



Our STN: BL 103948/5035

**MAY 19 2004**

ILEX Pharmaceuticals L.P.  
Attention: Michael Bernstein, MPH  
Senior Director, Regulatory Affairs  
4545 Horizon Hill Boulevard  
San Antonio, TX 78229

Dear Mr. Bernstein:

Your request to supplement your biologics license application for Alemtuzumab received on November 20, 2003, to revise the Adverse Reactions section of the package insert to include tumor lysis syndrome and autoimmune disorders, and to strengthen the Warnings section regarding infusion associated events has been approved.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels).

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see <http://www.fda.gov/cder/biologics/default.htm>. Until further notice, however, all correspondence, except as provided elsewhere in this letter, should continue to be addressed to:

CBER Document Control Center  
Attn: Office of Therapeutics Research and Review  
Suite 200N (HFM-99)  
1401 Rockville Pike  
Rockville, Maryland 20852-1448

This information will be included in your biologics license application file.

Sincerely,

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Patricia Keegan, M.D.  
Director  
Division of Therapeutic Biological Oncology Products  
Office of Drug Evaluation VI  
Office of New Drugs  
Center for Drug Evaluation and Research

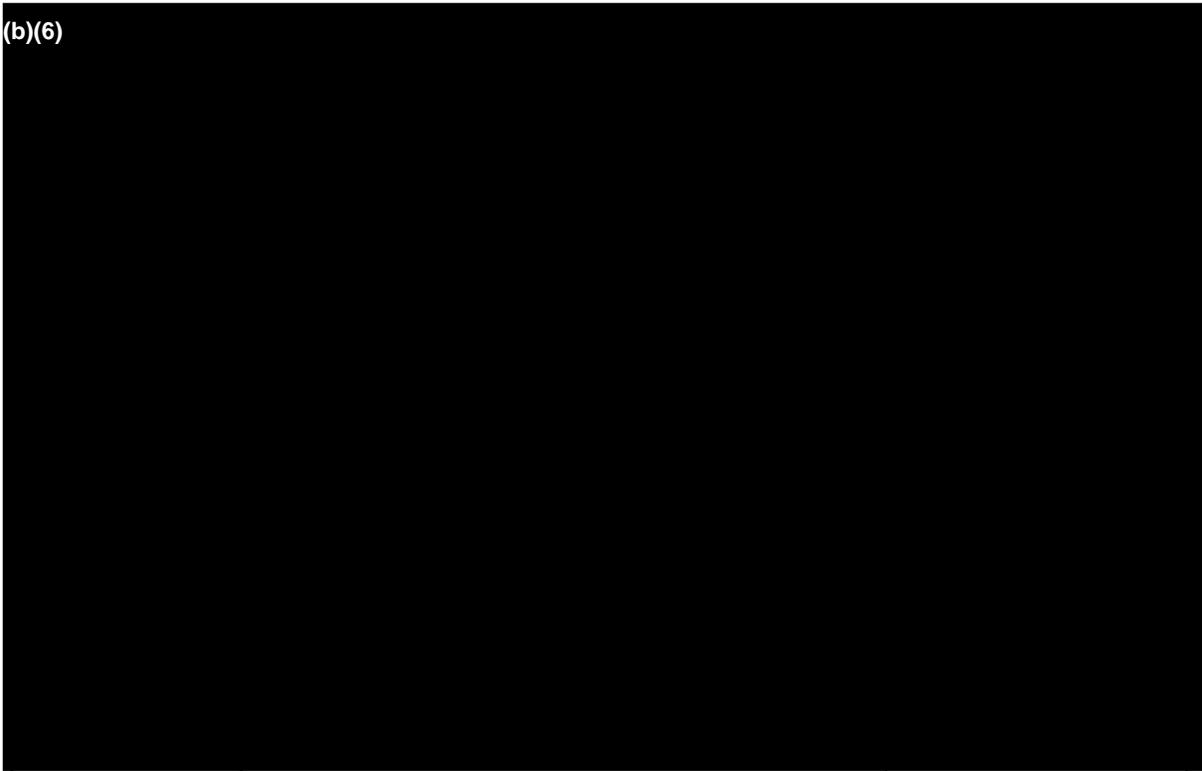
Enclosure: Package insert

**CONCURRENCE PAGE**

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**Campath® (Alemtuzumab)**

*Page 1 of 14*  
*Draft Package Insert*

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  
9 90 mg per week should not be administered because these doses are  
10 associated with a higher incidence of pancytopenia.**
- 11 • **Infusion Reactions:** Campath can result in serious, and in some instances fatal,  
12 infusion reactions. Patients should be carefully monitored during infusions and  
13 Campath discontinued if indicated. (See DOSAGE AND ADMINISTRATION.)  
14 **Gradual escalation to the recommended maintenance dose is required at the  
15 initiation of therapy 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  
18 Campath therapy. Prophylaxis directed against *Pneumocystis carinii* pneumonia  
19 (PCP) and herpes virus infections has been shown to decrease, but not eliminate,  
20 the 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  
27 IgG1 kappa with human variable framework and constant regions, and complementarity-  
28 determining regions from a murine (rat) monoclonal antibody (Campath-1G). The Campath-1H  
29 antibody has an approximate molecular weight of 150 kD.

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

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**Campath® (Alemtuzumab)**

**Page 2 of 14**  
**Draft Package Insert**

30 Campath contains 30 mg Alemtuzumab, 24.0 mg sodium chloride, 3.5 mg dibasic sodium  
31 phosphate, 0.6 mg potassium chloride, 0.6 mg monobasic potassium phosphate, 0.3 mg  
32 polysorbate 80, and 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  
37 a 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,  
44 but neither spermatogenic cells nor immature spermatozoa show evidence of staining.

#### 45 Human Pharmacokinetics:

46 Campath pharmacokinetics were characterized in a study of 30 Campath-naïve patients with  
47 chronic lymphocytic leukemia (B-CLL) who had failed previous therapy with purine analogs.  
48 Campath was administered as a 2 hour intravenous infusion, at the recommended dosing  
49 schedule, starting at 3 mg and increasing to 30 mg three times per week for up to 12 weeks.  
50 Campath pharmacokinetics displayed nonlinear elimination kinetics. After the last 30 mg dose,  
51 the mean volume of distribution at steady-state was 0.18 L/kg (range: 0.1 to 0.4 L/kg).  
52 Systemic clearance decreased with repeated administration due to decreased receptor-mediated  
53 clearance (i.e., loss of CD52 receptors in the periphery). After 12 weeks of dosing, patients  
54 exhibited a seven-fold increase in mean AUC. Mean half-life was 11 hours (range: 2 to 32  
55 hours) after the first 30 mg dose and was 6 days (range: 1 to 14 days) after the last 30 mg dose.

56 Comparisons of AUC in patients 65 years or older (n=6) versus patients less than 65 years  
57 (n=15) suggested that no dose adjustments are necessary for age. Comparisons of AUC in  
58 female patients (n=4) versus male patients (n=17) suggested that no dose adjustments are  
59 necessary for gender.

60 The pharmacokinetics of Campath in pediatric patients have not been studied. The effects of  
61 renal or hepatic impairment on the pharmacokinetics of Campath have not been studied.

### 62 CLINICAL STUDIES

63 The safety and efficacy of Campath were evaluated in a multicenter, open-label,  
64 noncomparative study (Study 1) of 93 patients with B-cell chronic lymphocytic leukemia  
65 (B-CLL) who had been previously treated with alkylating agents and had failed treatment with  
66 fludarabine. Fludarabine failure was defined as lack of an objective partial (PR) or complete  
67 (CR) response to at least one fludarabine-containing regimen, progressive disease (PD) while  
68 on fludarabine treatment, or relapse within 6 months of the last dose of fludarabine. Patients

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**Campath® (Alemtuzumab)**

**Page 3 of 14**  
**Draft Package Insert**

69 were gradually escalated to a maintenance dose of Campath 30 mg intravenously three times per  
 70 week for 4 to 12 weeks. Patients received premedication prior to infusion and anti-  
 71 *Pneumocystis carinii* and anti-herpes prophylaxis while on treatment and for at least 2 months  
 72 after the last dose of Campath.

73 Two supportive, multicenter, open-label, noncomparative studies of Campath enrolled a total of  
 74 56 patients with B-CLL (Studies 2 and 3). These patients had been previously treated with  
 75 fludarabine or other chemotherapies. In Studies 2 and 3, the maintenance dose of Campath was  
 76 30 mg three times per week with treatment cycles of 8 and 6 weeks respectively. A slightly  
 77 different dose escalation scheme was used in these trials. Premedication to ameliorate infusional  
 78 reactions and anti-*Pneumocystis carinii* and anti-herpes prophylaxis were optional.

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

84

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

	Study 1 (N = 93)	Study 2 (N = 32)	Study 3 (N = 24)
Median Age in Years (Range)	66 (32 - 68)	57 (46 - 75)	62 (44 - 77)
Median Number of Prior Regimens (Range)	3 (2 - 7)	3 (1 - 10)	3 (1 - 8)
<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</b>	<b>33%</b>	<b>21%</b>	<b>29%</b>
(95% Confidence Interval)	(23%, 43%)	(8%, 33%)	(11%, 47%)
Complete Response	2%	0%	0%
Partial Response	31%	21%	29%
<b>Median Duration of Response (months)</b>	<b>7</b>	<b>7</b>	<b>11</b>
(95% Confidence Interval)	(5, 8)	(5, 23)	(6, 19)
<b>Median Time to Response (months)</b>	<b>2</b>	<b>4</b>	<b>4</b>
(95% Confidence Interval)	(1, 2)	(1, 5)	(2, 4)
<b>Progression-Free Survival (months)</b>	<b>4</b>	<b>5</b>	<b>7</b>
(95% Confidence Interval)	(3, 5)	(3, 7)	(3, 9)

## 85 INDICATIONS AND USAGE

86 Campath is indicated for the treatment of B-cell chronic lymphocytic leukemia (B-CLL) in  
 87 patients who have been treated with alkylating agents and who have failed fludarabine therapy.  
 88 Determination of the effectiveness of Campath is based on overall response rates. (See

89 CLINICAL STUDIES.) Comparative, randomized trials demonstrating increased survival or  
90 clinical benefits such as improvement in disease-related symptoms have not yet been conducted.

## 91 **CONTRAINDICATIONS**

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

## 95 **WARNINGS (See BOXED WARNING.)**

### 96 **Infusion-Related Events:**

97 Campath has been associated with infusion-related events including hypotension, rigors, fever,  
98 shortness of breath, bronchospasm, chills, and/or rash. In post-marketing reports, the following  
99 serious infusion-related events were reported: syncope, pulmonary infiltrates, ARDS,  
100 respiratory arrest, cardiac arrhythmias, myocardial infarction and cardiac arrest. The cardiac  
101 adverse events have resulted in death in some cases. In order to ameliorate or avoid infusion-  
102 related events, patients should be premedicated with an oral antihistamine and acetaminophen  
103 prior to dosing and monitored closely for infusion-related adverse events. In addition, Campath  
104 should be initiated at a low dose with gradual escalation to the effective dose. Careful  
105 monitoring of blood pressure and hypotensive symptoms is recommended especially in patients  
106 with ischemic heart disease and in patients on antihypertensive medications. If therapy is  
107 interrupted for 7 or more days, Campath should be reinstated with gradual dose escalation.  
108 (See ADVERSE EVENTS and DOSAGE AND ADMINISTRATION.)

### 109 **Immunosuppression/Opportunistic Infections:**

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

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

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

### 122 **Hematologic Toxicity:**

123 Severe, prolonged, and in rare instances fatal, myelosuppression has occurred in patients with  
124 leukemia and lymphoma receiving Campath. Bone marrow aplasia and hypoplasia were  
125 observed in the clinical studies at the recommended dose. The incidence of these complications

126 increased with doses above the recommended dose. In addition, severe and fatal autoimmune  
127 anemia and thrombocytopenia were observed in patients with CLL. Campath should be  
128 discontinued for severe hematologic toxicity (see Table 3 Dose Modification and Reinitiation of  
129 Therapy for Hematologic Toxicity) or in any patient with evidence of autoimmune hematologic  
130 toxicity. Following resolution of transient, non-immune myelosuppression, Campath may be  
131 reinitiated with caution. (See DOSAGE AND ADMINISTRATION.) There is no information  
132 on the safety of resumption of Campath in patients with autoimmune cytopenias or marrow  
133 aplasia. (See ADVERSE REACTIONS.)

## 134 PRECAUTIONS

### 135 Laboratory Monitoring:

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

### 140 Drug/Laboratory Interactions:

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

### 143 Immunization:

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

### 148 Immunogenicity:

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

### 158 Carcinogenesis, Mutagenesis, Impairment of Fertility:

159 No long-term studies in animals have been performed to establish the carcinogenic or  
160 mutagenic potential of Campath, or to determine its effects on fertility in males or females.  
161 Women of childbearing potential and men of reproductive potential should use effective

162 contraceptive methods during treatment and for a minimum of 6 months following Campath  
163 therapy.

164 **Pregnancy Category C:**

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

170 **Nursing Mothers:**

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

174 **Pediatric Use:**

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

176 **Geriatric Use:**

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

181 **ADVERSE REACTIONS**

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

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

193 **Infusion-Related Adverse Events:**

194 Infusion-related adverse events ~~due to the release of cytokines~~ resulted in discontinuation of  
195 Campath therapy in 6% of the patients enrolled in Study 1. The most commonly reported  
196 infusion-related adverse events on this study included rigors in 89% of patients, drug-related  
197 fever in 83%, nausea in 47%, vomiting in 33%, and hypotension in 15%. Other frequently

198 reported infusion-related events include, rash in 30% of patients, fatigue in 22%, urticaria in  
199 22%, dyspnea in 17%, pruritus in 14%, headache in 13%, and diarrhea in 13%. Similar types of  
200 adverse events were reported on the supporting studies (see Table 2). Acute infusion-related  
201 events were most common during the first week of therapy. In post-marketing reports, the  
202 following serious infusion-related events have been reported: syncope, pulmonary infiltrates,  
203 ARDS, respiratory arrest, cardiac arrhythmias, myocardial infarction and cardiac arrest. The  
204 cardiac adverse events have resulted in death in some cases. Antihistamines, acetaminophen,  
205 antiemetics, meperidine, and corticosteroids as well as incremental dose escalation were used to  
206 prevent or ameliorate infusion-related events. (See WARNINGS and DOSAGE AND  
207 ADMINISTRATION.)

### 208 **Infections:**

209 On Study 1, all patients were required to receive anti-herpes and anti-PCP prophylaxis (see  
210 DOSAGE AND ADMINISTRATION) and were followed for infections for 6 months. Forty  
211 (43%) of 93 patients experienced 59 infections (one or more infections per patient) related to  
212 Campath during treatment or within 6 months of the last dose. Of these, 34 (37%) patients  
213 experienced 42 infections that were of Grade 3 or 4 severity; 11 (18%) were fatal. Fifty-five  
214 percent of the Grade 3 or 4 infections occurred during treatment or within 30 days of last dose.  
215 In addition one or more episodes of febrile neutropenia ( $ANC \leq 500/\mu L$ ) were reported in 10%  
216 of patients.

217 The following types of infections were reported in Study 1: Grade 3 or 4 sepsis in 12% of  
218 patients with one fatality, Grade 3 or 4 pneumonia in 15% with five fatalities, and opportunistic  
219 infections in 17% with four fatalities. Candida infections were reported in 5% of patients; CMV  
220 infections in 8% (4% of Grade 3 or 4 severity); Aspergillosis in 2% with fatal Aspergillosis in  
221 1%; fatal Mucormycosis in 2%; fatal Cryptococcal pneumonia in 1%; *Listeria monocytogenes*  
222 meningitis in 1%; disseminated *Herpes zoster* in 1%; Grade 3 *Herpes simplex* in 2%; and  
223 Torulopsis pneumonia in 1%. PCP pneumonia occurred in one (1%) patient who discontinued  
224 PCP prophylaxis.

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

### 230 **Hematologic Adverse Events:**

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

234 Anemia: Forty-four (47%) patients had one or more episodes of new onset NCI-CTC Grade 3 or  
235 4 anemia. Sixty-two (67%) patients required RBC transfusions. In addition, erythropoietin use  
236 was reported in nineteen (20%) patients. Autoimmune hemolytic anemia secondary to Campath

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**Page 8 of 14**  
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237 therapy was reported in 1% of patients. Positive Coombs test without hemolysis was reported in  
 238 2%. (See BOXED WARNING.)

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

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

247 Lymphopenia: The median CD4<sup>+</sup> count at 4 weeks after initiation of Campath therapy was 2  
 248 (two) /μL, at 2 months after discontinuation of Campath therapy, 207/μL, and 6 months after  
 249 discontinuation, 470/μL. The pattern of change in median CD8<sup>+</sup> lymphocyte counts was similar  
 250 to that of CD4<sup>+</sup> cells. In some patients treated with Campath, CD4<sup>+</sup> and CD8<sup>+</sup> lymphocyte  
 251 counts had not returned to baseline levels at longer than 1 year post therapy.

252  
 253

**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
Dyesthesias	15	--
Dizziness	12	1
Tremor	7	--

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**Page 9 of 14**  
**Draft Package Insert**

Adverse Event:	B-CLL STUDIES (N = 149)	
	ANY Grade (%)	Grade 3 or 4 (%)
<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
<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

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**Campath® (Alemtuzumab)**

**Page 10 of 14**  
**Draft Package Insert**

254 **Serious adverse events:**

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

261

262 ~~Additional Post Marketing Data: tumor lysis syndrome has occurred in rare cases.~~

263

264 ~~Autoimmune Disorders: graves disease has been reported in some multiple sclerosis patients~~  
265 ~~and in rare cases goodpastures, optic neuritis, guillain barre syndrome, serum sickness~~

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

268 Cardiovascular Disorders: cardiac failure, cyanosis, atrial fibrillation, cardiac arrest, ventricular  
269 arrhythmia, ventricular tachycardia, angina pectoris, coronary artery disorder, myocardial  
270 infarction, pericarditis

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

273 Endocrine Disorders: hyperthyroidism

274 Gastrointestinal System Disorders: duodenal ulcer, esophagitis, gingivitis, gastroenteritis, GI  
275 hemorrhage, hematemesis, hemorrhoids, intestinal obstruction, intestinal perforation, melena,  
276 paralytic ileus, peptic ulcer, pseudomembranous colitis, colitis, pancreatitis, peritonitis,  
277 hyperbilirubinemia, hepatic failure, hepatocellular damage, hypoalbuminemia, biliary pain

278 Hearing and Vestibular Disorders: decreased hearing

279 Metabolic and Nutritional Disorders: acidosis, aggravated diabetes mellitus, dehydration, fluid  
280 overload, hyperglycemia, hyperkalemia, hypokalemia, hypoglycemia, hyponatremia, increased  
281 alkaline phosphatase, respiratory alkalosis

282 Musculoskeletal System Disorders: arthritis or worsening arthritis, arthropathy, bone fracture,  
283 myositis, muscle atrophy, muscle weakness, osteomyelitis, polymyositis

284 Neoplasms: malignant lymphoma, malignant testicular neoplasm, prostatic cancer, plasma cell  
285 dyscrasia, secondary leukemia, squamous cell carcinoma, transformation to aggressive  
286 lymphoma, transformation to prolymphocytic leukemia

287 Platelet, Bleeding, and Clotting Disorders: coagulation disorder, disseminated intravascular  
288 coagulation, hematoma, pulmonary embolism, thrombocytopenia

289 Psychiatric Disorders: confusion, hallucinations, nervousness, abnormal thinking, apathy

**ILEX Pharmaceuticals, L.P.**  
**Campath® (Alemtuzumab)**

**Page 11 of 14**  
**Draft Package Insert**

- 290 White Cell and RES Disorders: agranulocytosis, aplasia, decreased haptoglobin,  
291 lymphadenopathy, marrow depression
- 292 Red Blood Cell Disorders: hemolysis, hemolytic anemia, splenic infarction, splenomegaly
- 293 Reproductive System Disorders: cervical dysplasia
- 294 Resistance Mechanism Disorders: abscess, bacterial infection, *Herpes zoster* infection,  
295 *Pneumocystis carinii* infection, otitis media, Tuberculosis infection, viral infection
- 296 Respiratory System Disorders: asthma, bronchitis, chronic obstructive pulmonary disease,  
297 hemoptysis, hypoxia, pleural effusion, pleurisy, pneumothorax, pulmonary edema, pulmonary  
298 fibrosis, pulmonary infiltration, respiratory depression, respiratory insufficiency, sinusitis,  
299 stridor, throat tightness
- 300 Skin and Appendages Disorders: angioedema, bullous eruption, cellulitis, purpuric rash
- 301 Special Senses Disorders: taste loss
- 302 Urinary System Disorders: abnormal renal function, acute renal failure, anuria, facial edema,  
303 hematuria, toxic nephropathy, ureteric obstruction, urinary retention, urinary tract infection
- 304 Vascular (Extracardiac) Disorders: cerebral hemorrhage, cerebrovascular disorder, deep vein  
305 thrombosis, increased capillary fragility, intracranial hemorrhage, phlebitis, subarachnoid  
306 hemorrhage, thrombophlebitis
- 307 Vision Disorders: endophthalmitis
- 308 **Post-marketing reports:**
- 309 Additional adverse reactions have been identified during post-marketing use of Campath.  
310 Because these reactions are reported voluntarily from a population of uncertain size, it is not  
311 always possible to reliably estimate their frequency or establish a causal relationship to  
312 Campath exposure. Decisions to include these reactions in labeling are typically based on one  
313 or more of the following factors: (1) seriousness of the reaction, (2) frequency of the reporting,  
314 or (3) strength of causal connection to Campath.
- 315 The following serious adverse events were identified in post-marketing reports: tumor lysis  
316 syndrome, Goodpasture's syndrome, Graves disease, Guillain-Barre syndrome, optic  
317 neuropathy, and serum sickness.
- 318 **OVERDOSAGE**
- 319 Initial doses of Campath of greater than 3 mg are not well-tolerated. One patient who received  
320 80 mg as an initial dose by IV infusion experienced acute bronchospasm, cough, and shortness  
321 of breath, followed by anuria and death. A review of the case suggested that tumor lysis  
322 syndrome may have played a role.
- 323 Single doses of Campath greater than 30 mg or a cumulative weekly dose greater than 90 mg  
324 should not be administered as higher doses have been associated with a higher incidence of  
325 pancytopenia. (See BOXED WARNING and DOSAGE AND ADMINISTRATION.)

*ILEX Pharmaceuticals, L.P.*  
**Campath® (Alemtuzumab)**

*Page 12 of 14*  
*Draft Package Insert*

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

## 328 **DOSAGE AND ADMINISTRATION**

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

### 331 **Dosing Schedule and Administration:**

332 Campath therapy should be initiated at a dose of 3 mg administered as a 2 hour IV infusion  
333 daily. (See ADVERSE EVENTS.) When the Campath 3 mg daily dose is tolerated (e.g.,  
334 infusion-related toxicities are  $\leq$  Grade 2), the daily dose should be escalated to 10 mg and  
335 continued until tolerated. When the 10 mg dose is tolerated, the maintenance dose of Campath  
336 30 mg may be initiated. The maintenance dose of Campath is 30 mg/day administered three  
337 times per week on alternate days (i.e., Monday, Wednesday, and Friday) for up to 12 weeks. In  
338 most patients, escalation to 30 mg can be accomplished in 3 - 7 days. **Dose escalation to the**  
339 **recommended maintenance dose of 30 mg administered three times per week is required.**  
340 **Single doses of Campath greater than 30 mg or cumulative weekly doses of greater than**  
341 **90 mg should not be administered since higher doses are associated with an increased**  
342 **incidence of pancytopenia.** (See BOXED WARNING.) Campath should be administered  
343 intravenously only. The infusion should be administered over a 2 hour period. **DO NOT**  
344 **ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.**

### 345 **Recommended Concomitant Medications:**

346 Premedication should be given prior to the first dose, at dose escalations, and as clinically  
347 indicated. The premedication used in clinical studies was diphenhydramine 50 mg and  
348 acetaminophen 650 mg administered 30 minutes prior to Campath infusion. ~~It is recommended~~  
349 ~~that patients be premedicated with intravenous steroids 30-60 minutes prior to each CAMPATH~~  
350 ~~infusion during dose escalation and as clinically indicated.~~ In cases where severe infusion-  
351 related events occur, treatment with hydrocortisone 200 mg was used in decreasing the  
352 infusion-related events.

353 Patients should receive anti-infective prophylaxis to minimize the risks of serious opportunistic  
354 infections. (See BOXED WARNING.) The anti-infective regimen used on Study 1 consisted of  
355 trimethoprim/sulfamethoxazole DS twice daily (BID) three times per week and famciclovir or  
356 equivalent 250 mg twice a day (BID) upon initiation of Campath therapy. Prophylaxis should be  
357 continued for 4-2 months after completion of Campath therapy or until the CD4<sup>+</sup> count is  $\geq$  200  
358 cells/ $\mu$ L, whichever occurs later.

### 359 **Dose Modification and Reinitiation of Therapy:**

360 Campath therapy should be discontinued during serious infection, serious hematologic toxicity,  
361 or other serious toxicity until the event resolves. (See WARNINGS.) Campath therapy should  
362 be permanently discontinued if evidence of autoimmune anemia or thrombocytopenia appears.

**ILEX Pharmaceuticals, L.P.**  
**Campath® (Alemtuzumab)**

**Page 13 of 14**  
**Draft Package Insert**

363 Table 3 includes recommendations for dose modification for severe neutropenia or  
 364 thrombocytopenia.

365 **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 is $\geq$ 7 days, initiate therapy at Campath 3 mg and escalate to 10 mg and then to 30 mg as tolerated.

366 **Preparation for Administration:**

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

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

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

378 **Incompatibilities:**

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

**ILEX Pharmaceuticals, L.P.**  
**Campath® (Alemtuzumab)**

**Page 14 of 14**  
**Draft Package Insert**

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384 **HOW SUPPLIED**

385 Campath (Alemtuzumab) is supplied in single-use clear glass ampoules containing 30 mg of  
386 Alemtuzumab in 3 mL of solution. Each box contains three Campath ampoules (NDC 50419-  
387 355-10).

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

390 **Rx only.**

391 U.S. Patents: 5,545,403; 5,545,405; 5,654,403; 5,846,534; 6,569,430

392 Other patents pending

393 Manufactured by: ILEX Pharmaceuticals, L.P., San Antonio, TX 78229

394 Distributed by: BERLEX® Laboratories, Montville, NJ 07045

395

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