

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-673**

**Approved Labeling**

1 **CLOLAR™ FOR INTRAVENOUS INFUSION**

2 (clofarabine)

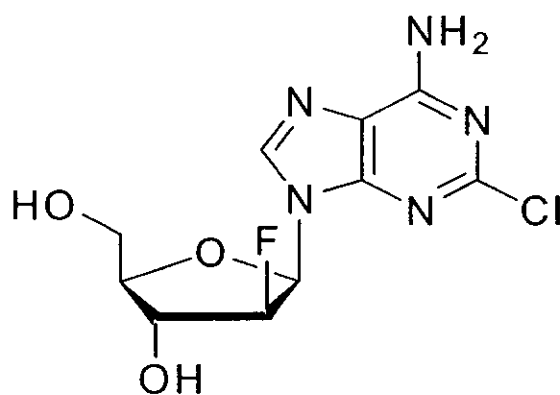
3 **DESCRIPTION**

4 CLOLAR™ For Intravenous Infusion (CLOLAR™; clofarabine) contains clofarabine, a  
5 purine nucleoside anti-metabolite. CLOLAR™ (1 mg/mL) is supplied in a 20 mL, single-use  
6 vial. The 20 mL vial contains 20 mg clofarabine formulated in 20 mL unbuffered normal  
7 saline (comprised of Water for Injection, USP, and Sodium Chloride USP). The pH range of  
8 the solution is 4.5 to 7.5. The solution is clear and practically colorless, and free from  
9 foreign matter.

10

11 The chemical structure of clofarabine is 2-chloro-9-(2-deoxy-2-fluoro-β-D-  
12 arabinofuranosyl)-9H-purin-6-amine. The molecular formula of clofarabine is  
13 C<sub>10</sub>H<sub>11</sub>ClFN<sub>5</sub>O<sub>3</sub> with a molecular weight of 303.68.

14



15 Clofarabine

16

17

18

18 **CLINICAL PHARMACOLOGY**

19 **Mechanism of Action:** Clofarabine is sequentially metabolized intracellularly to the 5'-  
20 monophosphate metabolite by deoxycytidine kinase and mono- and di-phosphokinases to the  
21 active 5'-triphosphate metabolite. Clofarabine has high affinity for the activating  
22 phosphorylating enzyme, deoxycytidine kinase, equal to or greater than that of the natural  
23 substrate, deoxycytidine. Clofarabine inhibits DNA synthesis by decreasing cellular  
24 deoxynucleotide triphosphate pools through an inhibitory action on ribonucleotide reductase,  
25 and by terminating DNA chain elongation and inhibiting repair through incorporation into  
26 the DNA chain by competitive inhibition of DNA polymerases. The affinity of clofarabine  
27 triphosphate for these enzymes is similar to or greater than that of deoxyadenosine  
28 triphosphate. In preclinical models, clofarabine has demonstrated the ability to inhibit DNA  
29 repair by incorporation into the DNA chain during the repair process. Clofarabine 5'-  
30 triphosphate also disrupts the integrity of mitochondrial membrane, leading to the release of  
31 the pro-apoptotic mitochondrial proteins, cytochrome C and apoptosis-inducing factor,  
32 leading to programmed cell death.

33

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

35

36 *Human Pharmacokinetics:* The population pharmacokinetics of CLOLAR™ were studied in  
37 40 pediatric patients aged 2 to 19 years (21 males/19 females) with relapsed or refractory  
38 ALL or AML. At the given 52 mg/m<sup>2</sup> dose, similar concentrations were obtained over a  
39 wide range of BSAs. Clofarabine was 47% bound to plasma proteins, predominantly to  
40 albumin. Based on non-compartmental analysis, systemic clearance and volume of  
41 distribution at steady-state were estimated to be 28.8 L/h/m<sup>2</sup> and 172 L/m<sup>2</sup>, respectively. The  
42 terminal half-life was estimated to be 5.2 hours. No apparent difference in pharmacokinetics  
43 was observed between patients with ALL and AML or between males and females.

44

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

47

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

51

52 Although no clinical drug-drug interaction studies have been conducted to date, on the basis  
53 of the *in vitro* studies, cytochrome p450 inhibitors and inducers are unlikely to affect the  
54 metabolism of clofarabine. The effect of clofarabine on the metabolism of cytochrome p450  
55 substrates has not been studied. The pharmacokinetics of clofarabine have not been  
56 evaluated in patients with renal or hepatic dysfunction.

57

## 58 **CLINICAL STUDIES**

59 Sixty-six (66) pediatric ALL patients were exposed to CLOLAR™. Fifty-eight (58) of the  
60 patients received the recommended pediatric dose of CLOLAR™ 52 mg/m<sup>2</sup> daily × 5 as an  
61 intravenous infusion (IVI).

62

63 The safety and efficacy of CLOLAR™ were evaluated in pediatric patients with refractory or  
64 relapsed hematologic malignancies in an open-label, dose-escalation, noncomparative study.  
65 The starting dose of CLOLAR™ was 11.25 mg/m<sup>2</sup>/day IVI daily × 5 and escalated to 70  
66 mg/m<sup>2</sup>/day IVI daily × 5. This dosing schedule was repeated every 2 to 6 weeks depending  
67 on toxicity and response. Nine of 17 ALL patients were treated with CLOLAR™ 52 mg/m<sup>2</sup>  
68 daily × 5. In the 17 ALL patients there were 2 complete remissions (12.5%) and 2 partial  
69 remissions (12.5%) at varying doses. Dose-limiting toxicities (DLTs) in this study were

70 reversible hyperbilirubinemia and elevated transaminase levels and skin rash, experienced at  
71 70 mg/m<sup>2</sup>. As a result of this study, the recommended dose for subsequent study in pediatric  
72 patients was determined to be 52 mg/m<sup>2</sup>/day for 5 days.

73

#### 74 **Single Arm Study in Pediatric ALL**

75 A single arm study was conducted in relapsed/refractory pediatric patients with ALL at a  
76 single dose. All patients had disease that had relapsed after and/or was refractory to two or  
77 more prior therapies. Most patients, 46/49 (93.8%), had received 2 to 4 prior regimens and  
78 15/49 (30.6%) of the patients had undergone at least 1 prior transplant. The median age of  
79 the treated patients was 12 years. There were more males, 29/49 (59.2%), than females,  
80 20/49 (40.8%). Most of the patients were either Caucasian (n=20, 40.8%) or Hispanic (n=20,  
81 40.8%), with 12.2% African-American (n=6), and 6.1% Other race (n=3). All patients  
82 received a dose of 52 mg/m<sup>2</sup> daily × 5 IVI. There was no dose modification during the  
83 remission induction phase of treatment (maximum of 2 cycles). Doses could be modified  
84 (reduced/delayed) during the post-induction phase. There was no dose escalation. The  
85 planned study endpoint was the rate of Complete Remission (CR), defined as no evidence of  
86 circulating blasts or extramedullary disease, an M1 bone marrow (<5% blasts), and recovery  
87 of peripheral counts (platelets > 100 × 10<sup>9</sup> L and absolute neutrophil count (ANC) > 1.0 ×  
88 10<sup>9</sup> L) and Complete Remission in the Absence of Total Platelet Recovery (CRp), defined as  
89 meeting all criteria for CR except for recovery of platelet counts to > 100 × 10<sup>9</sup> L. Partial  
90 Response (PR) was also determined, defined as complete disappearance of circulating blasts,  
91 an M2 bone marrow (> 5% and < 25% blasts), and appearance of normal progenitor cells or  
92 an M1 marrow that did not qualify for CR or CRp. Transplantation rate was not a study  
93 endpoint.

94

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

97

98 Table 1 summarizes results for the pediatric ALL study. Responses were seen in both pre-B  
99 and T-cell immunophenotypes of ALL. The median cumulative dose was 540 mg (range 29-  
100 1905 mg) in 1 (42.9%), 2 (38.8%) or 3 or more (18.4%) cycles.

101

102

**Table 1: Results in Pediatric ALL Study**

n=49			
Responses	n	%	95% CI
CR	6	12.2	4.6 to 24.8
CRp	4	8.2	2.3 to 19.6
PR	5	10.2	3.4 to 22.2

103

104 Of the 15 responding pediatric ALL patients, 6 had post-clofarabine bone marrow  
105 transplantation, so that duration of response could not be determined. In the 9 responding  
106 patients who were not transplanted, the response durations for CR were 43, 50, 82, 93+, and  
107 160+ days; for CRp the response duration was 32 days; and for PR the response durations  
108 were 7, 16, and 21 days.

109

**110 INDICATIONS AND USAGE**

111 CLOLAR™ is indicated for the treatment of pediatric patients 1 to 21 years old with relapsed  
112 or refractory acute lymphoblastic leukemia after at least two prior regimens. This use is  
113 based on the induction of complete responses. Randomized trials demonstrating increased  
114 survival or other clinical benefit have not been conducted.

115

116 **CONTRAINDICATIONS**

117 None

118

119 **WARNINGS**

120 CLOLAR™ should be administered under the supervision of a qualified physician  
121 experienced in the use of antineoplastic therapy. Suppression of bone marrow function  
122 should be anticipated. This is usually reversible and appears to be dose dependent. The use  
123 of CLOLAR™ is likely to increase the risk of infection, including severe sepsis, as a result of  
124 bone marrow suppression. Administration of CLOLAR™ results in a rapid reduction in  
125 peripheral leukemia cells. For this reason, patients undergoing treatment with CLOLAR™  
126 should be evaluated and monitored for signs and symptoms of tumor lysis syndrome, as well  
127 as signs and symptoms of cytokine release (eg, tachypnea, tachycardia, hypotension,  
128 pulmonary edema) that could develop into systemic inflammatory response syndrome  
129 (SIRS)/capillary leak syndrome, and organ dysfunction. Physicians are encouraged to give  
130 continuous IV fluids throughout the five days of CLOLAR™ administration to reduce the  
131 effects of tumor lysis and other adverse events. Allopurinol should be administered if  
132 hyperuricemia is expected. CLOLAR™ should be discontinued immediately in the event of  
133 clinically significant signs or symptoms of SIRS or capillary leak syndrome, either of which  
134 can be fatal, and use of steroids, diuretics, and albumin considered. CLOLAR™ can be re-  
135 instituted when the patient is stable, generally at a lower dose.

136

137 Severe bone marrow suppression, including neutropenia, anemia, and thrombocytopenia, has  
138 been observed in patients treated with CLOLAR™. At initiation of treatment, most patients  
139 in the clinical studies had hematological impairment as a manifestation of leukemia. Because  
140 of the pre-existing immunocompromised condition of these patients and prolonged  
141 neutropenia that can result from treatment with CLOLAR™, patients are at increased risk for

142 severe opportunistic infections. Careful hematological monitoring during therapy is  
143 important, and hepatic and renal function should be assessed prior to and during treatment  
144 with CLOLAR™ because of CLOLAR™'s predominantly renal excretion and because the  
145 liver is a target organ for CLOLAR™ toxicity. The respiratory status and blood pressure  
146 should be closely monitored during infusion of CLOLAR™.

147

#### 148 **Hepatic and Renal Impairment**

149 CLOLAR™ has not been studied in patients with hepatic or renal dysfunction. Its use in  
150 such patients should be undertaken only with the greatest caution.

151

#### 152 **Pregnancy – Teratogenic Effects: Pregnancy Category D**

153 CLOLAR™ (clofarabine) may cause fetal harm when administered to a pregnant woman.  
154 Clofarabine was teratogenic in rats and rabbits. Developmental toxicity (reduced fetal body  
155 weight and increased post-implantation loss) and increased incidences of malformations and  
156 variations (gross external, soft tissue, skeletal and retarded ossification) were observed in rats  
157 receiving 54 mg/m<sup>2</sup>/day (approximately equivalent to the recommended clinical dose on a  
158 mg/m<sup>2</sup> basis), and in rabbits receiving 12 mg/m<sup>2</sup>/day (approximately 23% of the  
159 recommended clinical dose on a mg/m<sup>2</sup> basis).

160

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

164

165 Women of childbearing potential should be advised to avoid becoming pregnant while  
166 receiving treatment with clofarabine.



167

168 **PRECAUTIONS**

169 **Information for Patients and Caregivers**

170 Physicians are advised to discuss the following with patients to whom CLOLAR™ will be  
171 administered and patient caregivers, as appropriate.

172

173 ***Dehydration/Hypotension***

174 Patients receiving CLOLAR™ may experience vomiting and diarrhea; they should therefore  
175 be advised regarding appropriate measures to avoid dehydration. Patients should be  
176 instructed to seek medical advice if they experience symptoms of dizziness, lightheadedness,  
177 fainting spells, or decreased urine output. CLOLAR™ administration should be stopped if  
178 the patient develops hypotension for any reason during the 5 days of administration. If  
179 hypotension is transient and resolves without pharmacological intervention, CLOLAR™  
180 treatment can be re-instituted, generally at a lower dose.

181

182 ***Concomitant Medications***

183 Since CLOLAR™ is excreted primarily by the kidneys, drugs with known renal toxicity  
184 should be avoided during the 5 days of CLOLAR™ administration. In addition, since the  
185 liver is a known target organ for CLOLAR™ toxicity, concomitant use of medications known  
186 to induce hepatic toxicity should also be avoided. Patients taking medications known to  
187 affect blood pressure or cardiac function should be closely monitored during administration  
188 of CLOLAR™.

189

190 **Pregnancy/Nursing**

191 All patients should be advised to use effective contraceptive measures to prevent pregnancy.  
192 Female patients should be advised to avoid breast feeding during treatment with CLOLAR™.

193

194 **Laboratory Tests**

195 Complete blood counts and platelet counts should be obtained at regular intervals during  
196 CLOLAR™ therapy, and more frequently in patients who develop cytopenias. In addition  
197 liver and kidney function should be monitored frequently during the 5 days of CLOLAR™  
198 administration.

199

200 **Drug Interactions**

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

205

206 **Drug/Laboratory Tests Interactions**

207 There are no known clinically significant interactions of CLOLAR™ with other medications  
208 or laboratory tests. No formal drug/laboratory test interaction studies have been conducted  
209 with CLOLAR™.

210

211 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

212 **Carcinogenesis**

213 Clofarabine has not been tested for carcinogenic potential.

214

215 **Mutagenesis**

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

219

220 **Impairment of Fertility**

221 Studies in mice, rats, and dogs have demonstrated dose-related adverse effects on male  
222 reproductive organs. Seminiferous tubule and testicular degeneration and atrophy were  
223 reported in male mice receiving IP doses of 3 mg/kg/day (9 mg/m<sup>2</sup>/day, approximately 17%  
224 of clinical recommended dose on a mg/m<sup>2</sup> basis). The testes of rats receiving 25 mg/kg/day  
225 (150 mg/m<sup>2</sup>/day, approximately 3 times the recommended clinical dose on a mg/m<sup>2</sup> basis) in  
226 a 6-month IV study had bilateral degeneration of the seminiferous epithelium with retained  
227 spermatids and atrophy of interstitial cells. In a 6-month IV dog study, cell degeneration of  
228 the epididymis and degeneration of the seminiferous epithelium in the testes were observed  
229 in dogs receiving 0.375 mg/kg/day (7.5 mg/m<sup>2</sup>/day, approximately 14% of the clinical  
230 recommended dose on a mg/m<sup>2</sup> basis). Ovarian atrophy or degeneration and uterine mucosal  
231 apoptosis were observed in female mice at 75 mg/kg/day (225 mg/m<sup>2</sup>/day, approximately  
232 4 fold of recommended human dose on a mg/m<sup>2</sup> basis), the only dose administered to female  
233 mice. The effect on human fertility is unknown.

234

235 **Pregnancy**

236 **Teratogenic Effects: Pregnancy Category D**

237 See **WARNINGS**.

238

239 **Nursing Mothers**

240 It is not known whether clofarabine or its metabolites are excreted in human milk. Because  
241 of the potential for tumorigenicity shown for clofarabine in animal studies and the potential  
242 for serious adverse reactions, women treated with clofarabine should not nurse.

243

244 **Other Special Population: Adults**

245 Safety and efficacy have not been established in adults. One study was performed in highly  
246 refractory and/or relapsed adult patients with hematologic malignancies. The Phase 2 dose of  
247 CLOLAR™ was determined to be 40 mg/m<sup>2</sup>/day administered as a 1- to 2-hour IVI daily × 5  
248 every 28 days.

249

250 **ADVERSE REACTIONS**

251 One hundred thirteen (113) pediatric patients with ALL (67) or AML (46) were exposed to  
252 CLOLAR™. Ninety six (96) of the pediatric patients treated in clinical trials received the  
253 recommended dose of CLOLAR™ 52 mg/m<sup>2</sup> daily × 5.

254

255 The most common adverse effects after CLOLAR™ treatment, regardless of causality, were  
256 gastrointestinal tract symptoms, including vomiting, nausea, and diarrhea; hematologic

257 effects, including anemia, leukopenia, thrombocytopenia, neutropenia, and febrile  
258 neutropenia; and infection.

259

260 Table 2 lists adverse events by System Organ Class regardless of causality, including severe  
261 or life threatening events (NCI CTC grade 3 or grade 4), reported in  $\geq 10\%$  of the 96 patients  
262 in the 52 mg/m<sup>2</sup>/day dose group. More detailed information and follow-up of certain events  
263 is given below.

264

265

<b>Table 2: Most Commonly Reported (&gt;=10% Overall) Adverse Events by System Organ Class (N=96)</b>						
System Organ Class Adverse Event <sup>1</sup>	52 mg/m <sup>2</sup> (N=96)					
	Total		Grade 3		Grade 4	
	N	%	n	%	n	%
<b>Blood and Lymphatic System Disorders</b>						
Febrile neutropenia	55	57	51	53	3	3
Neutropenia	10	10	3	3	7	7
Transfusion reaction	10	10	3	3	.	.
<b>Cardiac Disorders</b>						
Tachycardia NOS	33	34	6	6	.	.
<b>Gastrointestinal Disorders</b>						
Abdominal pain NOS	35	36	7	7	.	.
Constipation	20	21	.	.	.	.
Diarrhea NOS	51	53	10	10	.	.
Gingival bleeding	14	15	7	7	1	1
Nausea	72	75	14	15	1	1
Sore throat NOS	13	14	.	.	.	.
Vomiting NOS	80	83	8	8	1	1
<b>General Disorders and Administration Site Conditions</b>						
Edema NOS	19	20	1	1	2	2
Fatigue	35	36	3	3	1	1
Injection site pain	13	14	1	1	.	.
Lethargy	11	11	.	.	.	.
Mucosal inflammation NOS	17	18	3	3	.	.
Pain NOS	18	19	6	6	1	1
Pyrexia	39	41	15	16	.	.
Rigors	36	38	3	3	.	.
<b>Hepato-Biliary Disorders</b>						
Hepatomegaly	14	15	8	8	.	.
Jaundice NOS	14	15	2	2	.	.
<b>Infections and Infestations</b>						
Bacteremia	10	10	10	10	.	.
Cellulitis	11	11	9	9	.	.
Herpes simplex	11	11	6	6	.	.
Oral candidiasis	12	13	2	2	.	.
Pneumonia NOS	10	10	5	5	2	2
Sepsis NOS	14	15	7	7	7	7
Staphylococcal infection NOS	12	13	10	10	.	.
<b>Investigations</b>						
Weight decreased	10	10	1	1	.	.

<b>Table 2: Most Commonly Reported (<math>\geq 10\%</math> Overall) Adverse Events by System Organ Class (N=96) (continued)</b>						
<b>System Organ Class Adverse Event<sup>1</sup></b>	<b>52 mg/m<sup>2</sup> (N=96)</b>					
	<b>Total</b>		<b>Grade 3</b>		<b>Grade 4</b>	
	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>
<b>Metabolism and Nutrition Disorders</b>						
Anorexia	30	31	5	5	7	7
Appetite decreased NOS	11	11	.	.	.	.
<b>Musculoskeletal, Connective Tissue and Bone Disorders</b>						
Arthralgia	11	11	3	3	.	.
Back pain	12	13	3	3	.	.
Myalgia	13	14	.	.	.	.
Pain in limb	28	29	5	5	.	.
<b>Nervous System Disorders</b>						
Dizziness (exc vertigo)	15	16	.	.	.	.
Headache NOS	44	46	4	4	.	.
Somnolence	10	10	1	1	.	.
Tremor NEC	10	10	.	.	.	.
<b>Psychiatric Disorders</b>						
Anxiety NEC	21	22	2	2	.	.
Depression NEC	11	11	1	1	.	.
Irritability	11	11	1	1	.	.
<b>Renal and Urinary Disorders</b>						
Hematuria	16	17	2	2	.	.
<b>Respiratory, Thoracic and Mediastinal Disorders</b>						
Cough	18	19	.	.	.	.
Dyspnea NOS	12	13	4	4	2	2
Epistaxis	30	31	14	15	.	.
Pleural effusion	10	10	3	3	2	2
Respiratory distress	13	14	6	6	5	5
<b>Skin and Subcutaneous Tissue Disorders</b>						
Contusion	11	11	1	1	.	.
Dermatitis NOS	39	41	7	7	.	.
Dry skin	10	10	1	1	.	.
Erythema NEC	17	18	.	.	.	.
Palmar-plantar erythrodysesthesia syndrome	12	13	4	4	.	.
Petechiae	28	29	7	7	.	.
Pruritus NOS	45	47	1	1	.	.
<b>Vascular Disorders</b>						
Flushing	17	18	.	.	.	.
Hypertension NOS	11	11	4	4	.	.
Hypotension NOS	28	29	12	13	7	7

<sup>1</sup> Patients with more than one occurrence of the same preferred term are counted only once.  
Grade 4 includes deaths (Grade 5).

267

268 **Cardiovascular**

269 The most frequently reported cardiac disorder was tachycardia (34%), which was however,  
270 already present in 27.4% of patients at study entry. Most of the cardiac adverse events were  
271 reported in the first 2 cycles.

272

273 Pericardial effusion was a frequent finding in these patients on post-treatment studies, [19/55  
274 (35%)]. The effusion was almost always minimal to small and in no cases had hemodynamic  
275 significance.

276

277 Left ventricular systolic dysfunction (LVSD) was also noted. Fifteen out of fifty-five  
278 patients [15/55 (27%)] had some evidence of LVSD after study entry. In most cases where  
279 subsequent follow-up data were available, the LVSD appeared to be transient. The exact  
280 etiology for the LVSD is unclear because of previous therapy or serious concurrent illness.

281

282 **Hepatic**

283 Hepato-biliary toxicities were frequently observed in pediatric patients during treatment with  
284 CLOLAR™. Grade 3 or 4 elevated AST occurred in 38% of patients and grade 3 or 4  
285 elevated ALT occurred in 44% of patients. Grade 3 or 4 elevated bilirubin occurred in 15%  
286 of patients, with 2 cases of grade 4 hyperbilirubinemia resulting in treatment discontinuation.

287

288 For patients with follow-up data, elevations in AST and ALT were transient and typically of  
289 <2 weeks duration. The majority of AST and ALT elevations occurred within 1 week of  
290 CLOLAR™ administration and returned to baseline or ≤ grade 2 within several days.  
291 Although less common, elevations in bilirubin appeared to be more persistent. Where



292 follow-up data are available, the median time to recovery from grade 3 and grade 4  
293 elevations in bilirubin to  $\leq$  grade 2 was 6 days.

294

295 **Infection**

296 At baseline 47% of the patients had 1 or more concurrent infections. A total of 85% of  
297 patients experienced at least 1 infection after CLOLAR™ treatment, including fungal, viral  
298 and bacterial infections.

299

300 **Renal**

301 The most prevalent renal toxicity was elevated creatinine. Grade 3 or 4 elevated creatinine  
302 occurred in 6% of patients. Nephrotoxic medications, tumor lysis, and tumor lysis with  
303 hyperuricemia may contribute to renal toxicity.

304

305 **Systemic Inflammatory Response Syndrome (SIRS)/Capillary Leak Syndrome**

306 Capillary leak syndrome or SIRS (signs and symptoms of cytokine release, e.g., tachypnea,  
307 tachycardia, hypotension, pulmonary edema) occurred in 4 pediatric patients overall (3 ALL,  
308 1 AML). Several patients developed rapid onset of respiratory distress, hypotension,  
309 capillary leak (pleural and pericardial effusions), and multi-organ failure. Close monitoring  
310 for this syndrome and early intervention are recommended. The use of prophylactic steroids  
311 (eg, 100 mg/m<sup>2</sup> hydrocortisone on Days 1 through 3) may be of benefit in preventing signs or  
312 symptoms of SIRS or capillary leak. Physicians should be alert to early indications of this  
313 syndrome and should immediately discontinue CLOLAR™ administration if they occur and  
314 provide appropriate supportive measures. After the patient is stabilized and organ function  
315 has returned to baseline, re-treatment with CLOLAR™ can be considered at a lower dose.

316

317 **Overdosage**

318 There were no known overdoses of CLOLAR™. The highest daily dose administered to a  
319 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  
320 patients). The toxicities included in these 2 patients included grade 4 hyperbilirubinemia,  
321 grade 2 and 3 vomiting, and grade 3 maculopapular rash.

322

323 **DOSAGE AND ADMINISTRATION**

324 **Recommended Dose**

325 CLOLAR™ should be diluted per instructions below with 5% dextrose injection, USP or  
326 0.9% sodium chloride injection, USP prior to intravenous infusion (IVI).

327

328 The recommended pediatric dose and schedule is 52 mg/m<sup>2</sup> administered by intravenous  
329 infusion (IVI) over 2 hours daily for 5 consecutive days. Treatment cycles are repeated  
330 following recovery or return to baseline organ function, approximately every 2 to 6 weeks.  
331 The dosage is based on the patient's body surface area (BSA), calculated using the actual  
332 height and weight before the start of each cycle. To prevent drug incompatibilities, no other  
333 medications should be administered through the same intravenous line.

334

335 CLOLAR™ has not been studied in patients with hepatic or renal dysfunction. Its use in  
336 such patients should be undertaken only with the greatest caution.

337

338 Physicians are encouraged to give continuous IV fluids throughout the 5 days of CLOLAR™  
339 administration to reduce the effects of tumor lysis and other adverse events. The use of  
340 prophylactic steroids (e.g., 100 mg/m<sup>2</sup> hydrocortisone on Days 1 through 3) may be of

341 benefit in preventing signs or symptoms of SIRS or capillary leak (e.g., hypotension). If  
342 patients show early signs or symptoms of SIRS or capillary leak (e.g., hypotension), the  
343 physician should immediately discontinue CLOLAR™ administration and provide  
344 appropriate supportive measures. Close monitoring of renal and hepatic function during the  
345 5 days of CLOLAR™ administration is advised. If substantial increases in creatinine or  
346 bilirubin are noted, physicians should immediately discontinue administration of  
347 CLOLAR™. CLOLAR™ should be re-instituted when the patient is stable and organ  
348 function has returned to baseline, possibly at a lower dose. If hyperuricemia is anticipated  
349 (tumor lysis), patients should prophylactically receive allopurinol.

350

351

#### 352 **STORAGE AND HANDLING**

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

355

356 CLOLAR™ should be filtered through a sterile 0.2 µm syringe filter and then further diluted  
357 with 5% dextrose injection USP or 0.9% sodium chloride injection USP prior to intravenous  
358 infusion (IVI). The resulting admixture may be stored at room temperature, but must be used  
359 within 24 hours of preparation.

360

#### 361 **HOW SUPPLIED**

362 CLOLAR™ is formulated at a concentration of 1 mg/mL in sodium chloride (9 mg/mL),  
363 USP, and water for injection, USP, quantity sufficient (qs) to 1 mL. CLOLAR™ is supplied  
364 in 20 mL flint vials in a box of 4 (NDC 58468-0100-2). The 20 mL flint vials contain 20 mL  
365 (20 mg) of solution. The pH range of the solution is 4.5 to 7.5. The solution is clear and  
366 practically colorless, is preservative free, and is free from foreign matter.

367

368 **Rx only**

369 **U.S. Patents:** 4,751,221; 4, 918,179; 5,384,310; 5,661,136, 6,680,382 B2.

370 Other patents pending.

371

372 **NAME AND ADDRESS OF MANUFACTURER**

373 **Manufactured by:** AAI Development Services

374 Charleston, SC 29405

375 **Manufactured for:** Genzyme Corporation

376 4545 Horizon Hill Blvd

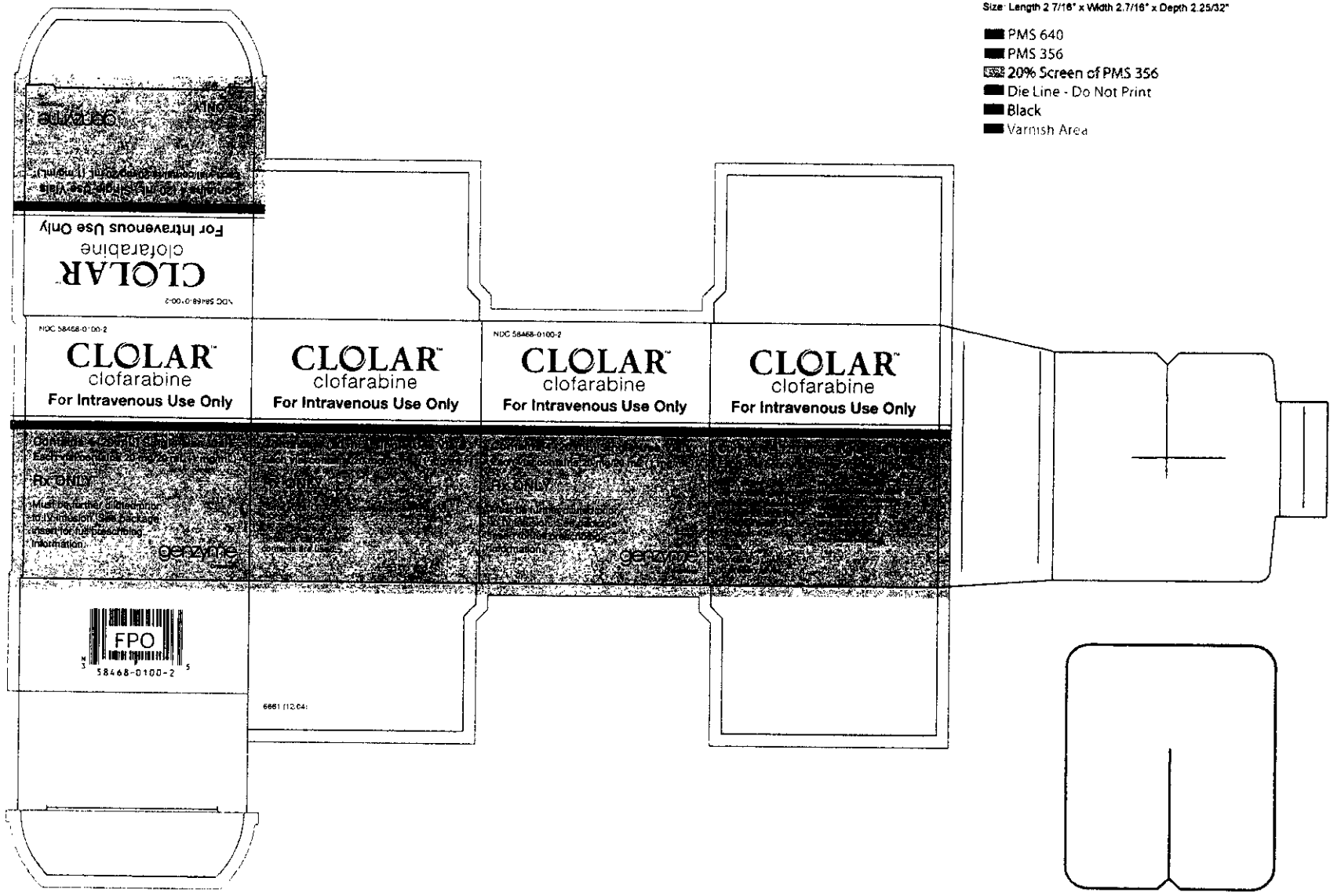
377 San Antonio, TX 78229

378 **Distributed by:** Genzyme Corporation

379 500 Kendall Street

380 Cambridge, MA 02142

381



Graphic Support: George D. @ X22618  
 6681 (12/04) R4  
 12-21-04, CLOLAR Carton  
 Size: Length 2 7/16" x Width 2.716" x Depth 2.25/32"

- PMS 640
- PMS 356
- ▨ 20% Screen of PMS 356
- Die Line - Do Not Print
- Black
- Varnish Area

CLOLAR  
 clofarabine  
 For Intravenous Use Only  
 NDC 58468-0100-2

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Rx ONLY  
 Must be used under the supervision of a physician. See package insert for full prescribing information.  
 genzyme

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 Must be used under the supervision of a physician. See package insert for full prescribing information.  
 genzyme

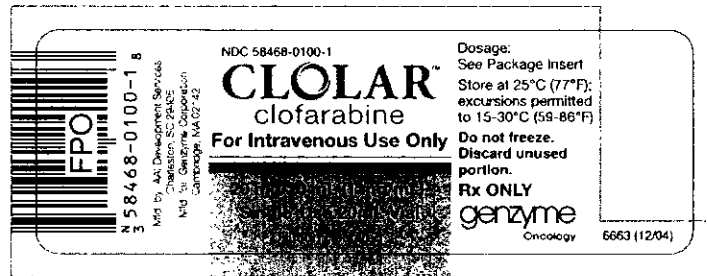
Rx ONLY  
 Must be used under the supervision of a physician. See package insert for full prescribing information.  
 genzyme

FPO  
 58468-0100-2

6681 (12/04)

Graphic Support: George D. @ X22618  
6663 (12/04) R6  
12-21-04, CLOLAR Vial Label  
Size: Width 3.625 " x Height 1.25"

- PMS 640
- 20% Screen of PMS 356
- PMS 356
- Die Line - Do Not Print
- Black
- Varnish & Knockout area



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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Robert Temple  
12/28/04 04:48:55 PM

**Cottrell, Christy**

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**From:** ONSlist [ONSlist@ons.org]  
**Sent:** Tuesday, January 04, 2005 8:34 AM  
**To:** ONS-l@Onsbulkmail.ons.org  
**Subject:** FDA Approves Clolar for Pediatric ALL

*In collaboration with the Food and Drug Administration (FDA), and as a service to our members, the Oncology Nursing Society will provide information about newly approved therapies for patients with cancer. This will allow the FDA to inform ONS members of recent approvals in a timely manner. Included in the email from the FDA will be a link to the product label, which will provide the relevant clinical information on the indication, contraindications, dosing, and safety. The following is a message from Dr. Richard Pazdur:*

To: ONS membership

From: Richard Pazdur, M.D.  
 Director, Division of Oncology Drug Products,  
 Center for Drug Evaluation and Research, FDA

On December 28, 2004 the U. S. Food and Drug Administration granted accelerated approval for clofarabine (Clolar<sup>TM</sup> For Intravenous Infusion, Genzyme Corporation), a purine nucleoside antimetabolite, for treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens. The approval of this indication is based on the induction of complete responses. Clinical studies demonstrating increased survival or other clinical benefit have not been conducted. Approval was granted under accelerated approval regulations that require the applicant to conduct and complete additional clinical studies to confirm clinical benefit.

Efficacy and safety were demonstrated in a single multicenter trial that enrolled 49 patients. Most patients had received 2 to 4 prior regimens and 15/49 (31%) had undergone at least one transplant. The median age was 12 years. Clofarabine was given at a dose of 52 mg/m<sup>2</sup>, intravenously, over 2 hours daily x 5 repeated every 2 to 6 weeks following recovery or return to baseline organ function. The study endpoints were the rate of complete response (CR) and the rate of complete response without platelet recovery (CRp). The former was defined as no evidence of circulating blasts or extramedullary disease, an M1 bone marrow, and recovery of peripheral platelet and absolute neutrophil counts; the latter was defined as meeting all criteria for CR except for platelet count recovery. Response rates were determined by an Independent Response Review Panel (IRRP).

Six patients (12%) achieved a CR and 4 patients (8%) achieved a CRp, and 5 patients (10%) achieved a PR. Of the 15 responding patients, 6 had post-clofarabine bone marrow transplantation. Hence, response durations could not be determined. In the patients who were not transplanted, the response durations for CR were 43, 50, 82, 93+, and 160+ days; for CRp the response duration was 32 days.

The principal clofarabine toxicities were nausea, vomiting, hematologic toxicity, febrile neutropenia, hepatobiliary toxicity, infections and renal toxicity. Clofarabine can produce systemic inflammatory response syndrome/capillary leak syndrome (SIRS), manifested by the rapid development of tachypnea, tachycardia, hypotension, shock, and multi-organ failure. Cardiac toxicity was characterized as left ventricular systolic dysfunction; tachycardia may also occur.

Full prescribing information, including clinical trial information, safety, dosing, drug-drug interactions



and contraindications is available at [www.fda.gov/cder/foi/label/2004/021673lbl.pdf](http://www.fda.gov/cder/foi/label/2004/021673lbl.pdf).

To unsubscribe from this email or change your preferences, visit <https://onsopcontent.ons.org/profile/>. Log in, select "Change your mailing, e-mailing, and privacy preferences", and follow the instructions on the screen. If you do not have a user name and password, you will need to create one. You may also unsubscribe by emailing [customer.service@ons.org](mailto:customer.service@ons.org) or calling 412-859-6100. Please include your full name and email address with your request.

We respect your privacy. Read our [privacy statement](#). Click [here](#) to review a list of FAQs regarding ONS and Internet security and emails.

This email was sent by the Oncology Nursing Society, 125 Enterprise Drive, Pittsburgh, PA 15275. 866-257-4ONS, 412-859-6100, [customer.service@ons.org](mailto:customer.service@ons.org), <http://www.ons.org>.

1 **CLOLAR™ FOR INTRAVENOUS INFUSION**

2 (clofarabine)

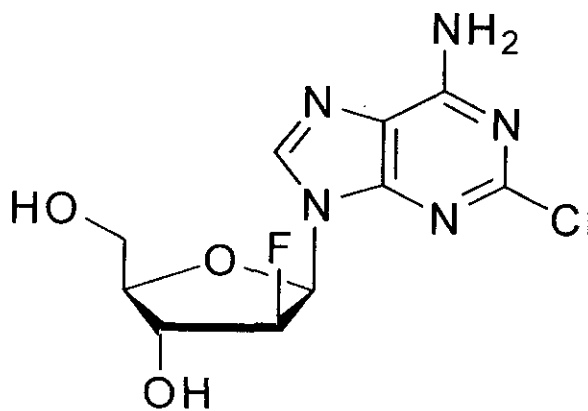
3 **DESCRIPTION**

4 CLOLAR™ For Intravenous Infusion (CLOLAR™; clofarabine) contains clofarabine, a  
5 purine nucleoside anti-metabolite. CLOLAR™ (1 mg/mL) is supplied in a 20 mL, single-use  
6 vial. The 20 mL vial contains 20 mg clofarabine formulated in 20 mL unbuffered normal  
7 saline (comprised of Water for Injection, USP, and Sodium Chloride USP). The pH range of  
8 the solution is 4.5 to 7.5. The solution is clear and practically colorless, and free from  
9 foreign matter.

10

11 The chemical structure of clofarabine is 2-chloro-9-(2-deoxy-2-fluoro-β-D-  
12 arabinofuranosyl)-9H-purin-6-amine. The molecular formula of clofarabine is  
13 C<sub>10</sub>H<sub>11</sub>ClFN<sub>5</sub>O<sub>3</sub> with a molecular weight of 303.68.

14



15 Clofarabine

16

17

18 **CLINICAL PHARMACOLOGY**

19 **Mechanism of Action:** Clofarabine is sequentially metabolized intracellularly to the 5'-  
20 monophosphate metabolite by deoxycytidine kinase and mono- and di-phosphokinases to the  
21 active 5'-triphosphate metabolite. Clofarabine has high affinity for the activating  
22 phosphorylating enzyme, deoxycytidine kinase, equal to or greater than that of the natural  
23 substrate, deoxycytidine. Clofarabine inhibits DNA synthesis by decreasing cellular  
24 deoxynucleotide triphosphate pools through an inhibitory action on ribonucleotide reductase,  
25 and by terminating DNA chain elongation and inhibiting repair through incorporation into  
26 the DNA chain by competitive inhibition of DNA polymerases. The affinity of clofarabine  
27 triphosphate for these enzymes is similar to or greater than that of deoxyadenosine  
28 triphosphate. In preclinical models, clofarabine has demonstrated the ability to inhibit DNA  
29 repair by incorporation into the DNA chain during the repair process. Clofarabine 5'-  
30 triphosphate also disrupts the integrity of mitochondrial membrane, leading to the release of  
31 the pro-apoptotic mitochondrial proteins, cytochrome C and apoptosis-inducing factor,  
32 leading to programmed cell death.

33

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

35

36 *Human Pharmacokinetics:* The population pharmacokinetics of CLOLAR™ were studied in  
37 40 pediatric patients aged 2 to 19 years (21 males/19 females) with relapsed or refractory  
38 ALL or AML. At the given 52 mg/m<sup>2</sup> dose, similar concentrations were obtained over a  
39 wide range of BSAs. Clofarabine was 47% bound to plasma proteins, predominantly to  
40 albumin. Based on non-compartmental analysis, systemic clearance and volume of  
41 distribution at steady-state were estimated to be 28.8 L/h/m<sup>2</sup> and 172 L/m<sup>2</sup>, respectively. The  
42 terminal half-life was estimated to be 5.2 hours. No apparent difference in pharmacokinetics  
43 was observed between patients with ALL and AML or between males and females.

44

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

47

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

51

52 Although no clinical drug-drug interaction studies have been conducted to date, on the basis  
53 of the *in vitro* studies, cytochrome p450 inhibitors and inducers are unlikely to affect the  
54 metabolism of clofarabine. The effect of clofarabine on the metabolism of cytochrome p450  
55 substrates has not been studied. The pharmacokinetics of clofarabine have not been  
56 evaluated in patients with renal or hepatic dysfunction.

57

## 58 CLINICAL STUDIES

59 Sixty-six (66) pediatric ALL patients were exposed to CLOLAR™. Fifty-eight (58) of the  
60 patients received the recommended pediatric dose of CLOLAR™ 52 mg/m<sup>2</sup> daily × 5.

61

62 The safety and efficacy of CLOLAR™ were evaluated in pediatric patients with refractory or  
63 relapsed hematologic malignancies in an open-label, dose-escalation, noncomparative study.  
64 The starting dose of CLOLAR™ was 11.25 mg/m<sup>2</sup>/day IVI daily × 5 and escalated to 70  
65 mg/m<sup>2</sup>/day IVI daily × 5. This dosing schedule was repeated every 2 to 6 weeks depending  
66 on toxicity and response. Nine of 17 ALL patients were treated with CLOLAR™ 52 mg/m<sup>2</sup>  
67 daily × 5. In the 17 ALL patients there were 2 complete remissions (12.5%) and 2 partial  
68 remissions (12.5%) at varying doses. Dose-limiting toxicities (DLTs) in this study were  
69 reversible hyperbilirubinemia and elevated transaminase levels and skin rash, experienced at

70 70 mg/m<sup>2</sup>. As a result of this study, the recommended dose for subsequent study in pediatric  
71 patients was determined to be 52 mg/m<sup>2</sup>/day for 5 days.

72

### 73 **Single Arm Study in Pediatric ALL**

74 A single arm study was conducted in relapsed/refractory pediatric patients with ALL at a  
75 single dose. All patients had disease that had relapsed after and/or was refractory to two or  
76 more prior therapies. Most patients, 46/49 (93.8%), had received 2 to 4 prior regimens and  
77 15/49 (30.6%) of the patients had undergone at least 1 prior transplant. The median age of  
78 the treated patients was 12 years. There were more males, 29/49 (59.2%), than females,  
79 20/49 (40.8%). Most of the patients were either Caucasian (n=20, 40.8%) or Hispanic (n=20,  
80 40.8%), with 12.2% African-American (n=6), and 6.1% Other race (n=3). All patients  
81 received a dose of 52 mg/m<sup>2</sup> daily × 5. There was no dose modification during the remission  
82 induction phase of treatment (maximum of 2 cycles). Doses could be modified  
83 (reduced/delayed) during the post-induction phase. There was no dose escalation. The  
84 planned study endpoint was the rate of Complete Remission (CR), defined as no evidence of  
85 circulating blasts or extramedullary disease, an M1 bone marrow (<5% blasts), and recovery  
86 of peripheral counts (platelets > 100 × 10<sup>9</sup> L and absolute neutrophil count (ANC) > 1.0 ×  
87 10<sup>9</sup> L) and Complete Remission in the Absence of Total Platelet Recovery (CRp), defined as  
88 meeting all criteria for CR except for recovery of platelet counts to > 100 × 10<sup>9</sup> L. Partial  
89 Response (PR) was also determined, defined as complete disappearance of circulating blasts,  
90 an M2 bone marrow (> 5% and < 25% blasts), and appearance of normal progenitor cells or  
91 an M1 marrow that did not qualify for CR or CRp. Transplantation rate was not a study  
92 endpoint.

93

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

96

97 Table 1 summarizes results for the pediatric ALL study. Responses were seen in both pre-B  
 98 and T-cell immunophenotypes of ALL. The median cumulative dose was 540 mg (range 29-  
 99 1905 mg) in 1 (42.9%), 2 (38.8%) or 3 or more (18.4%) cycles.

100

101

**Table 1: Results in Pediatric ALL Study**

n=49			
Responses	n	%	95% CI
CR	6	12.2	4.6 to 24.8
CRp	4	8.2	2.3 to 19.6
PR	5	10.2	3.4 to 22.2

102

103 Of the 15 responding pediatric ALL patients, 6 had post-clofarabine bone marrow  
 104 transplantation, so that duration of response could not be determined. In the 9 responding  
 105 patients who were not transplanted, the response durations for CR were 43, 50, 82, 93+, and  
 106 160+ days; for CRp the response duration was 32 days; and for PR the response durations  
 107 were 7, 16, and 21 days.

108

## 109 INDICATIONS AND USAGE

110 CLOLAR™ is indicated for the treatment of pediatric patients 1 to 21 years old with relapsed  
 111 or refractory acute lymphoblastic leukemia after at least two prior regimens. This use is  
 112 based on the induction of complete responses. Randomized trials demonstrating increased  
 113 survival or other clinical benefit have not been conducted.

114

115 **CONTRAINDICATIONS**

116 None

117

118 **WARNINGS**

119 CLOLAR™ should be administered under the supervision of a qualified physician  
120 experienced in the use of antineoplastic therapy. Suppression of bone marrow function  
121 should be anticipated. This is usually reversible and appears to be dose dependent. The use  
122 of CLOLAR™ is likely to increase the risk of infection, including severe sepsis, as a result of  
123 bone marrow suppression. Administration of CLOLAR™ results in a rapid reduction in  
124 peripheral leukemia cells. For this reason, patients undergoing treatment with CLOLAR™  
125 should be evaluated and monitored for signs and symptoms of tumor lysis syndrome, as well  
126 as signs and symptoms of cytokine release (eg, tachypnea, tachycardia, hypotension,  
127 pulmonary edema) that could develop into systemic inflammatory response syndrome  
128 (SIRS)/capillary leak syndrome, and organ dysfunction. Physicians are encouraged to give  
129 continuous IV fluids throughout the five days of CLOLAR™ administration to reduce the  
130 effects of tumor lysis and other adverse events. Allopurinol should be administered if  
131 hyperuricemia is expected. CLOLAR™ should be discontinued immediately in the event of  
132 clinically significant signs or symptoms of SIRS or capillary leak syndrome, either of which  
133 can be fatal, and use of steroids, diuretics, and albumin considered. CLOLAR™ can be re-  
134 instituted when the patient is stable, generally at a lower dose.

135

136 Severe bone marrow suppression, including neutropenia, anemia, and thrombocytopenia, has  
137 been observed in patients treated with CLOLAR™. At initiation of treatment, most patients  
138 in the clinical studies had hematological impairment as a manifestation of leukemia. Because  
139 of the pre-existing immunocompromised condition of these patients and prolonged  
140 neutropenia that can result from treatment with CLOLAR™, patients are at increased risk for  
141 severe opportunistic infections. Careful hematological monitoring during therapy is

142 important, and hepatic and renal function should be assessed prior to and during treatment  
143 with CLOLAR™ because of CLOLAR™'s predominantly renal excretion and because the  
144 liver is a target organ for CLOLAR™ toxicity. The respiratory status and blood pressure  
145 should be closely monitored during infusion of CLOLAR™.

146

#### 147 **Hepatic and Renal Impairment**

148 CLOLAR™ has not been studied in patients with hepatic or renal dysfunction. Its use in  
149 such patients should be undertaken only with the greatest caution.

150

#### 151 **Pregnancy – Teratogenic Effects: Pregnancy Category D**

152 CLOLAR™ (clofarabine) may cause fetal harm when administered to a pregnant woman.  
153 Clofarabine was teratogenic in rats and rabbits. Developmental toxicity (reduced fetal body  
154 weight and increased post-implantation loss) and increased incidences of malformations and  
155 variations (gross external, soft tissue, skeletal and retarded ossification) were observed in rats  
156 receiving 54 mg/m<sup>2</sup>/day (approximately equivalent to the recommended clinical dose on a  
157 mg/m<sup>2</sup> basis), and in rabbits receiving 12 mg/m<sup>2</sup>/day (approximately 23% of the  
158 recommended clinical dose on a mg/m<sup>2</sup> basis).

159

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

163

164 Women of childbearing potential should be advised to avoid becoming pregnant while  
165 receiving treatment with clofarabine.



166

167 **PRECAUTIONS**

168 **Information for Patients and Caregivers**

169 Physicians are advised to discuss the following with patients to whom CLOLAR™ will be  
170 administered and patient caregivers, as appropriate.

171

172 ***Dehydration/Hypotension***

173 Patients receiving CLOLAR™ may experience vomiting and diarrhea; they should therefore  
174 be advised regarding appropriate measures to avoid dehydration. Patients should be  
175 instructed to seek medical advice if they experience symptoms of dizziness, lightheadedness,  
176 fainting spells, or decreased urine output. CLOLAR™ administration should be stopped if  
177 the patient develops hypotension for any reason during the 5 days of administration. If  
178 hypotension is transient and resolves without pharmacological intervention, CLOLAR™  
179 treatment can be re-instituted, generally at a lower dose.

180

181 ***Concomitant Medications***

182 Since CLOLAR™ is excreted primarily by the kidneys, drugs with known renal toxicity  
183 should be avoided during the 5 days of CLOLAR™ administration. In addition, since the  
184 liver is a known target organ for CLOLAR™ toxicity, concomitant use of medications known  
185 to induce hepatic toxicity should also be avoided. Patients taking medications known to  
186 affect blood pressure or cardiac function should be closely monitored during administration  
187 of CLOLAR™.

188

189 **Pregnancy/Nursing**

190 All patients should be advised to use effective contraceptive measures to prevent pregnancy.  
191 Female patients should be advised to avoid breast feeding during treatment with CLOLAR™.

192

193 **Laboratory Tests**

194 Complete blood counts and platelet counts should be obtained at regular intervals during  
195 CLOLAR™ therapy, and more frequently in patients who develop cytopenias. In addition  
196 liver and kidney function should be monitored frequently during the 5 days of CLOLAR™  
197 administration.

198

199 **Drug Interactions**

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

204

205 **Drug/Laboratory Tests Interactions**

206 There are no known clinically significant interactions of CLOLAR™ with other medications  
207 or laboratory tests. No formal drug/laboratory test interaction studies have been conducted  
208 with CLOLAR™.

209

210 **Carcinogenesis, Mutagenesis, Impairment of Fertility**211 **Carcinogenesis**

212 Clofarabine has not been tested for carcinogenic potential.

213

214 **Mutagenesis**

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

218

219 **Impairment of Fertility**

220 Studies in mice, rats, and dogs have demonstrated dose-related adverse effects on male  
221 reproductive organs. Seminiferous tubule and testicular degeneration and atrophy were  
222 reported in male mice receiving IP doses of 3 mg/kg/day (9 mg/m<sup>2</sup>/day, approximately 17%  
223 of clinical recommended dose on a mg/m<sup>2</sup> basis). The testes of rats receiving 25 mg/kg/day  
224 (150 mg/m<sup>2</sup>/day, approximately 3 times the recommended clinical dose on a mg/m<sup>2</sup> basis) in  
225 a 6-month IV study had bilateral degeneration of the seminiferous epithelium with retained  
226 spermatids and atrophy of interstitial cells. In a 6-month IV dog study, cell degeneration of  
227 the epididymis and degeneration of the seminiferous epithelium in the testes were observed  
228 in dogs receiving 0.375 mg/kg/day (7.5 mg/m<sup>2</sup>/day, approximately 14% of the clinical  
229 recommended dose on a mg/m<sup>2</sup> basis). Ovarian atrophy or degeneration and uterine mucosal  
230 apoptosis were observed in female mice at 75 mg/kg/day (225 mg/m<sup>2</sup>/day, approximately  
231 4 fold of recommended human dose on a mg/m<sup>2</sup> basis), the only dose administered to female  
232 mice. The effect on human fertility is unknown.

233

234 **Pregnancy**

235 **Teratogenic Effects: Pregnancy Category D**

236 See **WARNINGS**.

237

238 **Nursing Mothers**

239 It is not known whether clofarabine or its metabolites are excreted in human milk. Because  
240 of the potential for tumorigenicity shown for clofarabine in animal studies and the potential  
241 for serious adverse reactions, women treated with clofarabine should not nurse.

242

243 **Other Special Population: Adults**

244 Safety and efficacy have not been established in adults. One study was performed in highly  
245 refractory and/or relapsed adult patients with hematologic malignancies. The Phase 2 dose of  
246 CLOLAR™ was determined to be 40 mg/m<sup>2</sup>/day administered as a 1- to 2-hour IVI daily × 5  
247 every 28 days.

248

249 **ADVERSE REACTIONS**

250 One hundred thirteen (113) pediatric patients with ALL (67) or AML (46) were exposed to  
251 CLOLAR™. Ninety six (96) of the pediatric patients treated in clinical trials received the  
252 recommended dose of CLOLAR™ 52 mg/m<sup>2</sup> daily × 5.

253

254 The most common adverse effects after CLOLAR™ treatment, regardless of causality, were  
255 gastrointestinal tract symptoms, including vomiting, nausea, and diarrhea; hematologic

256 effects, including anemia, leukopenia, thrombocytopenia, neutropenia, and febrile  
257 neutropenia; and infection.

258

259 Table 2 lists adverse events by System Organ Class regardless of causality, including severe  
260 or life threatening events (NCI CTC grade 3 or grade 4), reported in  $\geq 10\%$  of the 96 patients  
261 in the 52 mg/m<sup>2</sup>/day dose group. More detailed information and follow-up of certain events  
262 is given below.

263

264

<b>Table 2: Most Commonly Reported (&gt;=10% Overall) Adverse Events by System Organ Class (N=96)</b>						
System Organ Class Adverse Event <sup>1</sup>	52 mg/m <sup>2</sup> (N=96)					
	Total		Grade 3		Grade 4	
	N	%	n	%	n	%
<b>Blood and Lymphatic System Disorders</b>						
Febrile neutropenia	55	57	51	53	3	3
Neutropenia	10	10	3	3	7	7
Transfusion reaction	10	10	3	3	.	.
<b>Cardiac Disorders</b>						
Tachycardia NOS	33	34	6	6	.	.
<b>Gastrointestinal Disorders</b>						
Abdominal pain NOS	35	36	7	7	.	.
Constipation	20	21	.	.	.	.
Diarrhea NOS	51	53	10	10	.	.
Gingival bleeding	14	15	7	7	1	1
Nausea	72	75	14	15	1	1
Sore throat NOS	13	14	.	.	.	.
Vomiting NOS	80	83	8	8	1	1
<b>General Disorders and Administration Site Conditions</b>						
Edema NOS	19	20	1	1	2	2
Fatigue	35	36	3	3	1	1
Injection site pain	13	14	1	1	.	.
Lethargy	11	11	.	.	.	.
Mucosal inflammation NOS	17	18	3	3	.	.
Pain NOS	18	19	6	6	1	1
Pyrexia	39	41	15	16	.	.
Rigors	36	38	3	3	.	.
<b>Hepato-Biliary Disorders</b>						
Hepatomegaly	14	15	8	8	.	.
Jaundice NOS	14	15	2	2	.	.
<b>Infections and Infestations</b>						
Bacteremia	10	10	10	10	.	.
Cellulitis	11	11	9	9	.	.
Herpes simplex	11	11	6	6	.	.
Oral candidiasis	12	13	2	2	.	.
Pneumonia NOS	10	10	5	5	2	2
Sepsis NOS	14	15	7	7	7	7
Staphylococcal infection NOS	12	13	10	10	.	.
<b>Investigations</b>						
Weight decreased	10	10	1	1	.	.

<b>Table 2: Most Commonly Reported (&gt;=10% Overall) Adverse Events by System Organ Class (N=96) (continued)</b>						
<b>System Organ Class Adverse Event<sup>1</sup></b>	<b>52 mg/m<sup>2</sup> (N=96)</b>					
	<b>Total</b>		<b>Grade 3</b>		<b>Grade 4</b>	
	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>
<b>Metabolism and Nutrition Disorders</b>						
Anorexia	30	31	5	5	7	7
Appetite decreased NOS	11	11	.	.	.	.
<b>Musculoskeletal, Connective Tissue and Bone Disorders</b>						
Arthralgia	11	11	3	3	.	.
Back pain	12	13	3	3	.	.
Myalgia	13	14	.	.	.	.
Pain in limb	28	29	5	5	.	.
<b>Nervous System Disorders</b>						
Dizziness (exc vertigo)	15	16	.	.	.	.
Headache NOS	44	46	4	4	.	.
Somnolence	10	10	1	1	.	.
Tremor NEC	10	10	.	.	.	.
<b>Psychiatric Disorders</b>						
Anxiety NEC	21	22	2	2	.	.
Depression NEC	11	11	1	1	.	.
Irritability	11	11	1	1	.	.
<b>Renal and Urinary Disorders</b>						
Hematuria	16	17	2	2	.	.
<b>Respiratory, Thoracic and Mediastinal Disorders</b>						
Cough	18	19	.	.	.	.
Dyspnea NOS	12	13	4	4	2	2
Epistaxis	30	31	14	15	.	.
Pleural effusion	10	10	3	3	2	2
Respiratory distress	13	14	6	6	5	5
<b>Skin and Subcutaneous Tissue Disorders</b>						
Contusion	11	11	1	1	.	.
Dermatitis NOS	39	41	7	7	.	.
Dry skin	10	10	1	1	.	.
Erythema NEC	17	18	.	.	.	.
Palmar-plantar erythrodysesthesia syndrome	12	13	4	4	.	.
Petechiae	28	29	7	7	.	.
Pruritus NOS	45	47	1	1	.	.
<b>Vascular Disorders</b>						
Flushing	17	18	.	.	.	.
Hypertension NOS	11	11	4	4	.	.
Hypotension NOS	28	29	12	13	7	7

<sup>1</sup> Patients with more than one occurrence of the same preferred term are counted only once.  
Grade 4 includes deaths (Grade 5).

266

267 **Cardiovascular**

268 The most frequently reported cardiac disorder was tachycardia (34%), which was however,  
269 already present in 27.4% of patients at study entry. Most of the cardiac adverse events were  
270 reported in the first 2 cycles.

271

272 Pericardial effusion was a frequent finding in these patients on post-treatment studies, [19/55  
273 (35%)]. The effusion was almost always minimal to small and in no cases had hemodynamic  
274 significance.

275

276 Left ventricular systolic dysfunction (LVSD) was also noted. Fifteen out of fifty-five  
277 patients [15/55 (27%)] had some evidence of LVSD after study entry. In most cases where  
278 subsequent follow-up data were available, the LVSD appeared to be transient. The exact  
279 etiology for the LVSD is unclear because of previous therapy or serious concurrent illness.

280

281 **Hepatic**

282 Hepato-biliary toxicities were frequently observed in pediatric patients during treatment with  
283 CLOLAR™. Grade 3 or 4 elevated AST occurred in 38% of patients and grade 3 or 4  
284 elevated ALT occurred in 44% of patients. Grade 3 or 4 elevated bilirubin occurred in 15%  
285 of patients, with 2 cases of grade 4 hyperbilirubinemia resulting in treatment discontinuation.

286

287 For patients with follow-up data, elevations in AST and ALT were transient and typically of  
288 <2 weeks duration. The majority of AST and ALT elevations occurred within 1 week of  
289 CLOLAR™ administration and returned to baseline or ≤ grade 2 within several days.  
290 Although less common, elevations in bilirubin appeared to be more persistent. Where



291 follow-up data are available, the median time to recovery from grade 3 and grade 4  
292 elevations in bilirubin to  $\leq$  grade 2 was 6 days.

293

294 **Infection**

295 At baseline 47% of the patients had 1 or more concurrent infections. A total of 85% of  
296 patients experienced at least 1 infection after CLOLAR™ treatment, including fungal, viral  
297 and bacterial infections.

298

299 **Renal**

300 The most prevalent renal toxicity was elevated creatinine. Grade 3 or 4 elevated creatinine  
301 occurred in 6% of patients. Nephrotoxic medications, tumor lysis, and tumor lysis with  
302 hyperuricemia may contribute to renal toxicity.

303

304 **Systemic Inflammatory Response Syndrome (SIRS)/Capillary Leak Syndrome**

305 Capillary leak syndrome or SIRS (signs and symptoms of cytokine release, e.g., tachypnea,  
306 tachycardia, hypotension, pulmonary edema) occurred in 4 pediatric patients overall (3 ALL,  
307 1 AML). Several patients developed rapid onset of respiratory distress, hypotension,  
308 capillary leak (pleural and pericardial effusions), and multi-organ failure. Close monitoring  
309 for this syndrome and early intervention are recommended. The use of prophylactic steroids  
310 (eg, 100 mg/m<sup>2</sup> hydrocortisone on Days 1 through 3) may be of benefit in preventing signs or  
311 symptoms of SIRS or capillary leak. Physicians should be alert to early indications of this  
312 syndrome and should immediately discontinue CLOLAR™ administration if they occur and  
313 provide appropriate supportive measures. After the patient is stabilized and organ function  
314 has returned to baseline, re-treatment with CLOLAR™ can be considered at a lower dose.

315

316 **Overdosage**

317 There were no known overdoses of CLOLAR™. The highest daily dose administered to a  
318 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  
319 patients). The toxicities included in these 2 patients included grade 4 hyperbilirubinemia,  
320 grade 2 and 3 vomiting, and grade 3 maculopapular rash.

321

322 **DOSAGE AND ADMINISTRATION**

323 **Recommended Dose**

324 CLOLAR™ should be diluted per instructions below with 5% dextrose injection, USP or  
325 0.9% sodium chloride injection, USP prior to intravenous infusion (IVI).

326

327 The recommended pediatric dose and schedule is 52 mg/m<sup>2</sup> administered by intravenous  
328 infusion (IVI) over 2 hours daily for 5 consecutive days. Treatment cycles are repeated  
329 following recovery or return to baseline organ function, approximately every 2 to 6 weeks.  
330 The dosage is based on the patient's body surface area (BSA), calculated using the actual  
331 height and weight before the start of each cycle. To prevent drug incompatibilities, no other  
332 medications should be administered through the same intravenous line.

333

334 CLOLAR™ has not been studied in patients with hepatic or renal dysfunction. Its use in  
335 such patients should be undertaken only with the greatest caution.

336

337 Physicians are encouraged to give continuous IV fluids throughout the 5 days of CLOLAR™  
338 administration to reduce the effects of tumor lysis and other adverse events. The use of  
339 prophylactic steroids (e.g., 100 mg/m<sup>2</sup> hydrocortisone on Days 1 through 3) may be of

340 benefit in preventing signs or symptoms of SIRS or capillary leak (e.g., hypotension). If  
341 patients show early signs or symptoms of SIRS or capillary leak (e.g., hypotension), the  
342 physician should immediately discontinue CLOLAR™ administration and provide  
343 appropriate supportive measures. Close monitoring of renal and hepatic function during the  
344 5 days of CLOLAR™ administration is advised. If substantial increases in creatinine or  
345 bilirubin are noted, physicians should immediately discontinue administration of  
346 CLOLAR™. CLOLAR™ should be re-instituted when the patient is stable and organ  
347 function has returned to baseline, possibly at a lower dose. If hyperuricemia is anticipated  
348 (tumor lysis), patients should prophylactically receive allopurinol.

349

350

### 351 **STORAGE AND HANDLING**

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

354

355 CLOLAR™ should be filtered through a sterile 0.2 µm syringe filter and then further diluted  
356 with 5% dextrose injection USP or 0.9% sodium chloride injection USP prior to intravenous  
357 infusion (IVI). The resulting admixture may be stored at room temperature, but must be used  
358 within 24 hours of preparation.

359

### 360 **HOW SUPPLIED**

361 CLOLAR™ is formulated at a concentration of 1 mg/mL in sodium chloride (9 mg/mL),  
362 USP, and water for injection, USP, quantity sufficient (qs) to 1 mL. CLOLAR™ is supplied  
363 in 20 mL flint vials in a box of 4 (NDC 58468-0100-2). The 20 mL flint vials contain 20 mL  
364 (20 mg) of solution. The pH range of the solution is 4.5 to 7.5. The solution is clear and  
365 practically colorless, is preservative free, and is free from foreign matter.

366

367 **Rx only**

368 **U.S. Patents:** 4,751,221; 4, 918,179; 5,384,310; 5,661,136, 6,680,382 B2.

369 Other patents pending.

370

371 **NAME AND ADDRESS OF MANUFACTURER**

372 **Manufactured by:** AAI Development Services

373 Charleston, SC 29405

374 **Manufactured for:** Genzyme Corporation

375 4545 Horizon Hill Blvd

376 San Antonio, TX 78229

377 **Distributed by:** Genzyme Corporation

378 500 Kendall Street

379 Cambridge, MA 02142

380