

Fludara®

fludarabine phosphate

FOR INJECTION**FOR INTRAVENOUS USE ONLY****Rx Only**

WARNING: FLUDARA FOR INJECTION should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy. FLUDARA FOR INJECTION can severely suppress bone marrow function. When used at high doses in dose-ranging studies in patients with acute leukemia, FLUDARA FOR INJECTION was associated with severe neurologic effects, including blindness, coma, and death. This severe central nervous system toxicity occurred in 36% of patients treated with doses approximately four times greater (96 mg/m²/day for 5-7 days) than the recommended dose. Similar severe central nervous system toxicity, including coma, seizures, agitation and confusion, has been reported in patients treated at doses in the range of the dose recommended for chronic lymphocytic leukemia.

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

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

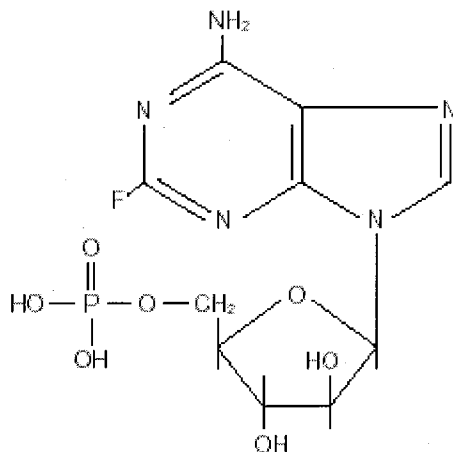
DESCRIPTION

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

The chemical name for fludarabine phosphate is 9H-Purin-6-amine, 2-fluoro-9-(5-β-D-phosphono-β-D-arabino-furanosyl) (2-fluoro-ara-AMP). The molecular formula of fludarabine phosphate is C₁₀H₁₃FN₅O₇P (MW 365.2) and the structure is:

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36



37

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/m² 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/m² 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/m² 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/mm³ to 103,300/mm³ 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**)

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/m²/day for 5 to 7 days) than that recommended for
107 CLL (25 mg/m²/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/m²/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.

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/m²) 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 (≥ 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/m²/day followed by a continuous infusion of 30.5 mg/m²/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/m²/day followed by a continuous infusion of 23.5 mg/m²/day for 5 days.
255 The maximum tolerated dose was a loading dose of 7 mg/m²/day followed by a continuous
256 infusion of 20 mg/m²/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/mm³ 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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PERCENT OF CLL PATIENTS REPORTING
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/m² 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 **Starting Dose Adjustment for Renal Impairment**
382

Creatinine Clearance	Starting Dose
≥ 80 mL/min	25 mg/m ² (full dose)
50 - 79 mL/min	20 mg/m ²
30 - 49 mL/min	15 mg/m ²
< 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.

PROPOSED TEXT OF THE LABELING OF THE DRUG

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.¹⁻⁴

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.**

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