

## 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<sup>2</sup> 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 alkalization 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](http://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]

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

1 **FULL PRESCRIBING INFORMATION**

2 **1. INDICATIONS AND USAGE**

3 Clolar<sup>®</sup> (clofarabine) Injection is indicated for the treatment of pediatric patients 1 to 21  
4 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior  
5 regimens. This indication is based upon response rate. There are no trials verifying an  
6 improvement in disease-related symptoms or increased survival with Clolar.

7 **2. DOSAGE AND ADMINISTRATION**

8 **2.1 Recommended Dosage**

9 Administer the recommended pediatric dose of 52 mg/m<sup>2</sup> as an intravenous infusion over  
10 2 hours daily for 5 consecutive days.

- 11 • Treatment cycles are repeated following recovery or return to baseline organ  
12 function, approximately every 2 to 6 weeks. The dosage is based on the patient's  
13 body surface area (BSA), calculated using the actual height and weight before the  
14 start of each cycle. To prevent drug incompatibilities, no other medications  
15 should be administered through the same intravenous line.
- 16 • Provide supportive care, such as intravenous fluids, antihyperuricemic treatment,  
17 and alkalinize urine throughout the 5 days of Clolar administration to reduce the  
18 effects of tumor lysis and other adverse events.
- 19 • Discontinue Clolar if hypotension develops during the 5 days of administration.
- 20 • Monitor renal and hepatic function during the 5 days of Clolar administration [see  
21 *Warnings and Precautions* (5.6, 5.7)].
- 22 • Monitor patients taking medications known to affect blood pressure. Monitor  
23 cardiac function during administration of Clolar.
- 24 • Reduce the dose by 50% in patients with creatinine clearance (CrCL) between 30  
25 and 60 mL/min. There is insufficient information to make a dosage  
26 recommendation in patients with CrCL less than 30 mL/min [see *Use in Specific*  
27 *Populations* (8.7)].

28 **2.2 Supportive Medications and Medications to Avoid**

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

- 35 • Consider avoiding concomitant use of medications known to induce hepatic toxicity.

36 **2.3 Dose Modifications and Reinitiation of Therapy**

- 37 • Hematologic Toxicity

- 38 • Administer subsequent cycles no sooner than 14 days from the starting day of  
39 the previous cycle and provided the patient's ANC is  $\geq 0.75 \times 10^9/L$ .
- 40 • If a patient experiences a Grade 4 neutropenia ( $ANC < 0.5 \times 10^9/L$ ) lasting  $\geq 4$   
41 weeks, reduce dose by 25% for the next cycle.
- 42 • Non-hematologic Toxicity
  - 43 • Withhold Clolar if a patient develops a clinically significant infection, until  
44 the infection is controlled, then restart at the full dose.
  - 45 • Withhold Clolar for a Grade 3 non-infectious non-hematologic toxicity  
46 (excluding transient elevations in serum transaminases and/or serum bilirubin  
47 and/or nausea/vomiting controlled by antiemetic therapy). Re-institute Clolar  
48 administration at a 25% dose reduction when resolution or return to baseline.
  - 49 • Discontinue Clolar administration for a Grade 4 non-infectious non-  
50 hematologic toxicity.
  - 51 • Discontinue Clolar administration if a patient shows early signs or symptoms  
52 of SIRS or capillary leak (e.g., hypotension, tachycardia, tachypnea, and  
53 pulmonary edema) occur and provide appropriate supportive measures.
  - 54 • Discontinue Clolar administration if Grade 3 or higher increases in creatinine  
55 or bilirubin are noted. Re-institute Clolar with a 25% dose reduction, when  
56 the patient is stable and organ function has returned to baseline. If  
57 hyperuricemia is anticipated (tumor lysis), initiate measures to control uric  
58 acid.

#### 59 **2.4 Reconstitution/Preparation**

60 Clolar should be filtered through a sterile 0.2 micron syringe filter and then diluted with  
61 5% Dextrose Injection, USP, or 0.9% Sodium Chloride Injection, USP, prior to  
62 intravenous (IV) infusion to a final concentration between 0.15 mg/mL and 0.4 mg/mL.  
63 Use within 24 hours of preparation. Store diluted Clolar at room temperature (15-30°C).

#### 64 **2.5 Incompatibilities**

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

### 66 **3. DOSAGE FORMS AND STRENGTHS**

67 20 mg/20 mL (1 mg/mL) single-use vial

### 68 **4. CONTRAINDICATIONS**

69 None

### 70 **5. WARNINGS AND PRECAUTIONS**

#### 71 **5.1 Hematologic Toxicity**

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

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

## 80 **5.2 Infections**

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

## 86 **5.3 Hyperuricemia (Tumor Lysis)**

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

## 92 **5.4 Systemic Inflammatory Response Syndrome (SIRS) and Capillary Leak** 93 **Syndrome**

94 Clolar may cause a cytokine release syndrome (e.g., tachypnea, tachycardia, hypotension,  
95 pulmonary edema) that may progress to the systemic inflammatory response syndrome  
96 (SIRS) with capillary leak syndrome and organ impairment which may be fatal. Monitor  
97 patients frequently for these conditions. In clinical trials, SIRS was reported in two  
98 patients (2%); capillary leak syndrome was reported in four patients (4%). Symptoms  
99 included rapid onset of respiratory distress, hypotension, pleural and pericardial effusion,  
100 and multi-organ failure. Close monitoring for this syndrome and early intervention may  
101 reduce the risk. Immediately discontinue Clolar and provide appropriate supportive  
102 measures. The use of prophylactic steroids (e.g., 100 mg/m<sup>2</sup> hydrocortisone on Days 1  
103 through 3) may be of benefit in preventing signs or symptoms of SIRS or capillary leak.  
104 Consider use of diuretics and/or albumin. After the patient is stabilized and organ  
105 function has returned to baseline, re-treatment with Clolar can be considered with a 25%  
106 dose reduction.

## 107 **5.5 Venous Occlusive Disease of the Liver**

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

## 115 116 **5.6 Hepatotoxicity**

117 Severe and fatal hepatotoxicity has occurred with the use of Clolar. In clinical studies,  
118 Grade 3-4 liver enzyme elevations were observed in pediatric patients during treatment  
119 with Clolar at the following rates: elevated aspartate aminotransferase (AST) occurred in  
120 36% of patients; elevated alanine aminotransferase (ALT) occurred in 44% of patients.  
121 AST and ALT elevations typically occurred within 10 days of Clolar administration and  
122 returned to Grade 2 or less within 15 days. Grade 3 or 4 elevated bilirubin occurred in  
123 13% of patients, with 2 events reported as Grade 4 hyperbilirubinemia (2%), one of  
124 which resulted in treatment discontinuation and one patient had multi-organ failure and  
125 died. Eight patients (7%) had Grade 3 or 4 elevations in serum bilirubin at the last time  
126 point measured; these patients died due to sepsis and/or multi-organ failure. Monitor  
127 hepatic function and discontinue Clolar for Grade 3 or greater liver enzyme elevations  
128 [see *Adverse Reactions (6.1)*].

### 129 **5.7 Renal Toxicity**

130 In clinical studies, Grade 3 or 4 elevated creatinine occurred in 8% of patients; acute  
131 renal failure was reported as Grade 3 in three patients (3%) and Grade 4 in two patients  
132 (2%). Hematuria was observed in 13% of patients overall. Monitor patients for renal  
133 toxicity and interrupt or discontinue Clolar as necessary.

### 134 **5.8 Embryo-fetal Toxicity**

135 Clolar can cause fetal harm when administered to a pregnant woman. Intravenous doses  
136 of clofarabine in rats and rabbits administered during organogenesis caused an increase in  
137 resorptions, malformations, and variations [see *Use in Specific Populations (8.1)*].  
138

## 139 **6. ADVERSE REACTIONS**

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

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

### 150 **6.1 Clinical Trials Experience**

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

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

157 In total, 115 pediatric patients treated in clinical trials received the recommended dose of  
158 Clolar  $52 \text{ mg/m}^2$  daily  $\times 5$ . The median number of cycles was 2. The median cumulative  
159 amount of Clolar received by pediatric patients during all cycles was 540 mg.

160 The most common adverse reactions occurring in 10% or more of patients treated with  
161 Clolar are: nausea, vomiting, diarrhea, febrile neutropenia, headache, rash, pruritus,  
162 pyrexia, fatigue, palmar-plantar erythrodysesthesia syndrome, anxiety, flushing, and  
163 mucosal inflammation.

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

168 **Table 1: Most Commonly Reported ( $\geq 5\%$  Overall)**  
169 **Adverse Reactions by System Organ Class (N=115 pooled analysis)**

System Organ Class <sup>1</sup>	Preferred Term <sup>1</sup>	ALL/AML (N=115)		Worst NCI Common Terminology Criteria Grade <sup>1</sup>					
				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	

170 <sup>1</sup> Patients with more than one preferred term within a SOC are counted only once in the SOC totals. Patients with  
171 more than one occurrence of the same preferred term are counted only once within that term and at the highest  
172 severity grade.

173  
174

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

System Organ Class <sup>1</sup>	Preferred Term <sup>1</sup>	ALL/AML (N=115)		Worst NCI Common Terminology Criteria Grade <sup>1</sup>					
		N	%	3		4		5	
				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	.	.

<sup>1</sup> 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.

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

177 *Gastrointestinal Disorders:* cecitis, pancreatitis

178 *Hepatobiliary Disorders:* hyperbilirubinemia

179 *Immune System Disorders:* hypersensitivity

180 *Infections and Infestations:* bacterial infection, Enterococcal bacteremia, Escherichia  
181 bacteremia, Escherichia sepsis, fungal infection, fungal sepsis, gastroenteritis adenovirus,  
182 infection, influenza, parainfluenza virus infection, pneumonia fungal, pneumonia primary  
183 atypical, Respiratory syncytial virus infection, sinusitis, staphylococcal infection  
184 *Investigations:* blood creatinine increased  
185 *Psychiatric Disorders:* mental status change  
186 *Respiratory, Thoracic and Mediastinal Disorder:* pulmonary edema

187 Table 2 lists the incidence of treatment-emergent laboratory abnormalities after Clolar  
188 administration at 52 mg/m<sup>2</sup> among pediatric patients with ALL and AML (N=115).

189 **Table 2: Incidence of Treatment-Emergent Laboratory Abnormalities**  
190 **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%)

191

192

193

## 194 **6.2 Post-marketing Experience**

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

- 201 • Gastrointestinal disorders: Gastrointestinal hemorrhage including  
202 fatalities.
- 203 • Skin and subcutaneous tissue disorders: Occurrences of Stevens-Johnson  
204 Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported  
205 in patients who were receiving or had recently been treated with Clolar  
206 and other medications (e.g., allopurinol or antibiotics) known to cause  
207 these syndromes. Other exfoliative conditions have also been reported.  
208

## 209 **7. DRUG INTERACTIONS**

210 No in-vivo drug interaction studies have been conducted [see *Clinical Pharmacology*  
211 (12.3)].

## 212 **8. USE IN SPECIFIC POPULATIONS**

### 213 **8.1 Pregnancy**

#### 214 **Pregnancy Category D**

215 Clolar (clofarabine) may cause fetal harm when administered to a pregnant woman.

216 Clofarabine was teratogenic in rats and rabbits. Developmental toxicity (reduced fetal  
217 body weight and increased post-implantation loss) and increased incidences of  
218 malformations and variations (gross external, soft tissue, skeletal and retarded  
219 ossification) were observed in rats receiving 54 mg/m<sup>2</sup>/day (approximately equivalent to  
220 the recommended clinical dose on a mg/m<sup>2</sup> basis), and in rabbits receiving 12 mg/m<sup>2</sup>/day  
221 (approximately 23% of the recommended clinical dose on a mg/m<sup>2</sup> basis).

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

225 Women of childbearing potential should be advised to avoid becoming pregnant while  
226 receiving treatment with clofarabine. All patients should be advised to use effective  
227 contraceptive measures to prevent pregnancy.

### 228 **8.3 Nursing Mothers**

229 It is not known whether clofarabine or its metabolites are excreted in human milk.

230 Because of the potential for tumorigenicity shown for clofarabine in animal studies and

231 the potential for serious adverse reactions, women treated with clofarabine should not  
232 nurse. Female patients should be advised to avoid breast-feeding during treatment with  
233 Clolar.

#### 234 **8.4 Pediatric Use**

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

#### 237 **8.5 Geriatric Use**

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

#### 240 **8.6 Adults with Hematologic Malignancies**

241 Safety and effectiveness have not been established in adults.

#### 242 **8.7 Renal Impairment**

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

246 The pharmacokinetics of clofarabine in patients with renal impairment and normal renal  
247 function were obtained from a population pharmacokinetic analysis of three pediatric and  
248 two adult studies. In patients with CrCL 60 to less than 90 mL/min (N = 47) and CrCL 30 to  
249 less than 60 mL/min (N = 30), the average AUC of clofarabine increased by 60% and 140%,  
250 respectively, compared to patients with normal (N = 66) renal function (CrCL greater than  
251 90 mL/min).

#### 252 **8.8 Hepatic Impairment**

253 Clolar has not been studied in patients with hepatic impairment.

### 254 **10. OVERDOSAGE**

255 There were no known overdoses of Clolar. The highest daily dose administered to a  
256 human to date (on a mg/m<sup>2</sup> basis) has been 70 mg/m<sup>2</sup>/day × 5 days (2 pediatric ALL  
257 patients). The toxicities included in these 2 patients included Grade 4  
258 hyperbilirubinemia, Grade 2 and 3 vomiting, and Grade 3 maculopapular rash.

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

### 261 **11. DESCRIPTION**

262 Clolar (clofarabine) Injection contains clofarabine, a purine nucleoside metabolic  
263 inhibitor. Clolar (1 mg/mL) is supplied in a 20 mL, single-use vial. The 20 mL vial  
264 contains 20 mg clofarabine formulated in 20 mL unbuffered normal saline (comprised of  
265 Water for Injection, USP, and Sodium Chloride, USP). The pH range of the solution is  
266 4.5 to 7.5. The solution is sterile, clear and practically colorless, and is preservative-free.

### 267 **12. CLINICAL PHARMACOLOGY**

268 **12.1 Mechanism of Action**

269 Clofarabine is sequentially metabolized intracellularly to the 5'-monophosphate  
270 metabolite by deoxycytidine kinase and mono- and di-phospho-kinases to the active  
271 5'-triphosphate metabolite. Clofarabine has affinity for the activating phosphorylating  
272 enzyme, deoxycytidine kinase, equal to or greater than that of the natural substrate,  
273 deoxycytidine. Clofarabine inhibits DNA synthesis by decreasing cellular  
274 deoxynucleotide triphosphate pools through an inhibitory action on ribonucleotide  
275 reductase, and by terminating DNA chain elongation and inhibiting repair through  
276 incorporation into the DNA chain by competitive inhibition of DNA polymerases. The  
277 affinity of clofarabine triphosphate for these enzymes is similar to or greater than that of  
278 deoxyadenosine triphosphate. In preclinical models, clofarabine has demonstrated the  
279 ability to inhibit DNA repair by incorporation into the DNA chain during the repair  
280 process. Clofarabine 5'-triphosphate also disrupts the integrity of mitochondrial  
281 membrane, leading to the release of the pro-apoptotic mitochondrial proteins, cytochrome  
282 C and apoptosis-inducing factor, leading to programmed cell death.

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

284 **12.3 Pharmacokinetics**

285 The population pharmacokinetics of Clolar were studied in 40 pediatric patients aged 2 to  
286 19 years (21 males/19 females) with relapsed or refractory acute lymphoblastic leukemia  
287 (ALL) or acute myelogenous leukemia (AML). At the given 52 mg/m<sup>2</sup> dose, similar  
288 concentrations were obtained over a wide range of body surface areas (BSAs).

289 Clofarabine was 47% bound to plasma proteins, predominantly to albumin. Based on  
290 non-compartmental analysis, systemic clearance and volume of distribution at steady-  
291 state were 28.8 L/h/m<sup>2</sup> and 172 L/m<sup>2</sup>, respectively. The terminal half-life was 5.2 hours.  
292 No apparent difference in pharmacokinetics was observed between patients with ALL  
293 and AML or between males and females.

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

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

300 *Drug-Drug Interactions*

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

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

309 determined, signs of Clolar toxicity should be monitored when administered with other  
310 hOAT1, hOAT3, hOCT1 and hOCT2 substrates or inhibitors.  
311

## 312 **13. NONCLINICAL TOXICOLOGY**

### 313 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

314 Clofarabine has not been tested for carcinogenic potential.

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

318 Studies in mice, rats, and dogs have demonstrated dose-related adverse effects on male  
319 reproductive organs. Seminiferous tubule and testicular degeneration and atrophy were  
320 reported in male mice receiving intraperitoneal (IP) doses of 3 mg/kg/day (9 mg/m<sup>2</sup>/day,  
321 approximately 17% of clinical recommended dose on a mg/m<sup>2</sup> basis). The testes of rats  
322 receiving 25 mg/kg/day (150 mg/m<sup>2</sup>/day, approximately 3 times the recommended  
323 clinical dose on a mg/m<sup>2</sup> basis) in a 6-month IV study had bilateral degeneration of the  
324 seminiferous epithelium with retained spermatids and atrophy of interstitial cells. In a 6-  
325 month IV dog study, cell degeneration of the epididymis and degeneration of the  
326 seminiferous epithelium in the testes were observed in dogs receiving 0.375 mg/kg/day  
327 (7.5 mg/m<sup>2</sup>/day, approximately 14% of the clinical recommended dose on a mg/m<sup>2</sup>  
328 basis). Ovarian atrophy or degeneration and uterine mucosal apoptosis were observed in  
329 female mice at 75 mg/kg/day (225 mg/m<sup>2</sup>/day, approximately 4-fold of recommended  
330 human dose on a mg/m<sup>2</sup> basis), the only dose administered to female mice. The effect on  
331 human fertility is unknown.

## 332 **14. CLINICAL STUDIES**

333 Seventy-eight (78) pediatric patients with ALL were exposed to Clolar. Seventy (70) of  
334 the patients received the recommended pediatric dose of Clolar 52 mg/m<sup>2</sup> daily for 5 days  
335 as an intravenous (IV) infusion.

### 336 **Dose Escalation Study in Pediatric Patients with Hematologic Malignancies**

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

### 348 **Single-Arm Study in Pediatric ALL**

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

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

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

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

370 Table 3 summarizes results for the pediatric ALL study. Responses were seen in both  
371 pre-B and T-cell immunophenotypes of ALL. The median cumulative dose was 530 mg  
372 (range 29-2815 mg) in 1 (41%), 2 (44%) or 3 or more (15%) cycles. The median number  
373 of cycles was 2 (range 1-12). The median time between cycles was 28 days with a range  
374 of 12 to 55 days.

375 **Table 3: Results in Single-Arm Pediatric ALL**

	<b>N = 61</b>
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) <sup>1</sup>	10.7 (4.3 to 58.6)

376 CR = Complete response

377 CRp = Complete response without platelet recovery

378 <sup>1</sup> Does not include 4 patients who were transplanted (duration of response, including response  
379 after transplant, in these 4 patients was 28.6 to 107.7 weeks).

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

382 Of 35 patients who were refractory to their immediately preceding induction regimen, 6  
383 (17%) achieved a CR or CRp. Of 18 patients who had at least 1 prior hematopoietic stem  
384 cell transplant (HSCT), 5 (28%) achieved a CR or CRp.

385 Among the 12 patients who achieved at least a CRp, 6 patients achieved the best response  
386 after 1 cycle of clofarabine, 5 patients required 2 courses and 1 patient achieved a CR  
387 after 3 cycles of therapy.  
388

## 389 **15. REFERENCES**

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

## 392 **16. HOW SUPPLIED/STORAGE AND HANDLING**

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

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

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

401 Procedures for proper handling and disposal should be utilized. Handling and disposal of  
402 Clolar should conform to guidelines issued for cytotoxic drugs. Several guidelines on this  
403 subject have been published.<sup>1</sup>

## 404 **17. PATIENT COUNSELING INFORMATION**

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

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

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

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

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

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

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

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

430

431 **Manufactured by:**

432 Teva Pharmachemie

433 Swensweg 5

434 Haarlem, The Netherlands

435

436 **Manufactured for:**

437 Genzyme Corporation

438 500 Kendall Street

439 Cambridge, MA 02142

440

441 **Distributed by:**

442 Genzyme Corporation

443 500 Kendall Street

444 Cambridge, MA 02142

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