

# 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.

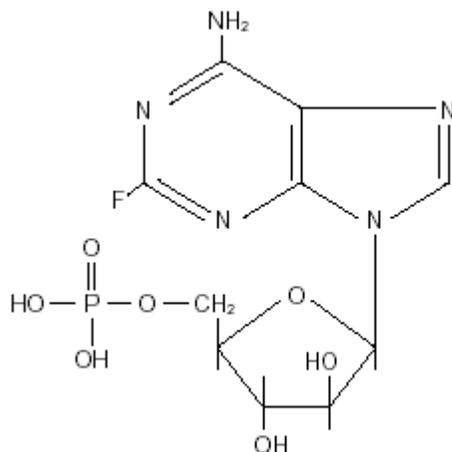
16 Instances of life-threatening and sometimes fatal autoimmune phenomena such as hemolytic  
17 anemia, autoimmune thrombocytopenia/thrombocytopenic purpura (ITP), Evan's syndrome, and  
18 acquired hemophilia have been reported to occur after one or more cycles of treatment with  
19 FLUDARA FOR INJECTION. 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:



36

### 37 **CLINICAL PHARMACOLOGY**

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

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

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

### 53 **Special Populations**

#### 54 *Pediatric Patients*

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

#### 60 *Patients with Renal Impairment*

61 The total body clearance of the principal metabolite 2-fluoro-ara-A correlated with the creatinine  
62 clearance, indicating the importance of the renal excretion pathway for the elimination of the  
63 drug. Renal clearance represents approximately 40% of the total body clearance. Patients with  
64 moderate renal impairment (17 - 41 mL/min/m<sup>2</sup>) receiving 20% reduced Fludara dose had a

65 similar exposure (AUC; 21 versus 20 nM • h/mL) compared to patients with normal renal  
66 function receiving the recommended dose. The mean total body clearance was 172 mL/min for  
67 normal and 124 mL/min for patients with moderately impaired renal function.

## 68 **CLINICAL STUDIES**

69 Two single-arm open-label studies of FLUDARA FOR INJECTION have been conducted in  
70 adult patients with CLL refractory to at least one prior standard alkylating-agent containing  
71 regimen. In a study conducted by M.D. Anderson Cancer Center (MDAH), 48 patients were  
72 treated with a dose of 22-40 mg/m<sup>2</sup> daily for 5 days every 28 days. Another study conducted by  
73 the Southwest Oncology Group (SWOG) involved 31 patients treated with a dose of 15-25  
74 mg/m<sup>2</sup> daily for 5 days every 28 days. The overall objective response rates were 48% and 32%  
75 in the MDAH and SWOG studies, respectively. The complete response rate in both studies was  
76 13%; the partial response rate was 35% in the MDAH study and 19% in the SWOG study.  
77 These response rates were obtained using standardized response criteria developed by the  
78 National Cancer Institute CLL Working Group<sup>3</sup> and were achieved in heavily pre-treated patients.  
79 The ability of FLUDARA FOR INJECTION to induce a significant rate of response in refractory  
80 patients suggests minimal cross-resistance with commonly used anti-CLL agents.

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

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

## 92 **INDICATIONS AND USAGE**

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

## 98 **CONTRAINDICATIONS**

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

## 101 **WARNINGS**

102 (See **BOXED WARNINGS**)

103 There are clear dose dependent toxic effects seen with FLUDARA FOR INJECTION. Dose  
104 levels approximately 4 times greater (96 mg/m<sup>2</sup>/day for 5 to 7 days) than that recommended for  
105 CLL (25 mg/m<sup>2</sup>/day for 5 days) were associated with a syndrome characterized by delayed  
106 blindness, coma and death. Symptoms appeared from 21 to 60 days following the last dose.  
107 Thirteen of 36 patients (36%) who received FLUDARA FOR INJECTION at high doses (96  
108 mg/m<sup>2</sup>/day for 5 to 7 days) developed this severe neurotoxicity. Similar severe central nervous

109 system toxicity, including coma, seizures, agitation and confusion, has been reported in patients  
110 treated at doses in the range of the dose recommended for chronic lymphocytic leukemia.

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

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

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

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

138 Transfusion-associated graft-versus-host disease has been observed after transfusion of non-  
139 irradiated blood in FLUDARA FOR INJECTION treated patients. Fatal outcome as a  
140 consequence of this disease has been reported. Therefore, to minimize the risk of transfusion-  
141 associated graft-versus-host disease, patients who require blood transfusion and who are  
142 undergoing, or who have received, treatment with FLUDARA FOR INJECTION should receive  
143 irradiated blood only.

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

148 Of the 133 adult CLL patients in the two trials, there were 29 fatalities during study.  
149 Approximately 50% of the fatalities were due to infection and 25% due to progressive disease.

#### 150 **Pregnancy Category D**

151 Based on its mechanism of action, fludarabine phosphate can cause fetal harm when  
152 administered to a pregnant woman. There are no adequate and well-controlled studies of  
153 Fludara in pregnant women. Fludarabine phosphate was embryoletal and teratogenic in both  
154 rats and rabbits. If FLUDARA FOR INJECTION is used during pregnancy, or if the patient

155 becomes pregnant while taking this drug, the patient should be apprised of the potential hazard  
156 to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.  
157 Women of childbearing potential and fertile males must take contraceptive measures during and  
158 at least for six months after cessation of treatment with FLUDARA FOR INJECTION.

159  
160 Fludarabine phosphate was embryolethal and teratogenic in rats and rabbits.  
161 Fludarabine phosphate was administered at doses of 0, 1, 10 or 30 mg/kg/day (0.24, 2.4 times  
162 and 7.2 times the recommended human dose on a mg/m<sup>2</sup> basis, respectively) to pregnant rats  
163 on days 6 to 15 of gestation. At 10 and 30 mg/kg/day administered during organogenesis,  
164 there was a dose-related increase in various skeletal variations and a decrease in mean fetal  
165 body weights. Maternal toxicity was not apparent at 10 mg/kg/day, and was limited to slight  
166 body weight decreases at 30 mg/kg/day. In a dose finding study malformations, such as limb  
167 and tail defects, were induced at 40 mg/kg/day (9.6 times the recommended human dose on a  
168 mg/m<sup>2</sup> basis). In a reproduction toxicity study on rabbits Fludarabine phosphate was  
169 administered intravenously at doses of 0, 1, 5 or 8 mg/kg/day (approximately 0.5, 2.4, and 3.8  
170 times the recommended human dose on a mg/m<sup>2</sup> basis) on days 6 to 18 of gestation. A dose  
171 of 8 mg/kg/day administered during organogenesis increased embryo and fetal lethality as  
172 indicated by a higher number of resorptions and a decrease in live fetuses. Compound-related  
173 teratogenic effects manifested by external deformities and skeletal malformations were  
174 observed at 8 mg/kg/day. The most frequent external malformations observed in rabbits were  
175 cleft palate, adactyly, brachydactyly and syndactyly along with skeletal malformations such as  
176 fused metatarsals, phalanges, sternebrae and limb bones and some soft tissue malformations  
177 (diaphragmatic herniae). Fetal body weights were decreased in rabbits given 8 mg/kg/day."

178

## 179 **PRECAUTIONS**

### 180 **General**

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

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

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

195 There are inadequate data on dosing of patients with renal insufficiency. FLUDARA FOR  
196 INJECTION must be administered cautiously in patients with renal insufficiency. The total body  
197 clearance of 2-fluoro-ara-A has been shown to be directly correlated with creatinine clearance.  
198 Patients with moderate impairment of renal function (creatinine clearance 30-70 mL/min/1.73  
199 m<sup>2</sup>) should have their Fludara dose reduced by 20% and be monitored closely. FLUDARA FOR  
200 INJECTION is not recommended for patients with severely impaired renal function (creatinine  
201 clearance less than 30 mL/min/1.73 m<sup>2</sup>).

202 Fludara may reduce the ability to drive or use machines, since fatigue, weakness, visual  
203 disturbances, confusion, agitation and seizures have been observed.

#### 204 **Laboratory Tests**

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

#### 207 **Drug Interactions**

208 The use of FLUDARA FOR INJECTION in combination with pentostatin is not recommended  
209 due to the risk of severe pulmonary toxicity (see WARNINGS section).

#### 210 **Carcinogenesis**

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

#### 212 **Mutagenesis**

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

#### 220 **Impairment of Fertility**

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

#### 226 **Pregnancy**

227 Pregnancy Category D: (see WARNINGS section).

228

#### 229 **Nursing Mothers**

230 It is not known whether fludarabine phosphate is excreted in human milk. Because many drugs  
231 are excreted in human milk and because of the potential for serious adverse reactions including  
232 tumorigenicity in nursing infants, a decision should be made to discontinue nursing or  
233 discontinue the drug, taking into account the importance of the drug to the mother.  
234

#### 235 **Pediatric Use**

236 Data submitted to the FDA was insufficient to establish efficacy in any childhood malignancy.  
237 Fludarabine was evaluated in 62 pediatric patients (median age 10, range 1-21) with refractory  
238 acute leukemia (45 patients) or solid tumors (17 patients). The fludarabine regimen tested for  
239 pediatric acute lymphocytic leukemia (ALL) patients was a loading bolus of 10.5 mg/m<sup>2</sup>/day  
240 followed by a continuous infusion of 30.5 mg/m<sup>2</sup>/day for 5 days. In 12 pediatric patients with  
241 solid tumors, dose-limiting myelosuppression was observed with a loading dose of 8 mg/m<sup>2</sup>/day  
242 followed by a continuous infusion of 23.5 mg/m<sup>2</sup>/day for 5 days. The maximum tolerated dose  
243 was a loading dose of 7 mg/m<sup>2</sup>/day followed by a continuous infusion of 20 mg/m<sup>2</sup>/day for 5  
244 days. Treatment toxicity included bone marrow suppression. Platelet counts appeared to be  
245 more sensitive to the effects of fludarabine than hemoglobin and white blood cell counts. Other  
246 adverse events included fever, chills, asthenia, rash, nausea, vomiting, diarrhea, and infection.

247 There were no reported occurrences of peripheral neuropathy or pulmonary hypersensitivity  
248 reaction.

#### 249 **Vaccination**

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

#### 252 **Disease Progression**

253 Disease progression and transformation (e.g. Richter's syndrome) have been reported in CLL  
254 patients.

#### 255 **ADVERSE REACTIONS**

256 The most common adverse events include myelosuppression (neutropenia, thrombocytopenia  
257 and anemia), fever and chills, infection, and nausea and vomiting. Other commonly reported  
258 events include malaise, fatigue, anorexia, and weakness. Serious opportunistic infections have  
259 occurred in CLL patients treated with FLUDARA FOR INJECTION. Adverse events, and those  
260 reactions which are more clearly related to the drug are arranged below according to body  
261 system.

262 **Hematopoietic Systems** Hematologic events (neutropenia, thrombocytopenia, and/or anemia)  
263 were reported in the majority of CLL patients treated with FLUDARA FOR INJECTION. During  
264 FLUDARA FOR INJECTION treatment of 133 patients with CLL, the absolute neutrophil count  
265 decreased to less than 500/mm<sup>3</sup> in 59% of patients, hemoglobin decreased from pretreatment  
266 values by at least 2 grams percent in 60%, and platelet count decreased from pretreatment  
267 values by at least 50% in 55%. Myelosuppression may be severe, cumulative, and may affect  
268 multiple cell lines. Bone marrow fibrosis occurred in one CLL patient treated with FLUDARA  
269 FOR INJECTION.

270 Several instances of trilineage bone marrow hypoplasia or aplasia resulting in pancytopenia,  
271 sometimes resulting in death, have been reported in postmarketing surveillance. The duration  
272 of clinically significant cytopenia in the reported cases has ranged from approximately 2 months  
273 to approximately 1 year. These episodes have occurred both in previously treated or untreated  
274 patients.

275 Life-threatening and sometimes fatal autoimmune phenomena such as hemolytic anemia,  
276 autoimmune thrombocytopenia/thrombocytopenic purpura (ITP), Evan's syndrome, and  
277 acquired hemophilia have been reported to occur in patients receiving FLUDARA FOR  
278 INJECTION (see WARNINGS section). The majority of patients rechallenged with FLUDARA  
279 FOR INJECTION developed a recurrence in the hemolytic process.

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

283 **Infections** Serious, and sometimes fatal infections, including opportunistic infections and  
284 reactivations of latent viral infections such as VZV (Herpes zoster), Epstein-Barr virus and JC  
285 virus (progressive multifocal leukoencephalopathy)) have been reported in patients treated with  
286 FLUDARA FOR INJECTION.

287 Rare cases of Epstein Barr Virus (EBV) associated lymphoproliferative disorders have been  
288 reported in patients treated with FLUDARA FOR INJECTION.

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

293 **Nervous System** (See WARNINGS section) Objective weakness, agitation, confusion,  
294 seizures, [visual disturbances, optic neuritis, optic neuropathy, blindness and coma have  
295 occurred in CLL patients treated with FLUDARA FOR INJECTION at the recommended dose.  
296 Peripheral neuropathy has been observed in patients treated with FLUDARA FOR INJECTION  
297 and one case of wrist-drop was reported.

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

302 **Pulmonary System** Pneumonia, a frequent manifestation of infection in CLL patients, occurred  
303 in 16%, and 22% of those treated with FLUDARA FOR INJECTION in the MDAH and SWOG  
304 studies, respectively. Pulmonary hypersensitivity reactions to FLUDARA FOR INJECTION  
305 characterized by dyspnea, cough and interstitial pulmonary infiltrate have been observed.

306 In post-marketing experience, cases of severe pulmonary toxicity have been observed with  
307 Fludara use which resulted in ARDS, respiratory distress, pulmonary hemorrhage, pulmonary  
308 fibrosis, and respiratory failure. After an infectious origin has been excluded, some patients  
309 experienced symptom improvement with corticosteroids.

310 **Gastrointestinal System** Gastrointestinal disturbances such as nausea and vomiting, anorexia,  
311 diarrhea, stomatitis and gastrointestinal bleeding have been reported in patients treated with  
312 FLUDARA FOR INJECTION.

313 **Cardiovascular** Edema has been frequently reported. One patient developed a pericardial  
314 effusion possibly related to treatment with FLUDARA FOR INJECTION. No other severe  
315 cardiovascular events were considered to be drug related.

316 **Genitourinary System** Rare cases of hemorrhagic cystitis have been reported in patients  
317 treated with FLUDARA FOR INJECTION.

318 **Skin** Skin toxicity, consisting primarily of skin rashes, has been reported in patients treated with  
319 FLUDARA FOR INJECTION.

320 Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and pemphigus  
321 have been reported, with fatal outcomes in some cases.

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

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

326

#### PERCENT OF CLL PATIENTS REPORTING NON-HEMATOLOGIC 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

**PERCENT OF CLL PATIENTS REPORTING  
NON-HEMATOLOGIC ADVERSE EVENTS**

<u>ADVERSE EVENTS</u>	<u>MDAH (N=101)</u>	<u>SWOG (N=32)</u>
INFECTION	33	44
PAIN	20	22
MALaise	8	6
DIAPHORESIS	1	13
ALOPECIA	0	3
ANAPHYLAXIS	1	0
HEMORRHAGE	1	0
HYPERGLYCEMIA	1	6
DEHYDRATION	1	0
<b>NEUROLOGICAL</b>	<b>21</b>	<b>69</b>
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
<b>PULMONARY</b>	<b>35</b>	<b>69</b>
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
<b>GASTROINTESTINAL</b>	<b>46</b>	<b>63</b>
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

**PERCENT OF CLL PATIENTS REPORTING  
NON-HEMATOLOGIC ADVERSE EVENTS**

<u>ADVERSE EVENTS</u>	<u>MDAH (N=101)</u>	<u>SWOG (N=32)</u>
DYSPHAGIA	1	0
CUTANEOUS	17	18
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

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

330 **OVERDOSAGE**

331 High doses of FLUDARA FOR INJECTION (see WARNINGS section) have been associated  
 332 with an irreversible central nervous system toxicity characterized by delayed blindness, coma  
 333 and death. High doses are also associated with severe thrombocytopenia and neutropenia due

334 to bone marrow suppression. There is no known specific antidote for FLUDARA FOR  
335 INJECTION overdose. Treatment consists of drug discontinuation and supportive therapy.

## 336 **DOSAGE AND ADMINISTRATION**

### 337 **Usual Dose**

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

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

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

### 350 **Renal Insufficiency**

351 Adult patients with moderate impairment of renal function (creatinine clearance 30-70  
352 mL/min/1.73 m<sup>2</sup>) should have a 20% dose reduction of FLUDARA FOR INJECTION. FLUDARA  
353 FOR INJECTION should not be administered to patients with severely impaired renal function  
354 (creatinine clearance less than 30 mL/min/1.73 m<sup>2</sup>).

### 355 **Preparation of Solutions**

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

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

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

### 367 **Handling and Disposal**

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

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

376 **HOW SUPPLIED**

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

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

382 NDC 50419-511-06

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

384 Manufactured for: Bayer HealthCare Pharmaceuticals Inc., Wayne, NJ 07470

385 U.S. Patent Number: 4,357,324

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