sampling Strategy - Request An Added Time Point Following Last Dosing & Request for Assay Validation Report	9/11/03
35	63,641	FDA Sub.	SN: 160 Information Amendment - Clinical: Final Clinical Study Reports - Protocol ID99-383: "Phase I Study of CL-F-Ara-A (Clofarabine) in Pediatric Patients with Hematologic Malignancies"; 12 Volumes Total - (Volume 1: Sections)	18-Sep-03
36	63,641	FDA Sub.	SN: 160 Information Amendment - Clinical: Final Clinical Study Reports - Protocol ID99-383: "Phase I Study of CL-F-Ara-A (Clofarabine) in Pediatric Patients with Hematologic Malignancies"; 12 Volumes Total - (Volume 2: Sections)	18-Sep-03
37	63,641	FDA Sub.	SN: 160 Information Amendment - Clinical: Final Clinical Study Reports - Protocol ID99-383: "Phase I Study of CL-F-Ara-A (Clofarabine) in Pediatric Patients with Hematologic Malignancies"; 12 Volumes Total - (Volume 3: Sections)	18-Sep-03
38	63,641	FDA Sub.	SN: 160 Information Amendment - Clinical: Final Clinical Study Reports - Protocol ID99-383: "Phase I Study of CL-F-Ara-A (Clofarabine) in Pediatric Patients with Hematologic Malignancies"; 12 Volumes Total - (Volume 4: Sections)	18-Sep-03
39	63,641	FDA Sub.	SN: 160 Information Amendment - Clinical: Final Clinical Study Reports - Protocol ID99-383: "Phase I Study of CL-F-Ara-A (Clofarabine) in Pediatric Patients with Hematologic Malignancies"; 12 Volumes Total - (Volume 5: Sections)	18-Sep-03
40	63,641	FDA Sub.	SN: 160 Information Amendment - Clinical: Final Clinical Study Reports - Protocol ID99-383: "Phase I Study of CL-F-Ara-A (Clofarabine) in Pediatric Patients with Hematologic Malignancies"; 12 Volumes Total - (Volume 6: Sections)	18-Sep-03

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41	63,641	FDA Sub.	SN: 160 Information Amendment - Clinical: Final Clinical Study Reports - Protocol ID99-383; "Phase I Study of CL-F-Ara-A (Clofarabine) in Pediatric Patients with Hematologic Malignancies"; 12 Volumes Total - (Volume 7: Sections) SN: 160 Information Amendment - Clinical: Final Clinical Study Reports - Protocol ID99-383; "Phase I Study of CL-F-Ara-A (Clofarabine) in Pediatric Patients with Hematologic Malignancies"; 12 Volumes Total - (Volume 8: Sections) SN: 160 Information Amendment - Clinical: Final Clinical Study Reports - Protocol ID99-383; "Phase I Study of CL-F-Ara-A (Clofarabine) in Pediatric Patients with Hematologic Malignancies"; 12 Volumes Total - (Volume 9: Sections)	18-Sep-03
42	63,641	FDA Sub.	SN: 160 Information Amendment - Clinical: Final Clinical Study Reports - Protocol ID99-383; "Phase I Study of CL-F-Ara-A (Clofarabine) in Pediatric Patients with Hematologic Malignancies"; 12 Volumes Total - (Volume 10: Sections) SN: 160 Information Amendment - Clinical: Final Clinical Study Reports - Protocol ID99-383; "Phase I Study of CL-F-Ara-A (Clofarabine) in Pediatric Patients with Hematologic Malignancies"; 12 Volumes Total - (Volume 11: Sections)	18-Sep-03
43	63,641	FDA Sub.	SN: 160 Information Amendment - Clinical: Final Clinical Study Reports - Protocol ID99-383; "Phase I Study of CL-F-Ara-A (Clofarabine) in Pediatric Patients with Hematologic Malignancies"; 12 Volumes Total - (Volume 12: Sections) SN: 160 Information Amendment - Clinical: Final Clinical Study Reports - Protocol ID99-383; "Phase I Study of CL-F-Ara-A (Clofarabine) in Pediatric Patients with Hematologic Malignancies"; 12 Volumes Total - (Volume 13: Sections)	18-Sep-03
44	63,641	FDA Sub.	SN: 160 Information Amendment - Clinical: Final Clinical Study Reports - Protocol ID99-383; "Phase I Study of CL-F-Ara-A (Clofarabine) in Pediatric Patients with Hematologic Malignancies"; 12 Volumes Total - (Volume 14: Sections) SN: 160 Information Amendment - Clinical: Final Clinical Study Reports - Protocol ID99-383; "Phase I Study of CL-F-Ara-A (Clofarabine) in Pediatric Patients with Hematologic Malignancies"; 12 Volumes Total - (Volume 15: Sections)	18-Sep-03
45	63,641	FDA Sub.	SN: 160 Information Amendment - Clinical: Final Clinical Study Reports - Protocol ID99-383; "Phase I Study of CL-F-Ara-A (Clofarabine) in Pediatric Patients with Hematologic Malignancies"; 12 Volumes Total - (Volume 16: Sections) SN: 160 Information Amendment - Clinical: Final Clinical Study Reports - Protocol ID99-383; "Phase I Study of CL-F-Ara-A (Clofarabine) in Pediatric Patients with Hematologic Malignancies"; 12 Volumes Total - (Volume 17: Sections)	18-Sep-03
46	63,641	FDA Sub.	SN: 160 Information Amendment - Clinical: Final Clinical Study Reports - Protocol ID99-383; "Phase I Study of CL-F-Ara-A (Clofarabine) in Pediatric Patients with Hematologic Malignancies"; 12 Volumes Total - (Volume 18: Sections) SN: 160 Information Amendment - Clinical: Final Clinical Study Reports - Protocol ID99-383; "Phase I Study of CL-F-Ara-A (Clofarabine) in Pediatric Patients with Hematologic Malignancies"; 12 Volumes Total - (Volume 19: Sections)	18-Sep-03
47	63,641	FDA Sub.	SN: 160 Information Amendment - Clinical: Final Clinical Study Reports - Protocol ID99-383; "Phase I Study of CL-F-Ara-A (Clofarabine) in Pediatric Patients with Hematologic Malignancies"; 12 Volumes Total - (Volume 20: Sections) SN: 160 Information Amendment - Clinical: Final Clinical Study Reports - Protocol ID99-383; "Phase I Study of CL-F-Ara-A (Clofarabine) in Pediatric Patients with Hematologic Malignancies"; 12 Volumes Total - (Volume 21: Sections)	18-Sep-03
48	63,641	FDA Sub.	SN: 160 Information Amendment - Clinical: Final Clinical Study Reports - Protocol ID99-383; "Phase I Study of CL-F-Ara-A (Clofarabine) in Pediatric Patients with Hematologic Malignancies"; 12 Volumes Total - (Volume 22: Sections) SN: 160 Information Amendment - Clinical: Final Clinical Study Reports - Protocol ID99-383; "Phase I Study of CL-F-Ara-A (Clofarabine) in Pediatric Patients with Hematologic Malignancies"; 12 Volumes Total - (Volume 23: Sections)	18-Sep-03
34	63,641	FDA Sub.	SN: 161 IND Safety Report - Initial Report: MedWatch No. 13107, Patient No. 0005-0037 (E-B) on CLO-212 Study "Initial report due to one event; ILEX notified on 9/19/03 of patient death; death included but awaiting causality" Minutes of Teleconference 13 Aug 2003 (in place of Face-To-Face pre-NDA meeting) to discuss pre-NDA package: FDA feedback on overall clinical data, the rolling NDA process & review; further patient accrual; further development/study design; safety & efficacy sections; timing of CMC submissions.....(minutes generated internally by ILEX)	19-Sep-03
49	63,641	FDA Corres.	SN: 162 Pre-NDA CMC Meeting Request: Proposed Week of 1 December or 8 December 2003 SN: 163 IND Safety Report, Follow Up Report, for Expedited, 7-day Report (SN: 149, submitted 1 Aug 2003), Patient 0001-0031 (K-J), CLO-212, Report No. 13065	29-Sep-03
34	63,641	FDA Sub.	Facsimile from Christy Cottrell/FDA: Confirmation of pre-NDA CMC Mtg Scheduled for 10 December 2003 at 2:00pm; Includes List of FDA Attendees (this is in response to SN: 162: Request for Meeting)	01-Oct-03
34	63,641	pre-NDA		08-Oct-03

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49	63,641	FDA Sub.	SN: 164 Protocol Amendments: Change In Protocols: CLO-212-A6 (Peds ALL)(rationale for change and CLO-222-A6 (Peds AML) Amendments Official Notification of an Amendment to the Formal Written Request for Pediatric Exclusivity issued on 7 March 2003 (refer to FDA correspondence of 27 August 2002) Facsimile from Christy Cottrell/CSO/FDA: Final Meeting Minutes from the CMC Teleconference between ILEX & FDA of 4 September 2003 (failed lot of clofarabine drug product, visible re-inspection, submission Serial No. 152)	10-Oct-03
49	63,641	FDA Corres.	Official Notification of Receipt of Part 1 of the Step-Wise NDA Submission: Non-clinical Sections (Pharmacology/Toxicology)	14-Oct-03
49	63,641	FDA Corres.	SN: 165 Revised Form FDA 1572 - Replacement PI: Michael Rydning, M.D., The University of Texas MD Anderson Cancer Center, Houston, Texas (dated 5/16/03) Replacing Dr. Sima Jeha in the CLO-212 Study (Peds ALL)	16-Oct-03
49	63,641	FDA Sub.	SN: 166 Revised Form FDA 1572: Charles Casey Cunningham, M.D., Mary Crowley Medical Research Center, Dallas, Texas (dated 8/1/03) for the CLO-152 Study (Adult Solid Tumor)	17-Oct-03
49	63,641	FDA Sub.	SN: 167 Revised Form FDA 1572s: Lori Luchtmann-Jones, M.D., Washington University School of Medicine, St. Louis, Missouri (dated 29 August 2003) and Kimmo Stine, M.D., Arkansas Children's Hospital, Little Rock, Arkansas (dated 7/24/03) both on CLO-212 (Peds ALL) Study	22-Oct-03
49	63,641	FDA Sub.	SN: 168 Revised Form FDA 1572s: Lon Luchtmann-Jones, M.D., Washington University School of Medicine, St. Louis, Missouri (dated 28 August 2003) and Kimmo Stine, M.D., Arkansas Children's Hospital, Little Rock, Arkansas (dated 7/24/03) and Bassem Razzouk, M.D., St. Jude's Children's Hospital, Memphis, Tennessee (2 1572s: one dated 8/26/03, the second form dated 10/03/03) on CLO-222 (Peds AML) Study	22-Oct-03
49	63,641	FDA Sub.	SN: 169 IND Safety Report, Initial 7-Day Expedited Report, Control No. 13147, Patient 0014-0029 (J-D), CLO-222 (Submitted & Faxed CIOMS as the 7-day Report)	22-Oct-03
49	63,641	FDA Sub.	SN: 170 Revised Form FDA 1572: David Rizzler, M.D., Duke University Medical Center, Durham, North Carolina (dated 8/4/03) for CLO-221 Study	24-Oct-03
49	63,641	FDA Sub.	SN: 171 IND Safety Report, Follow Up to 7-Day Expedited Report (SN: 169), CIOMS Form - Control No. 13147, Patient 0014-0029 (J-D), CLO-222 (Submitted & Faxed CIOMS as the 7-day Report)	30-Oct-03
49	63,641	FDA Sub.	SN: 172 Pre-NDA CMC Meeting Package - Meeting Scheduled for 10 December 2003: Several Questions; Proposed Table of Contents; Copies of Supporting FDA Correspondence Included	04-Nov-03
49	63,641	FDA Sub.	SN: 173 IND Safety Report - Initial Report: 15-Day Expedited Report, MedWatch No. 13155, Patient No. 0010-0041 (D-R), for CLO-212 Study	07-Nov-03
49	63,641	FDA Sub.	SN: 174 IND Safety Report - Follow Up Report: MedWatch No. 13090, Patient No.001-0034 (JMA), for CLO-212 Study (no further follow up information expected; Initial report was Serial No. 153 on 26 Aug 2003)	11-Nov-03
49	63,641	FDA Sub.	SN: 175 IND Safety Report - Follow Up Report: MedWatch No. 13080, Patient No. 0004-0024 (S-J), for CLO-222 Study (Initial report was Serial No. 155 on 29 Aug 2003)	13-Nov-03

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49	63,641	FDA Sub.	SN: 176 IND Safety Report - Follow Up Report: MedWatch No. 13107, Patient No. 0005-0037 (E-B) on CLO-212 Study additional details received on 25 Nov 2003	01-Dec-03
49	63,641	pre-NDA	Facsimile from Christy Cottrell/FDA: FDA Responses to Questions from ILEX's pre-NDA CMC Meeting Package: (If responses acceptable to ILEX, a meeting is not required)	04-Dec-03
49	63,641	pre-NDA	Call between Christy Cottrell and Edda Tschirhart: ILEX Request Teleconference to Discuss Responses to pre-NDA CMC Meeting Questions	04-Dec-03
49	63,641	FDA Sub.	SN: 177 IND Safety Report - Second Follow Up Report (Initial Expedited, 7-day Report SN: 149, submitted 1 Aug 2003), Patient 0001-0031 (K-J), CLO-212, MedWatch Report No. 13065 (1st Follow Up - SN: 163 submitted 1 October 2003)	05-Dec-03
49	63,641	FDA Sub.	SN: 178 Revised Form FDA 1572: Bassem Razzouk, M.D., St. Jude's Children's Hospital, Memphis, Tennessee (dated 11/12/03) CLO-222 Study	05-Dec-03
49	63,641	FDA Sub.	SN: 179 Response to FDA Facsimile of 4 December 2003 (FDA Responses to pre-NDA CMC Meeting Package (submitted as SN: 172 on 7 November 2003))	08-Dec-03
49	63,641	FDA Sub.	SN: 180 Cross-reference Authorization: James M. Foran, M.D., FRCP (C), Asst Professor of Medicine, Co-Director, Hematologic Malignancy Working Group, Director, BMT Clinical Research & Fellowship Training Program, Div. of Hematology/Oncology, Univ. of Alabama at Birmingham, Birmingham, AL for the Protocol titled "A Phase III Study of Clofarabine & Cytosine Arabinoside Remission Induction Therapy for Older Adults (≥ 60 years) with Newly Diagnosed Acute Myeloid Leukemia" (IST Study)	08-Dec-03
49	63,641	FDA Sub.	SN: 181 IND Safety Report - Initial Report: 15-Day Expedited Report, MedWatch No. 13172, Patient No. 0018-0044 (RMH), for CLO-212 Study	08-Dec-03
49	63,641	FDA Sub.	SN: 182 IND Safety Report - Initial Report: 7-Day, Expedited Report, CIOIMS Control No. 13170, Patient No. 0014-0040 (M-G), for CLO-212 Study	09-Dec-03
49	63,641	FDA Sub.	SN: 183 General Correspondence - Change in Medical Monitor: Change from Adam Craig, M.D., to Steve Weltman, MD; also added Vojo Vukovic, M.D. and Lisa Hammond, M.D. as Medical Monitors for Evaluating Safety	09-Dec-03
49	63,641	FDA Sub.	SN: 184 IND Safety Report - Follow Up Report: MedWatch No. 13090, Patient No. 007-0034 (JMA), for CLO-212 Study (Initial, 7-Day report was Serial No. 153 on 26 Aug 2003; Serial No. 154 on 26 Aug 2003, Serial No. 174 on 11 Nov 2003)	11-Dec-03
49	63,641	FDA Sub.	SN: 185 IND Safety Report - Follow Up Report: MedWatch Report No. 13026, Patient No. 0010-0022 (D-M), CLO-222 Peds AML Study (Initial, 15-Day Report submitted as Serial No. 137 on 10 June 2003	11-Dec-03
49	63,641	pre-NDA	Minutes of Teleconference (in place of Face-To-Face pre-NDA CMC meeting scheduled for 10 Dec 2003) to discuss pre-NDA CMC Information: FDA responses to SN: 172 pre-NDA CMC Meeting Package (fax of 4 December 2003 from FDA): Specifically extractables/leachables and validation of API & drug product.	10-Dec-03
49	63,641	FDA Sub.	SN: 186 IND Safety Report, Second Follow Up to 7-Day Expedited Report (SN: 169), CIOIMS Form - Control No. 13147, Patient 0014-0029 (J-D), CLO-222 (Submitted & Faxed CIOIMS as the 7-day Report) (First Follow Up Report submitted as SN: 171 on 4 Nov 2003)	12-Dec-03
49	63,641	FDA Sub.	SN: 187 IND Safety Report: Initial 7-Day Expedited Report CIOIMS Form - Control No. 13185, Patient 0009-0048 (TPR), CLO-212 (Submitted & Faxed CIOIMS as the 7-day Report)	17-Dec-03

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49	63,641	Meeting Minutes	Minutes of Teleconference between ILEX, ASI, FDA and FDA/District Office Regarding Acceptance of Conducting Concurrent Validation Runs on Three Consecutive Lots of Clofarabine: Response: Acceptable/Approved - Minutes Include Details of Discussion	17-Dec-03	
49	63,641	FDA Corres.	Facsimile from Christy Cottrell/FDA: Comments from the Chemistry Reviewer Regarding Starting Materials (Refer to Serial No. 156 dated 4 Sept. 2003, Fax from FDA dated 29 May 2003, Serial No. 087 dated 15 Nov. 2002, FDA Corres. dated 3 Oct 2002; Serial No. 028 dated 14 June 2002 Proposal for Drug Substance Starting Material - Additional Information Required	18-Dec-03	
49	63,641	FDA Corres.	Emails between Christy Cottrell, CSO/FDA and Mike Bernstein, Sr. Director Reg. Affairs: Outline for Clofarabine NDA (preparation of Clinical Statistical Section (i.e. CRTs by domain, Integrated ISS database, specific data tables, patient profiles, SAS database & SAS program files, etc.) Facsimile from Christy Cottrell/FDA: Meeting Minutes from 10 December 2003 pre-NDA CMC Teleconference with Addendum Added of Minutes from Teleconference of 17 December 2003 Between the FDA District Office, FDA Office of Compliance, ILEX and Ash Stevens, Inc.: Includes Minutes Provided by ILEX and Minutes Provided by Judith A. Putz, FDA District Office/Detroit: Concurrent Validation of API Process (Yes- accepted & approved) Several Details Included in Minutes Regarding Materials, Process, Validation, etc.	30-Dec-03	
49	63,641	FDA Sub.	SN: 188 IND Safety Report - Follow Up Report: MedWatch No. 13155, Patient No. 0010-0041 (D-R), (Initial Report was SN 173) for CLO-212 Study	09-Jan-04	
49	63,641	FDA Sub.	SN: 189 IND Safety Report - Follow Up: MedWatch No. 13172, Patient No. 0018-0044 (RMH), (Initial Report was SN 181) for CLO-212 Study	12-Jan-04	
51	63,641	FDA Sub.	SN: 190 Information Amendment - Pharmacology/Toxicology: Report No. 3569.4 Titled "A 5-Day Intravenous Toxicity Study in Female Fischer 344 Rats Comparing Two Lots of Clofarabine" by Charles Rivers Lab, Division of Springborn Laboratories (Report Date 9 Jan 2004)		
49	63,641	FDA Sub.	SN: 191 IND Safety Report-Follow Up Report MedWatch Report No. 12656, Patient No. 0013-0013 S B, (additional details, autopsy received), for CLO-221 Adult AML Study	15-Jan-04	
49	63,641	FDA Sub.	SN: 192 IND Safety Report - Follow Up: MedWatch No. 12724, Patient No. 0012-0017 (J-K) CLO-221 Adult AML Study (see also Initial report SN: 082, & follow up reports SN: 093 & SN: 117	16-Jan-04	
49	63,641	FDA Sub.	SN: 193 Revised Form FDA 1572s: Susan Blaney, MD, Texas Children's Hospital, Houston, Texas (dated 10/27/03) and A. Kim Ritchey, MD, Children's Hospital of Pittsburgh, Pittsburgh, PA (dated 11/10/03) CLO-222 Study Peds AML	20-Jan-04	
49	63,641	FDA Sub.	SN: 194 Revised Form FDA 1572s: Lori Luchman-Jones, MD, Washington Univ. School of Medicine, St. Louis Children's Hospital, St. Louis, MO (dated 10/10/03); Susan Blaney, MD, Texas Children's Hospital, Houston, Texas (dated 10/27/03) and A. Kim Ritchey, MD, Children's Hospital of Pittsburgh, Pittsburgh, PA (dated 11/10/03) CLO-212 Study Peds ALL	30-Jan-04	

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50	63,641	Report	Clinical Report: Independent Response Review Panel Report (IRRP) for CLO-221 "A Phase II, Open Label Study of Clofarabine in Adult Patients with Refractory or Relapsed Acute Myelogenous Leukemia" (Report Date 15 November 2002)(Includes CVS of Review Panel Members)	
50	63,641	Report	Clinical Report: Independent Response Review Panel Report (IRRP) for CLO-212 "A Phase II, Open Label Study of Clofarabine in Pediatric Patients with Refractory or Relapsed Acute Lymphoblastic Leukemia" (Report Date 10 March 2003)	
50	63,641	Report	Clinical Report: Independent Response Review Panel Report (IRRP) for CLO-212 "A Phase II, Open Label Study of Clofarabine in Pediatric Patients with Refractory or Relapsed Acute Lymphoblastic Leukemia" (Report Date 8 June 2003)	
50	63,641	Report	Clinical Report: Independent Response Review Panel Report (IRRP) for CLO-212 "A Phase II, Open Label Study of Clofarabine in Pediatric Patients with Refractory or Relapsed Acute Lymphoblastic Leukemia" (Report Date 19 December 2003)	
50	63,641	Report	Clinical Report: Independent Response Review Panel Report (IRRP) for CLO-212 "A Phase II, Open Label Study of Clofarabine in Pediatric Patients with Refractory or Relapsed Acute Lymphoblastic Leukemia" (Report Date 28 January 2004)	
50	63,641	Report	Clinical Report: Independent Response Review Panel Report (IRRP) for CLO-222 "A Phase II, Open Label Study of Clofarabine in Pediatric Patients with Refractory or Relapsed Acute Myelogenous Leukemia" (Report Date 28 August 2003)	
50	63,641	Report	Clinical Report: Independent Response Review Panel Report (IRRP) for CLO-222 "A Phase II, Open Label Study of Clofarabine in Pediatric Patients with Refractory or Relapsed Acute Myelogenous Leukemia" (Report Date 19 December 2003)	
50	63,641	Report	Clinical Report: Independent Response Review Panel Report (IRRP) for CLO-222 "A Phase II, Open Label Study of Clofarabine in Pediatric Patients with Refractory or Relapsed Acute Myelogenous Leukemia" (Report Date 28 January 2004)	
52	63,641	FDA Sub.	Request for Labeler Code - To Information Management Team (New Drug Coding) with Form 2656	05-Feb-04
52	63,641	FDA Sub.	SN: 195 'Dear Doctor' Safety Letter - Copies To All Principal Investigators: Guidance and Treatment Recommendations (RE: Capillary Leak Syndrome, SIRS) from Steve Weltman, MD, PhD	
52	63,641	FDA Sub.	SN: 196 2003 Annual Report covering period 08 November 2002 through 31 October 2003 - Covers the Following Studies: CLO-212, CLO-222, CLO-221, CLO-141 and CLO-151	06-Feb-04
52	63,641	Gen. Corres.	Amended Request for Labeler Code: Submitted to the Information Management Team (FDA, Standish Road) with Amended Form 2656 per Telephone Call from MAZ (at FDA)	06-Feb-04
52	63,641	FDA Corres.	Official Notification of the Assigned Labeler Code - No. 66646	10-Feb-04
52	63,641	FDA Corres.	To Marlene Haffner, M.D., Orphan Drug Division: Copy of SN: 196 2003 Annual Report covering period 08 November 2002 through 31 October 2003 for Orphan Drug Designation No. 01-1532 (ALL) and Orphan Drug Designation No. 02-1548 (AML)	10-Feb-04
52	63,641	FDA Corres.		15-Feb-04

Clotfarabine / No. 63,641

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52	63,641	FDA Sub.	SN: 197 Revised Form FDA 1572s: Timothy C. Griffin, MD, Cook Children's Hematology/Oncology Center, Fort Worth, Texas (two forms, both dated 1/29/04) - CLO-212 & CLO-222 Studies; Paul S. Gaynon, MD, Children's Hospital Los Angeles, Los Angeles, CA (two forms, both dated 1/21/04) CLO-212 & CLO-222 Studies	16-Feb-04
52	63,641	FDA Sub.	SN: 198 Revised Form FDA 1572s: Stefan F. Faderl, M.D., MD Anderson Cancer Center, Houston, Texas (two forms - dated 12/15/03 & 1/12/04) both CLO-141 Study	18-Feb-04
52	63,641	FDA Sub.	SN: 199 Information Amendment - Chemistry, Manufacturing and Control (CMC): Two New Lots of Drug Manufactured - Lot No. C03R068A and Lot No. C03R068B and Change to Container/Closure (New Stopper): Submission Includes C of A for each lot and the Comparability Study for the New Stopper	20-Feb-04
52	63,641	FDA Sub.	Official Notification of the Assigned Labeler Code - No. 68646 for Amended Labeler Code Request (Final): Official Signed Form 2656, Labeler Code 68646 Assigned to ILEX Products, Inc., Registration No. 3003288351	2/17/2004 (see 10 Feb 2004)
52	63,641	FDA Sub.	SN: 200 IND Safety Report - Initial Report: 7-Day, Expedited Report, CIOIMS Control No. 13249, Patient No. 0010-0052 (AMC), for CLO-212 Study	8-Mar-04
52	63,641	FDA Sub.	SN: 201 IND Safety Report - Second Follow Up: MedWatch No. 13172, Patient No. 0018-0044 (RMH), (Initial Report was SN 181, First Follow Up was SN: 189) for CLO-212 Study	11-Mar-04
52	63,641	FDA Sub.	SN: 202 Revised Form FDA 1572s: Charles Casey Cunningham, M.D., Mary Crowley Medical Research Center, Dallas, Texas (dated 10/13/03); and Donald A. Richards, M.D., Tyler Cancer Center, Tyler, Texas (dated 1/19/04)	11-Mar-04
52	63,641	FDA Sub.	SN: 203 IND Safety Report: Follow Up to a 7-Day Expedited Report (SN: 187 submitted on 17 Dec 2003) CIOIMS Form - Control No. 13185, Patient 0009-0048 (TPR), CLO-212	22-Mar-04
52	63,641	FDA Sub.	SN: 204 Information Amendment - Pharmacology/Toxicology: BioAnalytical Report No. MC03153 titled "Determination of Clotfarabine Concentrations in Monkey Plasma and CSF for a Study of Clotfarabine Delivered Intravenously in Monkeys" (dated 5 March 2004) (will be in support of a both oral and IV formulations of clotfarabine; not submitted in Initial eNDA for IV formulation)	23-Mar-04
52	63,641	FDA Sub.	SN: 205 IND Safety Report - Follow Up Report: Follow Up to a 7-Day, Expedited Report (submitted as Serial No. 200), CIOIMS Control No. 13349, Patient No. 0010-0052 (AMC), for CLO-212 Study	30-Mar-04
52	63,641	FDA Sub.	SN: 206 Request for Review and Comment, Expedited Review of Carton and Vial Label (submitted as Item 2, N21673 A3) and Review for approval of CLOLAR as Trade Name	1-Apr-04
52	63,641	FDA Sub.	SN: 206/207 (changed to SN 207 via fax) IND Safety Report - Initial Report: 7-Day, Expedited Report, CIOIMS Control No. 13291, Patient No. 0018-0053 (AMC), for CLO-212 Study	2-Apr-04
52	63,641	FDA Sub.	SN: 208 IND Safety Report - Follow Up Report, CIOIMS Control No. 13291, Patient No. 0018-0053 (AMC), (Initial Report submitted on 1 April 2004 - SN: 207) for CLO-212 Study	19-Apr-04
52	63,641	FDA Sub.	Facsimile from Christy Cottrell/FDA: Clinical Reviewer has Requested Copies of Patient CRFs for All CRs, Pts, and CRPs (Responders) on Studies CLO-212, CLO-222 and ID99-383 (this is a copy - the original fax is filed with the eNDA submissions)	20-Apr-04

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52	63,641	FDA Sub.	SN: 209 Protocol Amendment - Change in Protocol: CLO-212-A7 (Peds ALL) titled "A Phase II, Open-Label Study of Clotfarabine in Pediatric Patients with Refractory or Relapsed Acute Lymphoblastic Leukemia", (most notable change: additional information/requirement for pre- and post- clotfarabine treatment medications)	27-Apr-04
52	63,641	FDA Sub.	SN: 210 Revised Form FDA 1572s: Charles Casey Cunninham, M.D., Mary Crowley Medical Research Center, Dallas, Texas (dated 2/4/04) for the CLO-151 Study; and Stefano Tarantolo, M.D., University of Nebraska Medical Center, Omaha, Nebraska (dated 4/1/04) for the CLO-221 Study	12-May-04
52	63,641	FDA Sub.	SN: 211 Protocol Amendment - Change in Protocol: CLO-151-A1 titled "A Phase II, Open-Label Study of Clotfarabine in Adult Patients with Advanced Solid Tumors" Adult Phase I Solid Tumor Letter from M. Dianne Murphy, M.D., Director, Off. of Counter-Terrorism and Pediatric Drug Development, CDER: FDA is amending the requirements for the data to be captured for race & ethnicity under the "Format of Reports to be Submitted" under the Written Request (Pediatric Exclusivity) under the BPCA Act (Best Pharmaceuticals for Children Act): <i>Internal note - too late for ILEX to rewrite clinical study reports that were filed in the eNDA - CRFs were not designed to capture the data as the new format requires</i>	18-May-04
52	63,641	FDA Sub.	SN: 212 Cross-reference Authorization: IST - Kristie Blum, M.D., Asst. Professor, Div. of Hematology/Oncology, The Ohio State University, Columbus, Ohio for the Study titled "A Phase III Study of Clotfarabine in Patients with Aggressive Non-Hodgkin's Lymphoma"	7-May-04
52	63,641	FDA Sub.	SN: 213 Revised Form FDA 1572 - Stewart Goldman, M.D., Children's Memorial Hospital, Chicago, ILL. (each dated 6/10/04); • Peter Steinhilber, M.D., Memorial Sloan Kettering Cancer Center, New York, NY (each dated 5/14/04); • Arnold Altman, M.D., Connecticut Children's Medical Center, Hartford, CT (each dated 5/5/04); • Lori Luchtmann-Jones, M.D., Washington Univ. School of Medicine, St. Louis/Children's Hospital, St. Louis, MO (CLO-212 Study Only dated 5/4/04); CLO-212 & CLO-222 Studies	2-Jun-04
53	63,641	Report	Report No. MC02297.02 titled "The Determination of Clotfarabine in Human Plasma in ILEX Products Study CLO-141" Report Dated 19 May 2004, By MicroConstants, Inc.	22-Jun-04
53	63,641	Report	Report No. MC02298.02 titled "Validation of a Method for the Determination of Clotfarabine in Human Urine Using High-Performance Liquid Chromatography with Mass Spectrometric (MS/MS) Detection" (MC02298.02 is Revision No. 2 of this report; the original report was submitted in Serial No. 112 on 5 Feb 2003) By MicroConstants, Inc.	
52	63,641	FDA Sub.	SN: 214 Information Amendment - Pharmacology/Toxicology: Report No. MC02297.02 (dated 19 May 2004) and Report No. MC02298.02 (dated 1 June 2004)	23-Jun-04
52	63,641	FDA Sub.	SN: 215 Response to the Office of Counter-Terrorism and Pediatric Drug Development: Acknowledgement of Amendment: Written Request "Format of Reports to be Submitted" More Specific Race & Ethnic Data Requested for Clinical Reports	23-Jun-04

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52	63,641	FDA Sub.	SN: 216 IND Safety Report - Second Follow Up Report: Follow Up to a 7-Day, Expedited Report (submitted as Serial No. 200), CIOIMS Control No. 13349, Patient No. 0010-0052 (AMC), for CLO-212 Study	13-Jul-04
52	63,641	FDA Sub.	SN: 217 Revised Form FDA 1572s: Timothy C. Griffin, MD, Cook Children's Hematology/Oncology Center, Fort Worth, Texas (two forms, both dated 07/08/04) - CLO-212 & CLO-222 Studies SN: 218 Cross-reference Authorization Letter: Edward Agura, M.D., Blood and Marrow Transplantation Services, Baylor University Medical Center, Dallas, Texas for the study titled "A Phase II Trial of Clofarabine and Cytarabine in Relapsed Standard-Risk MDS in Adult Patients, and Untreated AML in Elderly Patients" (authorization includes the co-PI: Houston Holmes, M.D., Texas Oncology, P.A. (same office as Dr. Agura))	16-Jul-04
52	63,641	FDA Sub.	Telephone Contact Report with Mike Bernstein and Amy Baird, CSO/FDA: Approval Granted for Pediatric Exclusivity (6-months) (contingent upon market approval)	19-Jul-04
52	63,641	FDA Sub.	Official Notification from WHO (World Health Organization) Nomenclature Committee / USAN Council: Clofarabine Adopted (Approved) as the INN (International Proprietary Name) from Paul Hofmann, Administrative Secretary for the USAN (United States Adopted Name Council) Program	16-Jul-04
52	63,641	FDA Sub.	Telephone Contact Report with Dotti Pease (for Christy Cottrell): Withdraw of Single-named Patient IND No. 68,260 which was inadvertently Assigned to ILEX Products Instead of Investigator Dr. Leonard Sender (approval to treat one patient issued by FDA on 1/14/04); Clarification that IND No. 63,641 Still Open - Only Site Closed for CLO-221 Adult AML Study	28-Jul-04
52	63,641	FDA Sub.	Facsimile to Dotti Pease (for Christy Cottrell): Withdraw of Single-named Patient IND No. 68,260 which was inadvertently Assigned to ILEX Products Instead of Investigator Dr. Leonard Sender (approval to treat one patient issued by FDA on 1/14/04); Clarification that IND No. 63,641 Still Open - Only Site Closed for CLO-221 Adult AML Study	23-Aug-04
52	63,641	FDA Sub.	SN: 219 IND Safety Report - Initial, Expedited 7-day Report: CIOIMS report, Control No. 13435 (Case No. BIOV-018), Patient No. 1105-0006 on Bioenvision's Study, BIOV-111 (Peds ALL) (not an ILEX sponsored study - occurred under Bioenvision's CTX 19999/0001/A) (copy of facsimile to FDA also filed here)	23-Aug-04
52	63,641	FDA Sub.	SN: 220 Request for Meeting: Pre- and Post- Approval Trials in Adults (ILEX request for a mid-October meeting to discuss development of clofarabine in adults)	26-Aug-04
52	63,641	FDA Sub.	SN: 221 IND Safety Report - Second Follow Up Report, CIOIMS Control No. 13291, Patient No. 0018-0053 (AMC), (Initial Report submitted on 1 April 2004 - SN: 207, 1st Follow Up - SN: 208) for CLO-212 Study	31-Aug-04
52	63,641	FDA Sub.		01-Sep-04

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52	63,641	FDA Sub.	<p>SN: 222 Information Amendment - Pharmacology/Toxicology: Report No. 3254.01 Formulation Analysis Report: "The Determination of Clofarabine Concentrations in Dosing Formulations: A 5-Day Intravenous Toxicity Study in Female Fischer Rats Comparing Two Lots of Clofarabine" by MicroConstants, Inc.; Report No. MBU00008 - "A Primary Eye Irritation Study in Rabbits with Clofarabine (Raw Powder)", Report No. MBU00009 - "A Primary Skin Irritation Study in Rabbits with Clofarabine (Clinical Formulation)" and Report No. MBU00010 - "A Primary Eye Irritation Study in Rabbits with Clofarabine (Clinical Formulation)"</p> <p>SN: 223 IND Safety Report - Follow Up Report: CIOMS report, Control No. 13435 (Case No. BIOV-018), Patient No. 1105-0006 on Bioenvision's Study, BIOV-111 (Peds ALL) (not an ILEX sponsored study - occurred under Bioenvision's CTX 19999/0001/A) Additional Information Received 27 August 2004</p>	07-Sep-04
52	63,641	FDA Sub.	<p>Report No. 3254.01 Formulation Analysis Report: "The Determination of Clofarabine Concentrations in Dosing Formulations: A 5-Day Intravenous Toxicity Study in Female Fischer Rats Comparing Two Lots of Clofarabine" by MicroConstants, Inc.; dated 28 October 2003</p> <p>Report No. MBU00008 - "A Primary Eye Irritation Study in Rabbits with Clofarabine (Raw Powder)", by Charles River Laboratories, dated 11 August 2004 (original report)</p> <p>Report No. MBU00009 - "A Primary Skin Irritation Study in Rabbits with Clofarabine (Raw Powder)", by Charles River Laboratories, dated 31 August 2004 (original report)</p> <p>Report No. MBU00010 - "A Primary Eye Irritation Study in Rabbits with Clofarabine (Raw Powder)", by Charles River Laboratories, dated 11 August 2004 (original report)</p> <p>Report No. MBU00011 - "A Primary Eye Irritation Study in Rabbits with Clofarabine (Clinical Formulation)", by Charles River Laboratories, dated 11 August 2004 (original report)</p> <p>Report No. MBU00012 - "A Primary Eye Irritation Study in Rabbits with Clofarabine (Clinical Formulation)", by Charles River Laboratories, dated 11 August 2004 (original report)</p> <p>SN: 224 Revised Form FDA 1572s: Susan Rheingold, The Children's Hospital of Philadelphia, Philadelphia, PA (dated 08/13/04), Susan Rheingold, The Children's Hospital of Philadelphia, Philadelphia, PA (dated 01/30/03, 08/07/03, and 06/17/04), and A. Kim Ritchey, MD, Children's Hospital of Pittsburgh, PA (dated 06/24/04) CLO-222 Study Peds ALL</p> <p>SN: 225 Revised Form FDA 1572s: Susan Blaney, MD, Texas Children's Hospital, Houston, Texas (dated 08/13/04), Susan Rheingold, The Children's Hospital of Philadelphia, Philadelphia, PA (dated 01/30/03, 08/07/03, and 06/17/04), and A. Kim Ritchey, MD, Children's Hospital of Pittsburgh, PA (dated 06/24/04) CLO-212 Study Peds ALL</p> <p>SN: 226 Revised Form FDA 1572 - Donald A Richards, MD, Tyler Cancer Center, Tyler, Texas (dated 07/21/04) for the CLO-151 study</p>	07-Sep-04
53	63,641	Report	<p>Report No. MBU00008 - "A Primary Eye Irritation Study in Rabbits with Clofarabine (Raw Powder)", by Charles River Laboratories, dated 11 August 2004 (original report)</p>	
53	63,641	Report	<p>Report No. MBU00009 - "A Primary Skin Irritation Study in Rabbits with Clofarabine (Raw Powder)", by Charles River Laboratories, dated 31 August 2004 (original report)</p>	
53	63,641	Report	<p>Report No. MBU00010 - "A Primary Eye Irritation Study in Rabbits with Clofarabine (Raw Powder)", by Charles River Laboratories, dated 11 August 2004 (original report)</p>	
53	63,641	Report	<p>Report No. MBU00011 - "A Primary Eye Irritation Study in Rabbits with Clofarabine (Clinical Formulation)", by Charles River Laboratories, dated 11 August 2004 (original report)</p>	
54	63,641	FDA Sub.	<p>SN: 225 Revised Form FDA 1572s: Susan Blaney, MD, Texas Children's Hospital, Houston, Texas (dated 08/13/04), Susan Rheingold, The Children's Hospital of Philadelphia, Philadelphia, PA (dated 01/30/03, 08/07/03, and 06/17/04), and A. Kim Ritchey, MD, Children's Hospital of Pittsburgh, PA (dated 06/24/04) CLO-212 Study Peds ALL</p>	08-Sep-04
54	63,641	FDA Sub.	<p>SN: 226 Revised Form FDA 1572 - Donald A Richards, MD, Tyler Cancer Center, Tyler, Texas (dated 07/21/04) for the CLO-151 study</p>	08-Sep-04
54	63,641	FDA Sub.	<p>Facsimile from Amy Baird/CSO/FDA: Response to SN: 220 ILEX Request for Meeting: Pre- and Post- Approval Trials in Adults (to discuss development of clofarabine in adults) FDA Meeting Date Set for 2 November 2004 (10:30am)</p>	10-Sep-04
54	63,641	FDA Sub.		14-Sep-04

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54	63,641	FDA Sub.	<p>SN: 227 Cross-reference Authorization: CLL Research Consortium (CRC), for the Study Titled "Phase I Study of Weekly Clofarabine for the Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia" (CRC 006 Master Protocol); Contact CRC Principal Investigator Thomas J. Kipps, M.D., Director, CLL Research Consortium, Univ of California San Diego, School of Medicine, La Jolla, California</p> <p>SN: 228 Adult AML Meeting Package: Teleconference Scheduled for 2 November 2004; Adult Strategy - Clinical Development; Vol. 1 of 4: Meeting Package & Reference Articles</p> <p>SN: 228 Adult AML Meeting Package: Teleconference Scheduled for 2 November 2004; Adult Strategy - Clinical Development; Vol. 2 of 4: Reference Articles</p> <p>SN: 228 Adult AML Meeting Package: Teleconference Scheduled for 2 November 2004; Adult Strategy - Clinical Development; Vol. 3 of 4: Appendix - CLO-221 Clinical Study Report</p> <p>SN: 228 Adult AML Meeting Package: Teleconference Scheduled for 2 November 2004; Adult Strategy - Clinical Development; Vol. 4 of 4: Appendix - CLO-141 Clinical Study Report</p> <p>SN: 229 IND Safety Report: Initial, 7-Day Expedited Report, CIOMS Report, Control No. 13462, Patient No. 0001-2055 (MJP), CLO-151 Adult Solid Tumor Study</p> <p>Facsimile from Christy Cottrell/CSO/FDA: FDA Answers to Adult Strategy Submission, Serial No. 228 (Requesting a Teleconference to Discuss Future Adult Studies); Teleconference Set for 2 November 2004 is optional</p>	30-Sep-04
55	63,641	FDA Sub.	<p>SN: 228 Adult AML Meeting Package: Teleconference Scheduled for 2 November 2004; Adult Strategy - Clinical Development; Vol. 1 of 4: Meeting Package & Reference Articles</p> <p>SN: 228 Adult AML Meeting Package: Teleconference Scheduled for 2 November 2004; Adult Strategy - Clinical Development; Vol. 2 of 4: Reference Articles</p>	07-Oct-04
56	63,641	FDA Sub.	<p>SN: 228 Adult AML Meeting Package: Teleconference Scheduled for 2 November 2004; Adult Strategy - Clinical Development; Vol. 3 of 4: Appendix - CLO-221 Clinical Study Report</p> <p>SN: 228 Adult AML Meeting Package: Teleconference Scheduled for 2 November 2004; Adult Strategy - Clinical Development; Vol. 4 of 4: Appendix - CLO-141 Clinical Study Report</p>	07-Oct-04
57	63,641	FDA Sub.	<p>SN: 229 IND Safety Report: Initial, 7-Day Expedited Report, CIOMS Report, Control No. 13462, Patient No. 0001-2055 (MJP), CLO-151 Adult Solid Tumor Study</p>	07-Oct-04
58	63,641	FDA Sub.	<p>SN: 229 IND Safety Report: Initial, 7-Day Expedited Report, CIOMS Report, Control No. 13462, Patient No. 0001-2055 (MJP), CLO-151 Adult Solid Tumor Study</p>	07-Oct-04
54	63,641	FDA Sub.	<p>SN: 229 IND Safety Report: Initial, 7-Day Expedited Report, CIOMS Report, Control No. 13462, Patient No. 0001-2055 (MJP), CLO-151 Adult Solid Tumor Study</p>	13-Oct-04
54	63,641	FDA Corres.	<p>SN: 228 (Requesting a Teleconference to Discuss Future Adult Studies); Teleconference Set for 2 November 2004 is optional</p>	27-Oct-04
53	63,641	Report	<p>Report No. ILEX-26: "Toxicity Evaluation of Clofarabine (NSC 606869) with Ara-C (NSC 63878) in Male Scid Mice", by Southern Research Institute; Evaluation/Report date 2 September 2003</p>	
53	63,641	Report	<p>Report No. ILEX-37: "Response of RPMI-8226 Myeloma to Treatment with Vincristine, Fludarabine, Clofarabine, or ILX-651", by Southern Research Institute (SRI Report No. A542.10), report dated 19 July 2004 (this is the original report, a copy is filed to ILX-651/IND No. 61,748)</p> <p>Report No. MC02297.03 titled: "The Determination of Clofarabine in Human Plasma in ILEX Products Study CLO-141", Report Dated 27 September 2004, by MicroConstants, Inc. (this is a revised report for corrections to errors in sampling times/Report No. MC02297.02 was submitted in Serial No. 214 on 23 June 2004)</p> <p>SN: 230 Information Amendment - Pharmacology/Toxicology: Report No. ILEX-26: "Toxicity Evaluation of Clofarabine (NSC 606869) with Ara-C (NSC 63878) in Male Scid Mice", by Southern Research Institute; Evaluation/Report date 2 September 2003; Report No. ILEX-37: "Response of RPMI-8226 Myeloma to Treatment with Vincristine, Fludarabine, Clofarabine, or ILX-651", by Southern Research Institute (SRI Report No. A542.10), report dated 19 July 2004; Report No. MC02297.03 titled: "The Determination of Clofarabine in Human Plasma in ILEX Products Study CLO-141", Report Dated 27 September 2004, by MicroConstants, Inc.</p> <p>SN: 231 IND Safety Report - Initial, Expedited 7-day Report: CIOMS report, Control No. 13490 (Case No. B10V-028), Patient No. 1101-0012 on Bioenvision's Study, B10V-111 (Peds ALL) (not an ILEX sponsored study - occurred under Bioenvision's CTX 19999/0001/A)(copy of facsimile to FDA also filed here)</p>	
54	63,641	FDA Sub.	<p>SN: 231 IND Safety Report - Initial, Expedited 7-day Report: CIOMS report, Control No. 13490 (Case No. B10V-028), Patient No. 1101-0012 on Bioenvision's Study, B10V-111 (Peds ALL) (not an ILEX sponsored study - occurred under Bioenvision's CTX 19999/0001/A)(copy of facsimile to FDA also filed here)</p>	28-Oct-04
54	63,641	FDA Sub.	<p>SN: 231 IND Safety Report - Initial, Expedited 7-day Report: CIOMS report, Control No. 13490 (Case No. B10V-028), Patient No. 1101-0012 on Bioenvision's Study, B10V-111 (Peds ALL) (not an ILEX sponsored study - occurred under Bioenvision's CTX 19999/0001/A)(copy of facsimile to FDA also filed here)</p>	02-Dec-04

54	63,641	FDA Sub.	SN: 232 Revised Form FDA 1572s: Multiple Investigators: Edythe Albano, MD, The Children's Hospital, Denver Colorado (dated 08/03/04); Susan Blaney, MD, Texas Children's Hospital, Houston, Texas (dated 09/08/04); Bruce Gordon, MD, Pediatric Hematology/Oncology & Bone Marrow Transplantation Program, Omaha, Nebraska (dated 05/21/03); Bassem Razzouk, MD, St. Jude's Children Hospital, Memphis, Tennessee (dated 11/12/03); Susan Rheingold, The Children's Hospital of Philadelphia, Philadelphia, PA (dated 09/28/04); A. Kim Ritchey, MD, Children's Hospital of Pittsburgh, Pittsburgh, PA (dated 09/01/04); and Michael Rytting, MD, UTMADACC, Houston, Texas (dated 08/10/04) CLO-212 Study Peds ALL	06-Dec-04
54	63,641	FDA Sub.	SN: 233 Revised Form FDA 1572s: Multiple Investigators: Edythe Albano, MD, The Children's Hospital, Denver Colorado (dated 08/03/04); Susan Blaney, MD, Texas Children's Hospital, Houston, Texas (dated 09/08/04); Stewart Goldman, MD, Children's Memorial Hospital, Chicago, Illinois (dated 06/23/04); Bruce Gordon, MD, Pediatric Hematology/Oncology & Bone Marrow Transplantation Program, Omaha, Nebraska (dated 05/21/03); Bassem Razzouk, MD, St. Jude's Children Hospital, Memphis, Tennessee (dated 11/12/03); A. Kim Ritchey, MD, Children's Hospital of Pittsburgh, Pittsburgh, PA (dated 09/01/04); and Michael Rytting, MD, UTMADACC, Houston, Texas (dated 08/10/04) CLO-212 Study Peds ALL	06-Dec-04
54	63,641	FDA Sub.	SN: 234 Information Amendment - Clinical: Revised Investigator's Brochure (IB) Edition 4, dated 12/3/04	06-Dec-04
54	63,641	FDA Sub.	Facsimile from Christy Cottrell/CSO/FDA: Official Meeting Minutes from the 2 November 2004 Teleconference Discussing pre- and post Approval Trials in Adults (includes specific comments for defining the elderly patient population, endpoints, registration strategy, and acceptance as support of pediatric approval/confirmatory trial)	06-Dec-04
54	63,641	FDA Sub.	SN: 235 IND Safety Report - Follow Up Report to an Expedited 7-day Report (SN: 231): CIOMS BIOV-111 (Peds ALL) (not an ILEX sponsored study - occurred under Bioenvision's Study, 19999/0001/A)(copy of facsimile to FDA also filed here)	08-Dec-04
54	63,641	FDA Sub.	SN: 236 Response to FDA Request for Information - Post-Approval Commitments/ILEX Request for Comment: Includes CLO-216 Protocol titled " A Phase I/II Dose-Escalation Study of Clofarabine Plus Cytarabine and L-Asparaginase in Pediatric Patients With Refractory or Relapsed Acute Lymphoblastic Leukemia (FDA Draft): Post-Approval Development Timeline: COG Protocol No. AALL01P2 titled "Intensive Induction Therapy for Children with Acute Lymphoblastic Leukemia (ALL) Who Experience A Bone Marrow Relapse", CLO-312 Protocol Synopsis, study titled " A Randomized Trial of Clofarabine Plus Cytarabine and Asparaginase Versus Cytarabine and Asparaginase in Pediatric Patients With Acute Lymphoblastic Leukemia (ALL) in First Relapsed (see COG protocol AALL01P2)	09-Dec-04
59	63,641	FDA Sub.		13-Dec-04

BINDER

59	63,641	FDA Corres.	<p>Facsimile to Christy Cottrell/CSO: Copy of the Official Notification from American Medical Association/USAN Council: Clofarabine Adopted (Approved) as the USAN Name in Support of FDA's Comments to the Draft Package Insert that Clofarabine was not Published in the 2004 USP SN: 237 <u>Cross-reference authorization for Barry L. Powner, M.D., Director, Leukemia Service, Comprehensive Cancer Center of Wake Forest University, Winston-Salem, NC for the Study Titled "Phase III Open-Label Study of High-Dose Cytarabine and Clofarabine in Adult Patients with Refractory or Relapsed Acute Myelogenous Leukemia or Refractory or Relapsed Acute Lymphoblastic Leukemia"</u></p>	13-Dec-04
59	63,641	FDA Sub.	<p><u>SN: 238 Missed/Inadvertently not used</u> <u>SN: 239 IND Safety Report - Follow Up Report to an Expedited 7-day Report (SN: 231): CIOIMS Report, Control No. 13490 (Case No. BIOV-028), Patient No. 1101-0012 on Bioenvision's Study, BIOV-111 (Peds ALL) (not an ILEX sponsored study - occurred under Bioenvision's Study, 19999/0001/A)(copy of facsimile to FDA also filed here)</u></p>	20-Dec-04
59	63,641	FDA Sub.	<p><u>SN: 240 IND Safety Report - Initial, 15-day Expedited Report, CIOIMS Report, Control No. 13488 (Case No. BIOV-026), Patient No. 1301-0014 on Bioenvision's Study, BIOV-111 (Peds ALL) (not an ILEX sponsored study - occurred under Bioenvision's CTX 19999/0001/A)(copy of facsimile to FDA also filed here)</u></p>	20-Dec-04
59	63,641	FDA Sub.	<p><u>SN: 241 Request for PROTOCOL EXCEPTION: Treatment of Single, Named Patient Under IND No. 63,641 (per FDA - due to clofarabine approval & CLO-212 study closed to enrollment) for Patient R-S under Violet Shen, M.D. at Children's Hospital of Orange County, Orange, CA</u></p>	03-Jan-05

BINDER				
10	63,641	FDA Corres.	Telephone Contact Report: Discussion on CLOFAREX Pediatric Exclusivity, Timing of NDA Submission, etc. Official request (E-mail from Mike Bernstein) to USAN Council (Stephanie Schubat, Assoc. Secretary) to keep Clofarabine - not Clofarax - after USAN denial for ILEX to use both: see additional correspondence & approval of the name Clofarabine: 3 Oct. 2002, 13 Dec. 2002, 27 Dec. 2002, 29 May 2003 & 23 June 2003	27-Aug-02
13	63,641	FDA Corres.		
22	63,641	Tel. Contact Rep.	Telephone Contact Report Between Chrissy Cottrell/FDA, Mike Bernstein & Jenny Swalac: Discussion on Timing of NDA Submission for Pediatric ALL, Request/Application for Fast-Track Designation for Pediatric ALL, Pre-NDA Mtg Pkg (submission) & Rolling NDA Submission	28-Oct-02
24	63,641	FDA Sub.	SN: 136 Request for Pre-NDA Meeting for Clofarabine in Acute Lymphoblastic Leukemia (ALL): Proposed date of Meeting - First Week in August	1-May-03
22	63,641	FDA Corres.	Facsimile from Chrissy Cottrell/FDA: Confirmation of Pre-NDA, Scheduled for 13 August 2003 and List of Attendees	3-Jun-03
22	63,641	FDA Corres.	Official E-mail from Mike Bernstein to Chrissy Cottrell/FDA: Corrections to Serial No. 129 (Fast Track Application, 8 May 2003) Response Definition and Primary/Secondary Objectives	11-Jun-03
23	63,641	FDA Sub.	SN: 129 Request for Fast Track Designation and NDA Rolling Submission Strategy (ALL Indication)	20-Jun-03
24B	63,641	Report	Report No. MCO2470: Pharmacokinetics Report - "Intravenous and Oral Pharmacokinetic Study of Clofarabine in Male CD-1 Mice, Report Dated 8 May 2003 (ILEX Study No. 0212-01 (will be referenced in the Oral Formulation Initial IND and NDA Pkg)/(submitted as a stand alone report to the IND in Serial No. 144 on 15 July 2003)	8-May-03
24C	63,641	Report	NCI Screening Data: In Vitro Anti-Tumor Screening on 60-Tumor Cell Lines ... Referenced in the IB, Oral IND and IV NDA (Report Date: 16 April 2003; Test Date: 3 March 2003)	
32	63,641	FDA Sub.	SN: 143 Pre-NDA Meeting Package (Meeting Scheduled for 13 August 2003)	
34	63,641	FDA Corres.	Fast Track Designation Granted to Clofarabine for Acute Lymphoblastic Leukemia (ALL) Includes Acceptance of Rolling NDA Submission (now called a 'step-wise' submission)	11-Jul-03
34	63,641	FDA Corres.	Facsimile from Chrissy Cottrell/FDA: Comments Regarding the Pre-NDA Package Submitted for Meeting Set for 13 August 2003	8-Jul-03
34	63,641	FDA Corres.	Facsimile from Chrissy Cottrell/FDA: Pre-NDA Meeting Changed to a Teleconference for 13 August 2003 (in place of face-to-face meeting)	05-Aug-03
				07-Aug-03

34	63,641	Internal Corres	Minutes of Teleconference (in place of Face-To-Face pre-NDA CMC meeting scheduled for 13 Aug 2003) to discuss pre-NDA package; FDA feedback on overall clinical data, the rolling NDA sections; timing of CMC submissions....(minutes generated internally by ILEX)	13-Aug-03
34	63,641	FDA Sub.	SN: 162 Pre-NDA CMC Meeting Request: Proposed Week of 1 December or 8 December 2003 Facsimile from Christy Cottrell/FDA: Confirmation of pre-NDA CMC Mtg Scheduled for 10 December 2003 at 2:00pm; Includes List of FDA Attendees (this is in response to SN: 162: Request for Meeting)	01-Oct-03
34	63,641	pre-NDA	Request for Meeting)	08-Oct-03
49	63,641	FDA Sub.	SN: 172 Pre-NDA CMC Meeting Package - Meeting Scheduled for 10 December 2003: Several Questions; Proposed Table of Contents; Copies of Supporting FDA Correspondence Included Facsimile from Christy Cottrell/FDA: FDA Responses to Questions from ILEX's pre-NDA CMC Meeting Package: (If responses acceptable to ILEX, a meeting is not required)	07-Nov-03
49	63,641	pre-NDA	Call between Christy Cottrell and Edda Tschirhart: ILEX Request Teleconference to Discuss Responses to pre-NDA CMC Meeting Questions	04-Dec-03
49	63,641	FDA Sub.	SN: 179 Response to FDA Facsimile of 4 December 2003 (FDA Responses to pre-NDA CMC Meeting Package (submitted as SN: 172 on 7 November 2003))	04-Dec-03
49	63,641	pre-NDA	Minutes of Teleconference (in place of Face-To-Face pre-NDA CMC meeting scheduled for 10 Dec 2003) to discuss pre-NDA CMC Information: FDA responses to SN: 172 pre-NDA CMC Meeting Package (fax of 4 December 2003 from FDA): Specifically extractable/teachable and validation of API & drug product.	08-Dec-03
49	63,641	FDA Corres.	Facsimile from Christy Cottrell/FDA: Meeting Minutes from 10 December 2003 pre-NDA CMC Teleconference with Addendum Added of Minutes from Teleconference of 17 December 2003 Between the FDA District Office, FDA Office of Compliance, ILEX and Ash Stevens, Inc.: Includes Minutes Provided by ILEX and Minutes Provided by Judith A. Putz, FDA District Office/Detroit: Concurrent Validation of API Process (Yes- accepted & approved) Several Details Included in Minutes Regarding Materials, Process, Validation, etc. SN: 185 Dear Doctor Safety Letter - Copies To All Principal Investigators: Guidance and Treatment Recommendations (RE: Capillary Leak Syndrome, SIRS) from Steve Wetman, MD, PhD	10-Dec-03
52	63,641	FDA Sub.	Facsimile from Christy Cottrell/FDA: Clinical Reviewer has Requested Copies of Patient CMCs for All CRs, PRs, and CRPs (Responders) on Studies CL-O-212, CL-O-22 and ID99-383 (this is a copy - the original fax is filed with the eNDA submissions)	06-Jan-04
52	63,641	FDA Corres.		06-Feb-04
52	63,641	FDA Corres.		20-Apr-04

Clofarabir. JA 21-673

1	21-673	FDA Sub. - NDA	Original Application - Submission #1: Items 1(TOC), 5(Pharm/Tox), 13(Patent Info), 14(Patent Cert.), 16(Debarment Cert), and 18(User Fee Cover Sheet); binder includes those documents which were sent as hard copies, and a copy of the CD which contained the electronic submission	26-Sep-03
2	21-673	FDA Sub. - NDA	A1 - Submission #2: Resubmission of items included in submission #1, an electronic navigation file was left out of original submission therefore requiring the resubmission with inclusion of the navigation file (no other changes were made to the submission); binder includes those documents which were sent as hard copies, and a copy of the CD which contained the electronic submission (Pharmacology/Toxicology)	3-Oct-03
3	21-673 63,641	FDA Sub. - NDA FDA Sub. - NDA	A2 - Submission #3: Item 4 (CMC): binder includes those documents which were sent as hard copies, and a copy of the CD which contained the electronic submission	17-Oct-03
4	21-673	FDA Sub. - NDA	Official Notification of Receipt of Part 2 of the Step-Wise NDA Submission: CMC Sections 12(CRFs), 17(Field Copy Cert), and 19(Financial Disclosure, Claimed Exclusivity, Cert of Electronic Submission); binder includes those documents which were sent as hard copies, and a copy of the CD which contained the electronic submission	24-Feb-04 03-Mar-04
	21-673	FDA Sub. - NDA	Desk Copies of the Clinical Study Reports (CLO-212, CLO-222, ID99-383, ISS, ISE & ClinData - Only the Body of the Reports, Appendices not included) for the Clinical Reviewer (per request in email of 26 March 2004)	29-Mar-04
	21-673	FDA Sub. - NDA	Facsimile from Christy Cottrill/CSO/FDA: Request for Copies of CRFs for All PRs, CRs, and CRps for Patient in Studies CLO-212, CLO-222 and ID99-383	31-Mar-04
5	21-673	FDA Sub. - NDA	A4 - Submission #5: Response to FDA Request - Patient CRFs (Responders) (FDA Request dated 20 April 2004)	20-Apr-04
	21-673	FDA Sub. - NDA	Meeting Minutes of 13 May 2004 - Clofarabine NDA Presentation - Short Overview of Clinical, Nonclinical, Pharmacology & CMC; List of Attendees & Copy of PowerPoint Slides Included (email from Mike Bernstein attached - received minutes & presentation on 1 July 2004)	22-Apr-04
	21-673	FDA Sub. - NDA	Facsimile from Amy Baird/CSO/FDA: Analysis from the FDA Clinical Review Team of the Responders in Study CLO-222 (fax reads CLO-220) Pediatric AML Patients based on the aspirate database (this is a table with responses, conformed responses, duration of response, and death)	13-May-04
	21-673	FDA Sub. - NDA		28-May-04

Clofarabine DA 21-673

21-673	FDA Corres.	Official Filing Letter: Acknowledgement of Receipt of the Application: CLOLAR (clofarabine) Intravenous 52mg/m2 day; Priority (P) Classification: Appl. Date: 29 March 2004 (received letter on 4 June 2004)	28-May-04
21-673	FDA Corres.	Facsimile from Army Baird/CSO/FDA: Draft Comments to be forthcoming in Proposed Filing Letter (1) ALL & AML Protocols Require Confirmation of Responses by Bone Marrow Aspiration and (2) Provide Patient Listings for Patients Who Went On To Transplant or Biopsy with Results	
21-673	FDA Corres.	Facsimile from Army Baird/CSO/FDA: Page 33, Item 6.3.1.7 Confirmation of Responses from CLO-212 Protocol -sent per ILEX request as follow up to teleconference discussing response durations and response confirmations/ teleconference of 4 June 2004)	2-Jun-04
21-673	FDA Corres.	Facsimile from Army Baird/CSO/FDA: Full Tables Listing Responders per Request from ILEX (see fax of 28 May 2004 - some lines/patient info missing in fax of 28 May 2004)	4-Jun-04
21-673	FDA Corres.	Meeting Minutes (ILEX Generated) of Teleconference of 4 June 2004 Between FDA (Dr. Johnson, Dr. Cohen & Army Baird/CSO) and ILEX (Steve Weisman, Mike Bernstein, Francis Ruvana/Data Mgmt & Bret Wacker/Biostats): Discussion of Facsimile from FDA of 28 May 2004 Regarding Responders, Duration of Responses & Calculations/Analysis done: Proposed Submission of Additional Efficacy Data	4-Jun-04
21-673	FDA Corres.	Official Filing Letter: Acceptance of CLOLAR NDA - Sufficient for Review - Two Potential Review Issues Request for Response: (1) ALL & AML Protocols Require Confirmation of Responses by Bone Marrow Aspiration, Provide Data Listings for Bone Marrow Evaluations, and (2) Provide Patient Listings for Patients Who Went On To Transplant or Biopsy, with Results (received letter on 18 June 2004)	4-Jun-04
21-673	FDA Corres.	Facsimile from Army Baird/CSO/FDA: Copy of Official Filing Letter (hard copy to follow via mail): Acceptance of CLOLAR NDA - Sufficient for Review - Two Potential Review Issues - Request for Response: (1) ALL & AML Protocols Require Confirmation of Responses by Bone Marrow Aspiration, Provide Data Listings for Bone Marrow Evaluations, and (2) Provide Patient Listings for Patients Who Went On To Transplant or Biopsy, with Results (actual letter dated 8 June 2004)	8-Jun-04
21-673	FDA Corres.	Email from Mike Bernstein to Army Baird/CSO/FDA: Letter/Initial Response to FDA and the Two Review Issues Addressed in the Official Filing Letter (fax of 28 May 2004) and Discussion During Teleconference of 4 June 2004 (ILEX & FDA): ILEX Will Submit Additional Data on Responders as Requested and Additional Efficacy Data as an Updated ISE (under separate cover from responder information)	9-Jun-04
21-673	Gen. Corres.	Copy of Case Report Forms for All Responders on CD ROM (submitted to FDA as A4 - #5) to Mark Hayes at Genzyme	10-Jun-04
21-673	FDA Corres.	Email from Mike Bernstein to Army Baird/CSO/FDA: ILEX Will Submit Additional Efficacy Data on Original 70 Patients and Additional 14 Patients: Proposal to Submit by 9 July 2004; Submission will be an Updated ISE: ISS Will Follow Under Separate Cover	17-Jun-04
21-673	FDA Corres.		22-Jun-04

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21-673	FDA Corres.	Email from Amy Baird/CSO/FDA to Mike Bernstein: Official Confirmation to ILEX to Submit Provide the Patient CRFs for Follow Up Patients in Their Entirety (per FDA clinical reviewers Drs. Cohen and Johnson)	23-Jun-04
21-673	FDA Corres.	Email from Amy Baird/CSO/FDA to Mike Bernstein: Official Confirmation to ILEX to Submit the Data/Efficacy Data will be Recognized as a Major Amendment	23-Jun-04
21-673	FDA Sub. - NDA	A5 - Submission #8: Response to FDA File Letter of 8 June 2004, FDA Facsimile of 28 May 2004 and Teleconference of 4 June 2004: Assessments of FDA Responder Summary tables for CLO-212 Study and CLO-222 Study (includes copy of the CD)	23-Jun-04
21-673	FDA Corres.	Official Telephone Contact Report from Amy Baird/CSO/FDA: Pediatric Exclusivity Board Meeting Held 14 July 2004, Clofarabine Granted 6-Month Pediatric Exclusivity (contingent upon market approval) (formal response to phone call from Mike Bernstein inquiring about the status of pediatric exclusivity for clofarabine: telephone contact report by Mike Bernstein is attached)	7-Jul-04
21-673	FDA Sub. - NDA	A6 - Submission #7: Item 9 - 120-day Safety Update (includes an updated ISS report and updated CRFs for CLO-212 and CLO-222 Studies and a copy of the CD)	16-Jul-04
21-673	FDA Sub. - NDA	A7 - Submission #8: Efficacy and CMC Update (includes follow up data on patients presented in the original ISE; data on 14 additional patients [9 from CLO-212/ALL study and 5 from CLO-222/AML study]; and updated analysis and assessment of efficacy data)	2-Aug-04
21-643	FDA Corres.	Email: Confirmation from Amy Baird/CSO/FDA: New PDUFA date is 30 December 2004 - No Word on Advisory Committee Date (as of the email)	5-Aug-04
21-673	FDA Corres.	Facsimile from Amy Baird/CSO/FDA (filling in for Christy Cottrell): Acknowledgement of the Receipt of the Major Amendment(A7: Submission #8 - Efficacy & CMC Update) for the NDA	16-Aug-04
21-673	FDA Corres.	Official Notification of the Extension of the Review Period of the NDA under PDUFA Regulations: Extended User Fee Goal Date is now 31 December 2004	24-Aug-04
21-673	FDA Corres.	Facsimile from Amy Baird/CSO/FDA (filling in for Christy Cottrell): Summary Table from the Clinical Reviewers Describing Their Findings for Duration/Responses Based on Bone Marrow Aspirates for CLO-212 and CLO-222 Studies (requires ILEX response/concur or explain)	24-Aug-04
21-673	FDA Corres.	Email from Edda Tschirhart, ILEX Reg. Affairs to Amy Baird/CSO/FDA: Confirmation of the Receipt of the Facsimile of 10 Sept 2004 from FDA (Summary Table... Duration/Responses Based on Bone Marrow Aspirates for CLO-212 and CLO-222 Studies)...	10-Sep-04
21-673	FDA Corres.	Facsimile to Amy Baird/CSO/FDA: Request for Clarification of Start & Stop Dates Used for the Assessment of Response Duration and TTP for Patients from the CLO-212 & CLO-222 Studies as Presented in the Summary Table in the Facsimile from FDA of 10 September 2004 (also submitted as a formal amendment to the FDA) (fax resent on 17 Sept 2004)	14-Sep-04
21-673	FDA Corres.		15-Sep-04

9	21-673	FDA Sub. - NDA	A8 - Submission #9: Request for Clarification of Start & Stop Dates Used for the Assessment of Response Duration and TTP for Patients from the CLO-212 & CLO-222 Studies as Presented in the Summary Table in the Facsimile from FDA of 10 September 2004 Email from Johanna Clifford/Executive Secretary-ODAC/FDA: Specific Details for ODAC Meeting Scheduled for 8:00am, 1 December 2004 - 40 Paper Copies and 2 Electronic Copies in MicroSoft Word Format Due to FDA on 22 October 2004 (see email of 29 September 2004 for change in date) to Advisors and Consultants Staff, FDA, CDER, OEP, HFD-21, Room 1095, 5630 Fishers Lane, Rockville, MD, 20852-1734, Tel: 301-827-6761 Facsimile from Amy Baird/CSO/FDA: Request for Contact Information for AAI Development Services (3 Locations) per Chemistry Reviewers Facsimile from Mike Bernstein to Amy Baird/CSO/FDA: Response to FDA Request for Contact Information for AAI Development (see fax from FDA dated 9/21/04) Email from Mike Bernstein to Amy Baird/CSO/FDA: Inquiry as to FDA's Response to Request for Teleconference to Discuss Start and Stop Dates for Assessment of Response Durations and TTP (Submission of 15 September 2004)	15-Sep-04
	21-673	FDA Corres.	Emails between Mike Bernstein and Johanna Clifford/Exec. Secretary-ODAC/FDA: Request for Information Regarding ODAC Agenda/Meeting Location (for ILEX preparation for travel & hotel) Email from Johanna Clifford/Executive Secretary-ODAC/FDA: ODAC Package Due to FDA 28 October 2004 (change in date from previous email) Meeting Scheduled for 8:00am, 1 December 2004 - 40 Paper Copies and 2 Electronic Copies in MicroSoft Word Format Due to FDA on 22 October 2004 (Address Lane, Rockville, MD, 20852-1734, Tel: 301-827-6761)	22-Sep-04
	21-673	FDA Corres.	Submitted to the Nomenclature Committee (for approvability); Status on Acceptance of CLOLAR as the Marketed Name for Clofarabine	29-Sep-04
	21-673	FDA Corres.	Emails between Mike Bernstein and Amy Baird/CSO/FDA: Request for the Name CLOLAR to be Designation Now or to Wait for ODAC Meeting (Per Amy/FDA: Consensus is to Wait, Still Possibility of Full Approval vs. Accelerated Approval)	29-Sep-04
	21-673	FDA Corres.	Email: Confirmation from Amy Baird/CSO/FDA: New PDUFA date is 30 December 2004 - No Word on Advisory Committee #10: Response to Analysis of Response Duration and TTP for Patients from the CLO-212 & CLO-222 Studies as Presented in the Summary Table in the Facsimile from FDA of 10 September 2004; ILEX Requests Teleconference to Discuss	1-Oct-04
10	21-673	FDA Sub. - NDA	Email: From Edda Tschirhart to Johanna Clifford, Executive Secretary/ODAC: List of Consultants (List of Principal Investigators for Clofarabine Studies as Presented in Table 8.2 of the Clinical Section of the NDA; List does not include sub-investigators)	9-Oct-04
	21-673	FDA Corres.		19-Oct-04

	21-673	FDA Corres.	Facsimile from Mike Bernstein to Johanna Clifford/Executive Secretary/ODAC Meeting/FDA: List of Experts in Acute Leukemias in Pediatrics (with contact information)	
	21-673	FDA Sub. - NDA	ODAC Briefing Document: for Meeting scheduled for 1 December 2004: 40 paper copies and 2 electronic copies (CDs with Microsoft Word File of Volume 1) to Johanna Clifford, Executive Secretary for ODAC; Volume 1 of 2	27-Oct-04
	21-673	FDA Sub. - NDA	ODAC Briefing Document: for Meeting scheduled for 1 December 2004: 40 paper copies and 2 electronic copies (CDs with Microsoft Word File of Volume 1) to Johanna Clifford, Executive Secretary for ODAC; Volume 2 of 2 (Volume 2: Appendix A - Articles & Publications not referenced in document)	27-Oct-04
	21-673	FDA Corres.	Email from Mike Bernstein to Christy Cottrell/CSO/FDA: "Latest Update Package Insert (PI) with the 84 Patient Data" with commitment to submit official annotated PI as a formal submission	27-Oct-04
	21-673	FDA Sub. - NDA	A10 - Submission #11: Updated Components to NDA Sections; Item 2: Labeling (Proposed Labeling & Package Insert), Item 13: Patent Information and Item 14: Patent Certification	11-Nov-04
	21-673	FDA Corres.	Email from Mike Bernstein to Christy Cottrell/CSO/FDA: Slides Presented at ASH 2004 Conference (Presented by investigators: S. Jeha, M.D., B. Razouk, M.D., M. Rytting, M.D., et al.)	18-Nov-04
14	21-673	FDA Corres.	ODAC Briefing Document Created by CDER, FDA: Oncologic Drugs Advisory Committee Meeting Package - Note: FDA has marked a few 'Readactions'	24-Nov-04
	21-673	FDA Corres.	Email from Tracie Reed to Christy Cottrell: Confirmation of Dr. Pazdur's email address for forthcoming letter from Mike Bernstein & Steve Weltman	1-Dec-04
	21-673	FDA Corres.	Email from Christy Cottrell/CSO/FDA to Steve Weltman & Mike Bernstein: FDA's first set of comments/revisions to the dofarabine package insert; note: this does not include comments from Dr. Temple; per email, ILEX to respond by close of business 15 December 2004; attachments include tracked changes (FDA's revisions) & clean copy; ILEX to work from clean copy; see submission of 15 December 2004: A11 - Sub 12	3-Dec-04
	21-673	FDA Corres.	Email from Edda Tschlthart, ILEX Reg. Affairs to Christy Cottrell/CSO/FDA: A11 - Submission #12: Labeling Update - Revised Package Insert (PI) in response to FDA's first set of comments; (see email of 10 December 2004) (Tracked Changes & Clean Copy Versions/Microsoft Word)(Email Reply from Christy Cottrell also filed Here)	10-Dec-04
	21-673	FDA Sub. - NDA	A11 - Submission #12: Labeling Update - Revised Package Insert (PI) in response to FDA's first set of comments; (see email of 10 December 2004) (Tracked Changes & Clean Copy Versions/Microsoft Word)	15-Dec-04
15	21-673	FDA Sub. - NDA	Email from Christy Cottrell/CSO/FDA to Mike Bernstein: FDA's Comments from Chemistry Review Team: Deficiencies with Drug Substance and Drug Product (TMA407, Impurities/Degradants, etc.) ILEX to respond by close of business 21 December 2004	15-Dec-04
	21-673	FDA Corres.		17-Dec-04

16	21-673	FDA Sub. - NDA	A12 - Submission #13: Response to Request for Additional Information - CMC Comments/Deficiencies from NDA (email of 17 December 2004, Christy Cottrell on behalf of FDA Chemistry Reviewer)	21-Dec-04
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	21-673	FDA Corres.	Email from Christy Cottrell/CSO/FDA to Mike Bernstein: Clofarabir Labeling/Follow Up - Reminder to Submit Advertising Materials to DDMAC as Soon as Possible	23-Dec-04
17	21-673	FDA Sub. - NDA	A13 - Submission #14: Amendment to Pending Application - Addition of Genzyme Corporation to the Package Insert as the Distributor (actual package insert reflecting this change submitted in Amendment 16/Draft Labeling)	23-Dec-04
18	21-673	FDA Sub. - NDA	A14 - Submission #15: Transfer of Ownership: Acquisition of ILEX Oncology, Inc.; Submission Includes Transfer Letter from ILEX and Acceptance Letter from Genzyme Corporation (submitted together with approval from FDA)	27-Dec-04
19	21-673	FDA Sub. - NDA	A15 - Submission #16: Draft Labeling CLOLAR Package Insert - Updated Component of Item 2 of the NDA/Labeling - Accepted Changes from FDA with a Few Additional Revisions	27-Dec-04
20	21-673	FDA Sub. - NDA	A16 - Submission #17: Draft Labeling CLOLAR Vial Label and Carton Artwork, .pdf Versions, Labeling Includes Replacing the ILEX Logo with the Genzyme Oncology Logo; Labeling in Genzyme Font & Colors	27-Dec-04
21	21-673	FDA Sub. - NDA	A17 - Submission #18: Response to FDA Request for Additional Information - CMC Commitment	28-Dec-04
22	21-673	FDA Sub. - NDA	A18 - Submission #19: Post-Marketing Commitments - Commitment 1 - Completion of CLO-218 Study and Completion of a Controlled Clinical Study to Verify & Describe Clinical Benefit in Pediatric ALL (further protocol development & discussion with FDA needed); Commitment 2 - Completion of Additional Work for Drug Substance (Validation of Specified Impurities & Degradants) and Refining the Test Methods for Validation	28-Dec-04
	21-673	FDA Corres.	Approval Letter for NDA 21-673: Courtesy Copy Received Via Email with Approved Package Insert and Carton and Vial Labeling; Approval in Pediatric ALL (after two prior regimens)	28-Dec-04
	21-673	FDA Corres.	Official Approval Letter for NDA 21-673 with Approved Package Insert and Carton and Vial Labeling; Approval in Pediatric ALL (after two prior regimens)	28-Dec-04
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23	21-673	FDA Sub. - NDA	A19 - Submission #20: Promotional Materials - Submitted to CDER as Paper Copies Only - Includes Copies of Two Submissions Sent to DDMAC (dated 29 December 2004 & 30 December 2004)(CLOLAR Announcement Letter, CLOLAR Sales Aid, FDA Approval Letter, Package Insert, Genzyme Press Release, Information To Be Posted on Genzyme Websites)	3-Jan-05

[54] **2-HALO-2'-FLUORO ARA ADENOSINES AS ANTINOPLASTIC AGENTS**

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[73] **Assignee:** Southern Research Institute, Birmingham, Ala.

[21] **Appl. No.:** 320,879

[22] **Filed:** Sep. 21, 1994

Related U.S. Application Data

[63] Continuation of Ser. No. 693,646, May 10, 1991, Pat. No. 5,384,310, which is a continuation-in-part of Ser. No. 355,358, May 23, 1989, Pat. No. 5,034,518.

[51] **Int. Cl.⁶** **A61K 31/70**

[52] **U.S. Cl.** **514/46; 536/27.4; 536/27.63**

[58] **Field of Search** **514/46, 27.4; 536/27.63**

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[57] **ABSTRACT**

The present invention is directed to certain 2'-fluoro, 2-substituted purine nucleosides which are toxic to cancerous cell lines.

12 Claims, No Drawings

2-HALO-2'-FLUORO ARA ADENOSINES AS ANTINOPLASTIC AGENTS

The application is a continuation of application Ser. No. 07/693,646, filed May. 10, 1991, now U.S. Pat. No. 5,384,310 which is a continuation-in-part of application Ser. No. 07/355,358, filed May 23, 1989 now U.S. Pat. No. 5,034,518.

The research leading to the discovery of the present invention was funded, in part, by funds from the United States Department of Health and Human Services. Accordingly, the United States government has certain statutory rights to the present invention under 37 USC 200 et seq.

The development of effective anticancer agents is a complex problem for a number of reasons, but primarily because of the lack of an identifiable, exploitable biochemical difference between normal and malignant tumor cells, be they of animal or human origin.

The simplest and most used strategy for the discovery of new anticancer agents is by empirical search, which has been most successful in identifying useful antitumor antibiotics. The search for lead compounds among synthetics is somewhat different, since few clinically useful agents have resulted from strictly random screening, which in fact is not a truly random search since it reflects the status of organic chemistry and, largely, what synthetic chemists have found of interest for whatever reason. In fact, most synthetics found to have clinical activity were screened for a reason. A prime example is one of the first clinically useful agents, nitrogen mustard, which was tested because of its effects on the blood elements discovered in the chemical warfare program. Regardless of the method of discovery, anticancer agents can be classified in five broad groupings:

A. Antimetabolites

Glutamine antagonists
Inhibitors of dihydrofolic reductase
Purine and pyrimidine analogs
Nucleoside diphosphate inhibitors
B. Nucleic acid complexors

Actinomycins

Anthracyclines

Bleomycins

Mitomycins

Mithramycin

Neocarcinostatin

Anthramycins

C. Chemically reactive compounds

Nitrogen mustards

Aziridines

Sulfonates

Triazines

Nitrosoureas

Procarbazine

cis-Platinum

D. Mitotic inhibitors

Vinca alkaloids

Podophyllum derivatives

E. Hormones

Estrogens

Androgens

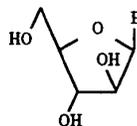
Progestogens

Glucocorticoids

Miscellaneous synthetics

From these groupings, it is clear that anticancer agents with proven utility interfere one way or another with cell division and, since cancer cells must divide or eventually die, they are cytotoxic agents with some degree of specificity for neoplastic cells. Thus it would seem logical that the search for new lead compounds should focus on new structural types that will also interfere with one or another of the processes of cell division. The most approachable of these is the design of enzyme inhibitors. There are at least 85 enzymatic reactions involved in the de novo synthesis of purine and pyrimidine nucleotides, in their interconversion, in their polymerization to nucleic acids, and in the so called salvage pathways. Of these 85 enzymes, approximately 14 are known to be inhibited by metabolic analogs or analogs thereof. These inhibitions are thought to be responsible for, or at least contribute to, the anticancer activity of these compounds.

Two such compounds are the arabinofuranosyl nucleosides, 9- β -D-arabinofuranosyladenine and 1- β -D-arabinofuranosylcytosine, of the formula:



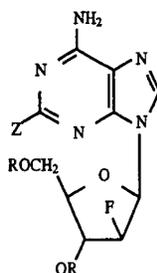
wherein B is adenine or cytosine, have well-known antiviral (B=adenine) and anticancer (B=cytosine) activity. In addition, other arabinofuranosyl nucleosides with 2'-substituents other than hydroxyl have also exhibited useful biological effects. All of these nucleosides require activation (phosphorylation) to be effective, and generally this is accomplished by different enzymes than the corresponding ribofuranosyl nucleosides.

In addition, a number of 2'-substituted-9- β -D-arabinofuranosyl-2-haloadenines [see J. Med. Chem. 31:405 (1988), and J. Med. Chem. 29:2389 (1986)] have also been developed along this general design. 9- β -D-arabinofuranosyl-2-fluoro-adenine monophosphate is, for example, is a drug of choice against chronic lymphocytic leukemia; and 2-chloro-2'-deoxyadenosine has shown some promise in a phase I trial against T-cell neoplasms and in phase II trials against chronic lymphocytic leukemia of B-cell origin that is refractory to conventional therapy, and against hairy-cell leukemia. However, the search for better and more effective, anticancer compounds continues.

Thus, in accordance with the present invention it has now been found that the incorporation of a 2-halo substituent onto the purine ring of these prior compounds significantly alters the metabolism of adenine nucleosides, specifically by reducing the ability of the compound to serve as a substrate for adenosine deaminase; that substituting a fluorine in the arabino configuration at C-2' makes these derivatives highly resistant to phosphorolytic cleavage; and that the combination of these two changes in the same molecule provide enhanced biological and anti cancer activity of the resulting compound.

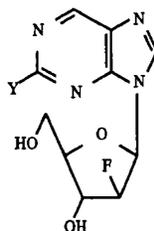
The present invention relates to a family of novel nucleoside compounds, and pharmaceutically acceptable salts thereof, represented by the general formula:

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in which R, which may be the same or different, is a hydrogen or acyl protecting group such as an alkanoyl protecting or blocking group such as benzoyl, and wherein Z is a halogen of the group F, Cl, and Br. In accordance with one aspect of the present invention, where R is acyl, the nucleoside compound acts as a prodrug in prolonging the in vivo life of the compound.

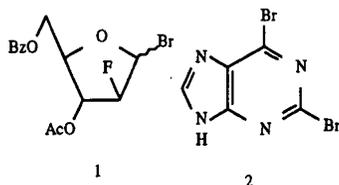
More specifically, the most preferred compounds of the present invention are those of formula:



wherein Y is F, Cl or Br, or the pharmaceutically acceptable salts thereof.

This and other aspects of the present invention will become clearer in the following discussion and description, both provided for purposes of clarification and not limitation as to the scope of the present invention.

In its broadest description, 2'-substituted purine arabinonucleosides are prepared from 2-haloadenosines via their 3',5'-O-(tetraisopropylsiloxane-2'-O-triflate derivatives according to the process discussed in *J. Med. Chem.* 31:405 (1988). Since this prior approaches failed to provide the 2'-fluoroarabinonucleosides in reasonable yields, these compounds had to be prepared by reaction of the appropriately blocked 2'-fluoro sugar (compound 1) with 2,6-dichloropurine followed by modification of the purine [see *J. Med. Chem.* 29:2389 (1986)].

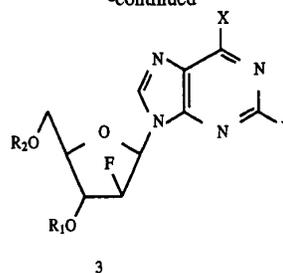


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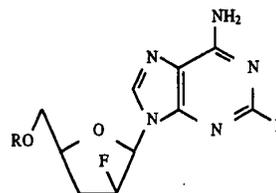
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- a) X = Y = Br, R₁ = Ac, R₂ = Bz a) R = Bz
 25 b) X = NH₂, Y = Br, R₁ = R₂ = H b) R = H
 c) X = Y = Cl, R₁ = Ac, R₂ = Bz
 d) X = NH₂, Y = Cl, R₁ = R₂ = H
 e) X = Y = NH₂, R₁ = Ac, R₂ = Bz
 f) X = NH₂, Y = F, R₁ = Ac, R₂ = Bz
 30 g) X = NH₂, Y = F, R₁ = R₂ = H
 h) X = NH₂, Y = F, R₁ = H, R₂ = Bz

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The same sequence was also applied to 2,6-dibromopurine (compound 2) for the preparation of the 2-bromoadenine nucleoside. The blocked 2'-fluoro sugar was condensed with 2,6-dibromopurine in refluxing 1,2-dichloroethane in the presence of 4A molecular sieves. The anomeric configuration and substitution positions for compound 3a were confirmed by ¹H NMR comparisons with compound 3c. Animation and deprotection of compound 3a or 3c done in ethanolic ammonia yielded a mixture of the desired product and the 5'-benzoyl protected compound. This residual blocking group may be removed if desired by treating the mixture with LiOH in MeCN—H₂O to give either compound 3b or 3d.

Non-aqueous diazotization of compound 3e with tert-butyl nitrite in 60% hydrogen fluoride/pyridine at -20° C. produced the 2-fluoro compound 3f. Deacylation of compound 3f was accomplished with LiOH in MeCN—H₂O, allowing a reasonable yield of compound 3g, free of any side products.

In order to prepare the dideoxy compound 4b, the 3'-acetyl of compound 3f was first selectively removed with NaHCO₃ in MeOH. The resulting product, compound 3h, was then treated with thiocarbonyldiimidazole followed by reduction with tri-n-butyltin hydride to give compound 4a. The 5'-benzoyl protecting group of compound 4a was then removed with LiOH to produce compound 4b.

The following examples, given for purposes of clarity in more fully demonstrating the methods by which the compounds of the present invention may be prepared, are provided. However, these examples are not meant to be limiting in any manner, and modifications and adaptations may be made to provide other routes, which are to be considered to be within the scope of the present invention, for the synthesis of the desired compounds.

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EXAMPLE I

2,6-Dibromo-9-(3-O-acetyl-5-O-benzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)-9H-purine

(compound 3a)

A solution of 3-acetyl-5-benzoyl-2-deoxy-2-fluoroarabinofuranosylbromide (33.2 mmol) in 400 mL of dry dichloroethane was stirred for 10 min with 4A molecular sieves (250 mL) before the addition of (9.3 g, 33.5 mmol) 2,6-dibromopurine. The mixture was vigorously stirred with an overhead stirrer and placed in a preheated 100° C. oil bath. Heating was continued for 32 h until all the bromo-sugar was consumed. (TLC 2:1 cyclohexane-ethyl acetate, using 4-(4-nitrobenzyl) pyridine spray for detection.) After the mixture had cooled to room temperature, it was filtered through Celite. The solids were washed with dichloroethane, and the combined filtrates were evaporated to dryness in vacuo. The residue (16.5 g) was a mixture of three nucleosides which were separated by flash chromatography on 150 g of silica gel (230-400 mesh) using 2:1 cyclohexane-ethyl acetate as the eluting solvent. By combining pure fractions, the desired compound was obtained as a glass 3.64 g (19.7%) which was chromatographically homogeneous but would not crystallize. A second column run on impure fractions gave 2.21 g (11.9%) more pure product for a total yield of 31.6%.

EXAMPLE II

2-Bromo-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-9H-purin-6-amine

(compound 3b)

A solution of the example I product (5.84 g, 10.5 mmol) in 400 mL of ethanolic ammonia (saturated at 0° C.) was sealed in a glass-lined stainless steel bomb and left at room temperature for 3 days. The solution was evaporated to dryness and evaporated with ethanol to remove ammonia. The residue, containing the desired product and 5'-benzoyl compound, was dissolved in 440 mL of acetonitrile and 120 mL of water. Lithium hydroxide monohydrate (881 mg, 21 mmol) was added, and the solution was stirred for 16 h at room temperature. Thin-layer chromatography (5:1 CHCl₃-MeOH) indicated complete reaction. The chilled solution was carefully neutralized with glacial acetic acid and evaporated to dryness. The white solid residue was recrystallized from water. The product was dried in vacuo at room temperature at 100° C. for 2 h: 2.15 g (59.2%); Mp 209-210° C.

EXAMPLE III

2-Chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-2,0 9H-purin-6-amine

(compound 3d)

A solution of the compound 3c [see J. Med. Chem. 29:2389 (1986)] (5.1 g, 10.9 mmol) in ethanol saturated (0° C.) with anhydrous ammonia (100 mL) was placed in a glass-lined stainless steel bomb and left at room temperature for three days. Thin layer chromatography (2:1 cyclohexane-ethyl acetate and 5:1 CHCl₃-MeOH) indicated the absence of starting material. However, two major products were present: the desired compound and its 5'-benzoyl analog. The solution was evaporated to dryness

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and co-evaporated with acetonitrile. The residue was dissolved in acetonitrile (100 mL) and diluted with water (60 mL) before the addition of lithium hydroxide monohydrate (915 mg, 21.8 mmol). The solution was stirred at room temperature for 3 h, at which time thin layer chromatography (5:1 CHCl₃-MeOH) indicated the reaction had gone to completion. The solution was cooled, neutralized with acetic acid, and evaporated to dryness. Three recrystallizations from water gave the pure compound: 1.4 g (42.3%); Mp 225°-226° C.

EXAMPLE IV

2-Fluoro-9-(3-O-acetyl-5-O-benzoyl-2-deoxy-2-fluoro-β-arabinofuranosyl)-9H-purin-6-amine

(compound 3f)

Diamino compound 3e [see J. Med. Chem. 29:2389 (1986)] (700 mg, 1.63 mmol) was dissolved in 3:2 HF-pyridine (15 mL) at -25° C. and treated with tert-butyl nitrite (271 μL, 2.28 mmol). After 1 h at -20° C., the reaction was incomplete as indicated by thin layer chromatography. Additional tert-butyl nitrite (70 μL, 0.59 mmol) was added, and the reaction was held at -20° C. for an additional 2 h. The cold reaction solution was added dropwise to saturated aqueous NaHCO₃ (1 L) containing ice. The foaming mixture was stirred vigorously for 20 min, then diluted with CHCl₃ (300 mL). The solution was allowed to layer, and the layers were separated, and the aqueous layer was extracted with additional CHCl₃ (2×175 mL). The combined organic extracts were washed with water (3×175 mL), dried (over MgSO₄), and evaporated to dryness. The resulting residue, in CHCl₃, was applied to a flash column containing 50 g of silica gel (230-400 mesh) with CHCl₃ as eluant. Fractions were combined to give essentially pure product (500 mg, 70%). Crystallization of a small sample from EtOH gave pure product: Mp 208°-209° C.

EXAMPLE V

2-Fluoro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-9H-purin-6-amine

(compound 3g)

A suspension of the example IV product (430 mg, 0.99 mmol) in 1:1 MeCN-H₂O (40 mL) was treated in one portion with solid lithium hydroxide monohydrate (125 mg, 2.97 mmol). The reaction became a clear solution after being stirred at room temperature for 20 min. A 3 h thin layer chromatography aliquot showed the deblocking to be complete. Glacial acetic acid (57 μL) was added, and the solution was evaporated until a white solid was deposited. After being chilled, the solid was collected, washed with cold water, and dried in vacuo at room temperature to give a crude solid (252 mg). This solid was dissolved in 40 mL of water and applied to a water-equilibrated SM-4 Bio-Bead column (1.5×32 cm). After initial elution with water, the product was eluted with a step-wise gradient, 5%→20% EtOH in water. The residue from the combined evaporated column fractions was crystallized from 25 mL of boiling water with charcoal treatment, and dried in vacuo at 56° C. for 16 h to yield a pure product: 178 mg (59%); Mp 207-209° C.

EXAMPLE VI

2-Fluoro-9-(5-O-benzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)-9H-purin-6-amine

(compound 3h)

A suspension of the example IV product (312 mg, 0.72 mmol) in MeOH (25 mL) at 10° C. was treated with solid

NaHCO₃ (181 mg, 2.16 mmol). After being stirred at room temperature for 2.5 h, the reaction was quenched by the addition of glacial acetic acid (170 μ L) and evaporated to dryness. This residue in hot EtOH was applied to two silica gel thick plates (Analtech, GF, 2000 μ m) and subsequently developed in 9:1 CHCl₃—MeOH. The product was extracted with hot EtOH and evaporated to dryness to give essentially pure product: 208 mg (74%).

EXAMPLE VII

2-Fluoro-9-(5-O-benzoyl-2,3-dideoxy-2-fluoro-8- β -arabinofuranosyl)-9H-purin-6-amine

(compound 4a)

191 mg (0.49 mmol) of the compound made in accordance with example VI was dissolved in dry acetonitrile (20 mL) at 45° C., and then treated with 1,1'-thiocarbonyldiimidazole (339 mg, 1.7 mmol). The resulting cloudy yellow solution was stirred under N₂ at 45° C. for 24 h at which time thin layer chromatography analysis (EtOAc) showed one major product. The reaction was evaporated to dryness, and the residue was dissolved in dry toluene (15 mL). Treatment with AIBN (13.7 mg, 0.08 mmol) and tri-n-butyltin hydride (1.3 mL, 4.7 mmol) produced a yellow mixture that was placed directly in a 120° C. bath. A clear solution was observed after a 5 min reflux, and at 1 h the reaction was complete as indicated by thin layer chromatography. The solvent was then removed in vacuo, and the resulting syrup was coevaporated once with EtOH. Trituration of this residue with petroleum ether (50 mL) produced a white solid that was collected and washed with fresh solvent to give 214 mg of crude solid. This material in hot EtOH was applied to two Analtech (GF, 2000 μ m) layer plates. After three developments in 9:1 CHCl₃—MeOH, the product band was extracted with boiling EtOH. The residue from evaporation of the combined extracts was crystallized from boiling EtOH to yield sufficiently pure product 160 mg (87%); Mp 215°–217° C. Without any further purification, this material was used in the deprotection step of example VIII.

Example VIII

2-Fluoro-9-(2-3-dideoxy-2-fluoro- β -D-arabinofuranosyl)-9H-purin-6-amine

(compound 4b)

A suspension of the example VII compound (135 mg, 0.36 mmol) in 3:1 MeCN—H₂O was treated in one portion at room temperature with solid LiOH·H₂O (38 mg, 0.9 mmol). The stirred mixture became a clear solution after 1/2 h. At 7 h an aliquot examined by TLC (5:1 CHCl₃—MeOH) showed the absence of the example VII compound. Glacial acetic acid (35 μ L) was added, and the reaction was evaporated to dryness. This residue in hot acetonitrile was applied to one silica gel thick plate (Analtech, GF, 2000 μ m). After the plate was developed three times in 5:1 CHCl₃—MeOH, the product band was extracted with boiling MeCN. Evaporation of this extract gave slightly impure material that was chromatographed as above on three prep plates (Analtech, GF, 1000 μ m). The resulting residue was crystallized from boiling H₂O (25 mL) containing EtOH (0.5 mL). After being chilled, the white solid was collected, washed with cold H₂O and dried in vacuo at 56° C. for 16 h to give pure product, 71 mg (73%); Mp 249°–250° C.

In contrast to the previously reported 2'-substituted 9- β -D-arabinofuranosyl-2-haloadenines, the 2'-fluoro com-

pounds were quite cytotoxic to three human cell lines, H.Ep.-2, CCRF-CEM, and K562, and the murine leukemia line, L1210. They, in fact, are significantly more cytotoxic than the corresponding 9- β -D-arabinofuranosyl-2-haloadenines, resembling more closely the 2'-deoxy-2-halodenosines (see Table 1).

Obviously, to be useful as anticancer agents, the nucleosides of the present invention must show the ability to kill cells in vitro. The results in Table 1, indicating the concentration required to inhibit cell proliferation to 50% of untreated controls, show that these nucleosides can, at reasonable concentrations, kill cells. One cell line (L1210) is a murine leukemia, whereas the other three are human neoplasms. Based on many years of experience, we believe that compounds that do not require activation by the liver must have an IC₅₀ of about 1–10 μ M or less to show useful activity in the in vivo animal models—and in man. Many people today emphasize the importance of toxicity to human cell lines.

TABLE I

Cytotoxicity [as IC₅₀ (μ M)] of 2-Haloadenine Nucleosides

Compound	H.Ep.-2	L1210	CCRF-CEM	K562
when Y = F				
X = OH	9	3	0.4	0.15
X = H	0.2	0.9	0.2	
X = F	0.34	0.38	0.14	0.3
when Y = Cl				
X = OH	3	<3	10	
X = H	0.03	0.07	0.003	
X = F	0.012	0.23	0.05	0.003
when Y = Br				
X = OH	4	3		
X = H	0.02	0.9	0.02	
X = F	0.22	0.26	0.02	0.05

The data in Table I (given in μ M amounts) clearly establishes the ability of the compounds according to the present invention to kill neoplastic cells.

Subsequently, the phosphorolysis of these compounds were compared by *E. coli* purine nucleoside phosphorylase. The arabino and 2'-deoxyribonucleosides are rapidly cleaved by this enzyme, whereas the arabino nucleosides substituted at 2' by Cl, N₃, or NH₂ are almost completely resistant. The 2'-fluoro compounds are less resistant to cleavage, being cleaved at roughly one-third the rate of the arabino and 2'-deoxynucleosides. This reduction in cleavage rate may be acceptable for pharmaceutical purposes as phosphorylation in mammalian cells is quite rapid.

More specifically, an enzyme reaction mixture consisting of 0.5 mM nucleoside substrate, 50 mM pH 8.0 phosphate buffer and purine nucleoside phosphorylase in a final vol-

ume of 1.0 mL was allowed to incubate for 30, 60, 120, 180 and 240 minutes, and the amounts of nucleoside and substrate remaining were determined by HPLC. The results of this experiment are tabulated in the following Table II.

TABLE II

Phosphorolysis of Nucleosides	
Compound	% Cleavage
3b	45
3d	39
3g	10
2-fluoro-9- β -D-arabinofuranosyladenine	99
2-chloro-2'-deoxyadenosine	>99
2-fluoro-2'-deoxyadenosine	>99

A recent report from our laboratory [see Cancer Research 51:2386 (May 1st 1991) which is incorporated in toto herein] indicates that the compound 3d of the present invention inhibits DNA synthesis due to the inhibition of ribonucleotide reductase activity and inhibition of chain elongation by DNA polymerase α . These inhibitions of the ribonucleotide reductase and DNA polymerase α enzymes by compound 3d were important to the development of the cancerous K562 cells. Although this finding is similar to observations with 9- β -D-arabinofuranosyl-2-fluoroadenine and 2-chloro-2'-deoxyadenosine, the degree of inhibition of these enzymes by the 5'-triphosphate of these nucleoside analogues is quite different. The inhibition of ribonucleoside reductase by 2-chloro-9-(2-deoxy-2-fluoro- β -D-arabinofuranosyl)adenine 5'triphosphate was the same as that seen with 2-chloro-2'-deoxyadenosine 5'-triphosphate, and the inhibition of DNA polymerase α by 2-chloro-9-(2-deoxy-2-fluoro- β -D-arabinofuranosyl) adenine 5' triphosphate was similar to that seen with 9-13-D-arabinofuranosyl-2-fluoroadenine 5'triphosphate. In contrast, 9- β -D-arabinofuranosyl-2-fluoroadenine 5'triphosphate was a much less potent inhibitor of ribonucleotide reductase than either 2-chloro-2'-deoxyadenosine 5'-triphosphate or 2-chloro-9-(2-deoxy-2-fluoro- β -D-arabinofuranosyl)adenine 5'triphosphate, and although all of the 2'-deoxyadenosine nucleotide analogues inhibit the incorporation of 2'-deoxyadenosine 5'triphosphate by DNA polymerase α into the DNA and were more efficient substrates for the polymerase, the incorporation of 2-chloro-2'-deoxyadenosine 5'monophosphate into DNA by DNA polymerase α did not inhibit the further elongation of the DNA chain to the degree that was seen with the incorporation of either 9- β -D-arabinofuranosyl-2-fluoroadenine 5'monophosphate or 2-chloro-9-(2-deoxy-2-fluoro- β -D-arabinofuranosyl) adenine 5'monophosphate. These results indicated that the 2-chloro-9-(2-deoxy-2-fluoro- β -D-arabinofuranosyl)adenine (compound 3d) incorporates properties of both 9- β -D-arabinofuranosyl-2-fluoroadenine and 2-chloro-2'-deoxyadenosine into one compound. Furthermore, in the cell the inhibition of DNA polymerase α by these nucleoside analogues is a function of the ratio of [analogue nucleoside triphosphate] to [2'-deoxyadenosine 5'triphosphate]. Because 9- β -D-arabinofuranosyl-2-fluoroadenine 5'triphosphate inhibits ribonucleotide reductase at a 10-fold higher concentration than that required with 2-chloro-9-(2-deoxy-2-fluoro- β -D-arabinofuranosyl) adenine 5' triphosphate, the 2'-deoxyadenosine 5'triphosphate pool should be lower and the inhibition of DNA polymerase α should be greater, in cells treated with 2-chloro-9-(2-deoxy-2-fluoro-8-D-arabinofuranosyl) adenine than in cells treated with equimolar concentrations

of 9- β -D-arabinofuranosyl-2-fluoroadenine, assuming equal conversion to the triphosphate. These metabolic features may contribute to the potent inhibition of K562 cell growth with compound 3d [2-chloro-9-(2-deoxy-2-fluoro- β -D-arabinofuranosyl) adenine] of the present invention. In addition, the solubility problems associated with the administration of 9- β -D-arabinofuranosyl-2-fluoroadenine should not occur with this compound because of its greater solubility and high potency.

The reason that the 2'-fluorine atom disrupts chain extension is not obvious because the 2'-carbon is not involved in the reaction and a fluorine has an atomic radius slightly larger than a hydrogen atom. Steric hindrance would be expected to be less than is believed to be in the case of arabinofuranosyl nucleotides. It is possible that the electron-withdrawing properties of fluorine may affect the reactivity of the 3'-hydroxyl and/or the three dimensional structure of the DNA chain such that extension of a DNA chain terminated with a 2'-fluoronucleoside by the polymerase is inhibited.

Studies with the P388 leukemia cell line in mice (see Table III) indicate that the most effective compound of the present invention is the compound according to general formula 3d, that is the 2-chloro-2'-fluoro substituted nucleoside. This, coupled with the lower toxicity of the cleavage product, 2-chloroadenine, relative to 2-fluoroadenine, make this compound a preferred compound of the present invention. The following Table III provides a summary of the in vivo activity of the 9-(2-fluoro-2-deoxy- β -D-arabinofuranosyl)-2-haloadenines vs P388 leukemia cell line in which CD2F1 mice were implanted ip with 10^6 P388 leukemia cells on day 0 in accordance with the protocol of Waud et al [*Cancer Res.* 50:3232 (1990)].

TABLE III

Compound	Optimal IP Dose	Schedule	Median % ILS (dying mice only)	Log ₁₀ change	Tumor-free Survivors
3d	100	qd 1-5	+38	-0.3	0/5
	200	qd 1-5	+59	-1.6	0/3
	20	q 3 h x 8 (Days 1, 5, 9)	+220	-6.6	1/6
	25	q 3 h x 8 (Days 1, 5, 9)	+118	-2.8	0/5
3g	100	qd 1-5	+63	-1.8	0/3
	25	q 3 h x 8 (Days 1, 5, 9)	+81	-0.1	0/6
3b	30	q 3 h x 8 (Days 1, 5, 9)	+100	-1.0	0/6
	50	q 3 h x 8 (Days 1, 5, 9)	+41	+1.6	0/6
	200	qd 1-5	+33	+0.1	0/6

In the above table, the optimal dose refers to mg/kg/dose (\leq LD₅₀); ILS refers to the increase in life span; and the log change refers to the change in viable tumor cell population at the end of therapy compared to that at the start of therapy, based on the median day of death among the animals that died. The data in this table is presented in accordance with the National Cancer Institute activity criteria for drug testing in which an ILS of 20-74% is considered moderate activity, and an ILS of 75% or more is considered good activity.

In addition to the above, the 2,3-dideoxynucleoside depicted as compound 4b showed slight activity against HIV (strain IIIB) in either CEM or MT cell lines in culture.

In a similar test, compound 3d was administered orally and evaluated for antitumor activity against ip P388 leuke-

nia cells. As the data in Table III indicates, the optimal regimen for the compound, administered ip, is in divided doses five on days 1, 5, and 9, a similar schedule was selected for the oral administration of this compound. In this set of experiments, an oral dosage of 67 mg/kg/dose, given q 6 h x 4 on days 1, 5, and 9, effected a reduction in tumor burden of 1.7 log₁₀ units, a figure which is approximately 2.5 log₁₀ units less than that obtained in studies using ip drug administration.

The compounds according to the present invention are useful for their cytotoxic effects, and thus are useful as anticancer compounds in the treatment of cancerous cells in mammals when administered in an amount sufficient to bring about their cytotoxic effect to the desired cancerous cell. The compounds may be administered in a wide range of regimens ranging from about 10 mg to about 1000 mg per day. These regimens may be designed to give the compounds as a single dose or as multiple doses over extended periods of time, and the regimen may be adapted to provide the optimum therapeutic response. For example, several divided doses may be administered daily, or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. The compounds according to the present invention may be administered in the form of the free purine nucleoside or as a nontoxic pharmaceutically acceptable salt thereof, and may be administered either alone or in combination with one or more compounds of the present invention or with additional pharmaceutically active compounds.

The active compounds of the present invention may be administered parenterally, e.g. by subcutaneous, intramuscular, or intravenous injection. Solutions or suspensions of the active compound as a pharmaceutically acceptable salt can be prepared in water or saline containing the appropriate buffers and additives for administration. The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability is provided; it must be stable under the conditions of manufacture and storage, and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier may be a solvent or dispersion medium containing, for example, water, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. Compositions suitable for intramuscular or subcutaneous injection may also contain minor amounts of salts, acids, and bases to adjust tonicity and buffer the pH.

The compounds according to the present invention may also be suitable for oral administration, for example with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard or soft shell gelatin capsules, or compressed into tablets. For oral therapeutic administration, the compounds may be incorporated with excipients commonly used in the formulation of oral pharmaceutical preparations as, for example, sweetening agents, and preservatives.

In addition, the compounds of the present invention may be formulated in accordance with acceptable pharmaceutical formulation techniques for administration by other routes such as administration within topical ointments, creams or salves, as suppositories, or as lozenges.

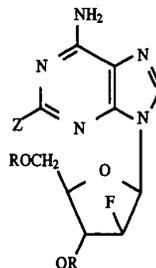
Thus, while we have illustrated and described the preferred embodiment of our invention, it is to be understood

that this invention is capable of variation and modification and we therefore do not wish to be limited to the precise terms set forth, but desire to avail ourselves of such changes and alterations which may be made for adapting the invention to various usages and conditions. Among such variations and modifications are, for example, and without limitation, the use of pharmaceutically acceptable salts of the disclosed purine nucleosides which may be designed for providing the purine nucleosides according to the present invention to a cell susceptible to cytotoxicity, to any minor substitution on the active nucleoside according to the present invention which results in no untoward effects upon the activity of the modified nucleoside from that of the depicted purine nucleosides or which results in the same or substantially the same activity as that found in the purine nucleosides depicted in accordance with the preceding disclosure; changes in formulation made due to the specific route of administration of the nucleosides according to the present invention; and changes made to the nucleoside molecule or composition formulation because of a specific salt form of the nucleoside according to the present invention. Accordingly, such changes, alterations and modifications are properly intended to be within the full range of equivalents, and therefore within the purview of the following claims.

Having thus described our invention and the manner and process of making and using the same in such full, clear, concise, and exact terms so as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same,

We claim:

1. A method for bringing about a cytotoxic effect in a mammalian cancerous cell which comprises contacting said cancerous cell with an effective amount of a cytotoxic compound having the formula



wherein R, each which may be the same or different, is hydrogen or a protecting group; wherein Z is a selected from the group consisting of F, Cl, and Br; and pharmaceutically acceptable salts thereof.

2. A method according to claim 1 which comprises contacting said cancerous cell with a compound wherein R is a protecting group.

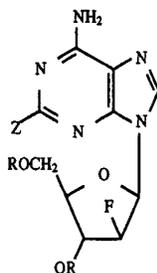
3. A method according to claim 1 which comprises contacting said cancerous cell with compound wherein R is hydrogen.

4. A method according to claim 1 which comprises contacting said cancerous cell with a compound wherein Z is Cl.

5. A method according to claim 1 which comprises contacting said cancerous cell with a compound wherein the compound is 2-Chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-9H-purin-6-amine.

6. A method for inhibiting ribonucleotide reductase and DNA polymerase α in a mammalian cell which comprises contacting said mammalian cell with of a cytotoxic compound having the formula

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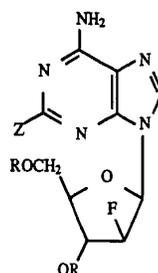
wherein R, each which may be the same or different, is hydrogen or a protecting group; wherein Z is a halogen selected from the group consisting of F, Cl, and Br; and pharmaceutically acceptable salts thereof.

7. A method according to claim 6 wherein R of said compound is a protecting group.

8. A method according to claim 6 wherein R of said a compound is hydrogen.

9. A method for inhibiting ribonucleotide reductase and DNA polymerase α in a mammalian cell which comprises contacting said mammalian cell with of a cytotoxic compound having the formula

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wherein R, each which may be the same or different, is hydrogen or a protecting group; wherein Z is a halogen selected from the group consisting of F, Cl, and Br; and the pharmaceutically acceptable salts thereof.

10. A method according to claim 9 wherein R of said compound is a protecting group.

11. A method according to claim 9 wherein R of said compound is hydrogen.

12. A method according claim 9 wherein said compound is 2-Chloro-9-(2-deoxy-2-fluoro- β -D arabinofuranosyl)-9H-purin-6-amine.

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