

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/m² 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 alkalization 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]

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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/m² 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 $\geq 0.75 \times 10^9/\text{L}$.
 - If a patient experiences a Grade 4 neutropenia (ANC $< 0.5 \times 10^9/\text{L}$) lasting ≥ 4 weeks, reduce dose by 25% for the next cycle.

- 37 • Non-hematologic Toxicity
- 38 • Withhold Clolar if a patient develops a clinically significant infection, until
- 39 the infection is clinically controlled and then restart at the full dose.
- 40 • Withhold Clolar if a Grade 3 non-infectious non-hematologic toxicity
- 41 (excluding transient elevations in serum transaminases and/or serum bilirubin
- 42 and/or nausea/vomiting that was controlled by antiemetic therapy) occurs.
- 43 Re-institute Clolar administration at a 25% dose reduction when resolution or
- 44 return to baseline.
- 45 • Discontinue Clolar administration if a Grade 4 non-infectious non-
- 46 hematologic toxicity occurs.
- 47 • Discontinue Clolar administration if a patient shows early signs or symptoms
- 48 of SIRS or capillary leak (e.g., hypotension, tachycardia, tachypnea, and
- 49 pulmonary edema) occur and provide appropriate supportive measures.
- 50 • Discontinue Clolar administration if Grade 3 or higher increases in creatinine
- 51 or bilirubin are noted. Re-institute Clolar when the patient is stable and organ
- 52 function has returned to baseline, generally with a 25% dose reduction. If
- 53 hyperuricemia is anticipated (tumor lysis), prophylactically administer
- 54 allopurinol.

55 **2.4 Reconstitution/Preparation**

56 Clolar should be filtered through a sterile 0.2 micron syringe filter and then diluted with
 57 5% Dextrose Injection, USP, or 0.9% Sodium Chloride Injection, USP, prior to
 58 intravenous (IV) infusion to a final concentration between 0.15 mg/mL and 0.4 mg/mL.
 59 Use within 24 hours of preparation. Store diluted Clolar at room temperature (15-30°C).

60 **2.5 Incompatibilities**

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

62 **3. DOSAGE FORMS AND STRENGTHS**

63 20 mg/20 mL (1 mg/mL) single use vial

64 **4. CONTRAINDICATIONS**

65 None

66 **5. WARNINGS AND PRECAUTIONS**

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

69 **5.1 Hematologic Toxicity**

70 Monitor complete blood counts and platelet counts during Clolar therapy.

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

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

79 **5.2 Infections**

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

83 **5.3 Hyperuricemia (Tumor Lysis)**

84 Administration of Clolar may result in a rapid reduction in peripheral leukemia cells.
 85 Evaluate and monitor patients undergoing treatment for signs and symptoms of tumor
 86 lysis syndrome. Provide intravenous infusion fluids throughout the five days of Clolar
 87 administration to reduce the effects of tumor lysis and other adverse events. Administer
 88 Allopurinol if hyperuricemia (tumor lysis) is expected.

89 **5.4 Systemic Inflammatory Response Syndrome (SIRS) and Capillary Leak Syndrome**

91 Evaluate and monitor patients undergoing treatment with Clolar for signs and symptoms
 92 of cytokine release (e.g., tachypnea, tachycardia, hypotension, pulmonary edema) that
 93 could develop into systemic inflammatory response syndrome (SIRS), capillary leak
 94 syndrome and organ dysfunction. Discontinue Clolar immediately in the event of
 95 clinically significant signs or symptoms of SIRS or capillary leak syndrome, either of
 96 which can be fatal, and consider use of steroids, diuretics, and albumin. Re-institute
 97 Clolar when the patient is stable, generally with a 25% dose reduction. The use of
 98 prophylactic steroids may be of benefit in preventing signs and symptoms of cytokine
 99 release.

100 **5.5 Hepatic Enzymes**

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

104 **5.6 Hepatic and Renal Impairment**

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

108 Patients who have previously received a hematopoietic stem cell transplant (HSCT) may
 109 be at higher risk for hepatotoxicity suggestive of veno-occlusive disease (VOD)
 110 following treatment with clofarabine (40 mg/m²) when used in combination with
 111 etoposide (100 mg/m²) and cyclophosphamide (440 mg/m²). Severe hepatotoxic events
 112 have been reported in an ongoing Phase 1/2 combination study of clofarabine in pediatric
 113 patients with relapsed or refractory acute leukemia.

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114 5.7 Use in Pregnancy

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

118 6. ADVERSE REACTIONS

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

- 121 • Severe Bone Marrow Suppression [see [WARNINGS AND PRECAUTIONS \(5.1\)](#)]
- 122 • Serious Infections [see [WARNINGS AND PRECAUTIONS \(5.2\)](#)]
- 123 • Hyperuricemia (Tumor Lysis) [see [WARNINGS AND PRECAUTIONS \(5.3\)](#)]
- 124 • Systemic Inflammatory Response Syndrome (SIRS) and Capillary Leak
125 Syndrome [see [WARNINGS AND PRECAUTIONS \(5.4\)](#)]
- 126 • Hepatic and Renal Impairment [see [WARNINGS AND PRECAUTIONS \(5.6\)](#)]
- 127 • Use in Pregnancy [see [WARNINGS AND PRECAUTIONS \(5.7\)](#)]

128 6.1 Clinical Trials Experience

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

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

135 One hundred and fifteen (115) of the pediatric patients treated in clinical trials received
136 the recommended dose of Clolar 52 mg/m² daily × 5. The median number of cycles was
137 2. The median cumulative amount of Clolar[®] received by pediatric patients during all
138 cycles was 540 mg.

139 The most common adverse reactions with Clolar are: nausea, vomiting, diarrhea, febrile
140 neutropenia, headache, rash, pruritus, pyrexia, fatigue, palmar-plantar erythrodysesthesia
141 syndrome, anxiety, flushing, and mucosal inflammation.

142 [Table 1](#) lists adverse events regardless of causality by System Organ Class, including
143 severe or life-threatening (NCI CTC grade 3 or grade 4), reported in ≥ 5% of the 115
144 patients in the 52 mg/m²/day dose group (pooled analysis of pediatric patients with ALL
145 and AML). More detailed information and follow-up of certain events is given below.

**Table 1: Most Commonly Reported ($\geq 5\%$ 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.

152 **Table 1: Most Commonly Reported ($\geq 5\%$ Overall)**
 153 **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.

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

156 *Gastrointestinal Disorders:* cecitis, pancreatitis

157 *Hepatobiliary Disorders:* hyperbilirubinemia

158 *Immune System Disorders:* hypersensitivity

159 *Infections and Infestations:* bacterial infection, Enterococcal bacteremia, Escherichia
 160 bacteremia, Escherichia sepsis, fungal infection, fungal sepsis, gastroenteritis adenovirus,
 161 infection, influenza, Parainfluenzae virus infection, pneumonia fungal, pneumonia
 162 primary atypical, Respiratory syncytial virus infection, sinusitis, staphylococcal infection
 163 *Investigations:* blood creatinine increased
 164 *Psychiatric Disorders:* mental status change
 165 *Respiratory, Thoracic and Mediastinal Disorder:* pulmonary edema
 166

167 Table 2 lists the incidence of treatment emergent laboratory abnormalities after Clolar
 168 administration at 52 mg/m² among pediatric patients with ALL and AML (n=115).

169 **Table 2: Incidence of Treatment Emergent Laboratory Abnormalities**
 170 **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%)

171 Hematologic Toxicity

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

174 Infection

175 At baseline, 48% of the pediatric patients had 1 or more concurrent infections. A total of
 176 83% of patients experienced at least 1 infection after Clolar treatment, including fungal,
 177 viral and bacterial infections.

178 Hepatic

179 Hepato-biliary toxicities were frequently observed in pediatric patients during treatment
 180 with Clolar. Grade 3 or 4 elevated aspartate aminotransferase (AST) occurred in 36% of
 181 patients and grade 3 or 4 elevated alanine aminotransferase (ALT) occurred in 44% of
 182 patients. Grade 3 or 4 elevated bilirubin occurred in 13% of patients, with 2 events

183 reported as grade 4 hyperbilirubinemia (2%), one of which resulted in treatment
 184 discontinuation, one patient had multi-organ failure and died. Two reports (2%) of veno-
 185 occlusive disease (VOD) were considered related to study drug.

186 For patients with follow-up data, elevations in AST and ALT were transient and typically
 187 ≤ 15 days duration. The majority of AST and ALT elevations occurred within 10 days of
 188 Clolar administration and returned to $\leq$ grade 2 within 15 days. Where follow-up data are
 189 available, the majority of bilirubin elevations returned to $\leq$ grade 2 within 10 days. Eight
 190 patients had grade 3 or 4 elevations in serum bilirubin at the last time point measured;
 191 these patients died due to sepsis and/or multi-organ failure.

192 Renal

193 The most prevalent renal toxicity in pediatric patients was elevated creatinine. Grade 3 or
 194 4 elevated creatinine occurred in 8% of patients. Acute renal failure was reported in 3
 195 patients (3%) at grade 3 and 2 patients (2%) with grade 4. Nephrotoxic medications,
 196 tumor lysis, and tumor lysis with hyperuricemia may contribute to renal toxicity.
 197 Hematuria was observed in 13% of patients overall.

198 Systemic Inflammatory Response Syndrome (SIRS)

199 Adverse reactions of SIRS were reported in 2 patients (2%) [See [WARNING AND](#)
 200 [PRECAUTIONS \(5.4\)](#)]

201 Capillary Leak Syndrome

202 Adverse reactions of capillary leak syndrome were reported in 4 patients (4%).
 203 Symptoms included rapid onset of respiratory distress, hypotension, pleural and
 204 pericardial effusion, and multi-organ failure.

205 Close monitoring for this syndrome and early intervention are recommended. The use of
 206 prophylactic steroids (e.g., 100 mg/m² hydrocortisone on Days 1 through 3) may be of
 207 benefit in preventing signs or symptoms of SIRS or capillary leak. Physicians should be
 208 alert to early indications of this syndrome and should immediately discontinue Clolar
 209 administration if they occur and provide appropriate supportive measures. After the
 210 patient is stabilized and organ function has returned to baseline, re-treatment with Clolar
 211 can be considered with a 25% dose reduction.

212 6.2 Post-marketing Experience

213 The following adverse reactions have been identified during post approval use of Clolar.
 214 Because these reactions are reported voluntarily from a population of uncertain size, it is
 215 not always possible to reliably estimate their frequency or establish a causal relationship
 216 to drug exposure. Decisions to include these reactions in labeling are typically based on
 217 one or more of the following factors: (1) seriousness of the reaction, (2) reported
 218 frequency of the reaction, or (3) strength of causal connection to Clolar.

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

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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/m²/day (approximately equivalent to the recommended clinical dose on a mg/m² basis), and in rabbits receiving 12 mg/m²/day (approximately 23% of the recommended clinical dose on a mg/m² 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.

genzyme

Clolar[®] (clofarabine) injection257 **8.4 Pediatric Use**

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

260 **8.5 Geriatric Use**

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

263 **8.6 Adults with Hematologic Malignancies**

264 Safety and effectiveness have not been established in adults.

265 **10. OVERDOSAGE**

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

270 In a Phase I study of adults with refractory and/or relapsed hematologic malignancies, the
 271 recommended pediatric dose of 52 mg/m²/day was not tolerated.

272 **11. DESCRIPTION**

273 Clolar (clofarabine) injection contains clofarabine, a purine nucleoside metabolic
 274 inhibitor. Clolar (1 mg/mL) is supplied in a 20 mL, single-use vial. The 20 mL vial
 275 contains 20 mg clofarabine formulated in 20 mL unbuffered normal saline (comprised of
 276 Water for Injection, USP, and Sodium Chloride USP). The pH range of the solution is 4.5
 277 to 7.5. The solution is sterile, clear and practically colorless, and is preservative free.

278

279 **12. CLINICAL PHARMACOLOGY**280 **12.1 Mechanism of Action**

281 Clofarabine is sequentially metabolized intracellularly to the 5'-monophosphate
 282 metabolite by deoxycytidine kinase and mono- and di-phospho-kinases to the active
 283 5'-triphosphate metabolite. Clofarabine has high affinity for the activating
 284 phosphorylating enzyme, deoxycytidine kinase, equal to or greater than that of the natural
 285 substrate, deoxycytidine. Clofarabine inhibits DNA synthesis by decreasing cellular
 286 deoxynucleotide triphosphate pools through an inhibitory action on ribonucleotide
 287 reductase, and by terminating DNA chain elongation and inhibiting repair through
 288 incorporation into the DNA chain by competitive inhibition of DNA polymerases. The
 289 affinity of clofarabine triphosphate for these enzymes is similar to or greater than that of
 290 deoxyadenosine triphosphate. In preclinical models, clofarabine has demonstrated the
 291 ability to inhibit DNA repair by incorporation into the DNA chain during the repair
 292 process. Clofarabine 5'-triphosphate also disrupts the integrity of mitochondrial
 293 membrane, leading to the release of the pro-apoptotic mitochondrial proteins, cytochrome
 294 C and apoptosis-inducing factor, leading to programmed cell death.

295 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/m² 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/m² and 172 L/m², 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/m²/day, approximately 17% of clinical recommended dose on a mg/m² basis). The testes of rats receiving 25 mg/kg/day (150 mg/m²/day, approximately 3 times the recommended clinical dose on a mg/m² 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/m²/day, approximately 14% of the clinical recommended dose on a mg/m² basis). Ovarian atrophy or degeneration and uterine mucosal apoptosis were observed in female mice at 75 mg/kg/day (225 mg/m²/day, approximately 4-fold of recommended human dose on a mg/m² basis), the only dose administered to female mice. The effect on human fertility is unknown.

334 14. CLINICAL STUDIES

335 Seventy-eight (78) pediatric patients with ALL were exposed to Clolar. Seventy (70) of
336 the patients received the recommended pediatric dose of Clolar 52 mg/m² daily x 5 as an
337 intravenous (IV) infusion.

338 Dose Escalation Study in Pediatric Patients with Hematologic Malignancies

339 The safety and efficacy of Clolar were evaluated in pediatric patients with refractory or
340 relapsed hematologic malignancies in an open-label, dose-escalation, noncomparative
341 study. The starting dose of Clolar was 11.25 mg/m²/day IV infusion daily x 5 and
342 escalated to 70 mg/m²/day IV infusion daily x 5. This dosing schedule was repeated
343 every 2 to 6 weeks depending on toxicity and response. Nine of 17 ALL patients were
344 treated with Clolar 52 mg/m² daily x 5. In the 17 ALL patients there were 2 complete
345 remissions (12%) and 2 partial remissions (12%) at varying doses. Dose-limiting
346 toxicities (DLTs) in this study were reversible hyperbilirubinemia and elevated
347 transaminase levels and skin rash, experienced at 70 mg/m². As a result of this study, the
348 recommended dose for subsequent study in pediatric patients was determined to be 52
349 mg/m²/day for 5 days.

350 Single Arm Study in Pediatric ALL

351 Clolar was evaluated in an open-label, single arm study of 61 pediatric patients with
352 relapsed/refractory ALL. Patients received a dose of 52 mg/m² over 2 hours for 5
353 consecutive days repeated every 2 to 6 weeks for up to 12 cycles. There was no dose
354 escalation in this study.

355 All patients had disease that had relapsed after and/or was refractory to two or more prior
356 therapies. Most patients, 38/61 (62%), had received > 2 prior regimens and 18/61 (30%)
357 of the patients had undergone at least 1 prior transplant. The median age of the treated
358 patients was 12 years, 61% were male, 39% were female, 44% were Caucasian, 38%
359 were Hispanic, 12% were African-American, 2% were Asian and 5% were Other race.

360 The overall remission (OR) rate (Complete Remission [CR] + CR in the absence of total
361 platelet recovery [CRp]) was evaluated. CR was defined as no evidence of circulating
362 blasts or extramedullary disease, an M1 bone marrow ($\leq 5\%$ blasts), and recovery of
363 peripheral counts [platelets $\geq 100 \times 10^9/L$ and absolute neutrophil count (ANC) $\geq 1.0 \times$
364 $10^9/L$]. CRp was defined as meeting all criteria for CR except for recovery of platelet
365 counts to $\geq 100 \times 10^9/L$. Partial Response (PR) was also determined, defined as complete
366 disappearance of circulating blasts, an M2 bone marrow ($\geq 5\%$ and $\leq 25\%$ blasts), and
367 appearance of normal progenitor cells or an M1 marrow that did not qualify for CR or
368 CRp. Duration of remission was also evaluated. Transplantation rate was not a study
369 endpoint.

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

372 [Table 3](#) summarizes results for the pediatric ALL study. Responses were seen in both
373 pre-B and T-cell immunophenotypes of ALL. The median cumulative dose was 530 mg
374 (range 29-2815 mg) in 1 (41%), 2 (44%) or 3 or more (15%) cycles. The median number

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Clolar® (clofarabine) injection

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

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2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999.
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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)

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411 or four Clolar vials (NDC 58468-0100-2). The 20mL flint vials contain 20 mL (20 mg)
 412 of solution. The pH range of the solution is 4.5 to 7.5.

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

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

417 Procedures for proper handling and disposal should be utilized. Handling and disposal of
 418 Clolar should conform to guidelines issued for cytotoxic drugs. Several guidelines on this
 419 subject have been published.¹⁻⁴

420 **17. PATIENT COUNSELING INFORMATION**

421 *Hematologic Toxicity:* Advise patients to return for regular blood counts and to report
 422 any symptoms associated with hematologic toxicity (such as weakness, fatigue, pallor,
 423 shortness of breath, easy bruising, petechiae, purpura, fever) to their physician [see
 424 [WARNINGS AND PRECAUTIONS \(5.1\)](#) and [ADVERSE REACTIONS \(6.1\)](#)].

425 *Infection:* Advise patients of the signs or symptoms of infection (eg. fever) and report to
 426 the physician immediately if any occur [see [WARNINGS AND PRECAUTIONS \(5.2\)](#) and
 427 [ADVERSE REACTIONS \(6.1\)](#)].

428 *Hepatic and Renal Impairment:* Advise patients to avoid medications including over the
 429 counter and herbal medications, which may be hepatotoxic or nephrotoxic, during the 5
 430 days of Clolar administration [see [WARNINGS AND PRECAUTIONS \(5.6\)](#)].

431 *Systemic Inflammatory Response Syndrome (SIRS)/Capillary Leak Syndrome:* Advise
 432 patients of the signs or symptoms of SIRS, such as fever, tachycardia, tachypnea,
 433 dyspnea and symptoms suggestive of hypotension [see [WARNINGS AND](#)
 434 [PRECAUTIONS \(5.4\)](#) and [ADVERSE REACTIONS \(6.1\)](#)].

435 Advise male and female patients with reproductive potential to use effective
 436 contraceptive measures to prevent pregnancy [see [WARNINGS AND PRECAUTIONS](#)
 437 [\(5.7\)](#), [USE IN SPECIFIC POPULATIONS \(8.1\)](#)]. Advise female patients to avoid breast
 438 feeding during Clolar treatment [see [USE IN SPECIFIC POPULATIONS \(8.3\)](#)].

439

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441

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444 Charleston, SC 29405

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