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

----------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. Randomized trials demonstrating increased survival or other clinical benefit have not been conducted. (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, allopurinol, and alkalinization of 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. (2.1)
- Monitor hepatic, renal, and cardiac function. (2.1)
- Avoid use of certain medications. (2.2)
- Use dose modification for toxicity. (2.3)
- Filter Clolar through a sterile 0.2 micron syringe filter and then dilute with 5% Dextrose Injection, USP, or 0.9% Sodium Chloride Injection, USP, prior to intravenous infusion to a final concentration between 0.15 mg/mL and 0.4 mg/mL. (2.4)
- To prevent drug incompatibilities, no other medications should be administered through the same intravenous line. (2.5)

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

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

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

- None. (4)

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

Hematologic Toxicity

- Monitor complete blood counts and platelet counts during Clolar therapy. (5.1)

Infections

- Clolar use is likely to increase the risk of infection, including severe sepsis, as a result of bone marrow suppression. Monitor patients for signs and symptoms of infection and treat promptly. (5.2)

Hyperuricemia (Tumor Lysis)

- Take precautions to prevent and monitor patients for signs and symptoms of tumor lysis syndrome, as well as signs and symptoms of cytokine release. (5.3)

Systemic Inflammatory Response Syndrome (SIRS) or Capillary Leak Syndrome

- Discontinue Clolar immediately in the event of signs or symptoms of SIRS or Capillary Leak Syndrome
- SIRS and Capillary Leak Syndrome may occur. Evaluate and monitor patients undergoing treatment for signs and symptoms of cytokine release. Consider use of steroids. (5.4)

Hepatic Enzymes

- Monitor and discontinue treatment if necessary. (5.5)

Hepatic/renal impairment

- Use with caution in patients with hepatic or renal impairment. Monitor hepatic and renal function. (5.6)

Use in Pregnancy

- Fetal harm can occur when administered to a pregnant woman. Women should be advised to avoid becoming pregnant when receiving Clolar. (5.7, 8.1)

----------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)

See 17 for PATIENT COUNSELING INFORMATION

Revised: [12/2010]

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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 use is based on the induction of complete responses. Randomized trials demonstrating increased survival or other clinical benefit have not been conducted.

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, allopurinol, 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)*].
- Monitor patients taking medications known to affect blood pressure. Monitor cardiac function during administration of Clolar.

2.2 Recommended Concomitant Medications and Medications to Avoid

- Consider prophylactic anti-emetic medications as Clolar is moderately emetogenic.
- Consider the use of prophylactic steroids to prevent signs or symptoms of Systemic Inflammatory Response Syndrome (SIRS) or capillary leak (e.g., hypotension, tachycardia, tachypnea, and pulmonary edema).
- Consider avoiding drugs with known renal toxicity during the 5 days of Clolar administration.
- 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 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 controlled and then restart at the full dose.
  - Withhold Clolar if a Grade 3 non-infectious non-hematologic toxicity (excluding transient elevations in serum transaminases and/or serum bilirubin and/or 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 a Grade 4 non-infectious non-hematologic toxicity occurs.
  - 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 when the patient is stable and organ function has returned to baseline, generally with a 25% dose reduction. If hyperuricemia is anticipated (tumor lysis), prophylactically administer allopurinol.

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

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

5.1 Hematologic Toxicity

Monitor complete blood counts and platelet counts during Clolar therapy.

Suppression of bone marrow function should be anticipated. This is usually reversible and appears to be dose dependent. Severe bone marrow suppression, including neutropenia, anemia, and thrombocytopenia, has been observed in patients treated with

Clolar. At initiation of treatment, most patients in the clinical studies had hematological impairment as a manifestation of leukemia. Because of the pre-existing immunocompromised condition of these patients and prolonged neutropenia that can result from treatment with Clolar, patients are at increased risk for severe opportunistic infections.

5.2 Infections

The use of Clolar is likely to increase the risk of infection, including severe sepsis, as a result of bone marrow suppression. Monitor patients for signs and symptoms of infection and treat promptly.

5.3 Hyperuricemia (Tumor Lysis)

Administration of Clolar may result in a rapid reduction in peripheral leukemia cells. 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. Administer Allopurinol if hyperuricemia (tumor lysis) is expected.

5.4 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 develop into systemic inflammatory response syndrome (SIRS), capillary leak syndrome and 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, generally with a 25% dose reduction. The use of prophylactic steroids may be of benefit in preventing signs and symptoms of cytokine release.

5.5 Hepatic Enzymes

Hepato-biliary enzyme elevations were frequently observed in pediatric patients during treatment with Clolar. Some patients discontinued treatment due to hepatic enzyme abnormalities. [see *ADVERSE REACTIONS (6.1)*].

5.6 Hepatic and Renal Impairment

Clolar has not been studied in patients with hepatic or renal dysfunction. Its use in such patients should be undertaken only with the greatest caution [see *DOSAGE AND ADMINISTRATION (2.2)*].

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 (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 an ongoing Phase 1/2 combination study of clofarabine in pediatric patients with relapsed or refractory acute leukemia.

5.7 Use in Pregnancy

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)*]
- Hepatic and Renal Impairment [see *WARNINGS AND PRECAUTIONS (5.6)*]
- Use in Pregnancy [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).

One hundred and fifteen (115) of the 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 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 events regardless of causality 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 Events Regardless of Causality 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 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.

Table 1: Most Commonly Reported (≥ 5% Overall) Adverse Events 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	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 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, 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

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%)

Hematologic Toxicity

The most frequently reported hematologic adverse reactions in pediatric patients included febrile neutropenia (55%) and non-febrile neutropenia (10%).

Infection

At baseline, 48% of the pediatric 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.

Hepatic

Hepato-biliary toxicities were frequently observed in pediatric patients during treatment with Clolar. Grade 3 or 4 elevated aspartate aminotransferase (AST) occurred in 36% of patients and grade 3 or 4 elevated alanine aminotransferase (ALT) occurred in 44% 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. Two reports (2%) of veno-occlusive disease (VOD) were 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. Where follow-up data are available, 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.

Renal

The most prevalent renal toxicity in pediatric patients was elevated creatinine. Grade 3 or 4 elevated creatinine occurred in 8% of patients. Acute renal failure was reported in 3 patients (3%) at grade 3 and 2 patients (2%) with grade 4. Nephrotoxic medications, tumor lysis, and tumor lysis with hyperuricemia may contribute to renal toxicity. Hematuria was observed in 13% of patients overall.

Systemic Inflammatory Response Syndrome (SIRS)

Adverse reactions of SIRS were reported in 2 patients (2%) [See *WARNING AND PRECAUTIONS (5.4)*]

Capillary Leak Syndrome

Adverse reactions of capillary leak syndrome were reported in 4 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 are recommended. 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. Physicians should be alert to early indications of this syndrome and should immediately discontinue Clolar administration if they occur and provide appropriate supportive measures. After the patient is stabilized and organ function has returned to baseline, re-treatment with Clolar can be considered with a 25% dose reduction.

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.

- Blood and lymphatic system disorders: bone marrow failure
- Hepatobiliary disorders: Serious hepatotoxic adverse reactions of veno-occlusive disease have been reported in adult patients following HSCT.

These patients received conditioning regimens that included busulfan, melphalan, and/or the combination of cyclophosphamide and total body irradiation.

- 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.

7. DRUG INTERACTIONS

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

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.

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

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

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.

The pharmacokinetics of clofarabine have not been evaluated in patients with renal or hepatic dysfunction.

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 x 5 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 × 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.

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 Study

	N = 61
CR % (n) [95% CI]	11.5 (4.7, 22.2)
CRp % (n) [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. 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.

Responses were seen in both pre-B and T-cell immunophenotypes of ALL.

15 REFERENCES

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.
2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html
3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm.* 2006; 63:1172-1193.
4. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

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. [1-4]

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 (eg. fever) and report to the physician immediately if any occur [see *WARNINGS AND PRECAUTIONS (5.2)* and *ADVERSE REACTIONS (6.1)*].

Hepatic and Renal Impairment: 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 [see *WARNINGS AND PRECAUTIONS (5.6)*].

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)*].

Advise male and female patients with reproductive potential to use effective contraceptive measures to prevent pregnancy [see *WARNINGS AND PRECAUTIONS (5.7), USE IN SPECIFIC POPULATIONS (8.1)*]. Advise female patients to avoid breast feeding during Clolar treatment [see *USE IN SPECIFIC POPULATIONS (8.3)*].

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