CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-673

Approved Labeling

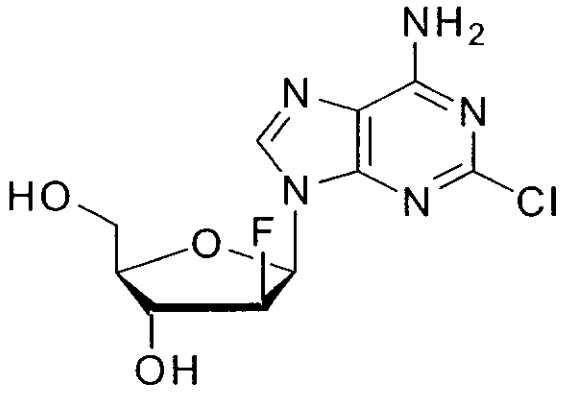
CLOLAR™ FOR INTRAVENOUS INFUSION

(clofarabine)

DESCRIPTION

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

The chemical structure of clofarabine is 2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-9H-purin-6-amine. The molecular formula of clofarabine is $C_{10}H_{11}ClFN_5O_3$ with a molecular weight of 303.68.



Clofarabine

CLINICAL PHARMACOLOGY

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

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

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

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

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

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

CLINICAL STUDIES

Sixty-six (66) pediatric ALL patients were exposed to CLOLAR™. Fifty-eight (58) of the patients received the recommended pediatric dose of CLOLAR™ 52 mg/m^2 daily × 5 as an intravenous infusion (IVI).

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

reversible hyperbilirubinemia and elevated transaminase levels and skin rash, experienced at 70 mg/m^2. As a result of this study, the recommended dose for subsequent study in pediatric patients was determined to be 52 mg/m^2/day for 5 days.

Single Arm Study in Pediatric ALL

A single arm study was conducted in relapsed/refractory pediatric patients with ALL at a single dose. All patients had disease that had relapsed after and/or was refractory to two or more prior therapies. Most patients, 46/49 (93.8%), had received 2 to 4 prior regimens and 15/49 (30.6%) of the patients had undergone at least 1 prior transplant. The median age of the treated patients was 12 years. There were more males, 29/49 (59.2%), than females, 20/49 (40.8%). Most of the patients were either Caucasian (n=20, 40.8%) or Hispanic (n=20, 40.8%), with 12.2% African-American (n=6), and 6.1% Other race (n=3). All patients received a dose of 52 mg/m^2 daily × 5 IVI. There was no dose modification during the remission induction phase of treatment (maximum of 2 cycles). Doses could be modified (reduced/delayed) during the post-induction phase. There was no dose escalation. The planned study endpoint was the rate of Complete Remission (CR), defined as no evidence of circulating blasts or extramedullary disease, an M1 bone marrow (<5% blasts), and recovery of peripheral counts (platelets > 100 × 10^9 L and absolute neutrophil count (ANC) > 1.0 × 10^9 L) and Complete Remission in the Absence of Total Platelet Recovery (CRp), defined as meeting all criteria for CR except for recovery of platelet counts to > 100 × 10^9 L. Partial Response (PR) was also determined, defined as complete disappearance of circulating blasts, an M2 bone marrow (> 5% and < 25% blasts), and appearance of normal progenitor cells or an M1 marrow that did not qualify for CR or CRp. Transplantation rate was not a study endpoint.

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

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

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

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

INDICATIONS AND USAGE

CLOLAR™ is indicated 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.

CONTRAINDICATIONS

None

WARNINGS

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

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

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

Hepatic and Renal Impairment

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

Pregnancy – Teratogenic Effects: Pregnancy Category D

CLOLAR™ (clofarabine) may cause fetal harm when administered to a pregnant woman. Clofarabine was teratogenic in rats and rabbits. Developmental toxicity (reduced fetal body weight and increased post-implantation loss) and increased incidences of malformations and variations (gross external, soft tissue, skeletal and retarded ossification) were observed in rats receiving 54 mg/m^2/day (approximately equivalent to the recommended clinical dose on a mg/m^2 basis), and in rabbits receiving 12 mg/m^2/day (approximately 23% of the recommended clinical dose on a mg/m^2 basis).

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

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

PRECAUTIONS

Information for Patients and Caregivers

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

Dehydration/Hypotension

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

Concomitant Medications

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

Pregnancy/Nursing

All patients should be advised to use effective contraceptive measures to prevent pregnancy. Female patients should be advised to avoid breast feeding during treatment with CLOLAR™.

Laboratory Tests

Complete blood counts and platelet counts should be obtained at regular intervals during CLOLAR™ therapy, and more frequently in patients who develop cytopenias. In addition liver and kidney function should be monitored frequently during the 5 days of CLOLAR™ administration.

Drug Interactions

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

Drug/Laboratory Tests Interactions

There are no known clinically significant interactions of CLOLAR™ with other medications or laboratory tests. No formal drug/laboratory test interaction studies have been conducted with CLOLAR™.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Clofarabine has not been tested for carcinogenic potential.

Mutagenesis

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

Impairment of Fertility

Studies in mice, rats, and dogs have demonstrated dose-related adverse effects on male reproductive organs. Seminiferous tubule and testicular degeneration and atrophy were reported in male mice receiving IP doses of 3 mg/kg/day (9 mg/m^2/day, approximately 17% of clinical recommended dose on a mg/m^2 basis). The testes of rats receiving 25 mg/kg/day (150 mg/m^2/day, approximately 3 times the recommended clinical dose on a mg/m^2 basis) in a 6-month IV study had bilateral degeneration of the seminiferous epithelium with retained spermatids and atrophy of interstitial cells. In a 6-month IV dog study, cell degeneration of the epididymis and degeneration of the seminiferous epithelium in the testes were observed in dogs receiving 0.375 mg/kg/day (7.5 mg/m^2/day, approximately 14% of the clinical recommended dose on a mg/m^2 basis). Ovarian atrophy or degeneration and uterine mucosal apoptosis were observed in female mice at 75 mg/kg/day (225 mg/m^2/day, approximately 4 fold of recommended human dose on a mg/m^2 basis), the only dose administered to female mice. The effect on human fertility is unknown.

Pregnancy

Teratogenic Effects: Pregnancy Category D

See **WARNINGS.**

Nursing Mothers

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

Other Special Population: Adults

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

ADVERSE REACTIONS

One hundred thirteen (113) pediatric patients with ALL (67) or AML (46) were exposed to CLOLAR™. Ninety six (96) of the pediatric patients treated in clinical trials received the recommended dose of CLOLAR™ 52 mg/m^2 daily × 5.

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

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

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

Table 2: Most Commonly Reported (>=10% Overall) Adverse Events by System Organ Class (N=96)

System Organ Class Adverse Event[1]	52 mg/m² (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	.	.

Table 2: Most Commonly Reported (>=10% Overall) Adverse Events by System Organ Class (N=96) (continued)

System Organ Class Adverse Event[1]	52 mg/m² (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).

Cardiovascular

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

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

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

Hepatic

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

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

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

Infection

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

Renal

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

Systemic Inflammatory Response Syndrome (SIRS)/Capillary Leak Syndrome

Capillary leak syndrome or SIRS (signs and symptoms of cytokine release, e.g., tachypnea, tachycardia, hypotension, pulmonary edema) occurred in 4 pediatric patients overall (3 ALL, 1 AML). Several patients developed rapid onset of respiratory distress, hypotension, capillary leak (pleural and pericardial effusions), and multi-organ failure. Close monitoring for this syndrome and early intervention are recommended. The use of prophylactic steroids (eg, 100 mg/m^2 hydrocortisone on Days 1 through 3) may be of benefit in preventing signs or symptoms of SIRS or capillary leak. Physicians should be alert to early indications of this syndrome and should immediately discontinue CLOLAR™ administration if they occur and provide appropriate supportive measures. After the patient is stabilized and organ function has returned to baseline, re-treatment with CLOLAR™ can be considered at a lower dose.

Overdosage

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

DOSAGE AND ADMINISTRATION

Recommended Dose

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

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

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

Physicians are encouraged to give continuous IV fluids throughout the 5 days of CLOLAR™ administration to reduce the effects of tumor lysis and other adverse events. The use of prophylactic steroids (e.g., 100 mg/m^2 hydrocortisone on Days 1 through 3) may be of

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

STORAGE AND HANDLING

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

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

HOW SUPPLIED

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

Rx only

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

Other patents pending.

NAME AND ADDRESS OF MANUFACTURER

Manufactured by: AAI Development Services

Charleston, SC 29405

Manufactured for: Genzyme Corporation

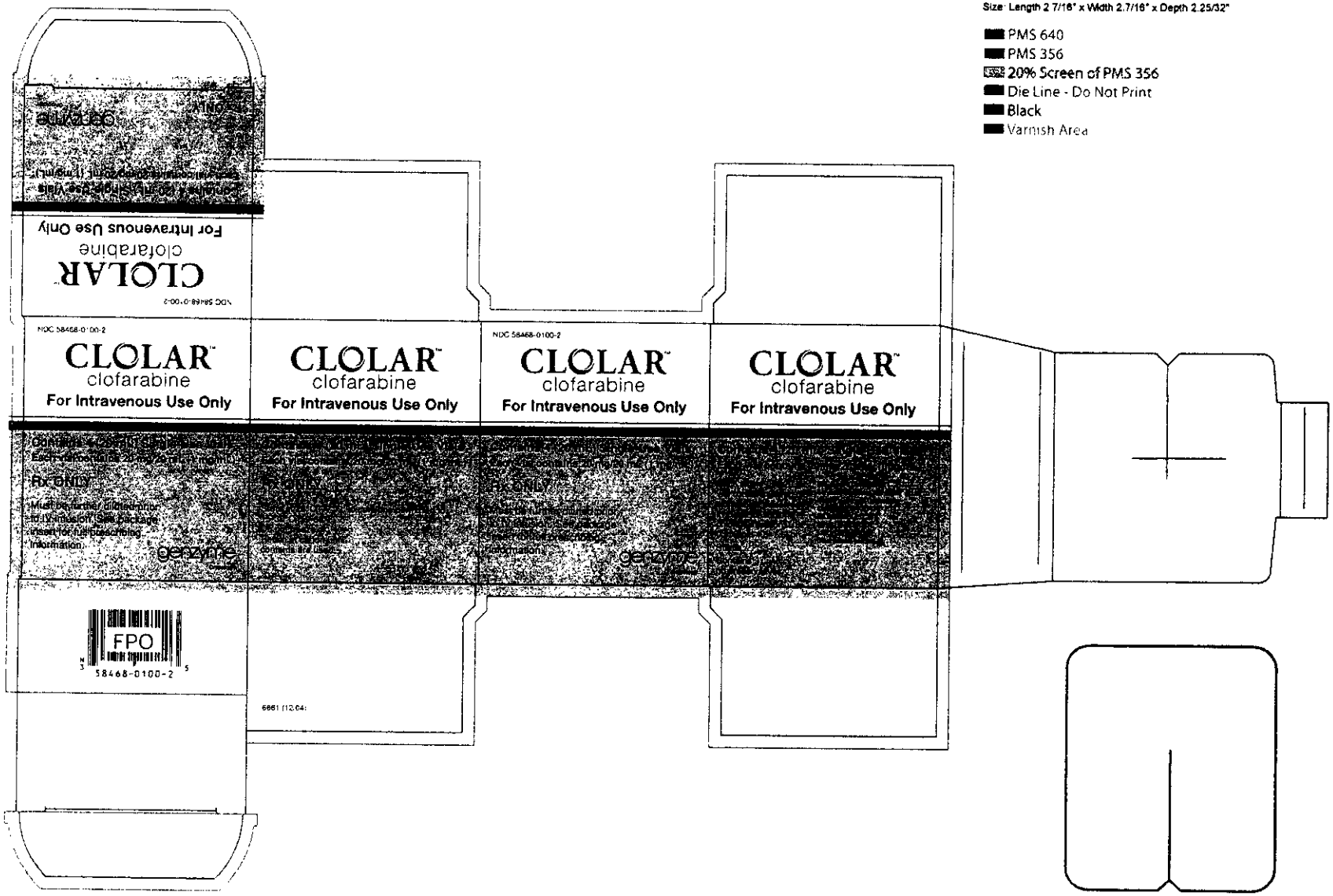
4545 Horizon Hill Blvd

San Antonio, TX 78229

Distributed by: Genzyme Corporation

500 Kendall Street

Cambridge, MA 02142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PMS 356
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clofarabine
For Intravenous Use Only
NDC 58468-0100-2
Rx ONLY
genzyme
FPO
58468-0100-2
6661 (12/04)

Graphic Support: ***George D. @ X22618***
6663 (12/04) R6
12-21-04, CLOLAR Vial Label
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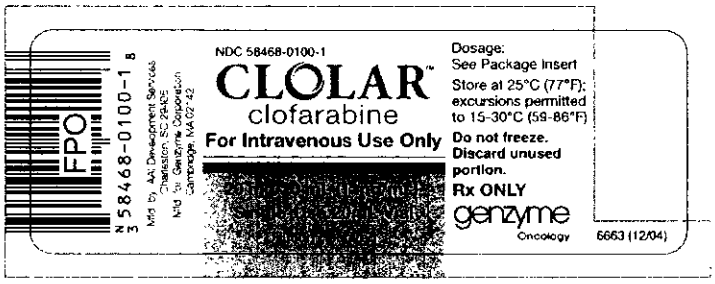

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/s/

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

Cottrell, Christy

From: ONSlist [ONSlist@ons.org]
Sent: Tuesday, January 04, 2005 8:34 AM
To: ONS-l@Onsbulkmail.ons.org
Subject: FDA Approves Clolar for Pediatric ALL

In collaboration with the Food and Drug Administration (FDA), and as a service to our members, the Oncology Nursing Society will provide information about newly approved therapies for patients with cancer. This will allow the FDA to inform ONS members of recent approvals in a timely manner. Included in the email from the FDA will be a link to the product label, which will provide the relevant clinical information on the indication, contraindications, dosing, and safety. The following is a message from Dr. Richard Pazdur:

To: ONS membership

From: Richard Pazdur, M.D.
Director, Division of Oncology Drug Products,
Center for Drug Evaluation and Research, FDA

On December 28, 2004 the U. S. Food and Drug Administration granted accelerated approval for clofarabine (Clolar™ For Intravenous Infusion, Genzyme Corporation), a purine nucleoside antimetabolite, for treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens. The approval of this indication is based on the induction of complete responses. Clinical studies demonstrating increased survival or other clinical benefit have not been conducted. Approval was granted under accelerated approval regulations that require the applicant to conduct and complete additional clinical studies to confirm clinical benefit.

Efficacy and safety were demonstrated in a single multicenter trial that enrolled 49 patients. Most patients had received 2 to 4 prior regimens and 15/49 (31%) had undergone at least one transplant. The median age was 12 years. Clofarabine was given at a dose of 52 mg/m^2, intravenously, over 2 hours daily x 5 repeated every 2 to 6 weeks following recovery or return to baseline organ function. The study endpoints were the rate of complete response (CR) and the rate of complete response without platelet recovery (CRp). The former was defined as no evidence of circulating blasts or extramedullary disease, an M1 bone marrow, and recovery of peripheral platelet and absolute neutrophil counts; the latter was defined as meeting all criteria for CR except for platelet count recovery. Response rates were determined by an Independent Response Review Panel (IRRP).

Six patients (12%) achieved a CR and 4 patients (8%) achieved a CRp, and 5 patients (10%) achieved a PR. Of the 15 responding patients, 6 had post-clofarabine bone marrow transplantation. Hence, response durations could not be determined. In the patients who were not transplanted, the response durations for CR were 43, 50, 82, 93+, and 160+ days; for CRp the response duration was 32 days.

The principal clofarabine toxicities were nausea, vomiting, hematologic toxicity, febrile neutropenia, hepatobiliary toxicity, infections and renal toxicity. Clofarabine can produce systemic inflammatory response syndrome/capillary leak syndrome (SIRS), manifested by the rapid development of tachypnea, tachycardia, hypotension, shock, and multi-organ failure. Cardiac toxicity was characterized as left ventricular systolic dysfunction; tachycardia may also occur.

Full prescribing information, including clinical trial information, safety, dosing, drug-drug interactions

and contraindications is available at www.fda.gov/cder/foi/label/2004/021673lbl.pdf.

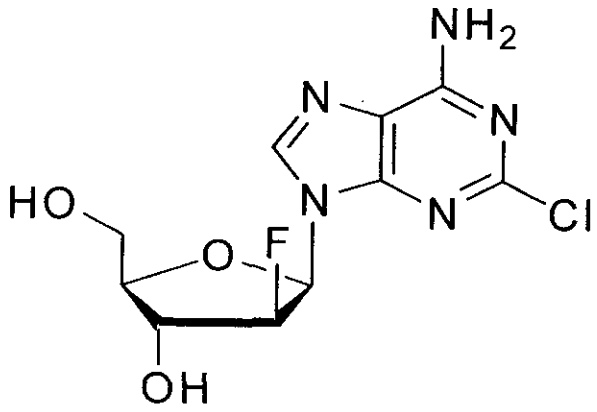
CLOLAR™ FOR INTRAVENOUS INFUSION

(clofarabine)

DESCRIPTION

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

The chemical structure of clofarabine is 2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-9H-purin-6-amine. The molecular formula of clofarabine is $C_{10}H_{11}ClFN_5O_3$ with a molecular weight of 303.68.



Clofarabine

CLINICAL PHARMACOLOGY

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

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

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

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

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

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

CLINICAL STUDIES

Sixty-six (66) pediatric ALL patients were exposed to CLOLAR™. Fifty-eight (58) of the patients received the recommended pediatric dose of CLOLAR™ 52 mg/m^2 daily × 5.

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

70 70 mg/m^2. As a result of this study, the recommended dose for subsequent study in pediatric
71 patients was determined to be 52 mg/m^2/day for 5 days.

72

73 **Single Arm Study in Pediatric ALL**

74 A single arm study was conducted in relapsed/refractory pediatric patients with ALL at a
75 single dose. All patients had disease that had relapsed after and/or was refractory to two or
76 more prior therapies. Most patients, 46/49 (93.8%), had received 2 to 4 prior regimens and
77 15/49 (30.6%) of the patients had undergone at least 1 prior transplant. The median age of
78 the treated patients was 12 years. There were more males, 29/49 (59.2%), than females,
79 20/49 (40.8%). Most of the patients were either Caucasian (n=20, 40.8%) or Hispanic (n=20,
80 40.8%), with 12.2% African-American (n=6), and 6.1% Other race (n=3). All patients
81 received a dose of 52 mg/m^2 daily × 5. There was no dose modification during the remission
82 induction phase of treatment (maximum of 2 cycles). Doses could be modified
83 (reduced/delayed) during the post-induction phase. There was no dose escalation. The
84 planned study endpoint was the rate of Complete Remission (CR), defined as no evidence of
85 circulating blasts or extramedullary disease, an M1 bone marrow (<5% blasts), and recovery
86 of peripheral counts (platelets > 100 × 10^9 L and absolute neutrophil count (ANC) > 1.0 ×
87 10^9 L) and Complete Remission in the Absence of Total Platelet Recovery (CRp), defined as
88 meeting all criteria for CR except for recovery of platelet counts to > 100 × 10^9 L. Partial
89 Response (PR) was also determined, defined as complete disappearance of circulating blasts,
90 an M2 bone marrow (> 5% and < 25% blasts), and appearance of normal progenitor cells or
91 an M1 marrow that did not qualify for CR or CRp. Transplantation rate was not a study
92 endpoint.

93

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

96

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

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

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

INDICATIONS AND USAGE

CLOLAR™ is indicated 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.

CONTRAINDICATIONS

None

WARNINGS

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

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

important, and hepatic and renal function should be assessed prior to and during treatment with CLOLAR™ because of CLOLAR™'s predominantly renal excretion and because the liver is a target organ for CLOLAR™ toxicity. The respiratory status and blood pressure should be closely monitored during infusion of CLOLAR™.

Hepatic and Renal Impairment

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

Pregnancy – Teratogenic Effects: Pregnancy Category D

CLOLAR™ (clofarabine) may cause fetal harm when administered to a pregnant woman. Clofarabine was teratogenic in rats and rabbits. Developmental toxicity (reduced fetal body weight and increased post-implantation loss) and increased incidences of malformations and variations (gross external, soft tissue, skeletal and retarded ossification) were observed in rats receiving 54 mg/m^2/day (approximately equivalent to the recommended clinical dose on a mg/m^2 basis), and in rabbits receiving 12 mg/m^2/day (approximately 23% of the recommended clinical dose on a mg/m^2 basis).

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

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

PRECAUTIONS

Information for Patients and Caregivers

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

Dehydration/Hypotension

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

Concomitant Medications

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

Pregnancy/Nursing

All patients should be advised to use effective contraceptive measures to prevent pregnancy. Female patients should be advised to avoid breast feeding during treatment with CLOLAR™.

Laboratory Tests

Complete blood counts and platelet counts should be obtained at regular intervals during CLOLAR™ therapy, and more frequently in patients who develop cytopenias. In addition liver and kidney function should be monitored frequently during the 5 days of CLOLAR™ administration.

Drug Interactions

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

Drug/Laboratory Tests Interactions

There are no known clinically significant interactions of CLOLAR™ with other medications or laboratory tests. No formal drug/laboratory test interaction studies have been conducted with CLOLAR™.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Clofarabine has not been tested for carcinogenic potential.

Mutagenesis

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

Impairment of Fertility

Studies in mice, rats, and dogs have demonstrated dose-related adverse effects on male reproductive organs. Seminiferous tubule and testicular degeneration and atrophy were reported in male mice receiving IP doses of 3 mg/kg/day (9 mg/m^2/day, approximately 17% of clinical recommended dose on a mg/m^2 basis). The testes of rats receiving 25 mg/kg/day (150 mg/m^2/day, approximately 3 times the recommended clinical dose on a mg/m^2 basis) in a 6-month IV study had bilateral degeneration of the seminiferous epithelium with retained spermatids and atrophy of interstitial cells. In a 6-month IV dog study, cell degeneration of the epididymis and degeneration of the seminiferous epithelium in the testes were observed in dogs receiving 0.375 mg/kg/day (7.5 mg/m^2/day, approximately 14% of the clinical recommended dose on a mg/m^2 basis). Ovarian atrophy or degeneration and uterine mucosal apoptosis were observed in female mice at 75 mg/kg/day (225 mg/m^2/day, approximately 4 fold of recommended human dose on a mg/m^2 basis), the only dose administered to female mice. The effect on human fertility is unknown.

Pregnancy

Teratogenic Effects: Pregnancy Category D

See **WARNINGS**.

Nursing Mothers

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

Other Special Population: Adults

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

ADVERSE REACTIONS

One hundred thirteen (113) pediatric patients with ALL (67) or AML (46) were exposed to CLOLAR™. Ninety six (96) of the pediatric patients treated in clinical trials received the recommended dose of CLOLAR™ 52 mg/m^2 daily × 5.

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

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

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

Table 2: Most Commonly Reported (>=10% Overall) Adverse Events by System Organ Class (N=96)

System Organ Class Adverse Event[1]	52 mg/m² (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	.	.

Table 2: Most Commonly Reported (>=10% Overall) Adverse Events by System Organ Class (N=96) (continued)

System Organ Class Adverse Event[1]	52 mg/m² (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).

Cardiovascular

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

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

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

Hepatic

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

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

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

Infection

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

Renal

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

Systemic Inflammatory Response Syndrome (SIRS)/Capillary Leak Syndrome

Capillary leak syndrome or SIRS (signs and symptoms of cytokine release, e.g., tachypnea, tachycardia, hypotension, pulmonary edema) occurred in 4 pediatric patients overall (3 ALL, 1 AML). Several patients developed rapid onset of respiratory distress, hypotension, capillary leak (pleural and pericardial effusions), and multi-organ failure. Close monitoring for this syndrome and early intervention are recommended. The use of prophylactic steroids (eg, 100 mg/m^2 hydrocortisone on Days 1 through 3) may be of benefit in preventing signs or symptoms of SIRS or capillary leak. Physicians should be alert to early indications of this syndrome and should immediately discontinue CLOLAR™ administration if they occur and provide appropriate supportive measures. After the patient is stabilized and organ function has returned to baseline, re-treatment with CLOLAR™ can be considered at a lower dose.

316 **Overdosage**

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

321

322 **DOSAGE AND ADMINISTRATION**

323 **Recommended Dose**

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

326

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

333

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

336

337 Physicians are encouraged to give continuous IV fluids throughout the 5 days of CLOLAR™
338 administration to reduce the effects of tumor lysis and other adverse events. The use of
339 prophylactic steroids (e.g., 100 mg/m^2 hydrocortisone on Days 1 through 3) may be of

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

STORAGE AND HANDLING

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

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

HOW SUPPLIED

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

Rx only

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

Other patents pending.

NAME AND ADDRESS OF MANUFACTURER

Manufactured by: AAI Development Services
Charleston, SC 29405

Manufactured for: Genzyme Corporation
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Distributed by: Genzyme Corporation
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Cambridge, MA 02142