HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CLOLAR safely and effectively. See full prescribing information for CLOLAR.

Clolar® (clofarabine) Injection for intravenous use
Initial U.S. Approval: 2004

---------- RECENT MAJOR CHANGES ----------

Dosage and Administration (2)	01/ 2013
Warnings and Precautions (5)	01/ 2013

----------INDICATIONS AND USAGE----------

Clolar (clofarabine) injection is a purine nucleoside metabolic inhibitor 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 indication is based upon response rate. There are no trials verifying an improvement in disease-related symptoms or increased survival with Clolar. (1)

----------DOSAGE AND ADMINISTRATION----------

- Administer the recommended pediatric dose of 52 mg/m^2 as an intravenous infusion over 2 hours daily for 5 consecutive days of a 28-day cycle. Repeat cycles every 2-6 weeks. (2.1)
- Provide supportive care, such as intravenous infusion fluids, antihyperuricemic treatment, and alkalinization of urine throughout the 5 days of Clolar administration to reduce the risk of tumor lysis and other adverse events. (2.1)
- Discontinue Clolar if hypotension develops during the 5 days of administration. (2.1)
- Reduce the dose in patients with renal impairment. (2.1)
- Use dose modification for toxicity. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- 20 mg/20 mL single-use vial. (3)

----------CONTRAINDICATIONS----------

- None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hematologic Toxicity: Clolar causes myelosuppression which may be severe and prolonged. Monitor complete blood counts and platelet counts during Clolar therapy. (5.1)
- Infections: Clolar increases the risk of infection, including severe and fatal sepsis, as a result of bone marrow suppression. Monitor patients for signs and symptoms of infection, discontinue Clolar, and treat promptly. (5.2)
- Tumor Lysis syndrome: Anticipate, monitor for signs and symptoms and treat promptly. (5.3)
- Systemic Inflammatory Response Syndrome (SIRS) or Capillary Leak Syndrome: Monitor for and discontinue Clolar immediately if suspected. (5.4)
- Venous Occlusive Disease of the Liver: Monitor for and discontinue Clolar if suspected. (5.5)
- Hepatotoxicity: Severe and fatal hepatotoxicity has occurred with Clolar; monitor liver enzymes and discontinue Clolar. (5.6)
- Renal Toxicity: Increased creatinine and acute renal failure; monitor renal function and interrupt or discontinue Clolar. (5.7)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥ 10%): nausea, vomiting, diarrhea, febrile neutropenia, headache, rash, pruritus, pyrexia, fatigue, palmar-plantar erythrodysesthesia syndrome, anxiety, flushing, and mucosal inflammation. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Genzyme Corporation at 1-800-RX-CLOLAR or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Safety and effectiveness have not been established in adults. (8.6)
- Embryo-fetal Toxicity: fetal harm can occur when administered to a pregnant woman. Women should be advised to avoid becoming pregnant when receiving Clolar. (5.8, 8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: [01/2013]

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
- 2.1 Recommended Dosage
- 2.2 Supportive Medications and Medications to Avoid
- 2.3 Dose Modifications and Reinitiation of Therapy
- 2.4 Reconstitution/Preparation
- 2.5 Incompatibilities

3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
- 5.1 Hematologic Toxicity
- 5.2 Infections
- 5.3 Hyperuricemia (Tumor Lysis)
- 5.4 Systemic Inflammatory Response Syndrome (SIRS) and Capillary Leak Syndrome
- 5.5 Venous Occlusive Disease of the Liver
- 5.6 Hepatotoxicity
- 5.7 Renal Toxicity
- 5.8 Embryo-fetal Toxicity

6 ADVERSE REACTIONS
- 6.1 Clinical Trials Experience
- 6.2 Post-marketing Experience

7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Adults with Hematologic Malignancies
- 8.7 Renal Impairment
- 8.8 Hepatic Impairment

10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

Clolar® (clofarabine) Injection 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 indication is based upon response rate. There are no trials verifying an improvement in disease-related symptoms or increased survival with Clolar.

2. DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Administer the recommended pediatric dose of 52 mg/m^2 as an intravenous infusion 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.
- Provide supportive care, such as intravenous fluids, antihyperuricemic treatment, and alkalinize urine throughout the 5 days of Clolar administration to reduce the effects of tumor lysis and other adverse events.
- Discontinue Clolar if hypotension develops during the 5 days of administration.
- Monitor renal and hepatic function during the 5 days of Clolar administration [see *Warnings and Precautions (5.6, 5.7)*].
- Monitor patients taking medications known to affect blood pressure. Monitor cardiac function during administration of Clolar.
- Reduce the dose by 50% in patients with creatinine clearance (CrCL) between 30 and 60 mL/min. There is insufficient information to make a dosage recommendation in patients with CrCL less than 30 mL/min [see *Use in Specific Populations (8.7)*].

2.2 Supportive Medications and Medications to Avoid

- Consider prophylactic anti-emetic medications as Clolar is moderately emetogenic.
- Consider the use of prophylactic steroids to mitigate Systemic Inflammatory Response Syndrome (SIRS) or capillary leak syndrome (e.g., hypotension, tachycardia, tachypnea, and pulmonary edema).
- Minimize exposure to drugs with known renal toxicity during the 5 days of Clolar administration since the risk of renal toxicity may be increased.
- Consider avoiding concomitant use of medications known to induce hepatic toxicity.

2.3 Dose Modifications and Reinitiation of Therapy

- Hematologic Toxicity

- Administer subsequent cycles no sooner than 14 days from the starting day of the previous cycle and 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 controlled, then restart at the full dose.
  - Withhold Clolar for a Grade 3 non-infectious non-hematologic toxicity (excluding transient elevations in serum transaminases and/or serum bilirubin and/or nausea/vomiting controlled by antiemetic therapy). Re-institute Clolar administration at a 25% dose reduction when resolution or return to baseline.
  - Discontinue Clolar administration for a Grade 4 non-infectious non-hematologic toxicity.
  - Discontinue Clolar administration if a patient shows early signs or symptoms of SIRS or capillary leak (e.g., hypotension, tachycardia, tachypnea, and pulmonary edema) occur and provide appropriate supportive measures.
  - Discontinue Clolar administration if Grade 3 or higher increases in creatinine or bilirubin are noted. Re-institute Clolar with a 25% dose reduction, when the patient is stable and organ function has returned to baseline. If hyperuricemia is anticipated (tumor lysis), initiate measures to control uric acid.

2.4 Reconstitution/Preparation

Clolar should be filtered through a sterile 0.2 micron 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 within 24 hours of preparation. Store diluted Clolar at room temperature (15-30ºC).

2.5 Incompatibilities

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

3. DOSAGE FORMS AND STRENGTHS

20 mg/20 mL (1 mg/mL) single-use vial

4. CONTRAINDICATIONS

None

5. WARNINGS AND PRECAUTIONS

5.1 Hematologic Toxicity

Clolar causes myelosuppression which may be severe and prolonged. Febrile neutropenia occurred in 55% and non-febrile neutropenia in an additional 10% of pediatric patients in clinical trials. At initiation of treatment, most patients in the clinical

studies had hematological impairment as a manifestation of leukemia. Myelosuppression is usually reversible with interruption of Clolar treatment and appears to be dose-dependent. Monitor complete blood counts and platelet counts daily during the 5 days of Clolar administration, then 1-2 times weekly or as clinically indicated [see *Dosage and Administration (2.3)*].

5.2 Infections

Clolar increases the risk of infection, including severe and fatal sepsis, and opportunistic infections. At baseline, 48% of the pediatric patients had one or more concurrent infections. A total of 83% of patients experienced at least one infection after Clolar treatment, including fungal, viral and bacterial infections. Monitor patients for signs and symptoms of infection, discontinue Clolar, and treat promptly.

5.3 Hyperuricemia (Tumor Lysis)

Administration of Clolar may result in tumor lysis syndrome associated with the break-down metabolic products from peripheral leukemia cell death. Monitor patients undergoing treatment for signs and symptoms of tumor lysis syndrome and initiate preventive measures including adequate intravenous fluids and measures to control uric acid.

5.4 Systemic Inflammatory Response Syndrome (SIRS) and Capillary Leak Syndrome

Clolar may cause a cytokine release syndrome (e.g., tachypnea, tachycardia, hypotension, pulmonary edema) that may progress to the systemic inflammatory response syndrome (SIRS) with capillary leak syndrome and organ impairment which may be fatal. Monitor patients frequently for these conditions. In clinical trials, SIRS was reported in two patients (2%); capillary leak syndrome was reported in four patients (4%). Symptoms included rapid onset of respiratory distress, hypotension, pleural and pericardial effusion, and multi-organ failure. Close monitoring for this syndrome and early intervention may reduce the risk. Immediately discontinue Clolar and provide appropriate supportive measures. 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. Consider use of diuretics and/or albumin. After the patient is stabilized and organ function has returned to baseline, re-treatment with Clolar can be considered with a 25% dose reduction.

5.5 Venous Occlusive Disease of the Liver

Patients who have previously received a hematopoietic stem cell transplant (HSCT) are at higher risk for veno-occlusive disease (VOD) of the liver following treatment with clofarabine (40 mg/m^2) when used in combination with etoposide (100 mg/m^2) and cyclophosphamide (440 mg/m^2). Severe hepatotoxic events have been reported in a combination study of clofarabine in pediatric patients with relapsed or refractory acute leukemia. Two cases (2%) of VOD in the mono-therapy studies were considered related to study drug. Monitor for and discontinue Clolar if VOD is suspected.

5.6 Hepatotoxicity

Severe and fatal hepatotoxicity has occurred with the use of Clolar. In clinical studies, Grade 3-4 liver enzyme elevations were observed in pediatric patients during treatment with Clolar at the following rates: elevated aspartate aminotransferase (AST) occurred in 36% of patients; elevated alanine aminotransferase (ALT) occurred in 44% of patients. AST and ALT elevations typically occurred within 10 days of Clolar administration and returned to Grade 2 or less within 15 days. 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 and one patient had multi-organ failure and died. Eight patients (7%) 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. Monitor hepatic function and discontinue Clolar for Grade 3 or greater liver enzyme elevations [see *Adverse Reactions (6.1)*].

5.7 Renal Toxicity

In clinical studies, Grade 3 or 4 elevated creatinine occurred in 8% of patients; acute renal failure was reported as Grade 3 in three patients (3%) and Grade 4 in two patients (2%). Hematuria was observed in 13% of patients overall. Monitor patients for renal toxicity and interrupt or discontinue Clolar as necessary.

5.8 Embryo-fetal Toxicity

Clolar can cause fetal harm when administered to a pregnant woman. Intravenous doses of clofarabine in rats and rabbits administered during organogenesis caused an increase in resorptions, malformations, and variations [see *Use in Specific Populations (8.1*)].

6. ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Severe Bone Marrow Suppression [see *Warnings and Precautions (5.1)*]
- Serious Infections [see *Warnings and Precautions (5.2)]*
- Hyperuricemia (Tumor Lysis) [see *Warnings and Precautions (5.3)*]
- Systemic Inflammatory Response Syndrome (SIRS) and Capillary Leak Syndrome [see *Warnings and Precautions (5.4)*]
- Venous Occlusive Disease of the Liver [*see Warnings and Precautions* (5.5)]
- Hepatotoxicity [*see Warnings and Precautions* (*5.6*)]
- Renal Toxicity [*see Warnings and Precautions* (*5.7*)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to Clolar in 115 pediatric patients with relapsed or refractory Acute Lymphoblastic Leukemia (ALL) (70 patients) or Acute Myelogenous Leukemia (AML) (45 patients).

In total, 115 pediatric patients treated in clinical trials received the recommended dose of Clolar 52 mg/m^2 daily × 5. 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 occurring in 10% or more of patients treated with Clolar are: nausea, vomiting, diarrhea, febrile neutropenia, headache, rash, pruritus, pyrexia, fatigue, palmar-plantar erythrodysesthesia syndrome, anxiety, flushing, and mucosal inflammation.

Table 1 lists adverse reactions by System Organ Class, including severe or life-threatening (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 1: Most Commonly Reported (≥ 5% Overall)
Adverse Reactions by System Organ Class (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 or mouth bleeding	20	17.4	8	7.0	1	0.9	.	.
	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.

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

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, including septic shock	19	16.5	6	5.2	4	3.5	9	7.8
	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 erythrodysesthesia 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.

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

Gastrointestinal Disorders: cecitis, pancreatitis
Hepatobiliary Disorders: hyperbilirubinemia
Immune System Disorders: hypersensitivity

Infections and Infestations: bacterial infection, Enterococcal bacteremia, Escherichia bacteremia, Escherichia sepsis, fungal infection, fungal sepsis, gastroenteritis adenovirus, infection, influenza, parainfluenza 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

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 2: Incidence of Treatment-Emergent Laboratory Abnormalities after Clolar Administration

Parameter	**Any Grade**	**Grade 3 or higher**
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%)

6.2 Post-marketing Experience

The following adverse reactions have been identified during post-approval use of Clolar. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically 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.

- Gastrointestinal disorders: Gastrointestinal hemorrhage including fatalities.
- Skin and subcutaneous tissue disorders: 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 Clolar and other medications (e.g., allopurinol or antibiotics) known to cause these syndromes. Other exfoliative conditions have also been reported.

7. DRUG INTERACTIONS

No in-vivo drug interaction studies have been conducted [see *Clinical Pharmacology (12.3)*].

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.3 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. Female patients should be advised to avoid breast-feeding during treatment with Clolar.

8.4 Pediatric Use

Safety and effectiveness have been established in pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia.

8.5 Geriatric Use

Safety and effectiveness of Clolar has not been established in geriatric patients aged 65 and older.

8.6 Adults with Hematologic Malignancies

Safety and effectiveness have not been established in adults.

8.7 Renal Impairment

Reduce the Clolar starting dose by 50% in patients with CrCL of 30 to 60 mL/min. There is insufficient information to make a dosage recommendation in patients with CrCL less than 30 mL/min or in patients on dialysis.

The pharmacokinetics of clofarabine in patients with renal impairment and normal renal function were obtained from a population pharmacokinetic analysis of three pediatric and two adult studies. In patients with CrCL 60 to less than 90 mL/min (N = 47) and CrCL 30 to less than 60 mL/min (N = 30), the average AUC of clofarabine increased by 60% and 140%, respectively, compared to patients with normal (N = 66) renal function (CrCL greater than 90 mL/min).

8.8 Hepatic Impairment

Clolar has not been studied in patients with hepatic impairment.

10. 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.

In a Phase 1 study of adults with refractory and/or relapsed hematologic malignancies, the recommended pediatric dose of 52 mg/m^2/day was not tolerated.

11. DESCRIPTION

Clolar (clofarabine) Injection contains clofarabine, a purine nucleoside metabolic inhibitor. 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 sterile, clear and practically colorless, and is preservative-free.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Clofarabine is sequentially metabolized intracellularly to the 5'-monophosphate metabolite by deoxycytidine kinase and mono- and di-phospho-kinases to the active 5'-triphosphate metabolite. Clofarabine has 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.*

12.3 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 acute lymphoblastic leukemia (ALL) or acute myelogenous leukemia (AML). At the given 52 mg/m^2 dose, similar concentrations were obtained over a wide range of body surface areas (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 28.8 $L/h/m^2$ and 172 L/m^2, respectively. The terminal half-life was 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%). The pathways of non-hepatic elimination remain unknown.

Drug-Drug Interactions

In vitro studies suggested that clofarabine undergoes limited metabolism and does not inhibit or induce major CYP enzymes. CYP inhibitors and inducers are unlikely to affect the metabolism of clofarabine. Clofarabine is unlikely to affect the metabolism of CYP substrates. However, no *in vivo* drug interaction studies have been conducted.

An *in vitro* transporter study suggested that clofarabine is a substrate of human transporters OAT1, OAT3, and OCT1. A preclinical study using perfused rat kidney demonstrated that the renal excretion of clofarabine was decreased by cimetidine, an inhibitor of the hOCT2. Although the clinical implications of this finding have not been

determined, signs of Clolar toxicity should be monitored when administered with other hOAT1, hOAT3, hOCT1 and hOCT2 substrates or inhibitors.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Clofarabine has not been tested for carcinogenic potential.

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).

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 intraperitoneal (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.

14. CLINICAL STUDIES

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 for 5 days as an intravenous (IV) infusion.

Dose Escalation 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 for 5 days. 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.

Single-Arm Study in Pediatric ALL

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. 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 18/61 (30%) 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]) was evaluated. CR was 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]. CRp was 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. Duration of remission 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).

Table 3 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 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 time between cycles was 28 days with a range of 12 to 55 days.

Table 3: Results in Single-Arm Pediatric ALL

	N = 61
CR % [95% CI]	11.5 (4.7, 22.2)
CRp % [95% CI]	8.2 (2.7, 18.1)
Median Duration of CR plus CRp (range in weeks)[1]	10.7 (4.3 to 58.6)

CR = Complete response
CRp = Complete response without platelet recovery
[1] Does not include 4 patients who were transplanted (duration of response, including response after transplant, in these 4 patients was 28.6 to 107.7 weeks).

Six (9.8%) patients achieved a PR; the clinical relevance of a PR in this setting is unknown.

Of 35 patients who were refractory to their immediately preceding induction regimen, 6 (17%) achieved a CR or CRp. Of 18 patients who had at least 1 prior hematopoietic stem cell transplant (HSCT), 5 (28%) achieved a CR or CRp.

Among the 12 patients who achieved at least a CRp, 6 patients achieved the best response after 1 cycle of clofarabine, 5 patients required 2 courses and 1 patient achieved a CR after 3 cycles of therapy.

15. REFERENCES

1. OSHA Hazardous Drugs. *OSHA.* http://www.osha.gov/SLTC/hazardousdrugs/index.html.

16. HOW SUPPLIED/STORAGE AND HANDLING

Clolar (clofarabine) Injection is supplied in single-use flint vials containing 20 mg of clofarabine in 20 mL of solution. Each box contains one Clolar vial (NDC 58468-0100-1) or four Clolar vials (NDC 58468-0100-2). The 20mL flint vials contain 20 mL (20 mg) of solution. The pH range of the solution is 4.5 to 7.5.

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

Diluted admixtures may be stored at room temperature, but must be used within 24 hours of preparation.

Procedures for proper handling and disposal should be utilized. Handling and disposal of Clolar should conform to guidelines issued for cytotoxic drugs. Several guidelines on this subject have been published. [1]

17. PATIENT COUNSELING INFORMATION

Hematologic Toxicity: Advise patients to return for regular blood counts and to report any symptoms associated with hematologic toxicity (such as weakness, fatigue, pallor, shortness of breath, easy bruising, petechiae, purpura, fever) to their physician [see *Warnings and Precautions (5.1)* and *Adverse Reactions (6.1)*].

Infection: Advise patients of the signs or symptoms of infection (e.g., fever) and report to the physician immediately if any occur [see *Warnings and Precautions (5.2)* and *Adverse Reactions (6.1)*].

Hepatic and Renal Toxicity: Advise patients to avoid medications including over the counter and herbal medications, which may be hepatotoxic or nephrotoxic, during the 5 days of Clolar administration. Also, advise patients of the possibility of developing liver function abnormalities and to immediately report signs or symptoms of jaundice [see *Warnings and Precautions (5.6) (5.7)*].

Systemic Inflammatory Response Syndrome (SIRS)/Capillary Leak Syndrome: Advise patients of the signs or symptoms of SIRS, such as fever, tachycardia, tachypnea, dyspnea and symptoms suggestive of hypotension [see *Warnings and Precautions (5.4)* and *Adverse Reactions (6.1)*].

Pregnancy and Breast-feeding: Advise male and female patients with reproductive potential to use effective contraceptive measures to prevent pregnancy [see *Warnings and*

Precautions (5.8), Use in Specific Populations (8.1)]. Advise female patients to avoid breast- feeding during Clolar treatment [see *Use in Specific Populations (8.3)*].

Gastrointestinal Disorders: Advise patients that they may experience nausea,vomiting, and/or diarrhea with Clolar. If these symptoms are significant, they should seek medical attention.

Rash: Advise patients that they may experience skin rash with Clolar. If this symptom is significant, they should seek medical attention.

Manufactured by:

Teva Pharmachemie

Swensweg 5

Haarlem, The Netherlands

Manufactured for:

Genzyme Corporation

500 Kendall Street

Cambridge, MA 02142

Distributed by:

Genzyme Corporation

500 Kendall Street

Cambridge, MA 02142

www.clolar.com

©2013 Genzyme Corporation. All rights reserved.

Clolar is a registered trademark of Genzyme Corporation.

8036 (mm/yy)