

1     **WARNING**

2  
3     Campath should be administered under the supervision of a physician experienced in  
4     the use of antineoplastic therapy.

5     • **Hematologic Toxicity:** Serious and, in rare instances fatal, pancytopenia/  
6     marrow hypoplasia, autoimmune idiopathic thrombocytopenia, and autoimmune  
7     hemolytic anemia have occurred in patients receiving Campath therapy. **Single  
8     doses of Campath greater than 30 mg or cumulative doses greater than 90 mg  
9     per week should not be administered because these doses are associated with  
10     a higher incidence of pancytopenia.**

11     • **Infusion Reactions:** Campath can result in serious infusion reactions. Patients  
12     should be carefully monitored during infusions and Campath discontinued if  
13     indicated. (See DOSAGE AND ADMINISTRATION.) **Gradual escalation to  
14     the recommended maintenance dose is required at the initiation of therapy  
15     and after interruption of therapy for 7 or more days.**

16     • **Infections, Opportunistic Infections:** Serious, sometimes fatal bacterial, viral,  
17     fungal, and protozoan infections have been reported in patients receiving Campath  
18     therapy. Prophylaxis directed against *Pneumocystis carinii* pneumonia (PCP) and  
19     herpes virus infections has been shown to decrease, but not eliminate, the  
20     occurrence of these infections.

21     **Campath® (ALEMTUZUMAB)**

22     **DESCRIPTION**

23     Campath® (Alemtuzumab) is a recombinant DNA-derived humanized monoclonal antibody  
24     (Campath-1H) that is directed against the 21-28 kD cell surface glycoprotein, CD52. CD52 is  
25     expressed on the surface of normal and malignant B and T lymphocytes, NK cells, monocytes,  
26     macrophages, and tissues of the male reproductive system. The Campath-1H antibody is an IgG1  
27     kappa with human variable framework and constant regions, and complementarity-determining  
28     regions from a murine (rat) monoclonal antibody (Campath-1G). The Campath-1H antibody has  
29     an approximate molecular weight of 150 kD.

30     Campath is produced in mammalian cell (Chinese hamster ovary) suspension culture in a medium  
31     containing neomycin. Neomycin is not detectable in the final product. Campath is a sterile, clear,  
32     colorless, isotonic pH 6.8-7.4 solution for injection. Each single use ampoule of Campath

30 contains 30 mg Alemtuzumab, 24.0 mg sodium chloride, 3.5 mg dibasic sodium phosphate,  
31 0.6 mg potassium chloride, 0.6 mg monobasic potassium phosphate, 0.3 mg polysorbate 80, and  
32 0.056 mg disodium edetate. No preservatives are added.

### 33 CLINICAL PHARMACOLOGY

#### 34 **General:**

35 Alemtuzumab binds to CD52, a non-modulating antigen that is present on the surface of  
36 essentially all B and T lymphocytes, a majority of monocytes, macrophages, and NK cells, and a  
37 subpopulation of granulocytes. Analysis of samples collected from multiple volunteers has not  
38 identified CD52 expression on erythrocytes or hematopoietic stem cells. The proposed  
39 mechanism of action is antibody-dependent lysis of leukemic cells following cell surface  
40 binding. Campath-1H Fab binding was observed in lymphoid tissues and the mononuclear  
41 phagocyte system. A proportion of bone marrow cells, including some CD34<sup>+</sup> cells, express  
42 variable levels of CD52. Significant binding was also observed in the skin and male  
43 reproductive tract (epididymis, sperm, seminal vesicle). Mature spermatozoa stain for CD52, but  
44 neither spermatogenic cells nor immature spermatozoa show evidence of staining.

#### 45 **Human Pharmacokinetics:**

46 The pharmacokinetic profile of Alemtuzumab was studied in a multicenter rising-dose trial in  
47 non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukemia (CLL). Campath was  
48 administered once weekly for a maximum of 12 weeks. Following intravenous infusions over a  
49 range of doses, the maximum serum concentration ( $C_{max}$ ) and the area under the curve (AUC)  
50 showed relative dose proportionality. The overall average half-life ( $t_{1/2}$ ) over the dosing interval  
51 was about 12 days. The pharmacokinetic profile of Campath administered as a 30 mg intravenous  
52 infusion three times per week was evaluated in CLL patients. Peak and trough levels of Campath  
53 rose during the first few weeks of treatment, and appeared to approach steady state by  
54 approximately week 6, although there was marked inter-patient variability. The rise in serum  
55 Campath concentration corresponded with the reduction in malignant lymphocytosis.

### 56 CLINICAL STUDIES

57 The safety and efficacy of Campath were evaluated in a multicenter, open-label, noncomparative  
58 study (Study 1) of 93 patients with B-cell chronic lymphocytic leukemia (B-CLL) who had been  
59 previously treated with alkylating agents and had failed treatment with fludarabine. Fludarabine  
60 failure was defined as lack of an objective partial (PR) or complete (CR) response to at least one  
61 fludarabine-containing regimen, progressive disease (PD) while on fludarabine treatment, or  
62 relapse within 6 months of the last dose of fludarabine. Patients were gradually escalated to a  
63 maintenance dose of Campath 30 mg intravenously three times per week for 4 to 12 weeks.  
64 Patients received premedication prior to infusion and anti-*Pneumocystis carinii* and anti-herpes  
65 prophylaxis while on treatment and for at least 2 months after the last dose of Campath.

66 Two supportive, multicenter, open-label, noncomparative studies of Campath enrolled a total of  
67 56 patients with B-CLL (Studies 2 and 3). These patients had been previously treated with  
68 fludarabine or other chemotherapies. In Studies 2 and 3, the maintenance dose of Campath was  
69 30 mg three times per week with treatment cycles of 8 and 6 weeks respectively. A slightly

70 different dose escalation scheme was used in these trials. Premedication to ameliorate infusional  
71 reactions and anti-*Pneumocystis carinii* and anti-herpes prophylaxis were optional.

72 Objective tumor response rates and duration of response were determined using the NCI Working  
73 Group Response Criteria (1996). A comparison of patient characteristics and the results for each  
74 of these studies is summarized in Table 1. Time to event parameters, except for duration of  
75 response, are calculated from initiation of Campath therapy. Duration of response is calculated  
76 from the onset of the response.

77 **Table 1: Summary of Patient Population and Outcomes**

	Study 1 (N = 93)	Study 2 (N = 32)	Study 3 (N = 24)
<b>Median Age in Years (Range)</b>	<b>66 (32 – 68)</b>	<b>57 (46 - 75)</b>	<b>62 (44 - 77)</b>
<b>Median Number of Prior Regimens (Range)</b>	<b>3 (2 – 7)</b>	<b>3 (1 – 10)</b>	<b>3 (1 – 8)</b>
<b>Prior Therapies:</b>			
Alkylating Agents	100%	100%	92%
Fludarabine	100%	34%	100%
<b>Disease Characteristics:</b>			
Rai Stage III / IV Disease	76%	72%	71%
B-Symptoms	42%	31%	21%
<b>Overall Response Rate (95% Confidence Interval)</b>	<b>33% (23%, 43%)</b>	<b>21% ( 8%, 33%)</b>	<b>29% (11%, 47%)</b>
Complete Response	2%	0%	0%
Partial Response	31%	21%	29%
<b>Median Duration of Response (months) (95% Confidence Interval)</b>	<b>7 (5, 8)</b>	<b>7 (5, 23)</b>	<b>11 (6, 19)</b>
<b>Median Time to Response (months) (95% Confidence Interval)</b>	<b>2 (1, 2)</b>	<b>4 (1, 5)</b>	<b>4 (2, 4)</b>
<b>Progression-Free Survival (months) (95% Confidence Interval)</b>	<b>4 (3, 5)</b>	<b>5 (3, 7)</b>	<b>7 (3, 9)</b>

78 **INDICATIONS AND USAGE**

79 Campath is indicated for the treatment of B-cell chronic lymphocytic leukemia (B-CLL) in  
80 patients who have been treated with alkylating agents and who have failed fludarabine therapy.  
81 Determination of the effectiveness of Campath is based on overall response rates. (See  
82 CLINICAL STUDIES.) Comparative, randomized trials demonstrating increased survival or  
83 clinical benefits such as improvement in disease-related symptoms have not yet been conducted.

84 **CONTRAINDICATIONS**

85 Campath is contraindicated in patients who have active systemic infections, underlying  
86 immunodeficiency (e.g., seropositive for HIV), or known Type I hypersensitivity or anaphylactic  
87 reactions to Campath or to any one of its components.

88 **WARNINGS (See BOXED WARNING.)**

89 **Infusion-Related Events:**

90 Campath has been associated with infusion-related events including hypotension, rigors, fever,  
91 shortness of breath, bronchospasm, chills, and/or rash. In order to ameliorate or avoid infusion-  
92 related events, patients should be premedicated with an oral antihistamine and acetaminophen  
93 prior to dosing and monitored closely for infusion-related adverse events. In addition, Campath  
94 should be initiated at a low dose with gradual escalation to the effective dose. Careful monitoring  
95 of blood pressure and hypotensive symptoms is recommended especially in patients with  
96 ischemic heart disease and in patients on antihypertensive medications. If therapy is interrupted  
97 for 7 or more days, Campath should be reinstated with gradual dose escalation. (See  
98 ADVERSE EVENTS and DOSAGE AND ADMINISTRATION.)

99 **Immunosuppression/Oppportunistic Infections:**

100 Campath induces profound lymphopenia. A variety of opportunistic infections have been reported  
101 in patients receiving Campath therapy (see ADVERSE EVENTS, Infections). If a serious  
102 infection occurs, Campath therapy should be interrupted and may be reinitiated following the  
103 resolution of the infection.

104 Anti-infective prophylaxis is recommended upon initiation of therapy and for a minimum of 2  
105 months following the last dose of Campath or until CD4<sup>+</sup> counts are  $\geq 200$  cells/ $\mu$ L. The median  
106 time to recovery of CD4<sup>+</sup> counts to  $\geq 200/\mu$ L was 2 months, however, full recovery (to baseline)  
107 of CD4<sup>+</sup> and CD8<sup>+</sup> counts may take more than 12 months. (See BOXED WARNING and  
108 DOSAGE AND ADMINISTRATION.)

109 Because of the potential for Graft versus Host Disease (GVHD) in severely lymphopenic  
110 patients, irradiation of any blood products administered prior to recovery from lymphopenia is  
111 recommended.

112 **Hematologic Toxicity:**

113 Severe, prolonged, and in rare instances fatal, myelosuppression has occurred in patients with  
114 leukemia and lymphoma receiving Campath. Bone marrow aplasia and hypoplasia were  
115 observed in the clinical studies at the recommended dose. The incidence of these complications  
116 increased with doses above the recommended dose. In addition, severe and fatal autoimmune  
117 anemia and thrombocytopenia were observed in patients with CLL. Campath should be  
118 discontinued for severe hematologic toxicity (see Table 3 Dose Modification and Reinitiation of  
119 Therapy for Hematologic Toxicity) or in any patient with evidence of autoimmune hematologic  
120 toxicity. Following resolution of transient, non-immune myelosuppression, Campath may be  
121 reinitiated with caution. (See DOSAGE AND ADMINISTRATION.) There is no information on  
122 the safety of resumption of Campath in patients with autoimmune cytopenias or marrow aplasia.  
123 (See ADVERSE REACTIONS.)

124 **PRECAUTIONS**

125 **Laboratory Monitoring:**

126 Complete blood counts (CBC) and platelet counts should be obtained at weekly intervals during  
127 Campath therapy and more frequently if worsening anemia, neutropenia, or thrombocytopenia is  
128 observed on therapy. CD4<sup>+</sup> counts should be assessed after treatment until recovery to ≥ 200  
129 cells/μL. (See WARNINGS and ADVERSE REACTIONS.)

130 **Drug/Laboratory Interactions:**

131 No formal drug interaction studies have been performed with Campath. An immune response to  
132 Campath may interfere with subsequent diagnostic serum tests that utilize antibodies.

133 **Immunization:**

134 Patients who have recently received Campath, should not be immunized with live viral vaccines,  
135 due to their immunosuppression. The safety of immunization with live viral vaccines following  
136 Campath therapy has not been studied. The ability to generate a primary or anamnestic humoral  
137 response to any vaccine following Campath therapy has not been studied.

138 **Immunogenicity:**

139 Four (1.9%) of 211 patients evaluated for development of an immune response were found to  
140 have antibodies to Campath. The data reflect the percentage of patients whose test results were  
141 considered positive for antibody to Campath in a kinetic enzyme immunoassay, and are highly  
142 dependent on the sensitivity and specificity of the assay. The observed incidence of antibody  
143 positivity may be influenced by several additional factors including sample handling,  
144 concomitant medications and underlying disease. For these reasons, comparison of the incidence  
145 of antibodies to Campath with the incidence of antibodies to other products may be misleading.  
146 Patients who develop hypersensitivity to Campath may have allergic or hypersensitivity reactions  
147 to other monoclonal antibodies.

148 **Carcinogenesis, Mutagenesis, Impairment of Fertility:**

149 No long-term studies in animals have been performed to establish the carcinogenic or mutagenic  
150 potential of Campath, or to determine its effects on fertility in males or females. Women of  
151 childbearing potential and men of reproductive potential should use effective contraceptive  
152 methods during treatment and for a minimum of 6 months following Campath therapy.

153 **Pregnancy Category C:**

154 Animal reproduction studies have not been conducted with Campath. It is not known whether  
155 Campath can affect reproductive capacity or cause fetal harm when administered to a pregnant  
156 woman. However, human IgG is known to cross the placental barrier and therefore Campath may  
157 cross the placental barrier and cause fetal B and T lymphocyte depletion. Campath should be  
158 given to a pregnant woman only if clearly needed.

159 **Nursing Mothers:**

160 Excretion of Campath in human breast milk has not been studied. Because many drugs including  
161 human IgG are excreted in human milk, breast-feeding should be discontinued during treatment  
162 and for at least 3 months following the last dose of Campath.

163 **Pediatric Use:**

164 The safety and effectiveness of Campath in children have not been established.

165 **Geriatric Use:**

166 Of the 149 patients with B-CLL enrolled in the three clinical studies, 66 (44%) were 65 and  
167 over, while 15 (10%) were 75 and over. Substantial differences in safety and efficacy related to  
168 age were not observed; however the size of the database is not sufficient to exclude important  
169 differences.

170 **ADVERSE REACTIONS**

171 Because clinical trials are conducted under widely varying conditions, adverse reaction rates  
172 observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials  
173 of another drug and may not reflect the rates observed in practice. The adverse reaction  
174 information from clinical trials does, however, provide a basis for identifying the adverse events  
175 that appear to be related to drug use and for approximating rates.

176 Safety data, except where indicated, are based on 149 patients with B-CLL enrolled in studies of  
177 Campath as a single agent administered at a maintenance dose of 30 mg intravenously three times  
178 weekly for 4 to 12 weeks. Table 2 lists adverse events including severe or life threatening (NCI-  
179 CTC Grade 3 or 4) adverse events reported in > 5% of the patients. More detailed information  
180 and follow-up were available for Study 1 (93 patients), therefore the narrative description of  
181 certain events, noted below, is based on this study.

182 **Infusion-Related Adverse Events:**

183 Infusion-related adverse events resulted in discontinuation of Campath therapy in 6% of the  
184 patients enrolled in Study 1. The most commonly reported infusion-related adverse events on this  
185 study included rigors in 89% of patients, drug-related fever in 83%, nausea in 47%, vomiting in  
186 33%, and hypotension in 15%. Other frequently reported infusion-related events include, rash in  
187 30% of patients, fatigue in 22%, urticaria in 22%, dyspnea in 17%, pruritus in 14%, headache in  
188 13%, and diarrhea in 13%. Similar types of adverse events were reported on the supporting  
189 studies (see Table 2). Acute infusion-related events were most common during the first week of  
190 therapy. Antihistamines, acetaminophen, antiemetics, meperidine, and corticosteroids as well as  
191 incremental dose escalation were used to prevent or ameliorate infusion-related events. (See  
192 WARNINGS and DOSAGE AND ADMINISTRATION.)

193 **Infections:**

194 On Study 1, all patients were required to receive anti-herpes and anti-PCP prophylaxis (see  
195 DOSAGE AND ADMINISTRATION) and were followed for infections for 6 months. Forty  
196 (43%) of 93 patients experienced 59 infections (one or more infections per patient) related to

197 Campath during treatment or within 6 months of the last dose. Of these, 34 (37%) patients  
198 experienced 42 infections that were of Grade 3 or 4 severity; 11 (18%) were fatal. Fifty-five  
199 percent of the Grade 3 or 4 infections occurred during treatment or within 30 days of last dose. In  
200 addition one or more episodes of febrile neutropenia (ANC  $\leq$  500/ $\mu$ L) were reported in 10% of  
201 patients.

202 The following types of infections were reported in Study 1: Grade 3 or 4 sepsis in 12% of  
203 patients with one fatality, Grade 3 or 4 pneumonia in 15% with five fatalities, and opportunistic  
204 infections in 17% with four fatalities. Candida infections were reported in 5% of patients; CMV  
205 infections in 8% (4% of Grade 3 or 4 severity); Aspergillosis in 2% with fatal Aspergillosis in  
206 1%; fatal Mucormycosis in 2%; fatal Cryptococcal pneumonia in 1%; *Listeria monocytogenes*  
207 meningitis in 1%; disseminated *Herpes zoster* in 1%; Grade 3 *Herpes simplex* in 2%; and  
208 Torulopsis pneumonia in 1%. PCP pneumonia occurred in one (1%) patient who discontinued  
209 PCP prophylaxis.

210 On Studies 2 and 3 in which anti-herpes and anti-PCP prophylaxis was optional, 37 (66%)  
211 patients had 47 infections while or after receiving Campath therapy. In addition to the  
212 opportunistic infections reported above, the following types of related events were observed on  
213 these studies: interstitial pneumonitis of unknown etiology and progressive multifocal  
214 leukoencephalopathy.

#### 215 **Hematologic Adverse Events:**

216 Pancytopenia/Marrow Hypoplasia: Campath therapy was permanently discontinued in six (6%)  
217 patients due to pancytopenia/marrow hypoplasia. Two (2%) cases of pancytopenia/ marrow  
218 hypoplasia were fatal.

219 Anemia: Forty-four (47%) patients had one or more episodes of new onset NCI-CTC Grade 3 or  
220 4 anemia. Sixty-two (67%) patients required RBC transfusions. In addition, erythropoietin use  
221 was reported in nineteen (20%) patients. Autoimmune hemolytic anemia secondary to Campath  
222 therapy was reported in 1% of patients. Positive Coombs test without hemolysis was reported in  
223 2%. (See BOXED WARNING.)

224 Neutropenia: Sixty-five (70%) patients had one or more episodes of NCI-CTC Grade 3 or 4  
225 neutropenia. Median duration of Grade 3 or 4 neutropenia was 28 days (range: 2 – 165 days).  
226 (See Infections.)

227 Thrombocytopenia: Forty-eight (52%) patients had one or more episodes of new onset Grade 3  
228 or 4 thrombocytopenia. Median duration of thrombocytopenia was 21 days (range: 2 – 165 days).  
229 Thirty-five (38%) patients required platelet transfusions for management of thrombocytopenia.  
230 Autoimmune thrombocytopenia was reported in 2% of patients with one fatal case of Campath-  
231 related autoimmune thrombocytopenia. (See BOXED WARNING.)

232 Lymphopenia: The median CD4<sup>+</sup> count at 4 weeks after initiation of Campath therapy was 2  
233 (two) / $\mu$ L, at 2 months after discontinuation of Campath therapy, 207/ $\mu$ L, and 6 months after  
234 discontinuation, 470/ $\mu$ L. The pattern of change in median CD8<sup>+</sup> lymphocyte counts was similar to  
235 that of CD4<sup>+</sup> cells. In some patients treated with Campath, CD4<sup>+</sup> and CD8<sup>+</sup> lymphocyte counts  
236 had not returned to baseline levels at longer than 1 year post therapy.

237  
238

**Table 2: Adverse Events in > 5% of the B-CLL Study Population  
During Treatment or Within 30 Days (N = 149)**

Adverse Event:	B-CLL STUDIES (N = 149)	
	ANY Grade (%)	Grade 3 or 4 (%)
<b>Body As A Whole</b>		
Rigors	86	16
Fever	85	19
Fatigue	34	5
Pain, Skeletal Pain	24	2
Anorexia	20	3
Asthenia	13	4
Edema, Peripheral Edema	13	1
Back Pain	10	3
Chest Pain	10	1
Malaise	9	1
Temperature Change Sensation	5	--
<b>Cardiovascular Disorders, General</b>		
Hypotension	32	5
Hypertension	11	2
<b>Heart Rate &amp; Rhythm Disorders</b>		
Tachycardia, SVT	11	3
<b>Central &amp; Peripheral Nervous System Disorders</b>		
Headache	24	1
Dysthesias	15	--
Dizziness	12	1
Tremor	7	--
<b>Gastrointestinal Disorders</b>		
Nausea	54	2
Vomiting	41	4
Diarrhea	22	1
Stomatitis, Ulcerative Stomatitis, Mucositis	14	1
Abdominal Pain	11	2
Dyspepsia	10	--
Constipation	9	1
<b>Hematologic Disorders</b>		
WBC Disorders: Neutropenia	85	64
RBC Disorders: Anemia	80	38
Pancytopenia	5	3
<b>Platelet, Bleeding &amp; Clotting Disorders:</b>		
Thrombocytopenia	72	50
Purpura	8	-
Epistaxis	7	1

Adverse Event:	B-CLL STUDIES (N = 149)	
	ANY Grade (%)	Grade 3 or 4 (%)
<b>Musculoskeletal Disorders</b>		
Myalgias	11	--
<b>Psychiatric Disorders</b>		
Insomnia	10	--
Depression	7	1
Somnolence	5	1
<b>Resistance Mechanism Disorders</b>		
Sepsis	15	10
Herpes Simplex	11	1
Moniliasis	8	1
Infection (other viral or unidentified)	7	1
<b>Respiratory System Disorders</b>		
Dyspnea	26	9
Cough	25	2
Bronchitis, Pneumonitis	21	13
Pneumonia	16	10
Pharyngitis	12	--
Bronchospasm	9	2
Rhinitis	7	--
<b>Skin &amp; Appendage Disorders</b>		
Rash, Maculopapular Rash, Erythematous Rash	40	3
Urticaria	30	5
Pruritus	24	1
Sweating increased	19	1

239 **Serious adverse events:**

240 The following serious adverse events, defined as events which result in death, requiring or  
241 prolonging hospitalization, requiring medical intervention to prevent hospitalization, or  
242 malignancy, were reported in at least one patient treated on studies where Campath was used as a  
243 single agent (and are not reported in Table 2). These studies were conducted in patients with  
244 lymphocytic leukemia and lymphoma (N = 745) and in patients with non-malignant diseases (N  
245 =152) such as rheumatoid arthritis, solid organ transplant, or multiple sclerosis.

246 Body As A Whole: allergic reactions, anaphylactoid reaction, ascites, hypovolemia, influenza-  
247 like syndrome, mouth edema, neutropenic fever, syncope

248 Cardiovascular Disorders: cardiac failure, cyanosis, atrial fibrillation, cardiac arrest, ventricular  
249 arrhythmia, ventricular tachycardia, angina pectoris, coronary artery disorder, myocardial  
250 infarction, pericarditis

251 Central and Peripheral Nervous System Disorders: abnormal gait, aphasia, coma, grand mal  
252 convulsions, paralysis, meningitis

- 253 Endocrine Disorders: hyperthyroidism
- 254 Gastrointestinal System Disorders: duodenal ulcer, esophagitis, gingivitis, gastroenteritis, GI  
255 hemorrhage, hematemesis, hemorrhoids, intestinal obstruction, intestinal perforation, melena,  
256 paralytic ileus, peptic ulcer, pseudomembranous colitis, colitis, pancreatitis, peritonitis,  
257 hyperbilirubinemia, hepatic failure, hepatocellular damage, hypoalbuminemia, biliary pain
- 258 Hearing and Vestibular Disorders: decreased hearing
- 259 Metabolic and Nutritional Disorders: acidosis, aggravated diabetes mellitus, dehydration, fluid  
260 overload, hyperglycemia, hyperkalemia, hypokalemia, hypoglycemia, hyponatremia, increased  
261 alkaline phosphatase, respiratory alkalosis
- 262 Musculoskeletal System Disorders: arthritis or worsening arthritis, arthropathy, bone fracture,  
263 myositis, muscle atrophy, muscle weakness, osteomyelitis, polymyositis
- 264 Neoplasms: malignant lymphoma, malignant testicular neoplasm, prostatic cancer, plasma cell  
265 dyscrasia, secondary leukemia, squamous cell carcinoma, transformation to aggressive  
266 lymphoma, transformation to prolymphocytic leukemia
- 267 Platelet, Bleeding, and Clotting Disorders: coagulation disorder, disseminated intravascular  
268 coagulation, hematoma, pulmonary embolism, thrombocytopenia
- 269 Psychiatric Disorders: confusion, hallucinations, nervousness, abnormal thinking, apathy
- 270 White Cell and RES Disorders: agranulocytosis, aplasia, decreased haptoglobin,  
271 lymphadenopathy, marrow depression
- 272 Red Blood Cell Disorders: hemolysis, hemolytic anemia, splenic infarction, splenomegaly
- 273 Reproductive System Disorders: cervical dysplasia
- 274 Resistance Mechanism Disorders: abscess, bacterial infection, *Herpes zoster* infection,  
275 *Pneumocystis carinii* infection, otitis media, Tuberculosis infection, viral infection
- 276 Respiratory System Disorders: asthma, bronchitis, chronic obstructive pulmonary disease,  
277 hemoptysis, hypoxia, pleural effusion, pleurisy, pneumothorax, pulmonary edema, pulmonary  
278 fibrosis, pulmonary infiltration, respiratory depression, respiratory insufficiency, sinusitis,  
279 stridor, throat tightness
- 280 Skin and Appendages Disorders: angioedema, bullous eruption, cellulitis, purpuric rash
- 281 Special Senses Disorders: taste loss
- 282 Urinary System Disorders: abnormal renal function, acute renal failure, anuria, facial edema,  
283 hematuria, toxic nephropathy, ureteric obstruction, urinary retention, urinary tract infection
- 284 Vascular (Extracardiac) Disorders: cerebral hemorrhage, cerebrovascular disorder, deep vein  
285 thrombosis, increased capillary fragility, intracranial hemorrhage, phlebitis, subarachnoid  
286 hemorrhage, thrombophlebitis
- 287 Vision Disorders: endophthalmitis

288 **OVERDOSAGE**

289 Initial doses of Campath of greater than 3 mg are not well-tolerated. One patient who received  
290 80 mg as an initial dose by IV infusion experienced acute bronchospasm, cough, and shortness of  
291 breath, followed by anuria and death. A review of the case suggested that tumor lysis syndrome  
292 may have played a role.

293 Single doses of Campath greater than 30 mg or a cumulative weekly dose greater than 90 mg  
294 should not be administered as higher doses have been associated with a higher incidence of  
295 pancytopenia. (See BOXED WARNING and DOSAGE AND ADMINISTRATION.)

296 There is no known specific antidote for Campath overdose. Treatment consists of drug  
297 discontinuation and supportive therapy.

298 **DOSAGE AND ADMINISTRATION**

299 Campath should be administered under the supervision of a physician experienced in the use of  
300 antineoplastic therapy.

301 **Dosing Schedule and Administration:**

302 Campath therapy should be initiated at a dose of 3 mg administered as a 2 hour IV infusion daily.  
303 (See ADVERSE EVENTS.) When the Campath 3 mg daily dose is tolerated (e.g., infusion-  
304 related toxicities are ≤ Grade 2), the daily dose should be escalated to 10 mg and continued until  
305 tolerated. When the 10 mg dose is tolerated, the maintenance dose of Campath 30 mg may be  
306 initiated. The maintenance dose of Campath is 30 mg/day administered three times per week on  
307 alternate days (i.e., Monday, Wednesday, and Friday) for up to 12 weeks. In most patients,  
308 escalation to 30 mg can be accomplished in 3 - 7 days. **Dose escalation to the recommended**  
309 **maintenance dose of 30 mg administered three times per week is required. Single doses of**  
310 **Campath greater than 30 mg or cumulative weekly doses of greater than 90 mg should not**  
311 **be administered since higher doses are associated with an increased incidence of**  
312 **pancytopenia.** (See BOXED WARNING.) Campath should be administered intravenously only.  
313 The infusion should be administered over a 2 hour period. **DO NOT ADMINISTER AS AN**  
314 **INTRAVENOUS PUSH OR BOLUS.**

315 **Recommended Concomitant Medications:**

316 Premedication should be given prior to the first dose, at dose escalations, and as clinically  
317 indicated. The premedication used in clinical studies was diphenhydramine 50 mg and  
318 acetaminophen 650 mg administered 30 minutes prior to Campath infusion. In cases where severe  
319 infusion-related events occur, treatment with hydrocortisone 200 mg was used in decreasing the  
320 infusion-related events.

321 Patients should receive anti-infective prophylaxis to minimize the risks of serious opportunistic  
322 infections. (See BOXED WARNING.) The anti-infective regimen used on Study 1 consisted of  
323 trimethoprim/sulfamethoxazole DS twice daily (BID) three times per week and famciclovir or  
324 equivalent 250 mg twice a day (BID) upon initiation of Campath therapy. Prophylaxis should be  
325 continued for 2 months after completion of Campath therapy or until the CD4<sup>+</sup> count is ≥ 200  
326 cells/μL, whichever occurs later.

327 **Dose Modification and Reinitiation of Therapy:**

328 Campath therapy should be discontinued during serious infection, serious hematologic toxicity, or  
329 other serious toxicity until the event resolves. (See WARNINGS.) Campath therapy should be  
330 permanently discontinued if evidence of autoimmune anemia or thrombocytopenia appears. Table  
331 3 includes recommendations for dose modification for severe neutropenia or thrombocytopenia.

332 **Table 3: Dose Modification and Reinitiation of Therapy for Hematologic Toxicity**

<u>Hematologic Toxicity</u>	<u>Dose Modification and Reinitiation of Therapy</u>
For first occurrence of ANC < 250/ $\mu$ L and/or platelet count $\leq$ 25,000/ $\mu$ L	Withhold Campath therapy. When ANC $\geq$ 500/ $\mu$ L and platelet count $\geq$ 50,000/ $\mu$ L, resume Campath therapy at same dose. If delay between dosing is $\geq$ 7 days, initiate therapy at Campath 3 mg and escalate to 10 mg and then to 30 mg as tolerated.
For second occurrence of ANC < 250/ $\mu$ L and/or platelet count $\leq$ 25,000/ $\mu$ L	Withhold Campath therapy. When ANC $\geq$ 500/ $\mu$ L and platelet count $\geq$ 50,000/ $\mu$ L, resume Campath therapy at <b>10 mg</b> . If delay between dosing is $\geq$ 7 days, initiate therapy at Campath 3 mg and escalate to <b>10 mg only</b> .
For third occurrence of ANC < 250/ $\mu$ L and/or platelet count $\leq$ 25,000/ $\mu$ L	Discontinue Campath therapy permanently.
For a decrease of ANC and/or platelet count to $\leq$ 50% of the baseline value in patients initiating therapy with a baseline ANC $\leq$ 500/ $\mu$ L and/or a baseline platelet count $\leq$ 25,000/ $\mu$ L	Withhold Campath therapy. When ANC and/or platelet count return to baseline value(s), resume Campath therapy. If the delay between dosing $\geq$ 7 days, initiate therapy at Campath 3 mg and escalate to 10 mg and then to 30 mg as tolerated.

333 **Preparation for Administration:**

334 Parenteral drug products should be inspected for visible particulate matter and discoloration  
335 prior to administration. If particulate matter is present or the solution is discolored, the vial  
336 should not be used. **DO NOT SHAKE AMPOULE PRIOR TO USE.** As with all parenteral  
337 drug products, aseptic technique should be used during the preparation and administration of  
338 Campath. Withdraw the necessary amount of Campath from the ampoule into a syringe. Filter  
339 with a sterile, low-protein binding, non-fiber releasing 5  $\mu$ m filter prior to dilution.

340 Inject into 100 mL sterile 0.9% Sodium Chloride USP or 5% Dextrose in Water USP. **Gently**  
341 **invert the bag to mix the solution.** Discard syringe and any unused drug product.

342 Campath contains no antimicrobial preservative. Campath should be used within 8 hours after  
343 dilution. Campath solutions may be stored at room temperature (15-30°C) or refrigerated.  
344 Campath solutions should be protected from light.

345 **Incompatibilities:**

346 No incompatibilities between Campath and polyvinylchloride (PVC) bags, PVC or polyethylene-  
347 lined PVC administration sets, or low-protein binding filters have been observed. No data are  
348 available concerning the incompatibility of Campath with other drug substances. Other drug  
349 substances should not be added or simultaneously infused through the same intravenous line.

*Millennium and ILEX Partners, LP*  
**Campath<sup>®</sup> (Alemtuzumab)**

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*Final Draft Package Insert*

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350 **HOW SUPPLIED**

351 Campath (Alemtuzumab) is supplied in single-use clear glass ampoules containing 30 mg of  
352 Alemtuzumab in 3 mL of solution. Each box contains either three Campath ampoules (NDC  
353 50419-355-10) or 12 Campath ampoules (NDC 50419-355-12).

354 **Campath should be stored at 2-8° C (36-46° F). Do not freeze. DISCARD IF AMPOULE**  
355 **HAS BEEN FROZEN. Protect from direct sunlight.**

356 **Rx only.**

357 U.S. Patents: 5,545,403; 5,545,405; 5,654,403; 5,846,534

358 Other patents pending

359 Manufactured by: Millennium and ILEX Partners, LP Cambridge, MA 02142

360 Distributed by: Berlex Laboratories, Richmond, CA 94804

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362 Issued: May 2001