

## 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<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, 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](http://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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Clolar<sup>®</sup> (clofarabine) injection

1 **1. INDICATIONS AND USAGE**

2 Clolar<sup>®</sup> (clofarabine) Injection is indicated for the treatment of pediatric patients 1 to 21  
3 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior  
4 regimens. This use is based on the induction of complete responses. Randomized trials  
5 demonstrating increased survival or other clinical benefit have not been conducted.

6 **2. DOSAGE AND ADMINISTRATION**

7 **2.1 Recommended Dosage**

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

- 10 • Treatment cycles are repeated following recovery or return to baseline organ  
11 function, approximately every 2 to 6 weeks. The dosage is based on the patient's  
12 body surface area (BSA), calculated using the actual height and weight before the  
13 start of each cycle. To prevent drug incompatibilities, no other medications  
14 should be administered through the same intravenous line.
- 15 • Provide supportive care, such as intravenous fluids, allopurinol, and alkalinize  
16 urine throughout the 5 days of Clolar administration to reduce the effects of tumor  
17 lysis and other adverse events.
- 18 • Discontinue Clolar if hypotension develops during the 5 days of administration.
- 19 • Monitor renal and hepatic function during the 5 days of Clolar administration [see  
20 [WARNINGS AND PRECAUTIONS \(5.6\)](#)].
- 21 • Monitor patients taking medications known to affect blood pressure. Monitor  
22 cardiac function during administration of Clolar.

23 **2.2 Recommended Concomitant Medications and Medications to Avoid**

- 24 • Consider prophylactic anti-emetic medications as Clolar is moderately emetogenic.
- 25 • Consider the use of prophylactic steroids to prevent signs or symptoms of Systemic  
26 Inflammatory Response Syndrome (SIRS) or capillary leak (e.g., hypotension,  
27 tachycardia, tachypnea, and pulmonary edema).
- 28 • Consider avoiding drugs with known renal toxicity during the 5 days of Clolar  
29 administration.
- 30 • Consider avoiding concomitant use of medications known to induce hepatic toxicity.

31 **2.3 Dose Modifications and Reinitiation of Therapy**

- 32 • Hematologic Toxicity
- 33 • Administer subsequent cycles no sooner than 14 days from the starting day of  
34 the previous cycle provided the patient's ANC is  $\geq 0.75 \times 10^9/L$ .
- 35 • If a patient experiences a Grade 4 neutropenia (ANC  $< 0.5 \times 10^9/L$ ) lasting  $\geq 4$   
36 weeks, reduce dose by 25% for the next cycle.

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- 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

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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 90 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  
107 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/m<sup>2</sup>) when used in combination with  
111 etoposide (100 mg/m<sup>2</sup>) and cyclophosphamide (440 mg/m<sup>2</sup>). 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/m<sup>2</sup> daily × 5. The median number of cycles was  
137 2. The median cumulative amount of Clolar<sup>®</sup> 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/m<sup>2</sup>/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.



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**Table 1: Most Commonly Reported (≥ 5% Overall)  
Adverse Events Regardless of Causality 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>					
		N	%	3		4		5	
				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

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<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.



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**Table 1: Most Commonly Reported (≥ 5% Overall)**

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**Adverse Events 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	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	.	.

<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.

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The following less common adverse reactions have been reported in 1-4% of the 115

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pediatric patients with ALL or AML:

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*Gastrointestinal Disorders:* cecitis, pancreatitis

157

*Hepatobiliary Disorders:* hyperbilirubinemia

158

*Immune System Disorders:* hypersensitivity

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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/m<sup>2</sup> among pediatric patients with ALL and AML (n=115).

169 **Table 2: Incidence of Treatment Emergent Laboratory Abnormalities**  
170 **After Clolar<sup>®</sup> 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

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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 ≤ grade 2 within 15 days. Where follow-up data are  
189 available, the majority of bilirubin elevations returned to ≤ 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/m<sup>2</sup> 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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222                    These patients received conditioning regimens that included busulfan,  
223                    melphalan, and/or the combination of cyclophosphamide and total body  
224                    irradiation.

225                    • Skin and subcutaneous tissue disorders: Occurrences of Stevens-Johnson  
226                    Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported  
227                    in patients who were receiving or had recently been treated with Clolar  
228                    and other medications (e.g. allopurinol or antibiotics) known to cause  
229                    these syndromes.

## 230    **7.      DRUG INTERACTIONS**

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

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

### 236    **8.1     Pregnancy**

#### 237    **Pregnancy Category D**

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

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

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

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

### 251    **8.3     Nursing Mothers**

252    It is not known whether clofarabine or its metabolites are excreted in human milk.  
253    Because of the potential for tumorigenicity shown for clofarabine in animal studies and  
254    the potential for serious adverse reactions, women treated with clofarabine should not  
255    nurse. Female patients should be advised to avoid breast-feeding during treatment with  
256    Clolar.

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257 **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/m<sup>2</sup> basis) has been 70 mg/m<sup>2</sup>/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/m<sup>2</sup>/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*.

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296 **12.3 Pharmacokinetics**

297 The population pharmacokinetics of Clolar were studied in 40 pediatric patients aged 2 to  
298 19 years (21 males/19 females) with relapsed or refractory acute lymphoblastic leukemia  
299 (ALL) or acute myelogenous leukemia (AML). At the given 52 mg/m<sup>2</sup> dose, similar  
300 concentrations were obtained over a wide range of body surface areas (BSAs).

301 Clofarabine was 47% bound to plasma proteins, predominantly to albumin. Based on  
302 non-compartmental analysis, systemic clearance and volume of distribution at steady-  
303 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.  
304 No apparent difference in pharmacokinetics was observed between patients with ALL  
305 and AML or between males and females.

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

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

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

314 **13. NONCLINICAL TOXICOLOGY**

315 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

316 Clofarabine has not been tested for carcinogenic potential.

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

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

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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/m<sup>2</sup> 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/m<sup>2</sup>/day IV infusion daily x 5 and  
342 escalated to 70 mg/m<sup>2</sup>/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/m<sup>2</sup> 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/m<sup>2</sup>. As a result of this study, the  
348 recommended dose for subsequent study in pediatric patients was determined to be 52  
349 mg/m<sup>2</sup>/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/m<sup>2</sup> 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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375 of cycles was 2 (range 1-12). The median time between cycles was 28 days with a range  
376 of 12 to 55 days.

377 **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) <sup>1</sup>	10.7 (4.3 to 58.6)

378 CR = Complete response

379 CRp = Complete response without platelet recovery

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

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

384 Of 35 patients who were refractory to their immediately preceding induction regimen, 6  
385 (17%) achieved a CR or CRp. Of 18 patients who had at least 1 prior hematopoietic stem  
386 cell transplant (HSCT), 5 (28%) achieved a CR or CRp.

387 Among the 12 patients who achieved at least a CRp, 6 patients achieved the best response  
388 after 1 cycle of clofarabine, 5 patients required 2 courses and 1 patient achieved a CR  
389 after 3 cycles of therapy. Seven patients received an HSCT after the first dose of  
390 clofarabine. The median time to transplant was 40 days, and median survival was 358  
391 days.

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

## 393 **15 REFERENCES**

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395 hazardous drugs in healthcare settings. 2004. U.S. Department of Health and  
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398 (NIOSH) Publication No. 2004-165.
- 399 2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling  
400 Occupational Exposure to Hazardous Drugs. OSHA, 1999.  
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405 biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh,  
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## 408 **16. HOW SUPPLIED/STORAGE AND HANDLING**

409 Clolar (clofarabine) injection is supplied in single-use flint vials containing 20 mg of  
410 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.<sup>1-4</sup>

## 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

### 440 **Rx Only**

441

#### 442 **Manufactured by:**

443 AAIPharma Services

444 Charleston, SC 29405

445

#### 446 **Manufactured for:**

447 Genzyme Corporation

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Clolar<sup>®</sup> (clofarabine) injection

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448 500 Kendall Street  
449 Cambridge, MA 02142

450

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452 Genzyme Corporation  
453 500 Kendall Street  
454 Cambridge, MA 02142

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455

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Graphic Support: George Dias @ 508-271-2618 or x22618

05-02-11

Size: 1-11/32" x 1-11/32" x 3" (20cc)

Clolar Single-Vial Carton

6139 (05/11) rD

**DRAFT**

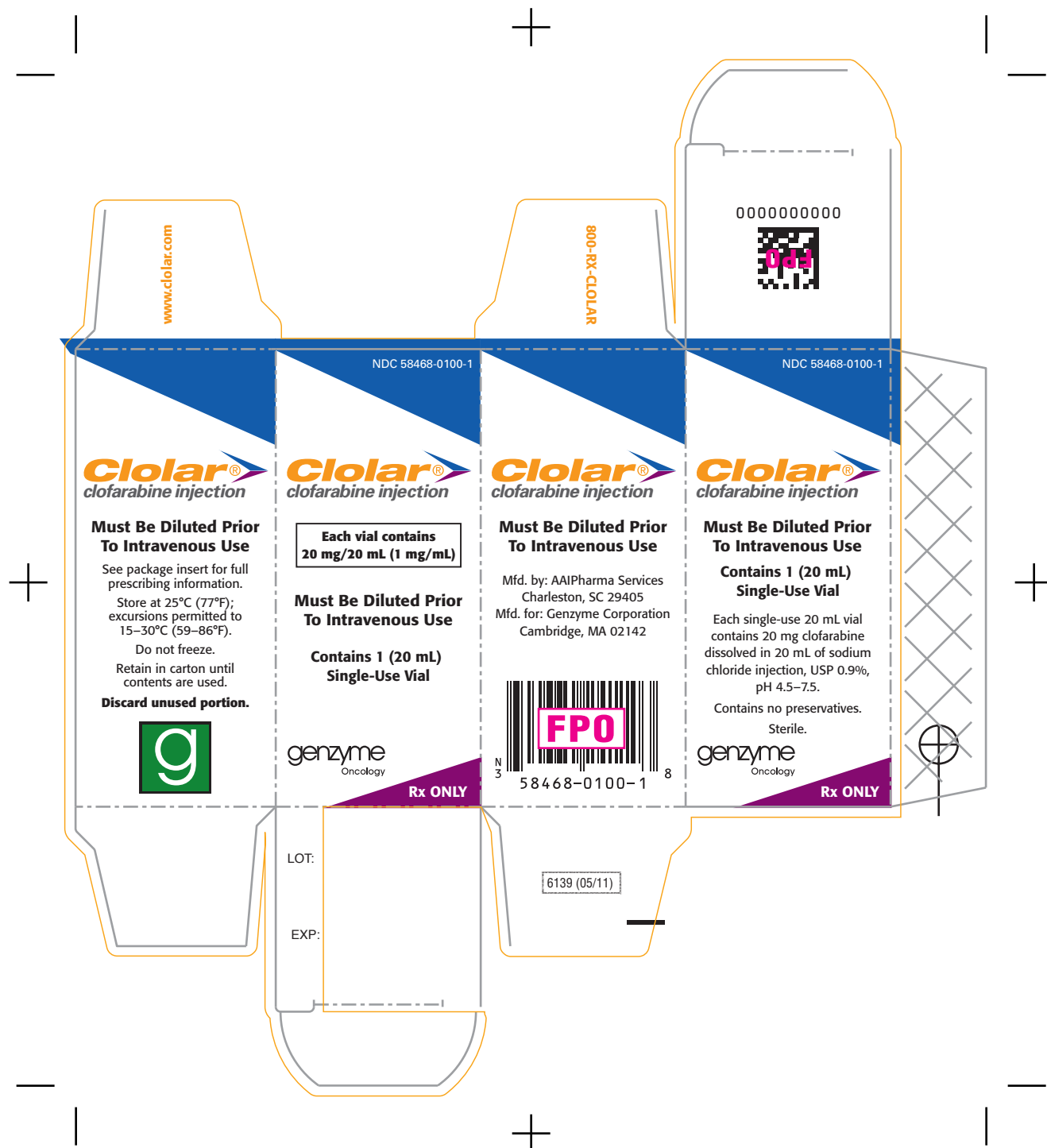
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- PMS 144
- PMS 2425
- Black
- Die Line - Do Not Print
- Varnish Area
- For Position Only
- Color Shifting Ink



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 05-02-11  
 Size: 1-11/32" x 1-11/32" x 3" (20cc)  
 Clolar Single-Vial Carton  
 6139 (05/11) rE

- PMS 2728**
- PMS 144**
- PMS 2425**
- Black**
- Die Line - Do Not Print**
- Varnish Area**
- For Position Only**
- Color Shifting Ink**

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**Graphic Support:** George Dias @ 508-271-2618 or x22618

05-02-11

Size: Width 3.625" x Height 1.25"

Clolar Vial Label

6663 (05/11) rD

**DRAFT**

 **PMS 2728**

 **PMS 144**

 **PMS 2425**

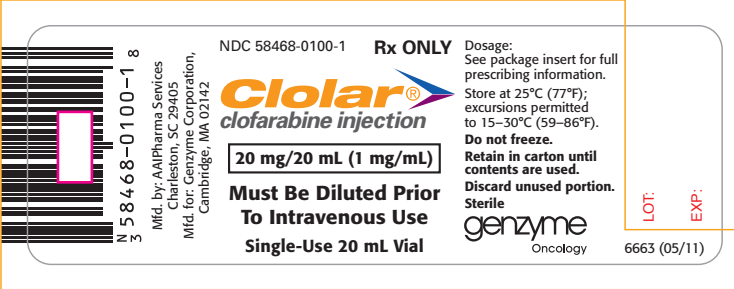
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 **Die Line - Do Not Print**

 **Varnish Area**

 **For Position Only**

 **LOT: & EXP: - Do Not Print**



NDC 58468-0100-1 **Rx ONLY** Dosage:  
See package insert for full  
prescribing information.  
Store at 25°C (77°F);  
excursions permitted  
to 15–30°C (59–86°F).  
**Do not freeze.**  
Retain in carton until  
contents are used.  
Discard unused portion.  
Sterile

**Clolar**<sup>®</sup>  
clofarabine injection

**20 mg/20 mL (1 mg/mL)**

**Must Be Diluted Prior  
To Intravenous Use**

**Single-Use 20 mL Vial**

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Charleston, SC 29405  
Mfd. for: Genzyme Corporation,  
Cambridge, MA 02142

3 N 58468-0100-1 8

LOT:  
EXP: