PRODUCT MONOGRAPH

PrCLOLAR®

Clofarabine for injection

1 mg/mL (20 mg/20 mL)

Antineoplastic Agent

sanofi-aventis Canada Inc.
2905 Place Louis-R.-Renaud
Laval, Quebec H7V 0A3

Date of Preparation:
August 31, 2016

Submission Control No: 195475

s-a version 4.0 dated August 31, 2016

Table of Contents

PrCLOLAR®

Clofarabine for injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Intravenous infusion	Injection/ 1 mg/mL	unbuffered normal saline (water for injection, USP, and sodium chloride, USP)

INDICATIONS AND CLINICAL USE

CLOLAR® (clofarabine) 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. Approval is based on objective response rates. No survival advantage has been demonstrated and palliative benefit was not evaluated.

CONTRAINDICATIONS

- Hypersensitivity to clofarabine or any of the excipients (see DOSAGE FORMS, COMPOSITION AND PACKAGING).
- Symptomatic central nervous system involvement (see CLINICAL TRIALS)
- History of serious heart, liver, kidney or pancreas disease (see ADVERSE DRUG REACTIONS).
- Severe hepatic impairment (defined as elevated transaminases (AST and/or ALT) > 5 x ULN, and/or elevated bilirubin > 3 x ULN) or severe renal insufficiency (defined as creatinine clearance < 30 mL/min).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

CLOLAR (clofarabine) must be administered under the supervision of a physician qualified in the use of antineoplastic agents.

CLOLAR is associated with:

- Tumor Lysis Syndrome (TLS) (see Hyperuricemia below)
- Systemic Inflammatory Response Syndrome (SIRS)/Capillary Leak Syndrome, including fatal cases (see Systemic Inflammatory Response Syndrome (SIRS) and Capillary Leak Syndrome below)
- Enterocolitis, including fatal cases (see Gastro-intestinal below)
- Hemorrhage, including fatal cases (see Hematologic below)
- Stevens-Johnson syndrome, toxic epidermal necrolysis, including fatal cases (see Skin below)
- Hepatotoxicity, including fatal cases (see Hepatic/Biliary/Pancreatic below)
- Renal failure/acute renal failure due to infections, sepsis, and TLS; some cases had a fatal outcome (see Renal below)

General

CLOLAR should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy.

Carcinogenesis and Mutagenesis

Carcinogenicity studies have not been conducted. Clofarabine was clastogenic in mammalian cells in the *in vitro* chromosomal aberration assay and in the *in vivo* micronucleus assay in rats. Clofarabine was not mutagenic in bacteria (Ames assay) (see TOXICOLOGY).

Dehydration/Hypotension

As with other chemotherapeutic agents, 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 with a dose reduction (see DOSAGE AND ADMINISTRATION).

Gastro-intestinal

Occurrences of enterocolitis, including neutropenic colitis, cecitis, and *C. difficile* colitis, have been reported during treatment with clofarabine. This has occurred more frequently within 30 days of treatment, and in the setting of combination chemotherapy. Enterocolitis may lead to necrosis, perforation, hemorrhage or sepsis complications and may be associated with fatal outcome (see ADVERSE REACTIONS). Patients should be monitored for signs and symptoms of enterocolitis.

Hematologic

Obtain complete blood counts and platelet counts at regular intervals during CLOLAR therapy. Suppression of bone marrow function should be anticipated. 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.

These patients are at risk of prolonged neutropenia when treated with CLOLAR. For all subsequent courses, recovery of absolute neutrophil count (ANC) to $> 0.5 \times 10^9$/L prior to restarting therapy is recommended. In clinical trials, no dose reductions were permitted for hematological toxicities, including thrombocytopenia, except for neutropenia ($\leq 0.5 \times 10^9$/L) lasting for more than 28 days (see DOSAGE AND ADMINISTRATION). Patients with prolonged neutropenia (ANC $\leq 0.5 \times 10^9$/L for > 28 days) should undergo a bone marrow examination to exclude progressive disease.

Hemorrhage, including cerebral, gastrointestinal and pulmonary hemorrhage, has been reported and may be fatal. The majority of the cases were associated with thrombocytopenia (see ADVERSE REACTIONS).

Hepatic/Biliary/Pancreatic

CLOLAR has not been studied in patients with hepatic impairment (serum billirubin > 1.5 x ULN plus ALT and AST > 5 x ULN). In patients with mild to moderate hepatic impairment CLOLAR should be used with the greatest caution. Avoid concomitant use of medications known to induce hepatic toxicity (see ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION).

Patients who have previously received a hematopoietic stem cell transplant (HSCT) may be at higher risk for hepatotoxicity suggestive of veno-occlusive disease (VOD) following treatment with clofarabine when used in combination (etoposide and cyclophosphamide). Severe hepatotoxic events have been reported in an ongoing Phase 1/2 combination study of clofarabine in pediatric patients with relapsed or refractory acute leukemia.

Severe and fatal hepatotoxicity has occurred with the use of CLOLAR. Cases of hepatitis and hepatic failure, including fatal outcomes, have been reported with CLOLAR treatment. Patients should be monitored for liver functions, and signs and symptoms of hepatitis and hepatic failure.

CLOLAR should be discontinued immediately if substantial increases in liver enzymes (≥ Grade 3) and/or bilirubin are observed.

Hyperuricemia (Tumor Lysis Syndrome)

Administration of CLOLAR may result in a rapid destruction of peripheral leukemia cells that may lead to tumor lysis syndrome. Evaluate and monitor patients undergoing treatment for signs and symptoms of tumor lysis syndrome. Provide intravenous infusion fluids throughout the five days of CLOLAR administration to reduce the effects of tumor lysis and other adverse events. The initiation of measures to prevent tumor lysis syndrome (such as the administration of alkalinized intravenous fluids, allopurinol and/or other uric acid-lowering agents) may be considered prior to clofarabine administration. Institutional guidelines should be followed in regards to the dosing and schedule of administration of these agents.

Systemic Inflammatory Response Syndrome (SIRS) and Capillary Leak Syndrome

Evaluate and monitor patients undergoing treatment with CLOLAR for signs and symptoms of cytokine release (e.g., tachypnea, tachycardia, hypotension, pulmonary edema) that could progress to systemic inflammatory response syndrome (SIRS), capillary leak syndrome and multi-organ dysfunction. Discontinue CLOLAR immediately in the event of clinically significant signs or symptoms of SIRS or capillary leak syndrome, either of which can be fatal, and consider use of steroids, diuretics, and albumin. Re-institute CLOLAR when the patient is stable (see DOSAGE AND ADMINISTRATION). The use of prophylactic steroids may be of benefit in preventing signs and symptoms of cytokine release (see DOSAGE AND ADMINISTRATION).

Immune

The use of CLOLAR is likely to increase the risk of infection, including severe sepsis, as a result of bone marrow suppression. 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.

Renal

CLOLAR has not been studied in patients with renal dysfunction (serum creatinine ≥2 ULN) and it is predominantly excreted via the kidney. Therefore, CLOLAR should be used with caution in patients with mild to moderate renal insufficiency. Avoid drugs with known renal toxicity during the 5 days of CLOLAR administration (see DRUG INTERACTIONS, DOSAGE AND ADMINISTRATION). CLOLAR should not be administered in patients with severe renal insufficiency (see CONTRAINDICATIONS; ACTIONS AND CLINICAL PHARMACOLOGY, Pharmacokinetics-Elimination).

Cases of renal failure/acute renal failure have been observed as a consequence of infections, sepsis and tumor lysis syndrome; some cases had a fatal outcome (see ADVERSE REACTIONS). Monitor patients for renal toxicity and interrupt or discontinue CLOLAR as necessary.

Sexual Function/Reproduction

Fertility studies with clofarabine have not been performed in animals. Degenerative effects on reproductive organs in the general toxicity studies suggest a potential effect on male and female fertility (see TOXICOLOGY). The effect of CLOLAR treatment on human fertility is unknown.

Skin

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), including fatal cases, have been reported (see ADVERSE REACTIONS). CLOLAR must be discontinued for exfoliative or bullous rash, or if SJS or TEN is suspected.

Special Populations

Pregnant Women: CLOLAR may cause fetal harm when administered to a pregnant woman.

Clofarabine was teratogenic in rats and rabbits at doses much lower than recommended human dose (see TOXICOLOGY).

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

Nursing Women: It is not known whether clofarabine or its metabolites are excreted in human milk. The excretion of clofarabine in milk has not been studied in animals. Because of the potential for serious adverse reactions in nursing infants, women treated with clofarabine should not nurse. Female patients should be advised to discontinue breast-feeding during treatment with CLOLAR.

Pediatrics (*1-21* years of age): Safety and effectiveness have been established in pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia.

Geriatrics (> *65* years of age): Safety and effectiveness of CLOLAR has not been established in geriatric patients aged 65 and older.

Adults (*>21 and <65 years of age*): Safety and effectiveness 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 IV infusion daily x 5 every 28 days.

Monitoring and Laboratory Tests:

The following parameters should be closely monitored in patients undergoing treatment with CLOLAR:

- Complete blood cells and platelets counts on Days 1, 3, and 5 of each cycle. Repeat 1 to 2 times weekly, as clinically indicated (more frequently in patients who develop cytopenia) thereafter.
- Bone marrow aspiration and/or biopsy: prior to each cycle. If the bone marrow has not recovered and there is no evidence of leukemia, a bone marrow aspiration and/or biopsy should be repeated within 14 days.
- Renal and hepatic function daily during the 5 days of CLOLAR administration and at regular intervals throughout the entire treatment cycle.
- Respiratory status, blood pressure, fluid balance and weight at least daily for the 5 days of CLOLAR administration and at regular intervals throughout the entire treatment cycle.
- Uric acid, potassium, phosphate, signs and symptoms of TLS, SIRS/capillary leak syndrome (see WARNINGS AND PRECAUTIONS)
- Serum electrolytes (including sodium)

Close monitoring of patients taking medications known to affect blood pressure or cardiac function during administration of CLOLAR is advised (see DRUG INTERACTIONS).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most common toxicities observed during exposure to CLOLAR were gastrointestinal system adverse events (AEs) (including vomiting, nausea, and diarrhea), adverse hematologic effects (including anemia, leukopenia, thrombocytopenia, neutropenia, and febrile neutropenia), and infection. It should be noted that a large number of the adverse effects were already present in many of the patients at baseline. Other significant groups of AEs observed for CLOLAR are found in the hepatobiliary, renal, and gastrointestinal organ systems. In addition, tumor lysis syndrome, capillary leak syndrome or SIRS have been reported.

The following serious adverse reactions have been reported with CLOLAR (see also WARNINGS AND PRECAUTIONS):

- Enterocolitis
- Severe bone marrow suppression
- Hemorrhage
- Hepatotoxicity
- Hyperuricemia (Tumor Lysis Syndrome)
- Systemic Inflammatory Response Syndrome (SIRS) and Capillary Leak Syndrome

- Infections, including severe sepsis
- Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

Clinical Trial Adverse Drug Reactions

Open-label single arm studies: Phase I Study ID99-383 (ALL/AML), Phase II CLO212 (ALL) and CLO222 (AML)

The data described below reflect exposure to CLOLAR in 115 pediatric patients with relapsed or refractory ALL (70) or AML (45).

One hundred and fifteen (115) of the pediatric patients treated in clinical trials received at least 1 infusion of CLOLAR at 52 mg/m^2. The data for these patients were combined into an integrated database. The patients in the integrated database participated in the 3 clinical trials presented (CLO-212, N=61 ALL, CLO-222, N=41 AML and ID99-383N=13). Treatment cycle comprised a 5-day course of Clolar 52 mg/m^2 /day followed by the recovery period of approximately 2 to 6 weeks from the starting day of the previous cycle (see DOSAGE AND ADMINISTRATION).

The median number of cycles was 2. The median cumulative amount of CLOLAR received by pediatric patients during all cycles was 540 mg.

The most common adverse reactions with CLOLAR are: nausea, vomiting, diarrhea, febrile neutropenia, headache, rash, pruritus, pyrexia, fatigue, palmar-plantar erythrodysesthesia syndrome, anxiety, flushing, and mucosal inflammation. Of 29 deaths on-study within 30 days of the last CLOLAR dose, 19 were disease related 7 were multifactorial (both disease and CLOLAR -related) and 3 were possibly CLOLAR -related by investigator.

Table 1 lists adverse reactions by System Organ Class, including severe or life-threatening events (NCI CTC grade 3 or grade 4), reported in ≥ 5% of the 115 patients in the 52 mg/m^2/day dose group (pooled analysis of pediatric patients with ALL and AML). More detailed information and follow-up of certain events is given below.

Table 2 lists the incidence of treatment emergent laboratory abnormalities after CLOLAR administration at 52 mg/m^2 among pediatric patients with ALL and AML (n=115).

Table 1: **Most Commonly Reported (≥ 5% Overall) Adverse Reactions by System Organ Class Regardless of Causality (N=115 pooled analysis)**

System Organ Class[1]	Preferred Term[1]	ALL/AML (N=115)		Worst NCI Common Terminology Criteria Grade[1]					
				3		4		5	
		N	%	N	%	N	%	N	%
Blood and Lymphatic System Disorders	Febrile neutropenia	63	54.8	59	51.3	3	2.6	.	.
	Neutropenia	11	9.6	3	2.6	8	7.0	.	.
Cardiac Disorders	Pericardial effusion	9	7.8	.	.	1	0.9	.	.
	Tachycardia	40	34.8	6	5.2	.	.	.	.
Gastrointestinal Disorders	Abdominal pain	40	34.8	8	7.0	.	.	.	.
	Abdominal pain upper	9	7.8	1	0.9	.	.	.	.
	Diarrhea	64	55.7	14	12.2	.	.	.	.
	Gingival bleeding	16	13.9	7	6.1	1	0.9	.	.
	Mouth hemorrhage	6	5.2	2	1.7	.	.	.	.
	Nausea	84	73.0	16	13.9	1	0.9	.	.
	Oral mucosal petechiae	6	5.2	4	3.5	.	.	.	.
	Proctalgia	9	7.8	2	1.7	.	.	.	.
	Stomatitis	8	7.0	1	0.9	.	.	.	.
	Vomiting	90	78.3	9	7.8	1	0.9	.	.
General Disorders and Administration Site Conditions	Asthenia	12	10.4	1	0.9	1	0.9	.	.
	Chills	39	33.9	3	2.6	.	.	.	.
	Fatigue	39	33.9	3	2.6	2	1.7	.	.
	Irritability	11	9.6	1	0.9	.	.	.	.
	Mucosal inflammation	18	15.7	2	1.7	.	.	.	.
	Edema	14	12.2	2	1.7	.	.	.	.
	Pain	17	14.8	7	6.1	1	0.9	.	.
	Pyrexia	45	39.1	16	13.9	.	.	.	.
Hepatobiliary Disorder	Jaundice	9	7.8	2	1.7	.	.	.	.
Infections and Infestations	Bacteremia	10	8.7	10	8.7	.	.	.	.
	Candidiasis	8	7.0	1	0.9	.	.	.	.
	Catheter related infection	14	12.2	13	11.3	.	.	.	.
	Cellulitis	9	7.8	7	6.1	.	.	.	.
	Clostridium colitis	8	7.0	6	5.2	.	.	.	.
	Herpes simplex	11	9.6	6	5.2	.	.	.	.
	Herpes zoster	8	7.0	6	5.2	.	.	.	.
	Oral candidiasis	13	11.3	2	1.7	.	.	.	.
	Pneumonia	11	9.6	6	5.2	1	0.9	1	0.9

[1]Patients with more than one preferred term within a SOC are counted only once in the SOC totals. Patients with more than one occurrence of the same preferred term are counted only once within that term and at the highest severity grade.

System Organ Class[1]	Preferred Term[1]	ALL/AML (N=115)		Worst NCI Common Terminology Criteria Grade[1] 3		4		5	
		N	%	N	%	N	%	N	%
Infections and Infestations (continued)	Sepsis	11	9.6	5	4.4	2	1.7	4	3.5
	Septic shock	8	7.0	1	0.9	2	1.7	5	4.4
	Staphylococcal bacteremia	7	6.1	5	4.4	1	0.9	.	.
	Staphylococcal sepsis	6	5.2	5	4.4	1	0.9	.	.
	Upper respiratory tract infection	6	5.2	1	0.9	.	.	.	.
Metabolism and Nutrition Disorders	Anorexia	34	29.6	6	5.2	8	7.0	.	.
Musculoskeletal and Connective Tissue Disorders	Arthralgia	10	8.7	3	2.6	.	.	.	.
	Back pain	12	10.4	3	2.6	.	.	.	.
	Bone pain	11	9.6	3	2.6	.	.	.	.
	Myalgia	16	13.9	.	.	.	.	.	.
	Pain in extremity	34	29.6	6	5.2	.	.	.	.
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	Tumor lysis syndrome	7	6.1	7	6.1	.	.	.	.
Nervous System Disorders	Headache	49	42.6	6	5.2	.	.	.	.
	Lethargy	12	10.4	1	0.9	.	.	.	.
	Somnolence	11	9.6	1	0.9	.	.	.	.
Psychiatric Disorders	Agitation	6	5.2	1	0.9	.	.	.	.
	Anxiety	24	20.9	2	1.7	.	.	.	.
Renal and Urinary Disorders	Hematuria	15	13.0	2	1.7	.	.	.	.
Respiratory, Thoracic and Mediastinal Disorders	Dyspnea	15	13.0	6	5.2	2	1.7	.	.
	Epistaxis	31	27.0	15	13.0	.	.	.	.
	Pleural effusion	14	12.2	4	3.5	2	1.7	.	.
	Respiratory distress	12	10.4	5	4.4	4	3.5	1	0.9
	Tachypnea	10	8.7	4	3.5	1	0.9	.	.
Skin and Subcutaneous Tissue Disorders	Erythema	13	11.3	.	.	.	.	.	.
	Palmar-plantar erythrodysaesthesia syndrome	18	15.7	8	7.0	.	.	.	.
	Petechiae	30	26.1	7	6.1	.	.	.	.
	Pruritus	49	42.6	1	0.9	.	.	.	.
	Rash	44	38.3	8	7.0	.	.	.	.
	Rash pruritic	9	7.8	.	.	.	.	.	.
Vascular Disorders	Flushing	22	19.1	.	.	.	.	.	.
	Hypertension	15	13.0	6	5.2	.	.	.	.
	Hypotension	33	28.7	13	11.3	9	7.8	.	.

[1]Patients with more than one preferred term within a SOC are counted only once in the SOC totals. Patients with more than one occurrence of the same preferred term are counted only once within that term and at the highest severity grade.

Less Common Clinical Trial Adverse Drug Reactions (1-4%)

The following less common adverse reactions have been reported in 1-4% of the 115 pediatric patients with ALL or AML:

Gastrointestinal Disorders: cecitis

General Disorders: SIRS

Hepatobiliary Disorders: hyperbilirubinemia, jaundice, VOD

Immune System Disorders: hypersensitivity

Infections and Infestations: bacterial infection, Enterococcal bacteremia, Escherichia bacteremia, Escherichia sepsis, fungal infection, fungal sepsis, gastroenteritis adenovirus, infection, influenza, Parainfluenzae virus infection, pneumonia fungal, pneumonia primary atypical, Respiratory syncytial virus infection, sinusitis, staphylococcal infection

Investigations: blood creatinine increased

Psychiatric Disorders: mental status change

Respiratory, Thoracic and Mediastinal Disorder: pulmonary edema

Vascular Disorders: capillary leak syndrome

Uncommon occurrences of Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients who were receiving or had recently been treated with other medications (e.g. allopurinol or antibiotics) known to cause these syndromes.

Abnormal Hematologic and Clinical Chemistry Findings

Table 2: Incidence of Treatment Emergent Laboratory Abnormalities After CLOLAR Administration

Parameter	Any Grade	Grade 3 or higher
Hematology		
Anemia (N=114)	95 (83.3%)	86 (75.4%)
Leukopenia (N=114)	100 (87.7%)	100 (87.7%)
Lymphopenia (N=113)	93 (82.3%)	93 (82.3%)
Neutropenia (N=113)	72 (63.7%)	72 (63.7%)
Thrombocytopenia (N=114)	92 (80.7%)	91 (79.8%)
Elevated Creatinine (N=115)	57 (49.5%)	9 (7.8%)
Elevated SGOT (N=100)	74 (74.0%)	36 (36.0%)
Elevated SGPT (N=113)	91 (80.5%)	49 (43.4%)
Elevated Total Bilirubin (N=114)	51 (44.7%)	15 (13.2%)

Open-label single arm Phase II BIOV-111 Study

In an additional pediatric ALL study, "A phase II, open-label study of clofarabine in pediatric patients with refractory/relapsed acute lymphoblastic leukemia" (BIOV-111 Study), 71 patients received CLOLAR. Of these, 65 patients received at least one full course of CLOLAR and 32 received at least two full courses at the recommended dose of 52 mg/m^2 daily × 5 days. Small numbers of patients (6, 4, 1) started third, fourth and sixth courses, respectively.

There were 43/71 (61%) in this study who experienced severe or life-threatening events (NCI CTC grade 3 or grade 4) adverse reactions related to CLOLAR. The most common event was febrile neutropenia (43.7%).

The most frequent AEs (incidence of > 50%) were vomiting in 52 (73.2%) patients, headache in 40 (56.3%) patients, pyrexia in 38 (53.5%) patients, and nausea and febrile neutropenia each in 37 (52.1%) patients. Sixty-two out of 71 (87.3%) patients died during the course of the study; 42 of these deaths occurred > 30 days after the last dose of CLOLAR. Seven (9.9%) deaths were considered to be CLOLAR related in this study.

Table 3 lists adverse reactions by System Organ Class, including severe or life-threatening events (NCI CTC grade 3 or grade 4), reported in ≥ 5% of the 71 patients.

Table 3: BIOV-111 Study Most Commonly Reported (≥ 5% Overall) Adverse Events by System Organ Class Regardless of Causality (N=71)*

		ALL/AML (N=71)		Worst NCI Common Terminology Criteria Grade[1]					
				3		4		5	
System Organ Class[1]	Preferred Term[1]	N	%	N	%	N	%	N	%
Blood and lymphatic System disorders	Anemia	5	7.0	3	4.2	1	1.4	.	.
	Febrile neutropenia	37	52.1	31	43.7	5	7.0	.	.
	Neutropenia	7	9.9	3	4.2	4	5.6	.	.
	Thrombocytopenia	6	8.5	.	.	6	8.5	.	.
Cardiac disorders	Tachycardia	5	7.0	.	.	.	.	1	1.4
Ear and labyrinth disorders	Ear pain	4	5.6	.	.	.	.	.	.
Gastrointestinal disorders	Abdominal pain	26	36.6	6	8.5	.	.	.	.
	Constipation	10	14.1	.	.	.	.	.	.
	Diarrhea	27	38.0	5	7.0	1	1.4	.	.
	Nausea	37	52.1	5	7.0	.	.	.	.
	Vomiting	52	73.2	3	4.2	.	.	.	.

System Organ Class[1]	Preferred Term[1]	ALL/AML (N=71)		Worst NCI Common Terminology Criteria Grade[1]					
				3		4		5	
		N	%	N	%	N	%	N	%
General disorders and administration site conditions	Asthenia	6	8.5	2	2.8	.	.	.	.
	Chills	5	7.0	.	.	.	.	.	.
	Fatigue	11	15.5	.	.	.	.	.	.
	Mucosal inflammation	13	18.3	4	5.6	.	.	.	.
	Pain	7	9.9	4	5.6	.	.	.	.
	Pyrexia	38	53.5	9	12.7	1	1.4	.	.
Immune system disorders	Hypersensitivity	7	9.9	4	5.6	.	.	.	.
Infections and infestations	Bronchopulmonary aspergillosis	4	5.6	2	2.8	1	1.4	1	1.4
	Herpes zoster	5	7.0	1	1.4	.	.	.	.
	Sepsis	7	9.9	3	4.2	2	2.8	1	1.4
Investigations	Alanine aminotransferase increased	5	7.0	4	5.6	.	.	.	.
	Aspartate aminotransferase increased	4	5.6	1	1.4	1	1.4	.	.
	Platelet count decreased	5	7.0	.	.	4	5.6	.	.
	Weight decreased	6	8.5	.	.	.	.	.	.
Metabolism and nutrition disorders	Anorexia	11	15.5	3	4.2	.	.	.	.
Musculoskeletal and connective tissue disorders	Arthralgia	6	8.5	4	5.6	.	.	.	.
	Back pain	8	11.3	1	1.4	.	.	.	.
	Bone pain	12	16.9	6	8.5	.	.	.	.
	Musculoskeletal pain	5	7.0	2	2.8	.	.	.	.
	Pain in extremity	18	25.4	3	4.2	.	.	.	.
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Malignant neoplasm progression	13	18.3	.	.	.	.	13	18.3
Nervous systems disorders	Convulsion	6	8.5	2	2.8	.	.	.	.
	Headache	30	42.3	7	9.9	.	.	.	.
Psychiatric disorders	Anxiety	7	9.9	3	4.2	.	.	.	.
	Depression	6	8.5	2	2.8	.	.	.	.
	Mood altered	7	9.9	1	1.4	.	.	.	.
Respiratory, thoracic and mediastinal disorders	Cough	13	18.3	.	.	.	.	.	.
	Dyspnea	4	5.6	1	1.4	.	.	.	.
	Epistaxis	10	14.1	3	4.2	.	.	.	.
	Pharyngolaryngeal pain	5	7.0	.	.	.	.	.	.

System Organ Class[1]	Preferred Term[1]	ALL/AML (N=71)		Worst NCI Common Terminology Criteria Grade[1]					
				3		4		5	
		N	%	N	%	N	%	N	%
Skin and subcutaneous tissue disorders	Erythema	4	5.6	.	.	.	.	.	.
	Palmar-plantar erythrodysesthesia syndrome	5	7.0	4	5.6	.	.	.	.
	Petechiae	4	5.6	.	.	.	.	.	.
	Pruritus	20	28.2	1	1.4	.	.	.	.
	Rash	27	38.0	4	5.6	.	.	.	.
Vascular disorders	Flushing	5	7.0	.	.	.	.	.	.
	Hypertension	8	11.3	2	2.8	.	.	.	.
	Hypotension	10	14.1	.	.	.	.	2	2.8

[1]Patients with more than one preferred term within a SOC are counted only once in the SOC totals. Patients with more than one occurrence of the same preferred term are counted only once within that term and at the highest severity grade.

The following sections provide more detailed information regarding the incidence of the most commonly occurring adverse events and/or laboratory abnormalities observed in all the pediatric clinical studies mentioned above:

Hematologic Toxicity
In the integrated safety population (n=115), the most frequently reported hematologic adverse reactions in pediatric patients included febrile neutropenia (55%) and neutropenia (10%). One (1) report of grade 4 bone marrow depression, and 1 report of grade 4 thrombocytopenia were considered related to study drug.

In the BIOV-111 Study more than 90% of patients experienced Grade 3 or 4 leukopenia, lymphopenia, neutropenia or thrombocytopenia.

Infection
In the integrated safety population (n=115), at baseline, 48% of the pediatric ALL and AML patients had 1 or more concurrent infections. A total of 83% of patients experienced at least 1 infection after CLOLAR treatment, including fungal, viral and bacterial infections.

Infections occurred in 25.4% of patients on the BIOV-111 Study.

Hepatic
The liver is a potential target organ of CLOLAR, and in the integrated safety population (n=115), 25% of patients experienced at least one hepato-biliary disorders adverse event. Grade 3 or 4 elevated aspartate aminotransferase (AST) occurred in 36% of patients and grade 3 or 4 elevated alanine aminotransferase (ALT) occurred in 43% of patients. Grade 3 or 4 elevated bilirubin occurred in 13% of patients, with 2 events reported as grade 4 hyperbilirubinemia (2%), one of which resulted in treatment discontinuation, one patient had multi-organ failure and died. One report (1%) of veno-occlusive disease (VOD) was considered related to study drug.

For patients with follow-up data, elevations in AST and ALT were transient and typically ≤ 15 days duration. The majority of AST and ALT elevations occurred within 10 days of CLOLAR administration and returned to ≤ grade 2 within 15 days while the majority of bilirubin elevations returned to ≤ grade 2 within 10 days. Eight patients had grade 3 or 4 elevations in serum bilirubin at the last time point measured, these patients died due to sepsis and/or multi-organ failure.

In the BIOV-111 Study elevated ALT (60.9%) was the most common chemistry abnormality, while other liver function abnormalities (AST increased: 41.1%; total bilirubin increased: 7.6%) also occurred at lower frequencies.

Renal
In the integrated safety population (n=115), a total of 53% (61/115) of patients experienced the onset or worsening of elevated creatinine. Grade 3 or 4 elevated creatinine occurred in 8% of patients. Nephrotoxic medications, tumor lysis, and tumor lysis with hyperuricemia may contribute to renal toxicity. Hematuria was observed in 13% of patients overall. This event likely reflects thrombocytopenia that is a pre-existing condition in these patients.

In the BIOV-111 Study, elevated creatinine occurred in 8.9% of patients. Renal failure and renal impairment were each reported in 2 (2.8%) patients and considered to be CLOLAR -related in 1 (1.4%) patient each.

Systemic Inflammatory Response Syndrome (SIRS)/Capillary Leak Syndrome
In the integrated safety population (n=115), other concurrent medical conditions, including sepsis, disease progression and/or prior therapies may also have contributed to the incidence of capillary leak syndrome.

There were no cases of SIRS or Capillary leak syndrome in the BIOV-111 Study.

Gastrointestinal Disorders
In the integrated safety population (n=115), gastrointestinal disorders were the most frequently affected system organ class with 97% of patients overall experiencing at least one AE in this class. Vomiting (78%) was the most frequent adverse event, followed by nausea (73%), diarrhea (56%), and abdominal pain (35%), constipation (17%), and gingival bleeding (14%).

In the BIOV-111 Study, 78.9% of patients experienced gastrointestinal disorders. Among patients with Gastrointestinal disorders, vomiting, nausea, diarrhea, abdominal pain, and anorexia occurred in 66.2%, 47.9% , 26.8%, 21.1% and 41.1%, respectively.

Cardiovascular
In the integrated safety population (n=115), the most frequently reported cardiac disorder was tachycardia (35%), which was, however, already present in 35% of patients at study entry. Most of the cardiac adverse events were reported in the first 2 cycles of CLOLAR treatment. Pericardial effusion was a finding in these patients on post-treatment studies, [9/115 (8%)]. The effusion was almost always minimal to small and in no cases had hemodynamic significance.

In the BIOV-111 Study, 7/71 patients (9.9%) experienced cardiac disorders. Preferred Terms (PTs) for adverse events in this System Organ Class (SOC) include, tachycardia, LV dysfunction, sinus arrhythmia, and cardiac failure.

Post-Market Adverse Drug Reactions

The following list of post market adverse reactions is based on one or more of the following factors: (1) seriousness of the reaction, (2) reported frequency of the reaction, or (3) strength of causal connection to CLOLAR.

Blood and lymphatic system disorders: bone marrow failure, cytopenias (thrombocytopenia, anemia, neutropenia and lymphopenia), pancytopenia. Bleeding events have been observed in the setting of thrombocytopenia. Hemorrhage, including cerebral and pulmonary hemorrhage, has been reported and may be fatal.

Cardiac: pericardial effusion and tachycardia.

Gastrointestinal disorders: Gastrointestinal hemorrhage has been observed and may be associated with a fatal outcome. Enterocolitis, including neutropenic colitis, cecitis, and *C. difficile* colitis; enterocolitis may lead to necrosis, perforation or sepsis complications and may be associated with fatal outcome.

General disorders: mucosal inflammation, SIRS.

Hepatobiliary disorders: hepatic function abnormal, hepatotoxicity, and hyperbilirubinemia. Serious hepatotoxic events of VOD have been reported in patients who had previous HSCT and who received conditioning regimens that included busulfan, melphalan, and/or the combination of cyclophosphamide and total body irradiation. Cases of hepatitis and hepatic failure have been reported, including fatal outcomes (see WARNINGS AND PRECAUTIONS, Hepatic).

Immune system disorders: hypersensitivity.

Infections and infestations:
Systemic:

- *sepsis*: neutropenic sepsis, due to bacterial (e.g. Streptococcus, Enterococcus, Klebsiella) or fungal infections (e.g.Candida), bacteremia (e.g.Streptococcus).

Respiratory: bronchopulmonary fungal (Aspergillus) infection, lung abscess, bacterial pneumonia (Klebsiella), lower respiratory tract infection, respiratory tract infection fungal.

GI: tonsillitis, hepatosplenic fungal infection (Candida), Clostridium difficile colitis.

Neurological: brain abscess, central nervous system infection.

Musculoskeletal: necrotizing fasciitis.

Skin: bacterial wound infection (Staphylococcus).

Unspecified: CMV, Fusarium, Pseudomonas, central line infection, vaginal cellulitis, Herpes simplex, Herpes zoster.

Metabolism and nutrition disorders: hyponatremia.

Nervous system disorders: syncope.

Psychiatric disorders: confusional state, agitation, mental status changes.

Renal disorders: Cases of renal failure/acute renal failure have been observed as a consequence of infections, sepsis and tumor lysis syndrome; some cases had a fatal outcome.

Skin and subcutaneous disorders: Occurrences of fatal cases of Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients who were receiving or had recently been treated with clofarabine and other medications (e.g. allopurinol or antibiotics) known to cause these syndromes. Other exfoliative conditions have also been reported.

Vascular disorders: capillary leak syndrome has been reported and may be fatal.

DRUG INTERACTIONS

Interactions with other drugs have not been established. However, the concomitant use of medicinal products that have been associated with hepatic and /or renal toxicity should be avoided wherever possible. Patients taking medicinal products known to affect blood pressure or cardiac function should be closely monitored during treatment with clofarabine.

Clofarabine is not detectably metabolized by the cytochrome P450 (CYP) enzyme system. In *in vitro* studies, clofarabine was not a substrate and did not significantly inhibit 5 human CYP isoforms (1A2, 2C9, 2C19, 2D6 and 3A4) or induce 2 of these isoforms (1A2 and 3A4). Thus, clofarabine is not expected to affect the metabolism of active substances which are known substrates for these enzymes.

Clofarabine is predominantly excreted via the kidneys; renal clearance is higher than glomerular filtration rates. Studies of the mechanisms of clearance in isolated rat kidney are consistent with elimination of clofarabine by a combination of filtration, tubular secretion and reabsorption. In this model, co-infusion with cimetidine reduced clearance of clofarabine, an effect that was confirmed *in vivo* in the rat. Hence, the concomitant use of drugs that have been associated with renal toxicity and those eliminated by tubular secretion or reabsorption should be avoided particularly during the 5 day clofarabine administration period.

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.

DOSAGE AND ADMINISTRATION

Recommended Concomitant Medications

- Provide IV infusion fluids throughout the 5 days of CLOLAR administration to reduce the effects of tumor lysis and other adverse events. Consider prophylactic anti-emetic medications as CLOLAR is moderately emetogenic. 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 syndrome (e.g., hypotension, tachycardia, tachypnea, and pulmonary edema).

- The administration of alkalinized intravenous fluids, allopurinol and/or other uric acid-lowering agents may be considered prior to clofarabine administration to prevent tumor lysis syndrome. Institutional guidelines should be followed in regards to the dosing and schedule of administration of these agents.

Recommended Dose and Dosage Adjustment

Dosing Schedule and Administration

- The pediatric (ages 1-21) dose of 52 mg/m^2 of body surface area is administered by intravenous infusion over 2 hours daily for 5 consecutive days.
    - Longer infusion times should be considered in children weighing < 20 kg (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics)
- Treatment cycle comprises a 5-day course of CLOLAR followed by the recovery period of 2 to 6 weeks (median 4 weeks) from the starting day of the previous cycle.
- The cycles are repeated following recovery or return to baseline organ function. In clinical trials in pediatric acute leukemias, the median duration of a cycle was 28 days (range of 12-55 days) (see CLINICAL TRIALS).
- The majority of patients who respond to CLOLAR achieve a response after 1 or 2 treatment cycles (see CLINICAL TRIALS). Therefore the potential benefit and risks associated with continued therapy in patients who do not show hematological or clinical improvement after 2 treatment cycles should be assessed by treating physicians.
- Close monitoring of fluid status, and renal and hepatic function during the 5 days of CLOLAR administration is advised (see WARNINGS AND PRECAUTIONS). CLOLAR should not be administered in patients with severe hepatic impairment or severe renal insufficiency (see CONTRAINDICATIONS).
- Close monitoring of patients taking medications known to affect blood pressure or cardiac function during administration of CLOLAR is advised.

Dose Modifications and Reinitiation of Therapy

- Hematologic Toxicity
    - Administer subsequent cycles no sooner than 14 days from the starting day of the previous cycle provided the patient's ANC is $\geq 0.75 \times 10^9$/L.
    - If a patient experiences a Grade 4 neutropenia (ANC $< 0.5 \times 10^9$/L) lasting ≥ 4 weeks, reduce dose by 25% for the next cycle.
- Non-hematologic Toxicity
    - Withhold CLOLAR if a patient develops a clinically significant infection, until the infection is clinically resolved and then restart at the full dose.
    - Withhold CLOLAR if a Grade 3 non-infectious non-hematologic toxicity (excluding nausea/vomiting that was controlled by antiemetic therapy) occurs. Re-institute CLOLAR administration at a 25% dose reduction when resolution or return to baseline.
    - Discontinue CLOLAR administration if $\geq$ Grade 3 liver enzyme elevations occurs.
    - Discontinue CLOLAR administration if a Grade 4 non-infectious non-hematologic toxicity occurs.
    - Withhold CLOLAR administration if a patient shows early signs or symptoms of SIRS or capillary leak syndrome (e.g., hypotension, tachycardia, tachypnea, and pulmonary edema) and provide appropriate supportive measures. Re-institute CLOLAR when the patient is stable, generally with a 25% dose reduction.
    - 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 with a 25% dose reduction.
    - Withhold CLOLAR administration if a substantial increase in creatinine is noted. Re-institute CLOLAR when the patient is stable and organ function has returned to baseline, possibly with a 25% dose reduction. If hyperuricemia is anticipated (tumor lysis), prophylactically administer allopurinol or other uric acid lowering medications. Institutional guidelines should be followed in regards to the dosing and schedule of administration of these agents.
    - Use in patients with hepatic and renal dysfunction: CLOLAR has not been studied in patients with renal or hepatic dysfunction. Its use in such patients should be undertaken only with the greatest caution.

Administration

CLOLAR should be filtered through a sterile 0.2 µm syringe filter and then diluted with 5% Dextrose Injection, USP, or 0.9% Sodium Chloride Injection, USP, prior to intravenous (IV)

infusion to a final concentration between 0.15 mg/mL and 0.4 mg/mL. Use diluted preparation immediately.

Do not administer any other medications through the same intravenous line.

As with all parenteral drug products, CLOLAR injection and diluted IV infusion should be inspected visually for clarity, haziness, particulate matter or precipitate and leakage prior to administration. Solution showing discoloration, haziness, precipitate, particulate, or leakage should not be used. Discard unused portion.

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 in these 2 patients included grade 4 hyperbilirubinemia, grade 2 and 3 vomiting, and grade 3 maculopapular rash.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Clofarabine is transported into target cells by both diffusion and facilitated diffusion. Intracellular clofarabine is mono-phosphorylated by deoxycytidine kinase (dCK) and then serially phosphorylated by other kinases to form clofarabine triphosphate, the active moiety. Clofarabine has high affinity for the dCK, which is equal or exceeds that of deoxycytidine, the natural substrate. Clofarabine is a prodrug and exerts its activity through active metabolites. Clofarabine triphosphate inhibits DNA synthesis via: (1) reduction of deoxynucleotide triphosphate pools by inhibiting ribonucleotide reductase; (2) by competitive inhibition of DNA polymerase alpha (IC50= 3.9 µM), and (3) by terminating DNA chain elongation. In addition, the triphosphate induces apoptosis through the disruption of mitochondrial membrane integrity with the release of cytochrome C and other pro-apoptotic factors. Clofarabine monophosphate has been shown to inhibit DNA repair through incorporation into the DNA chain during the repair process.

Pharmacodynamics

Based on its cellular mechanism of action, clofarabine is expected to demonstrate anticancer activity and also produce adverse effects such as damage to rapidly proliferating tissues (e.g. bone marrow, lymphoid tissue and the gastrointestinal tract) (see TOXICOLOGY).

The inhibitory effect of clofarabine on DNA synthesis in leukemia blast cells was observed in 4 pediatric patients who received doses of 11.25, 15, 40, or 52 mg/m^2. Generally, DNA synthesis declined rapidly after each infusion with a 10 to 50% recovery 24 hours later. The recovery of DNA synthesis appeared to be inversely related to clofarabine dose. Doses less than 52 mg/m^2 MTD) showed breakthrough DNA synthesis prior to the second infusion. At the MTD, the inhibition of DNA synthesis was maintained throughout the therapy cycle. Administration of 52 mg/m^{2}clofarabine resulted in dramatic and rapid reduction in peripheral leukemia cells in 94% (31/33) of pediatric ALL patients (33/61) who had measurable absolute blast count at baseline. No relationship between clofarabine or clofarabine triphosphate exposure and either efficacy or toxicity has been established in this population.

A dose-dependent inhibition of DNA synthesis was also reported in adult patients with acute leukemia treated with clofarabine. The pretreatment capacity of mononuclear cells to synthesize DNA was compared to their capacities after 3 to 4 days of therapy. At a dose of 22.5 mg/m^2/day, a 60% decrease in DNA synthesis was observed. At 30 mg/m^2/day, the DNA synthesis inhibition was almost complete, but not sustainable. And only at 55 mg/m^2/day the complete sustainable DNA synthesis inhibition was achieved. The decrease in DNA synthesis was accompanied by a decrease in white blood cell (WBC) counts. For the 12 adult patients at the MTD of 40 mg/m^2/day, the WBC count at pre-treatment ranged from 1000 to 78000/μL with a blast percentage of 80 to 97%. After 5 days of therapy, WBC counts declined a median of 97% (range 68-99%).

The anti-cancer activity of clofarabine appeared to be dose and schedule dependent, and greater antitumor activity was associated with more frequent administration.

Pharmacokinetics

Population pharmacokinetics of clofarabine were studied in 32 patients (M/F 18/14). Of these, 17 patients had ALL and 15 had AML. Patients aged between 2.9 to 17.8 years old (median 11.8 years old) were predominantly Caucasian (n=15) with an equal number of Blacks and Hispanics (n=6). Of the remaining patients, 1 was Asian and 4 were classified as other. Patient's average weigh was 45.0 kg (range 15.6 to 129.9 kg). Body surface area averaged 1.32 m^2 (range 0.65 to 2.58 m^2). All patients received a dose adjusted by BSA of 52 mg/m^2. Total doses administered ranged from 12.3 to 134 mg /day. The PK was best described by a 2-compartment model. In this analysis, weight was the most important predictor for all primary pharmacokinetic parameters. Sex, disease type, and race were not predictive of clofarabine pharmacokinetics. Although WBC negatively correlated with Cmax, this effect did not appear clinically relevant to individualize a patient's dosage regimen based on their WBC count. Cmax was inversely proportional to patient's weight, and therefore, small children may have a higher Cmax at the end of infusion than a typical 40 kg child given the same dose of clofarabine per m^2. Accordingly, longer infusion times should be considered in children weighing < 20 kg.

Pharmacokinetics parameters of clofarabine were estimated in 22 ALL patients (M/F: 12/10) with mean age of 12.3 years old, weight of 48.1 kg, and BSA of 1.38 m^2. All patients received 52 mg/m^2 clofarabine daily. Clofarabine was administered by IV infusion over 2-hours for 5 consecutive days.

Pharmacokinetic parameters were estimated on Day 1 and on Day 5 of Cycle 1, as well as at steady-state, (Typical*). Plasma clofarabine concentrations were generally maximal by the end of infusion. Little accumulation in plasma was observed by the end of a 5-day cycle.

Table 4. Pharmacokinetics in pediatric patients with relapsed/refractory ALL following IV administration of clofarabine at 52 mg/m^2 on Day1, Day 5 and Typical Across Days.

	C_{max} (ng/mL)	$t_{½\ \alpha}$ (h)	$t_{½\ \beta}$ (h)	$AUC_{0\text{-}inf}$ (ng.h/mL)	Clearance (L/h)	Volume of distribution (L)
Day1						
Mean	452.9	0.434	6.2	2480	34.0	195
SD	186.7	0.171	3.7	1290	15.8	118.2
Day 5						
Mean	600.6	0.430	4.3	2379	33.0	145
SD	280.7	0.186	1.3	995	13.4	80.3
Typical*						
Mean		0.432	5.3	2451	31.8	173.4
SD	N/A	0.172	1.5	828	13.3	87.4

***** The average of the daily values

Distribution

Only 47% of clofarabine is bound to human plasma proteins, predominantly to albumin. Clofarabine shows high tissue distribution. There is no evidence that intracellular uptake of clofarabine is cell specific.

Metabolism

Clofarabine is not detectably metabolized by the cytochrome P450 (CYP) enzyme system. Clofarabine undergoes step-wise intracellular phosphorylation. The *in vitro* studies suggest that once clofarabine triphosphate is formed it remains trapped in the cell until incorporated into DNA. There is very little to no metabolism of the triphosphate. The metabolic pathways of clofarabine in humans were not characterized. The pharmacokinetics of the active metabolite, clofarabine triphosphate, were not estimated in any studies. The triphosphate concentrations were measured in peripheral mononuclear cells of 10 pediatric patients with acute leukemia. Sustainable intracellular clofarabine triphosphate concentrations (mean of 15.7 µM, range 2.9 to 42.3 µM) were rapidly achieved and maintained over 24 hours with no indication that triphosphate concentrations declined.

Elimination

The mean clofarabine renal clearance was 15.1 L/h (90% CI: 11.1 to 20.6 L/h) with an observed minimum and maximum of 1.34 and 55.0 L/h, respectively.

Approximately 60% of clofarabine dose is eliminated by renal excretion as unchanged drug within 24 hours after dosing. Clofarabine renal clearance rates appear to be much higher than glomerular filtration rates suggesting filtration and tubular secretion as kidney elimination mechanism. Studies in the isolated perfused rat model suggest that the human Organic Cation Transporter Type 2 (hOCT2) may be the transporter responsible for tubular secretion. The pathways of non-renal elimination of the 40% of the administered dose remain unknown.

Although the pharmacokinetics of clofarabine have not been studied in patients with severe renal dysfunction, given the percent of dose excreted in urine as unchanged clofarabine, it is recommended that clofarabine should not be administered in this sub-population.

STORAGE AND STABILITY

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

Diluted admixtures must be used immediately.

SPECIAL HANDLING INSTRUCTIONS

Caution should be used during handling, preparation and disposal of CLOLAR. Use of gloves and other protective clothing to prevent skin contact is recommended. Proper aseptic technique should be used.

Guidelines on the proper handling and disposal of anticancer drugs should be consulted.

DOSAGE FORMS, COMPOSITION AND PACKAGING

CLOLAR injection (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).

Available single-pack and four-pack cartons. Not all package sizes may be marketed.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

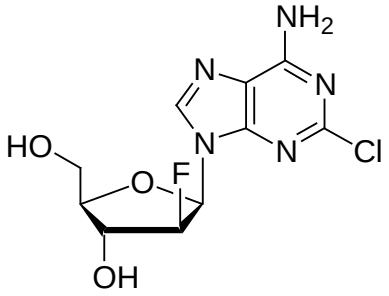
Common name: Clofarabine

Chemical name: 2-chloro-9-(2-deoxy-2-fluoro-ß-D-arabinofuranosyl)-9H-purin-6-amine

Molecular formula: $C_{10}H_{11}ClFN_5O_3$

Molecular mass: 303.68

Structural formula:



Clofarabine

Physicochemical properties:

pH:	The pH of clofarabine in normal saline at a concentration of 1 mg/mL is about 6.5 to 7.0
Solubility:	Soluble in saline up to 1.5 mg/mL at room temperature.
Appearance:	Off-white to white solid
Optical Rotation:	+ 39.93°
Melting Point:	237°C
Thermal Stability:	Clofarabine is thermally stable in both the dry state and in aqueous solutions.

CLINICAL TRIALS

Study demographics and trial design

Seventy-eight (78) pediatric patients with ALL were exposed to CLOLAR. Seventy (70) of the patients received the recommended pediatric dose of CLOLAR 52 mg/m^2 daily x 5 as an intravenous (IV) infusion.

Phase I Study in Pediatric Patients with Hematologic Malignancies

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 IV infusion daily × 5 and escalated to 70 mg/m^2/day IV infusion 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%) and 2 partial remissions (12%) 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.

Phase II Single Arm Study in Pediatric Patients with Refractory or Relapsed Acute Lymphoblasitc Leukemia (Study CLO-212):

CLOLAR was evaluated in an open-label, single arm study of 61 pediatric patients with relapsed/refractory ALL. Patients received a dose of 52 mg/m^2 over 2 hours for 5 consecutive days repeated every 2 to 6 weeks for up to 12 cycles. Responses were seen in both pre-B and T-cell immunophenotypes of ALL. The median cumulative dose was 530 mg (range 29-2815 mg) in 1 (41%), 2 (44%) or 3 or more (15%) cycles. The median number of cycles was 2 (range 1-12). The median duration of one cycle was 28 days with a range of 12 to 55 days. There was no dose escalation in this study.

All patients had disease that had relapsed after and/or was refractory to two or more prior therapies. Most patients, 38/61 (62%), had received > 2 prior regimens and 15/61 (25%) of the patients had undergone at least 1 prior transplant. The median age of the treated patients was 12 years, 61% were male, 39% were female, 44% were Caucasian, 38% were Hispanic, 12% were African-American, 2% were Asian and 5% were Other race.

The overall remission (OR) rate (Complete Remission [CR] + CR in the absence of total platelet recovery [CRp]), 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 CRp, defined as meeting all criteria for CR except for recovery of platelet counts to > 100 × 10^9/L was evaluated. 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. Duration of remission and overall survival was also evaluated. Transplantation rate was not a study endpoint.

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

Of 35 patients who were refractory to their immediately preceding induction regimen, 6 (17.1%) achieved a CR or CRp. Of 18 patients who had at least 1 prior hematopoietic stem cell transplant (HSCT), 5 (27.8%) achieved a CR or CRp.

Among the 18 patients who achieved at least a PR, 13 patients achieved the best response after 1 cycle of clofarabine, 4 patients required 2 courses and 1 patient achieved a CR after 3 cycles of therapy. Of these 18 responding patients, 9 had post-clofarabine bone marrow transplantation (3 CR, 3 CRp, 3 PR). Four of these patients who achieved CR or CRp received HSCT while in continued remission, one patient proceeded to transplant following relapse. One additional patient who achieved a CRp proceeded to transplant following alternative therapy. Duration of response was censored at the time of transplant.

Table 5 lists the efficacy results observed in the CLO-212 study.

Table 5 : Efficacy results from CLO-212 study in patients (≤ 21 years old at initial diagnosis) with relapsed or refractory ALL after at least two prior regimens

Response category	**Best objective response (IRRP) on ITT* patients (n = 61)**	**Median duration of remission (weeks) (95% CI)**	**Median time to progression (weeks)** (95% CI)**	**Median overall survival (weeks) (95% CI)**
Overall remission (CR + CRp)	12 (20%)	32.0 (9.7 to 47.9)	38.2 (15.4 to 56.1)	69.5 (58.6 to -)
CR	7 (12%)	47.9 (6.1 to -)	56.1 (13.7 to -)	72.4 (66.6 to -)
CRp	5 (8%)	28.6 (4.6 to 38.3)	37.0 (9.1 to 42.0)	53.7 (9.1 to -)
PR	6 (10%)	11.0 (5.0 to -)	14.4 (7.0 to -)	33.0 (18.1 to -)
CR + CRp + PR	18 (30%)	21.5 (7.6 to 47.9)	28.7 (13.7 to 56.1)	66.6 (42.0 to -)
Treatment failure	33 (54%)	N/A	4.0 (3.4 to 5.1)	7.6 (6.7 to 12.6)
Not evaluable	10 (16%)	N/A		
All patients	N/A	N/A	5.4 (4.0 to 6.1)	12.9 (7.9 to 18.1)

*ITT = intention to treat.
**Patients alive and in remission at the time of last follow up were censored at that time point for the analysis.
N/A = Not applicable/available

Median overall survival for CR, CR + CRp, or CR + CRp + PR was 72.4, 69.5, 66.6 weeks respectively. Median overall survival for all patients (n=61) was 12.9 weeks.

Among the 6 responders who did not receive a transplant, duration of remission ranged from 4.3 weeks to 58.6 weeks with 2 patients maintaining CR for 47.9 and 58.6 weeks. Three patients with CR were taken from the study: two due to disease progression (CR, CRp duration of 4.3 and 11.7 weeks respectively) and the third (CR duration of 6.1 weeks) due to hyperbillirubinemia. Another patient (CRp duration of 4.6 weeks) died due to multi-organ failure 21 days after the last clofarabine administration.

Phase II Single Arm Study in Pediatric Patients with Refractory or Relapsed Acute Lymphoblastic Leukemia (BIOV-111 Study)

CLOLAR was also evaluated in a second Phase II, open-label, single arm study of 71 pediatric (≤ 21 years of age at initial diagnosis) patients with relapsed/refractory ALL. Patients received a dose of 52 mg/m^2 over 2 hours for 5 consecutive days (one course), repeated every 21 ± 7 days, for up to 12 courses (the term course is equivalent to the term cycle as defined in DOSING SCHEDULE AND ADMINISTRATION). There was no dose escalation in this study. Eligible patients were to have failed to achieve primary response on conventional treatment regimens, or failed to achieve a response at first relapse. Patients were also eligible at second and subsequent relapse. All 71 patients who received any amount of study drug were included in the safety analyses, whereas only the 65 patients who received one full 5-day course of clofarabine were included in the primary efficacy analyses.

The majority of patients (n=69) had received at least two prior therapies, and 20/71 (28%) had undergone at least 1 prior bone marrow transplant. The mean age of the patients was 10.4 years, 63% were male and 37% were female, 85% were Caucasian, 3% were African-American, 6% were Asian, and 7% were classified as Other race.

The primary objective of the study was to determine the overall remission (OR) rate, which was defined as in the CLO-212 study above. Partial Response (PR) was also determined and defined as in the CLO-212 study. Response rates were determined by an Independent Response Review Panel (IRRP). Additional study endpoints included evaluation of the duration of remission and overall survival, as well as the number of patients proceeding to HSCT and the time to bone marrow transplantation.

Of the 9 patients who were refractory to their immediately preceding induction regimen, 1 (11.1%) achieved a CR or CRp. Of 25 patients who had at least 1 prior HSCT, 9 (36%) achieved a CR or CRp.

Of note, among 32 patients who received 2 or more courses, 11 patients achieved a response (CR, CRp or PR) with an OR rate of 31.1%: 2 achieved a CR (6.3%), 8 achieved a CRp (25%) and 1 achieved a PR (3.1%).

Seven patients received an HSCT after the first dose of clofarabine. The median time to transplant was 40 days, and median survival was 358 days.

Table 6 lists the efficacy results observed in the BIOV-111 Study:

Table 6: Efficacy results from the BIOV-111 Study in pediatric patients with relapsed or refractory ALL after at least two prior regimens

Response category	Best objective response (IRRP) on C1EE* patients (n = 65)	Median duration of remission (days) (95% CI)	Median time to progression (days)** (95% CI)	Median overall survival (days) (95% CI)
Overall remission (CR + CRp)	15 (23%)	190.0 (92.0 to -)	240.0 (199.0 to -)	282.0 (199.0 to -)
CR	3 (5%)	- (- to -)	- (- to -)	- (- to -)
CRp	12 (19%)	129.0 (65.0 to 191.0)	199.0 (127.0 to 265.0)	211.0 (186.0 to -)
PR	1 (2%)	43.0 (- to -)	64.0 (- to -)	192.0 (- to -)
CR + CRp + PR	16 (25%)	170.0 (65.0 to -)	211.0 (127.0 to -)	263.0 (192.0 to -)
Treatment failure	31 (48%)	N/A	28.0 (21.0 to 31.0)	67.0 (48.0 to 94.0)
Not evaluable	18 (28%)	N/A	N/A	N/A
All patients	N/A	N/A	33.0 (29.0 to 53.0)	86.0 (62.0 to 123.0)

*C1EE = course 1 efficacy-evaluable population.
**Patients alive and in remission at the time of last follow up were censored at that time point for the analysis.
N/A = Not applicable/available

All three patients with a CR were alive and free of progressive disease at the time of last follow-up with survival times since first administration of clofarabine of 358, 941 and 954 days. Two of these patients had received a bone marrow transplant between the first dose of clofarabine and the date of last follow-up.

DETAILED PHARMACOLOGY

Non-clinical pharmacology

Clofarabine, is a purine nucleoside anti-metabolite. Its antineoplastic activity has been studied in model systems *in vitro* and *in vivo.* Clofarabine has demonstrated *in vitro* growth inhibitory and cytotoxic activity with IC_{50} values ranging from 0.028 to 0.29 μM in susceptible leukemia and solid tumor cell lines. Clofarabine was also active against quiescent lymphocytes and macrophages and proliferating lymphoblasts. In animal models, clofarabine administered intraperitoneally showed significant activity against a wide variety of human tumor xenografts implanted subcutaneously into immuno-compromised mice. The characterization of kinetics of clofarabine in these models is limited. In the mouse models the administered dose-effect relationship indicated that more frequent divided doses are more efficacious than less frequent dosing with higher doses.

Non-clinical safety pharmacology

The effects of single dose IV administration on respiratory and renal function and behavioral and physiological effects have been determined in the rat. The effect on heart rate and blood pressure were determined after 5 daily IV injections in instrumented rats. ECGs intervals and morphology were not evaluated in this study. The *in vitro* data from the hERG assay does not indicate that clofarabine interacts with the I_{Kr} channel as there was no effect at concentrations of up to 300 µM (91.1 µg/mL). Study design and results are summarized in Table 7.

Table 7 : Safety Pharmacology Studies

Brief Description	**Species/ Number of Animals**	**Dosing/Route**	**Principal finding**	**Plasma concentrations**
Behavioral effects	Wistar rats/4 males/ group	Single bolus IV dose at 37.5, 150, and 300 mg/m^2 (6.25, 25 and 50 mg/kg)	No effects at low and mid dose. At 300 mg/m^2, tremor, sedation, marked motor signs and hypothermia, generally, from 0 to 120 minutes after administration. One male died 30 minutes after dosing	Not determined
Respiratory function	Wistar rats/8 males/ group	Single bolus IV dose at 37.5, 150, and 300 mg/m^2 (6.25, 25 and 50 mg/kg)	No effects at low dose. Findings are suggestive of transient bronchodilatory properties at 150 and 300 mg/m^2. One death at 300 mg/m^2.	1 hour post dose 37.5 mg/m^2 – 1210 ng/mL 150 mg/m^2 – 5101 ng/mL 300 mg/m^2 – 13880 ng/mL
Renal effect	Wistar rats/12 males/ group	Single bolus IV dose at 37.5, 150, and 300mg/m^2 (6.25, 25 and 50 mg/kg)	No significant effects on urinary volume, urinary pH, potassium excretion or creatinine excretion. Decreased sodium excretion at all doses.	Not determined
CV effects	Fischer 344 rats/11 males/ group	Daily 2-hour infusion at 60 or 150 mg/m^2 (10 or 25 mg/kg) daily for 5 days	At both doses, peak decreases in blood pressure occurred between 1 h following the start of the infusion and 0.5 h following the end of the infusion. Recovery was noted 3 h after the end of the infusion. The decreases in blood pressure was associated with compensatory increases in heart rate The effects on blood pressure were similar over the 5 days of dosing.	60 mg/mg^2 – 699 – 1215 ng/mL at end of infusion 150 mg/mg^2 - 65 – 2816 ng/mL at end of infusion

Non-clinical pharmacokinetics

After IV administration, clofarabine is widely and rapidly distributed in mouse and rat with highest concentrations in well perfused tissues and/or excretory/metabolic organs. The volume of distribution is also high in rat and mouse, as it is in dogs and humans supporting wide distribution in all species. Clofarabine was detectable in the brain but at much lower concentrations than in well perfused tissues and organs. Clofarabine is largely eliminated unchanged (~75%) with the remaining as metabolites. The *in vivo* metabolism has been characterized in the rat; the most abundant metabolite is a 6-ketoclofarabine, formed via oxidative deamination, a reaction that is not catalyzed by cytochrome P450. The lack of CYP metabolism of clofarabine in human, rat and dog is supported by a number of *in vitro* studies. Clofarabine is not a CYP substrate, does not inhibit CYP catalyzed reactions and no CYP mediated metabolites were detected in isolated primary cultures of hepatocytes. In preclinical studies, the active phosphorylated metabolites have only been detected *in vivo* at very low concentrations and were not formed in the isolated hepatocyte preparations. There may be methodological issues in tissues that relate to detection of phosphorylated metabolites rather than actual lack of phosphorylation but there is no nonclinical information on correlation between plasma clofarabine and the cellular concentrations of the active metabolites. Clofarabine showed triphasic elimination in the radiolabelled study with an alpha half-life of 0.3 h, a beta half-life of 1.4 h, and a gamma half-life of 18.4 h. This did not result in any accumulation and the radiolabelled clearance was complete 30 hours after infusion with no indication of accumulation following daily administration for 5 days. The major route of elimination following IV administration is as unchanged clofarabine in the urine; the renal clearance far exceeds GFR at therapeutic dose levels. The plasma beta half life in mice, rats and dogs ranged from 1 to 2 hours. Mechanistic studies indicate that clofarabine undergoes renal elimination by a combination of filtration, active tubular excretion and reabsorption. Increases in exposure of clofarabine due to decreased clearance were shown with cimetidine. Co-infusion with other nucleosides in the isolated kidney preparation resulted in increased clofarabine clearance possibly due to competition at nucleoside reabsorption transporters in the kidney. The lack of effect on CYP suggests that interactions with drugs metabolized by CYPs would not be expected. Linear plasma pharmacokinetics were observed for mice at doses up to 39.9 mg/m^2, rats at doses up to 75 mg/m^2, and dogs at doses up to 60 mg/m^2. Nonlinear plasma pharmacokinetics (as evidenced by a decrease in clearance and an increase in Cmax) were observed between 75 and 150 mg/m^2/day in female rats in the 6-month study (Table 8).

Table 8: Mean kinetic values in mouse, rat and dog

			Cmax ng/mL		AUC(0-inf) ng·h/mL		AUC(0-12 h) ng·h/mL		Clearance (L/h/kg)	
mg/kg	mg/m^2	Day	Male	Female	Male	Female	Male	Female	Male	Female
					Mouse					
1.3	3.9	1	ND	-	4108.2	-	-	-	2.32	-
13.3	39.9	1	ND	-	5091.6	-	-	-	2.61	-
					Rat					
6.25	37.5	1	1277	1477	3041	3600	-	-	2.06	1.74
12.5	75	1	2348	2905	6662	8565	-	-	1.88	1.46
25	150	1	6722	14979	13461	22968	-	-	1.86	1.09
6.25	37.5	145	3688	4021	-	-				
12.5	75	145	6114	6409	-	-				
25	150	145	NC	NC						
					Dog					
0.375	7.5	5	310	286	-	-	850	703	0.45	0.54
0.75	15	5	625	617	-	-	1755	1668	0.44	0.47
1.5	30	5	1206	1270	-	-	2874	3083	0.55	0.49
3	60	5	2368	2329	-	-	5331	5457	0.57	0.56
0.375	7.5	145	297	301	-	-	811	899		
0.75	15	145	563	563	-	-	1484	1370		
1.5	30	145	1096	1143	-	-	2610	2621		
3	60	145	ND	ND	-	-	ND	ND		

ND Not determined, NC No sample collected

TOXICOLOGY

Toxicology studies of clofarabine in mice, rats and dogs showed the expected effects on rapidly proliferating tissues (e.g. gastrointestinal tract, bone marrow hematopoietic cells; lymphoid tissues; testes) and circulating blood cells. However, target organs of toxicity in rats also included kidney, liver and heart (Table 9).

Significant cardiac toxicity associated with death was identified in rats administered clofarabine at dose levels of equal to or greater than 150 mg/m^2 which is approximately 3-times higher than the proposed human dose of 52 mg/m^2. Cardiac effects were observed in rats consistent with cardiomyopathy often resulting in signs of cardiac failure. The incidence and severity of cardiac toxicity was dependent on both the dose of clofarabine administered and the duration of treatment. Deaths occurred early in 5-day intravenous studies at 300 and 600 mg/m^2 while the majority of deaths attributable to cardiac toxicity commenced just after the end of the third cycle of dosing at 150 mg/m^2 in the rat intravenous multicycle study. Overt toxicity was observed at 150 mg/m^2 at exposure levels (C_{max}) of 6722-14979 ng/mL and AUC of 13461 to22968 ng·h/mL.

Glomerulonephropathy was reported in rats at 75 and 150 mg/m^2 in the multicycle intravenous study. Glomerulopathy was characterized by minor thickening of the glomerular basement

membrane with only slight tubular damage and was not associated with changes in serum chemistry or applicable proteinuria.

Dose-related hepatic pathologic effects were observed in rats following multicycle intravenous administration at 37.5, 75 and 150 mg/m^2. Treatment-related histopathologic findings included hepatocellular eosinophilia, single-cell degeneration/necrosis, periportal vacuolation, diffuse hypertrophy, karyomegaly/cytomegaly, regenerative hyperplasia, as well as liver fibrosis and/or bile duct/oval cell hyperplasia. These likely represent the superimposition of degenerative and regenerative changes on the liver as a result of treatment cycles, and were not associated with consistent changes in serum chemistry markers of hepato-biliary integrity. There was no histopathologic evidence of overt treatment-related liver pathology in dogs administered 0.375 to 1.5 mg/m^2 intravenously in the multicycle study, and no liver lesions to corroborate with occasional instances of increases in serum transaminases in treated dogs.

Dose related toxicities on male reproductive organs were observed in mice, rats and dogs. These effects included bilateral degeneration of the seminiferous epithelium with retained spermatids and atrophy of interstitial cells in rats at exaggerated exposure levels (150 mg/m^2), and cell degeneration of the epididymis and degeneration of the seminiferous epithelium in dogs at clinically relevant exposure levels (≥7.5 mg/ m^2/day clofarabine). Delayed ovarian atrophy or degeneration and uterine mucosal apoptosis were observed in female mice at the only dose used of 225 mg/m^2/day clofarabine.

Pathologic changes were present in the eye cornea of rats administered 150 mg/m^2 intravenously. These changes (generally minimal single cell necrosis) are considered to reflect the pharmacologic activity of clofarabine on the corneal epithelium.

Table 9: Summary of Repeat-Dose Toxicology Studies

Study Title	Species/ No Animals	Dosage/Route	Principal Findings
Clofarabine Mouse Studies[ξ]	Balb/c mice/2 or 3/group	9-600 mg/m^2 IP once daily for 7 days (male) 225 mg/ m^2 IP once daily for 7 days (male and female).	Lethal ≥300 mg/m^2 , GI toxicity dose limiting Seminiferous tubule degeneration ≥9 mg/m^2 and atrophy ≥30 mg/m^2 , ovarian atrophy 225 mg/m^2 (not reversible with 28 non dosing days). Degeneration and/or atrophy of bone marrow and lymphoid tissue at the end of dosing, reversible after 7-28 days
Clofarabine: A Multicycle (Five Days' Dosing Plus 23 Days' Recovery Per Cycle) Intravenous Toxicity and Toxicokinetics Study in Fischer 344 Rats[†]	Fischer 344 Rats/ 15-30/sex/group	37.5, 75 or 150 mg/m^2 IV once daily for 5 days, 23 non-dosing days, one cycle Phase A: Two cycles and one 5 days dosing (5/sex/group) Phase B: Five cycles and one 5 days dosing (5/sex/group) Phase C: Five cycles and one 5 days with 17 days withdrawal (5/sex/group) TK (15/sex/group)	Lethality at 150 mg/m^2 after 3 cycles due to cardiac toxicity Dose-related mild to marked ↓ in WBC and ↓ RBC at all doses, persisted with 17 days withdrawal. Degeneration, atrophy and/or decreased cellularity of spleen and thymus at 37.5 mg/m^2 and lymphoid tissue and bone marrow at ≥75 mg/m^2 and epithelia of GI tract (premature sacrifice and decedent rats) and testes at 150 mg/m^2. Heart changes (degeneration, necrosis, fibrosis, hypertrophy and ventricular dilation of left side) at 150 mg/m^2. Liver effects (single cell necrosis and hypertrophy) at all doses and Glomerulonephropathy at 75 mg/m^2 after 6 cycles and at 150 mg/m^2.
Clofarabine: A Multi-Cycle (Five Days' Dosing Plus 23 Days' Recovery Per Cycle) Intravenous Toxicity and Toxicokinetics Study in Beagle Dogs[†]	Beagle dogs/ 4-9/sex/group	7.5, 15 or 30 mg/m^2 IV once daily for 5 days, 23 non-dosing days, one cycle Phase A: Two cycles and one 5 days dosing (2/sex; 15 mg/m^2) Phase B: Five cycles and one 5 days dosing (2-3/sex/group) Phase C: Five cycles and one 5 days with 17 days withdrawal (2-3/sex/group)	Lethality at 30 mg/m^2 after 1 cycle due to GI toxicity. Histological lesions also in adrenals, liver, bone marrow, lymph tissue Dose-related marked ↓ in WBC and moderate ↓ RBC at ≥ 15 mg/m^2, evidence of some recovery during non-dosing days Decreased cellularity of bone marrow and lymphoid tissue at ≥7.5 mg/m^2. Degeneration of seminiferous testicular tubules at ≥15 mg/m^2.

[ξ] Non GLP study
[†] GLP study
TK = toxicokinetic

Genotoxicity

As summarized in Table 10, clofarabine showed clastogenic activity (structural chromosomal aberrations) in the *in vitro* chromosomal aberration assay using Chinese hamster ovary cells and *in vivo* in the rat micronucleus assay. Clofarabine was not mutagenic when tested in the *in vitro* mutagenicity assay (Ames test).

Table 10 : Summary of Genotoxicity Studies

Study Title	Species/ Number of Animals	Dosage/Route	Principal Findings
In vitro Mammalian Chromosome Aberration Test †	Chinese Hamster Ovary cell line	1, 5 and 10 μg/mL	Clofarabine was positive for induction of structural chromosome aberrations ≥ 5 μg/mL
In Vivo Mammalian Erythrocyte Micronucleus Test†	Sprague Dawley rats /5/sex/group	Single dose IV at 0, 52.5, 105 and 210 mg/m^2	Clofarabine was clastogenic at ≥ 105 μg/m^2.
In Vitro Bacterial Reverse Mutation Assay†	*Salmonella typlimurium* and *Escherichia coli*	≤ 5000 μg/plate	Clofarabine was not mutagenic under the test conditions.

† GLP study

Reproductive and Developmental Toxicity

Clofarabine was teratogenic in rats and rabbits. Dose-related developmental toxicity (reduced fetal body weight and increased post-implantation loss) and/or increased incidences of malformations and variations (gross external, soft tissue, skeletal and retarded ossification) were observed in rats at 18 mg/m^2/day and above (approximately 33% of the recommended clinical dose on a mg/m^2 basis), and in rabbits at 3.6 mg/m^2/day and above (approximately 6% of the recommended clinical dose on a mg/m^2 basis).

There are no dedicated studies to assess effects on fertility but with degenerative effects of the reproductive organs (general toxicology above), reduced fertility is expected. Embryo fetal development studies were conducted in rats and rabbits with daily IV administration during organogenesis (Table 11).

Table 11: Summary of Embryo Fetal Development Studies

Study Title	Species/ Number of Animals	Dosage/Route	Principal Findings
Intravenous Developmental Toxicity Study of Clofarabine in Rats†	Time-mated Sprague-Dawley Rats/25 females/group	Daily IV from gestation day 6 to 17 inclusive at 0, 6, 18 and 54 mg/m^2.	54 mg/m^2: ↑ Post implantation loss. Litter size and fetal weight↓. 19.7 % fetuses with anomalies (other groups 1-2%). Multiple clofarabine-related external, skeletal and soft tissue malformations and variations. 18 mg/m^2: One fetus with clofarabine related malformations 6 mg/m^2: Threshold for developmental toxicity
Intravenous Developmental Toxicity Study of Clofarabine in Rabbits†	Time-mated New Zealand White rabbits/20 females/group	Daily IV administration from gestation Day 7 to 19 inclusive at 0, 1.2, 3.6, and 12 mg/m^2.	12 mg/m^2: ↑ Post implantation loss. Litter size and fetal weight↓. 100 % fetuses with anomalies (11-16 %). Multiple clofarabine-related external, skeletal and soft tissue malformations and variations. 3.6 mg/m^2: One fetus with clofarabine related malformations 1.2 mg/m^2: No effect dose level

† GLP study

REFERENCES

1. Carson DA, Wasson DB, Esparza LM, Carrera CJ, Kipps TJ, Cottam HB. Oral antilymphocyte activity and induction of apoptosis by 2-chloro-2′-arabino-fluoro-2′-deoxyadenosine. Proc Natl Acad Sci *USA* 1992; 89: 2970-2974.
2. Cooper T, Nowak B, Gandhi V. Biochemical modulation of cytarabine triphosphate by clofarabine. Proceedings of the American Association for Cancer Research 2003; 44. Abstract 621.
3. Faderl S, Ravandi F, Ferrajoli A, et al. Clofarabine and clofarabine plus low-dose cytarabine (ara-C) as induction therapy for patients (pts) ≥60 years with newly diagnosed acute myeloid leukemia (AML). Blood 2005;106(11) Abstract 2804.
4. Gandhi V, Kantarjian H, Faderl S, Bonate P, *et al*. Pharmacokinetics and Pharmacodynamis of Plasma Clofarabine and Cellular Clofarabine Triphosphate in Patients with Acute Leukemias. Clin Can Res 2003; 9:6335-6342.
5. Gaynon P (2005). Childhood acute lymphoblastic leukaemia and relapse. Br J Haematol 131(5):579-87.
6. Genini D, Adachi S, Chao Q, Rose DW, Carrera CJ, Cottam HB, *et al*. Deoxyadenosine analogs induce programmed cell death in chronic lymphocytic leukemia cells by damaging the DNA and by directly affecting the mitochondria. Blood 2000; 96: 3537-3543.
7. Jeha S, Gandhi V, Chan K, McDonald L, *et al*. Clofarabine, a novel nucleoside analog, is active in pediatric patients with advanced leukemia. Blood 2004; 103(3) 784-789.
8. Jeha S, Kantarjian H (2007). Clofarabine for the treatment of acute lymphoblastic leukemia. Expert Rev Anticancer Ther 7(2):113-8.
9. King KM, Vickers MF, Damaraju V, Mowles DA, Lang T, Young JD *et al*. Nucleoside transporter proteins are determinants of cytotoxicity of clofarabine (Clofarex™) in cultured leukemic cell lines. Blood 2002;100. Abstract 1247.
10. King KM, Damaraju V, Mowles DA, Lang T, Vickers MF, Young JD *et al*. Clofarabine and fludarabine cytotoxicity in cultured leukemic cell lines can be correlated with the activity of the human equilibrative nucleoside transport process hENT1. Proceedings of the American Association for Cancer Research 2003; 44. Abstract LB-115.
11. Parker WB, Shaddix SC, Chang CH, White EL, Rose LM, Brockman RW *et al*. Effects of 2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl) adenine on K562 cellular metabolism and the inhibition of human ribonucleotide reductase and DNA polymerases by its 5′-triphosphate. Cancer Res 1991; 51: 2386-2394.
12. Pui CH, Relling MV, Downing JR (2004). Mechanisms of Disease: Acute Lymphoblastic Leukemia. N Eng J Med 350(15):1535-48.
13. Qian M, Wang X, Shanmuganathan K, Chu CK, Gallo JM. Pharmacokinetics of the anticancer agent 2-chloro-9-(2-deoxy-2-fluoro-beta-D-arabinofuranosyl)adenine in rats. Cancer Chemother Pharmacol 1994;33(6):484-488.

14. Takahashi T, Kanazawa J, Akinaga S, Tamaoki T, Okabe M. Antitumor activity of 2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl) adenine, a novel deoxyadenosine analog, against human colon tumor xenografts by oral administration. Cancer Chemother Pharmacol 1999; 43: 233-240.

15. Waud WR, Schmid SM, Montgomery JA, Secrist JA III. Preclinical antitumor activity of 2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl) adenine (Cl-F-ara-A). Nucleosides, Nucleotides and Nucleic Acids 2000; 19(1-2): 447-460.

16. Weitman S, Ochoa S, Sullivan J, et al. (1997). Pediatric phase II cancer chemotherapy trials: A Pediatric Oncology Group study. J Pediatr Hematol Oncol 19:187-91.

17. Xie C, Plunkett W. Metabolism and actions of 2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-adenine in human lymphoblastoid cells. Cancer Res 1995; 55: 2847-2852.

18. Xie KC, Plunkett W. Deoxynucleotide pool depletion and sustained inhibition of ribonucleotide reductase and DNA synthesis after treatment of human lymphoblastoid cells with 2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl) adenine. Cancer Res 1996; 56: 3030-3037.

PART III: CONSUMER INFORMATION

PrCLOLAR®
(Clofarabine for injection)

This leaflet is part III of a three-part "Product Monograph" published when CLOLAR was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CLOLAR. Read this information carefully before you or your child starts taking CLOLAR. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
CLOLAR is used to treat young patients (1 – 21 years of age) with acute lymphoblastic leukemia (ALL) when previous treatments have not worked or have stopped working. Approval is based on objective response rates. No survival advantage has been demonstrated and palliative benefit was not evaluated.

What it does:
CLOLAR damages rapidly proliferating (fast producing) cells and kills them.

When it should not be used:

- If you or your child have ever had an allergic reaction (for example, rash, or itchiness) to clofarabine or any ingredient in CLOLAR.
- If you or your child have leukemia cells in the fluid that surrounds the brain and spinal cord.
- If you or your child have had serious heart, liver, kidney or pancreas problems.
- If you or your child have severe liver or kidney disease that results in decreased function of these organs.

What the medicinal ingredient is:
CLOLAR Injection contains clofarabine.

What the nonmedicinal ingredients are:
Water for Injection and Sodium Chloride.

What dosage forms it comes in:
CLOLAR is available as a sterile solution for injection. CLOLAR is diluted (thinned) before being given as an intravenous infusion**.** Each mL contains 1 mg clofarabine.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
CLOLAR must be administered under the supervision of a physician qualified in the use of antineoplastic agents.

CLOLAR is associated with:

- Tumor Lysis Syndrome (TLS) due to rapid destruction of leukemia cells
- Systemic Inflammatory Response Syndrome (SIRS)/Capillary Leak Syndrome
- Inflammation of the intestines (enterocolitis)
- Bleeding (hemorrhage) (such as bleeding into the brain, stomach, intestines or lung)
- Severe skin reaction (such as Stevens-Johnson syndrome, toxic epidermal necrolysis)
- Liver injury
- Kidney failure, due to TLS or infections.

BEFORE using CLOLAR talk to your doctor or pharmacist if:

- You or your child have had liver and/or kidney problems
- You are pregnant or plan to become pregnant. CLOLAR may harm an unborn baby, effective birth control methods must be used while receiving CLOLAR. Talk to your doctor about your choices.
- You are breastfeeding. It is not known if CLOLAR passes through breast milk. Women should not breastfeed while taking CLOLAR.
- You or your child are allergic to clofarabine, or any ingredient in this medicine or the components of the container.
- You or your child are taking other medications or treatments, including any products you buy, such as over-the-counter medicines and herbal or home remedies.
- You or your child have low blood cell counts.

INTERACTIONS WITH THIS MEDICATION

Tell your or your child's doctor or pharmacist about any medications or treatments you or your child are taking, including medicines prescribed by a doctor, any products you buy, such as such as over-the-counter medicines, vitamins, and herbal or home remedies.

PROPER USE OF THIS MEDICATION

Usual dose:
The recommended pediatric dose of CLOLAR is 52 mg/m^2 as an intravenous (IV) infusion over 2 hours each day for 5 days one after another.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, CLOLAR can have side effects.

Some possible side effects of CLOLAR are listed below:

The following side effects have been reported very commonly (reported in more than 10 out of every 100 people):

- Nausea, vomiting and diarrhea can result in dehydration
- Fatigue
- Loss of appetite
- Anxiety
- Itching
- Headache
- Rash
- Cough
- Flushing
- Constipation
- Inflammation of the mucus membranes with symptoms of mouth soreness, sore throat and inflamed gums
- Muscle aches

The following side effects have been reported commonly (reported in 1 to10 out of every 100 people):

- Weakness, irritability, generally feeling unwell, feeling sleepy, depression
- Joint aches

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharma-cist
		Only if severe	In all cases	
Very Common	Decreased production of blood cells (tiredness, weakness, easy bruising and bleeding, gum bleed, blood in urine)		✓	
	Infection (fever or chill)		✓	
	Feeling unwell		✓	
	Rapid heart rate (tachycardia)		✓	
	Shortness of breath or difficulty breathing		✓	
	Changes in blood pressure (drowsiness, dizziness, headache, light headedness or fainting spells)		✓	
	Pain in extremity (hand and foot)	✓		
	Inflammation of the mucus membranes with symptoms such as: mouth soreness, sore throat and inflamed gums	✓		
Common	Hand and foot syndrome (redness, tenderness, blisters and possibly peeling of the skin on palms and soles with numbness or tingling)	✓		
	Muscle and joint pain, back pain, bone pain, rectal pain		✓	
	Serious liver problems (yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite, rectal bleeding, vomiting blood, increase in weight, and build up of fluid in the abdomen)		✓	
	Tumor lysis syndrome (rapid breathing, rapid heartbeat, and low blood pressure) which can lead to acute kidney failure (generalised swelling, decrease in urination)		✓	
	Accumulation of fluid around the heart, with symptoms such as: chest pain, shortness of breath, difficulty breathing, shortness of breath when lying down, painful breathing or fainting.		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharma-cist**
		Only if severe	**In all cases**	
	Irritability, feeling sleepy, depression	✓		
Uncommon	Stevens-Johnson syndrome or toxic epidermal necrolysis (severe skin reaction, blistering or red and flaky skin)		✓	
	Allergic reaction (rash, itching, difficulty breathing)		✓	
	Accumulation of water in the lung (shortness of breath, rapid breathing, chest pain)		✓	
	Systemic Inflammatory Response Syndrome/Capillary Leak Syndrome (Rapid breathing, rapid heartbeat, low blood pressure, high or low temperature, swelling, mental confusion)		✓	
Unknown frequency	Inflammation of the intestines (enterocolitis), with symptoms such as: abdominal pain, vomiting, diarrhea, fever		✓	
	Kidney problems, with symptoms such as: decrease in urination, swelling of feet and ankles, fatigue, drowsiness, nausea, vomiting		✓	

This is not a complete list of side effects. For any unexpected effects while taking CLOLAR, contact your or your child's doctor or pharmacist.

HOW TO STORE IT

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

Once diluted, use preparation immediately.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug, you may notify Canada Vigilance:

You can report any suspected adverse reactions associated with the use of health products in the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free telephone at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701 E
    Ottawa, ON, K1A 0K9

  Postage paid labels, Canada Vigilance Report Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of the side effect, please contact your health care professional. The Canada Vigilance program does not provide medical advice.

MORE INFORMATION

This leaflet provides important information about CLOLAR. If you have questions or concerns, talk to your or your child's doctor or other healthcare provider.

This document plus the full product monograph, prepared for health professionals can be found at: www.sanofi.ca or by contacting the sponsor, sanofi-aventis Canada Inc., at: 1-800-265-7927

This leaflet was prepared by sanofi-aventis Canada Inc.

Last revised: August 31, 2016