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Fludara<sup>®</sup> (fludarabine phosphate)

PROPOSED TEXT OF THE LABELING OF THE DRUG

1 **Fludara<sup>®</sup>**

2 **fludarabine phosphate**

3 **FOR INJECTION**

4 **FOR INTRAVENOUS USE ONLY**

5 **Rx Only**

6 **WARNING:** FLUDARA FOR INJECTION should be administered under the supervision of a  
7 qualified physician experienced in the use of antineoplastic therapy. FLUDARA FOR  
8 INJECTION can severely suppress bone marrow function. When used at high doses in dose-  
9 ranging studies in patients with acute leukemia, FLUDARA FOR INJECTION was associated  
10 with severe neurologic effects, including blindness, coma, and death. This severe central  
11 nervous system toxicity occurred in 36% of patients treated with doses approximately four times  
12 greater (96 mg/m<sup>2</sup>/day for 5-7 days) than the recommended dose. Similar severe central  
13 nervous system toxicity, including coma, seizures, agitation and confusion, has been reported in  
14 patients treated at doses in the range of the dose recommended for chronic lymphocytic  
15 leukemia.

16 Instances of life-threatening and sometimes fatal autoimmune phenomena such as hemolytic  
17 anemia, autoimmune thrombocytopenia/thrombocytopenic purpura (ITP), Evans syndrome, and  
18 acquired hemophilia have been reported to occur after one or more cycles of treatment with  
19 FLUDARA FOR INJECTION. Patients undergoing treatment with FLUDARA FOR INJECTION  
20 should be evaluated and closely monitored for hemolysis.

21 In a clinical investigation using FLUDARA FOR INJECTION in combination with pentostatin  
22 (deoxycoformycin) for the treatment of refractory chronic lymphocytic leukemia (CLL), there was  
23 an unacceptably high incidence of fatal pulmonary toxicity. Therefore, the use of FLUDARA  
24 FOR INJECTION in combination with pentostatin is not recommended.

25 **DESCRIPTION**

26 FLUDARA FOR INJECTION contains fludarabine phosphate, a fluorinated nucleotide analog of  
27 the antiviral agent vidarabine, 9-β-D-arabinofuranosyladenine (ara-A) that is relatively resistant  
28 to deamination by adenosine deaminase. Each vial of sterile lyophilized solid cake contains 50  
29 mg of the active ingredient fludarabine phosphate, 50 mg of mannitol, and sodium hydroxide to  
30 adjust pH to 7.7. The pH range for the final product is 7.2-8.2. Reconstitution with 2 mL of  
31 Sterile Water for Injection, USP, results in a solution containing 25 mg/mL of fludarabine  
32 phosphate intended for intravenous administration.

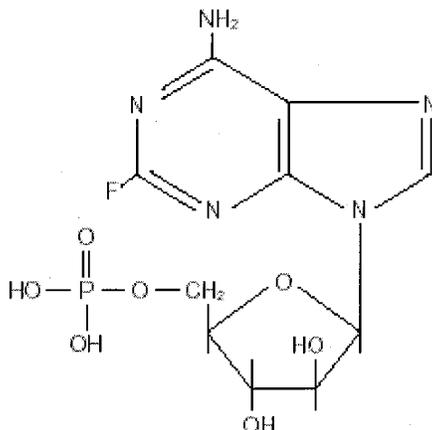
33 The chemical name for fludarabine phosphate is 9H-Purin-6-amine, 2-fluoro-9-(5-0-phosphono-  
34 β-D-arabino-furanosyl) (2-fluoro-ara-AMP). The molecular formula of fludarabine phosphate is  
35 C<sub>10</sub>H<sub>13</sub>FN<sub>5</sub>O<sub>7</sub>P (MW 365.2) and the structure is:

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38 **CLINICAL PHARMACOLOGY**

39 Fludarabine phosphate is rapidly dephosphorylated to 2-fluoro-ara-A and then phosphorylated  
40 intracellularly by deoxycytidine kinase to the active triphosphate, 2-fluoro-ara-ATP. This  
41 metabolite appears to act by inhibiting DNA polymerase alpha, ribonucleotide reductase and  
42 DNA primase, thus inhibiting DNA synthesis. The mechanism of action of this antimetabolite is  
43 not completely characterized and may be multi-faceted.

44 Phase I studies in humans have demonstrated that fludarabine phosphate is rapidly converted  
45 to the active metabolite, 2-fluoro-ara-A, within minutes after intravenous infusion.  
46 Consequently, clinical pharmacology studies have focused on 2-fluoro-ara-A pharmacokinetics.  
47 After the five daily doses of 25 mg 2-fluoro-ara-AMP/m<sup>2</sup> to cancer patients infused over 30  
48 minutes, 2-fluoro-ara-A concentrations show a moderate accumulation. During a 5-day  
49 treatment schedule, 2-fluoro-ara-A plasma trough levels increased by a factor of about 2. The  
50 terminal half-life of 2-fluoro-ara-A was estimated as approximately 20 hours. *In vitro*, plasma  
51 protein binding of fludarabine ranged between 19% and 29%.

52 A correlation was noted between the degree of absolute granulocyte count nadir and increased  
53 area under the concentration x time curve (AUC).

54 **Special Populations**

55 *Pediatric Patients*

56 Limited pharmacokinetic data for FLUDARA FOR INJECTION are available from a published  
57 study of children (ages 1-21 years) with refractory acute leukemias or solid tumors (Children's  
58 Cancer Group Study 097). When FLUDARA FOR INJECTION was administered as a loading  
59 dose over 10 minutes immediately followed by a 5-day continuous infusion, steady-state  
60 conditions were reached early.

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61 *Patients with Renal Impairment*

62 The total body clearance of the principal metabolite 2-fluoro-ara-A correlated with the creatinine  
63 clearance, indicating the importance of the renal excretion pathway for the elimination of the  
64 drug. Renal clearance represents approximately 40% of the total body clearance. Patients  
65 with creatinine clearance 30-79 mL/min should have their FLUDARA FOR INJECTION dose  
66 reduced and be monitored closely for excessive toxicity. Due to insufficient data, FLUDARA  
67 FOR INJECTION should not be administered to patients with creatinine clearance less than 30  
68 mL/min. (See **DOSAGE AND ADMINISTRATION** section).

69 **CLINICAL STUDIES**

70 Two single-arm, open-label studies of FLUDARA FOR INJECTION have been conducted in  
71 adult patients with CLL refractory to at least one prior standard alkylating-agent containing  
72 regimen. In a study conducted by M.D. Anderson Cancer Center (MDAH), 48 patients were  
73 treated with a dose of 22-40 mg/m<sup>2</sup> daily for 5 days every 28 days. Another study conducted by  
74 the Southwest Oncology Group (SWOG) involved 31 patients treated with a dose of 15-25  
75 mg/m<sup>2</sup> daily for 5 days every 28 days. The overall objective response rates were 48% and 32%  
76 in the MDAH and SWOG studies, respectively. The complete response rate in both studies was  
77 13%; the partial response rate was 35% in the MDAH study and 19% in the SWOG study.  
78 These response rates were obtained using standardized response criteria developed by the  
79 National Cancer Institute CLL Working Group and were achieved in heavily pretreated patients.  
80 The ability of FLUDARA FOR INJECTION to induce a significant rate of response in refractory  
81 patients suggests minimal cross-resistance with commonly used anti-CLL agents.

82 The median time to response in the MDAH and SWOG studies was 7 weeks (range of 1 to 68  
83 weeks) and 21 weeks (range of 1 to 53 weeks), respectively. The median duration of disease  
84 control was 91 weeks (MDAH) and 65 weeks (SWOG). The median survival of all refractory CLL  
85 patients treated with FLUDARA FOR INJECTION was 43 weeks and 52 weeks in the MDAH  
86 and SWOG studies, respectively.

87 Rai stage improved to Stage II or better in 7 of 12 MDAH responders (58%) and in 5 of 7 SWOG  
88 responders (71%) who were Stage III or IV at baseline. In the combined studies, mean  
89 hemoglobin concentration improved from 9.0 g/dL at baseline to 11.8 g/dL at the time of  
90 response in a subgroup of anemic patients. Similarly, average platelet count improved from  
91 63,500/mm<sup>3</sup> to 103,300/mm<sup>3</sup> at the time of response in a subgroup of patients who were  
92 thrombocytopenic at baseline.

93 **INDICATIONS AND USAGE**

94 FLUDARA FOR INJECTION is indicated for the treatment of adult patients with B-cell chronic  
95 lymphocytic leukemia (CLL) who have not responded to or whose disease has progressed  
96 during treatment with at least one standard alkylating-agent containing regimen. The safety and  
97 effectiveness of FLUDARA FOR INJECTION in previously untreated or non-refractory patients  
98 with CLL have not been established.

99 **CONTRAINDICATIONS**

100 FLUDARA FOR INJECTION is contraindicated in those patients who are hypersensitive to this  
101 drug or its components.

102 **WARNINGS**

103 (See **BOXED WARNINGS**)

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104 **Dose Dependent Neurologic Toxicities**

105 There are clear dose-dependent toxic effects seen with FLUDARA FOR INJECTION. Dose  
106 levels approximately 4 times greater (96 mg/m<sup>2</sup>/day for 5 to 7 days) than that recommended for  
107 CLL (25 mg/m<sup>2</sup>/day for 5 days) were associated with a syndrome characterized by delayed  
108 blindness, coma and death. Symptoms appeared from 21 to 60 days following the last dose.  
109 Thirteen of 36 patients (36%) who received FLUDARA FOR INJECTION at high doses (96  
110 mg/m<sup>2</sup>/day for 5 to 7 days) developed this severe neurotoxicity. Similar severe central nervous  
111 system toxicity, including coma, seizures, agitation and confusion, has been reported in patients  
112 treated at doses in the range of the dose recommended for chronic lymphocytic leukemia.

113 In postmarketing experience neurotoxicity has been reported to occur either earlier or later than  
114 in clinical trials (range 7 to 225 days).

115 The effect of chronic administration of FLUDARA FOR INJECTION on the central nervous  
116 system is unknown; however, patients have received the recommended dose for up to 15  
117 courses of therapy.

118 **Bone Marrow Suppression**

119 Severe bone marrow suppression, notably anemia, thrombocytopenia and neutropenia, has  
120 been reported in patients treated with FLUDARA FOR INJECTION. In a Phase I study in adult  
121 solid tumor patients, the median time to nadir counts was 13 days (range, 3-25 days) for  
122 granulocytes and 16 days (range, 2-32) for platelets. Most patients had hematologic impairment  
123 at baseline either as a result of disease or as a result of prior myelosuppressive therapy.  
124 Cumulative myelosuppression may be seen. While chemotherapy-induced myelosuppression is  
125 often reversible, administration of FLUDARA FOR INJECTION requires careful hematologic  
126 monitoring.

127 Several instances of trilineage bone marrow hypoplasia or aplasia resulting in pancytopenia,  
128 sometimes resulting in death, have been reported in adult patients. The duration of clinically  
129 significant cytopenia in the reported cases has ranged from approximately 2 months to  
130 approximately 1 year. These episodes have occurred both in previously treated or untreated  
131 patients.

132 **Autoimmune Reactions**

133 Instances of life-threatening and sometimes fatal autoimmune phenomena such as hemolytic  
134 anemia, autoimmune thrombocytopenia/thrombocytopenic purpura (ITP), Evans syndrome, and  
135 acquired hemophilia have been reported to occur after one or more cycles of treatment with  
136 FLUDARA FOR INJECTION in patients with or without a previous history of autoimmune  
137 hemolytic anemia or a positive Coombs' test and who may or may not be in remission from their  
138 disease. Steroids may or may not be effective in controlling these hemolytic episodes. The  
139 majority of patients rechallenged with FLUDARA FOR INJECTION developed a recurrence in  
140 the hemolytic process. The mechanism(s) which predispose patients to the development of this  
141 complication has not been identified. Patients undergoing treatment with FLUDARA FOR  
142 INJECTION should be evaluated and closely monitored for hemolysis. Discontinuation of  
143 therapy with FLUDARA FOR INJECTION is recommended in case of hemolysis.

144 **Transfusion Associated Graft-Versus-Host Disease**

145 Transfusion-associated graft-versus-host disease has been observed after transfusion of non-  
146 irradiated blood in FLUDARA FOR INJECTION treated patients. Fatal outcome as a  
147 consequence of this disease has been reported. Therefore, to minimize the risk of transfusion-  
148 associated graft-versus-host disease, patients who require blood transfusion and who are

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149 undergoing, or who have received, treatment with FLUDARA FOR INJECTION should receive  
150 irradiated blood only.

151 **Pulmonary Toxicity**

152 In a clinical investigation using FLUDARA FOR INJECTION in combination with pentostatin  
153 (deoxycoformycin) for the treatment of refractory chronic lymphocytic leukemia (CLL) in adults,  
154 there was an unacceptably high incidence of fatal pulmonary toxicity. Therefore, the use of  
155 FLUDARA FOR INJECTION in combination with pentostatin is not recommended.

156 **Pregnancy Category D**

157 Based on its mechanism of action, fludarabine phosphate can cause fetal harm when  
158 administered to a pregnant woman. There are no adequate and well-controlled studies of  
159 FLUDARA FOR INJECTION in pregnant women. Fludarabine administered to rats and rabbits  
160 during organogenesis caused an increase in resorptions, skeletal and visceral malformations  
161 and decreased fetal body weights. If FLUDARA FOR INJECTION is used during pregnancy, or  
162 if the patient becomes pregnant while taking this drug, the patient should be apprised of the  
163 potential hazard to the fetus. Women of childbearing potential should be advised to avoid  
164 becoming pregnant.

165 **Male Fertility and Reproductive Outcomes**

166 Males with female sexual partners of childbearing potential should use contraception during and  
167 after cessation of FLUDARA FOR INJECTION therapy. Fludarabine may damage testicular  
168 tissue and spermatozoa. Possible sperm DNA damage raises concerns about loss of fertility  
169 and genetic abnormalities in fetuses. The duration of this effect is uncertain. [See  
170 **PRECAUTIONS, Impairment of Fertility**]

171 **PRECAUTIONS**

172 **General**

173 FLUDARA FOR INJECTION is a potent antineoplastic agent with potentially significant toxic  
174 side effects. Patients undergoing therapy should be closely observed for signs of hematologic  
175 and nonhematologic toxicity. Periodic assessment of peripheral blood counts is recommended  
176 to detect the development of anemia, neutropenia and thrombocytopenia.

177 In patients with impaired state of health, FLUDARA FOR INJECTION should be given with  
178 caution and after careful risk/benefit consideration. This applies especially for patients with  
179 severe impairment of bone marrow function (thrombocytopenia, anemia, and/or  
180 granulocytopenia), immunodeficiency or with a history of opportunistic infection. Prophylactic  
181 treatment should be considered in patients at increased risk of developing opportunistic  
182 infections.

183 FLUDARA FOR INJECTION may reduce the ability to drive or use machines, since fatigue,  
184 weakness, visual disturbances, confusion, agitation and seizures have been observed.

185 **Tumor Cell Lysis**

186 Tumor lysis syndrome has been associated with FLUDARA FOR INJECTION treatment. This  
187 syndrome has been reported in CLL patients with large tumor burden. Since FLUDARA FOR  
188 INJECTION can induce a response as early as the first week of treatment, precautions should  
189 be taken in those patients at risk of developing this complication.

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190 **Renal Impairment**

191 FLUDARA FOR INJECTION must be administered cautiously in patients with renal impairment.  
192 The total body clearance of 2-fluoro-ara-A has been shown to be directly correlated with  
193 creatinine clearance. Patients with creatinine clearance 30-79 mL/min should have their  
194 FLUDARA FOR INJECTION dose reduced and be monitored closely for excessive toxicity.  
195 FLUDARA FOR INJECTION should not be administered to patients with creatinine clearance  
196 less than 30 mL/min. (See **DOSAGE AND ADMINISTRATION** section).

197 In patients aged 65 years or older, creatinine clearance should be measured before start of  
198 treatment.

199 **Laboratory Tests**

200 During treatment, the patient's hematologic profile (particularly neutrophils and platelets) should  
201 be monitored regularly to determine the degree of hematopoietic suppression.

202 **Drug Interactions**

203 The use of FLUDARA FOR INJECTION in combination with pentostatin is not recommended  
204 due to the risk of fatal pulmonary toxicity (see **WARNINGS** section).

205 **Carcinogenesis**

206 No animal carcinogenicity studies with FLUDARA FOR INJECTION have been conducted.

207 **Mutagenesis**

208 Fludarabine phosphate was not mutagenic to bacteria (Ames test) or mammalian cells (HGRPT  
209 assay in Chinese hamster ovary cells) either in the presence or absence of metabolic activation.  
210 Fludarabine phosphate was clastogenic *in vitro* to Chinese hamster ovary cells (chromosome  
211 aberrations in the presence of metabolic activation) and induced sister chromatid exchanges  
212 both with and without metabolic activation. In addition, fludarabine phosphate was clastogenic  
213 *in vivo* (mouse micronucleus assay) but was not mutagenic to germ cells (dominant lethal test in  
214 male mice).

215 **Impairment of Fertility**

216 Studies in mice, rats and dogs have demonstrated dose-related adverse effects on the male  
217 reproductive system. Observations consisted of a decrease in mean testicular weights in mice  
218 and rats with a trend toward decreased testicular weights in dogs and degeneration and  
219 necrosis of spermatogenic epithelium of the testes in mice, rats and dogs. The possible adverse  
220 effects on fertility in humans have not been adequately evaluated.

221 **Pregnancy**

222 Pregnancy Category D (see **WARNINGS** section).

223 Based on its mechanism of action, fludarabine phosphate can cause fetal harm when  
224 administered to a pregnant woman. There are not adequate and well-controlled studies of  
225 fludarabine phosphate in pregnant women. Fludarabine phosphate was embryoletal and  
226 teratogenic in rats and rabbits. If FLUDARA FOR INJECTION is used during pregnancy, or if the  
227 patient becomes pregnant while taking this drug, the patient should be apprised of the potential  
228 hazard to the fetus. Women of childbearing potential should be advised to avoid becoming  
229 pregnant.

230 In rats, repeated intravenous doses of fludarabine phosphate at 2.4 times and 7.2 times the  
231 recommended human IV dose (25 mg/m<sup>2</sup>) administered during organogenesis caused an  
232 increase in resorptions, skeletal and visceral malformations (cleft palate, exencephaly, and fetal

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233 vertebrae deformities) and decreased fetal body weights. Maternal toxicity was not apparent at  
234 2.4 times the human IV dose, and was limited to slight body weight decreases at 7.2 times the  
235 human IV dose. In rabbits, repeated intravenous doses of fludarabine phosphate at 3.8 times  
236 the human IV dose administered during organogenesis increased embryo and fetal lethality as  
237 indicated by increased resorptions and a decrease in live fetuses. A significant increase in  
238 malformations including cleft palate, hydrocephaly, adactyly, brachydactyly, fusions of the digits,  
239 diaphragmatic hernia, heart/great vessel defects, and vertebrae/rib anomalies were seen in all  
240 dose levels ( $\geq 0.5$  times the human IV dose).

241

242

**Nursing Mothers**

243 It is not known whether fludarabine phosphate is excreted in human milk. Because many drugs  
244 are excreted in human milk and because of the potential for serious adverse reactions including  
245 tumorigenicity in nursing infants, a decision should be made to discontinue nursing or  
246 discontinue the drug, taking into account the importance of the drug to the mother.

247

**Pediatric Use**

248 Data submitted to the FDA was insufficient to establish efficacy in any childhood malignancy.  
249 FLUDARA FOR INJECTION was evaluated in 62 pediatric patients (median age 10, range 1-21)  
250 with refractory acute leukemia (45 patients) or solid tumors (17 patients). The FLUDARA FOR  
251 INJECTION regimen tested for pediatric acute lymphocytic leukemia (ALL) patients was a  
252 loading bolus of 10.5 mg/m<sup>2</sup>/day followed by a continuous infusion of 30.5 mg/m<sup>2</sup>/day for 5 days.  
253 In 12 pediatric patients with solid tumors, dose-limiting myelosuppression was observed with a  
254 loading dose of 8 mg/m<sup>2</sup>/day followed by a continuous infusion of 23.5 mg/m<sup>2</sup>/day for 5 days.  
255 The maximum tolerated dose was a loading dose of 7 mg/m<sup>2</sup>/day followed by a continuous  
256 infusion of 20 mg/m<sup>2</sup>/day for 5 days. Treatment toxicity included bone marrow suppression.  
257 Platelet counts appeared to be more sensitive to the effects of FLUDARA FOR INJECTION than  
258 hemoglobin and white blood cell counts. Other adverse events included fever, chills, asthenia,  
259 rash, nausea, vomiting, diarrhea, and infection. There were no reported occurrences of  
260 peripheral neuropathy or pulmonary hypersensitivity reaction.

261

**Vaccination**

262 During and after treatment with FLUDARA FOR INJECTION, vaccination with live vaccines  
263 should be avoided.

264

**Disease Progression**

265 Richter's syndrome has been reported in CLL patients.

266

**ADVERSE REACTIONS**

267 Very common adverse events include myelosuppression (neutropenia, thrombocytopenia and  
268 anemia), fever and chills, fatigue, weakness, infection, pneumonia, cough, nausea, vomiting,  
269 and diarrhea. Other commonly reported events include malaise, mucositis and anorexia.  
270 Serious opportunistic infections (such as latent viral reactivation, herpes zoster virus, Epstein-  
271 Barr virus, and progressive multifocal leukoencephalopathy) have occurred in CLL patients  
272 treated with FLUDARA FOR INJECTION. Adverse events and those reactions which are more  
273 clearly related to the drug are arranged below according to body system.

274

**Hematopoietic Systems**

275 Hematologic events (neutropenia, thrombocytopenia, and/or anemia) were reported in the  
276 majority of CLL patients treated with FLUDARA FOR INJECTION. During FLUDARA FOR  
277 INJECTION treatment of 133 patients with CLL, the absolute neutrophil count decreased to less

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278 than 500/mm<sup>3</sup> in 59% of patients, hemoglobin decreased from pretreatment values by at least 2  
279 grams percent in 60%, and platelet count decreased from pretreatment values by at least 50%  
280 in 55%. Myelosuppression may be severe, cumulative, and may affect multiple cell lines. Bone  
281 marrow fibrosis occurred in one CLL patient treated with FLUDARA FOR INJECTION.

282 Several instances of trilineage bone marrow hypoplasia or aplasia resulting in pancytopenia,  
283 sometimes resulting in death, have been reported in post-marketing surveillance. The duration  
284 of clinically significant cytopenia in the reported cases has ranged from approximately 2 months  
285 to approximately 1 year. These episodes have occurred both in previously treated or untreated  
286 patients.

287 Life-threatening and sometimes fatal autoimmune phenomena such as hemolytic anemia,  
288 autoimmune thrombocytopenia/thrombocytopenic purpura (ITP), Evans syndrome, and acquired  
289 hemophilia have been reported to occur in patients receiving FLUDARA FOR INJECTION (see  
290 **WARNINGS** section). The majority of patients rechallenged with FLUDARA FOR INJECTION  
291 developed a recurrence in the hemolytic process.

292 In post-marketing experience, cases of myelodysplastic syndrome and acute myeloid leukemia,  
293 mainly associated with prior, concomitant or subsequent treatment with alkylating agents,  
294 topoisomerase inhibitors, or irradiation have been reported.

295 **Infections**

296 Serious and sometimes fatal infections, including opportunistic infections and reactivations of  
297 latent viral infections such as VZV (herpes zoster), Epstein-Barr virus and JC virus (progressive  
298 multifocal leukoencephalopathy) have been reported in patients treated with FLUDARA FOR  
299 INJECTION.

300 Rare cases of Epstein-Barr virus (EBV) associated lymphoproliferative disorders have been  
301 reported in patients treated with FLUDARA FOR INJECTION.

302 In post-marketing experience, cases of progressive multifocal leukoencephalopathy have been  
303 reported. Most cases had a fatal outcome. Many of these cases were confounded by prior  
304 and/or concurrent chemotherapy. The time to onset has ranged from a few weeks to  
305 approximately one year after initiating treatment.

306 Of the 133 adult CLL patients in the two trials, there were 29 fatalities during study,  
307 approximately 50% of which were due to infection.

308 **Metabolic**

309 Tumor lysis syndrome has been reported in CLL patients treated with FLUDARA FOR  
310 INJECTION. This complication may include hyperuricemia, hyperphosphatemia, hypocalcemia,  
311 metabolic acidosis, hyperkalemia, hematuria, urate crystalluria, and renal failure. The onset of  
312 this syndrome may be heralded by flank pain and hematuria.

313 **Nervous System** (see **WARNINGS** section)

314 Objective weakness, agitation, confusion, seizures, visual disturbances, optic neuritis, optic  
315 neuropathy, blindness and coma have occurred in CLL patients treated with FLUDARA FOR  
316 INJECTION at the recommended dose. Peripheral neuropathy has been observed in patients  
317 treated with FLUDARA FOR INJECTION and one case of wrist-drop was reported. There have  
318 been additional reports of cerebral hemorrhage though the frequency is not known.

319 **Pulmonary System**

320 Pneumonia, a frequent manifestation of infection in CLL patients, occurred in 16% and 22% of  
321 those treated with FLUDARA FOR INJECTION in the MDAH and SWOG studies, respectively.

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322 Pulmonary hypersensitivity reactions to FLUDARA FOR INJECTION characterized by dyspnea,  
323 cough and interstitial pulmonary infiltrate have been observed.

324 In post-marketing experience, cases of severe pulmonary toxicity have been observed with  
325 FLUDARA FOR INJECTION use which resulted in ARDS, respiratory distress, pulmonary  
326 hemorrhage, pulmonary fibrosis, pneumonitis and respiratory failure. After an infectious origin  
327 has been excluded, some patients experienced symptom improvement with corticosteroids.

328 **Gastrointestinal System**

329 Gastrointestinal disturbances such as nausea and vomiting, anorexia, diarrhea, stomatitis and  
330 gastrointestinal bleeding and hemorrhage have been reported in patients treated with  
331 FLUDARA FOR INJECTION. Elevations of pancreatic enzyme levels have also been reported.

332 **Cardiovascular**

333 Edema has been frequently reported. One patient developed a pericardial effusion possibly  
334 related to treatment with FLUDARA FOR INJECTION. There have been additional reports of  
335 heart failure and arrhythmia though the frequency is rare. No other severe cardiovascular  
336 events were considered to be drug related.

337 **Genitourinary System**

338 Rare cases of hemorrhagic cystitis have been reported in patients treated with FLUDARA FOR  
339 INJECTION.

340 **Skin**

341 Skin toxicity, consisting primarily of skin rashes, has been reported in patients treated with  
342 FLUDARA FOR INJECTION. Erythema multiforme, Stevens-Johnson syndrome, toxic  
343 epidermal necrolysis and pemphigus have been reported, with fatal outcomes in some cases.

344 **Neoplasms**

345 Worsening or flare-up of pre-existing skin cancer lesions, as well as new onset of skin cancer,  
346 has been reported in patients during or after treatment with FLUDARA FOR INJECTION.

347 **Hepatobiliary Disorders**

348 Elevations of hepatic enzyme levels have been reported.

349 Data in the following table are derived from the 133 patients with CLL who received FLUDARA  
350 FOR INJECTION in the MDAH and SWOG studies.

351

**PERCENT OF CLL PATIENTS REPORTING  
NONHEMATOLOGIC ADVERSE EVENTS**

<u>ADVERSE EVENTS</u>	<u>MDAH (N=101)</u>	<u>SWOG (N=32)</u>
ANY ADVERSE EVENT	88%	91%
BODY AS A WHOLE	72	84
FEVER	60	69
CHILLS	11	19
FATIGUE	10	38
INFECTION	33	44
PAIN	20	22
MALAISE	8	6

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PERCENT OF CLL PATIENTS REPORTING  
 NONHEMATOLOGIC ADVERSE EVENTS

<u>ADVERSE EVENTS</u>	<u>MDAH (N=101)</u>	<u>SWOG (N=32)</u>
DIAPHORESIS	1	13
ALOPECIA	0	3
ANAPHYLAXIS	1	0
HEMORRHAGE	1	0
HYPERGLYCEMIA	1	6
DEHYDRATION	1	0
NEUROLOGICAL	21	69
WEAKNESS	9	65
PARESTHESIA	4	12
HEADACHE	3	0
VISUAL DISTURBANCE	3	15
HEARING LOSS	2	6
SLEEP DISORDER	1	3
DEPRESSION	1	0
CEREBELLAR SYNDROME	1	0
IMPAIRED MENTATION	1	0
PULMONARY	35	69
COUGH	10	44
PNEUMONIA	16	22
DYSPNEA	9	22
SINUSITIS	5	0
PHARYNGITIS	0	9
UPPER RESPIRATORY INFECTION	2	16
ALLERGIC PNEUMONITIS	0	6
EPISTAXIS	1	0
HEMOPTYSIS	1	6
BRONCHITIS	1	0
HYPOXIA	1	0
GASTROINTESTINAL	46	63
NAUSEA/VOMITING	36	31
DIARRHEA	15	13
ANOREXIA	7	34
STOMATITIS	9	0
GI BLEEDING	3	13
ESOPHAGITIS	3	0
MUCOSITIS	2	0
LIVER FAILURE	1	0
ABNORMAL LIVER FUNCTION TEST	1	3
CHOLELITHIASIS	0	3
CONSTIPATION	1	3
DYSPHAGIA	1	0
CUTANEOUS	17	18

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 NONHEMATOLOGIC ADVERSE EVENTS**

<u>ADVERSE EVENTS</u>	<u>MDAH (N=101)</u>	<u>SWOG (N=32)</u>
RASH	15	15
PRURITUS	1	3
SEBORRHEA	1	0
GENITOURINARY	12	22
DYSURIA	4	3
URINARY INFECTION	2	15
HEMATURIA	2	3
RENAL FAILURE	1	0
ABNORMAL RENAL FUNCTION TEST	1	0
PROTEINURIA	1	0
HESITANCY	0	3
CARDIOVASCULAR	12	38
EDEMA	8	19
ANGINA	0	6
CONGESTIVE HEART FAILURE	0	3
ARRHYTHMIA	0	3
SUPRAVENTRICULAR TACHYCARDIA	0	3
MYOCARDIAL INFARCTION	0	3
DEEP VENOUS THROMBOSIS	1	3
PHLEBITIS	1	3
TRANSIENT ISCHEMIC ATTACK	1	0
ANEURYSM	1	0
CEREBROVASCULAR ACCIDENT	0	3
MUSCULOSKELETAL	7	16
MYALGIA	4	16
OSTEOPOROSIS	2	0
ARTHRALGIA	1	0
TUMOR LYSIS SYNDROME	1	0

352 More than 3000 adult patients received FLUDARA FOR INJECTION in studies of other  
 353 leukemias, lymphomas, and other solid tumors. The spectrum of adverse effects reported in  
 354 these studies was consistent with the data presented above.

355 **OVERDOSAGE**

356 High doses of FLUDARA FOR INJECTION (see **WARNINGS** section) have been associated  
 357 with an irreversible central nervous system toxicity characterized by delayed blindness, coma  
 358 and death. High doses are also associated with severe thrombocytopenia and neutropenia due  
 359 to bone marrow suppression. There is no known specific antidote for FLUDARA FOR  
 360 INJECTION overdose. Treatment consists of drug discontinuation and supportive therapy.

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361 **DOSAGE AND ADMINISTRATION**

362 **Usual Dose**

363 The recommended adult dose of FLUDARA FOR INJECTION is 25 mg/m<sup>2</sup> administered  
364 intravenously over a period of approximately 30 minutes daily for five consecutive days. Each 5  
365 day course of treatment should commence every 28 days. Dosage may be decreased or  
366 delayed based on evidence of hematologic or nonhematologic toxicity. Physicians should  
367 consider delaying or discontinuing the drug if neurotoxicity occurs.

368 A number of clinical settings may predispose to increased toxicity from FLUDARA FOR  
369 INJECTION. These include advanced age, renal impairment, and bone marrow impairment.  
370 Such patients should be monitored closely for excessive toxicity and the dose modified  
371 accordingly.

372 The optimal duration of treatment has not been clearly established. It is recommended that  
373 three additional cycles of FLUDARA FOR INJECTION be administered following the  
374 achievement of a maximal response and then the drug should be discontinued.

375 **Renal Impairment**

376 Adjustments to the starting dose are recommended to provide appropriate drug exposure in  
377 patients with creatinine clearance 30-79 mL/min, as estimated by the Cockcroft-Gault equations.  
378 These adjustments are based on a pharmacokinetic study in patients with renal impairment.  
379 FLUDARA FOR INJECTION should not be administered to patients with creatinine clearance  
380 less than 30 mL/min.

381  
382 **Starting Dose Adjustment for Renal Impairment**

Creatinine Clearance	Starting Dose
≥ 80 mL/min	25 mg/m <sup>2</sup> (full dose)
50 - 79 mL/min	20 mg/m <sup>2</sup>
30 - 49 mL/min	15 mg/m <sup>2</sup>
< 30 mL/min	do not administer

383  
384 Renally impaired patients should be monitored closely for excessive toxicity and the dose  
385 modified accordingly.

386 **Preparation of Solutions**

387 FLUDARA FOR INJECTION should be prepared for parenteral use by aseptically adding Sterile  
388 Water for Injection, USP. When reconstituted with 2 mL of Sterile Water for Injection, USP, the  
389 solid cake should fully dissolve in 15 seconds or less; each mL of the resulting solution will  
390 contain 25 mg of fludarabine phosphate, 25 mg of mannitol, and sodium hydroxide to adjust the  
391 pH to 7.7. The pH range for the final product is 7.2-8.2. In clinical studies, the product has been  
392 diluted in 100 cc or 125 cc of 5% Dextrose Injection, USP, or 0.9% Sodium Chloride, USP.

393 Reconstituted FLUDARA FOR INJECTION contains no antimicrobial preservative and thus  
394 should be used within 8 hours of reconstitution. Care must be taken to assure the sterility of  
395 prepared solutions. Parenteral drug products should be inspected visually for particulate matter  
396 and discoloration prior to administration.

397 FLUDARA FOR INJECTION should not be mixed with other drugs.

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398 **Handling and Disposal**

399 Procedures for proper handling and disposal should be considered. Consideration should be  
400 given to handling and disposal according to guidelines issued for cytotoxic drugs. Several  
401 guidelines on this subject have been published.<sup>1-4</sup>

402 Caution should be exercised in the handling and preparation of FLUDARA FOR INJECTION  
403 solution. The use of latex gloves and safety glasses is recommended to avoid exposure in case  
404 of breakage of the vial or other accidental spillage. If the solution contacts the skin or mucous  
405 membranes, wash thoroughly with soap and water; rinse eyes thoroughly with plain water.  
406 Avoid exposure by inhalation or by direct contact of the skin or mucous membranes.

407 **HOW SUPPLIED**

408 FLUDARA FOR INJECTION is supplied as a white, lyophilized solid cake. Each vial contains 50  
409 mg of fludarabine phosphate, 50 mg of mannitol, and sodium hydroxide to adjust pH to 7.7. The  
410 pH range for the final product is 7.2-8.2. Store under refrigeration, between 2°-8°C (36°-46°F).

411 FLUDARA FOR INJECTION is supplied in a clear glass single dose vial (6 mL capacity) and  
412 packaged in a single dose vial carton in a shelf pack of five.

413 NDC 58468-0170-1

414 Manufactured by: Ben Venue Laboratories, Bedford, OH 44146

415 Manufactured for: Genzyme Corporation, Cambridge, MA 02142

416 **FLUDARA is a registered trademark exclusively licensed to Genzyme Corporation.**

417 **REFERENCES**

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