WARNING

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

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

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

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

Campath® (ALEMTUZUMAB)

DESCRIPTION

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

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

30 Campath contains 30 mg Alemtuzumab, 8.0 mg sodium chloride, 1.44 mg dibasic sodium
31 phosphate, 0.2 mg potassium chloride, 0.2 mg monobasic potassium phosphate, 0.1 mg
32 polysorbate 80, and .0187 mg disodium edetate dihydrate. 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 hematopoetic 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 $CD34^+$ 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

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)
Prior Therapies:			
Alkylating Agents	100%	100%	92%
Fludarabine	100%	34%	100%
Disease Characteristics:			
Rai Stage III / IV Disease	76%	72%	71%
B-Symptoms	42%	31%	21%
Overall Response Rate	33%	21%	29%
(95% Confidence Interval)	(23%, 43%)	(8%, 33%)	(11%, 47%)
Complete Response	2%	0%	0%
Partial Response	31%	21%	29%
Median Duration of Response (months)	7	7	11
(95% Confidence Interval)	(5, 8)	(5, 23)	(6, 19)
Median Time to Response (months)	2	4	4
(95% Confidence Interval)	(1, 2)	(1, 5)	(2, 4)
Progression-Free Survival (months)	4	5	7
(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

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

CONTRAINDICATIONS

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

WARNINGS (See BOXED WARNING.)

Infusion-Related Events:

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

Immunosuppression/Opportunistic Infections:

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

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

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

Hematologic Toxicity:

Severe, prolonged, and in rare instances fatal, myelosuppression has occurred in patients with leukemia and lymphoma receiving Campath. Bone marrow aplasia and hypoplasia were observed in the clinical studies at the recommended dose. The incidence of these complications increased with doses above the recommended dose. In addition, severe and fatal autoimmune

anemia and thrombocytopenia were observed in patients with CLL. Campath should be discontinued for severe hematologic toxicity (see Table 3 Dose Modification and Reinitiation of Therapy for Hematologic Toxicity) or in any patient with evidence of autoimmune hematologic toxicity. Following resolution of transient, non-immune myelosuppression, Campath may be reinitiated with caution. (See DOSAGE AND ADMINISTRATION.) There is no information on the safety of resumption of Campath in patients with autoimmune cytopenias or marrow aplasia. (See ADVERSE REACTIONS.)

PRECAUTIONS

Laboratory Monitoring:

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

Drug/Laboratory Interactions:

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

Immunization:

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

Immunogenicity:

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

Carcinogenesis, Mutagenesis, Impairment of Fertility:

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

Pregnancy Category C:

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

Nursing Mothers:

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

Pediatric Use:

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

Geriatric Use:

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

ADVERSE REACTIONS

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

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

Infusion-Related Adverse Events:

Infusion-related adverse events resulted in discontinuation of Campath therapy in 6% of the patients enrolled in Study 1. The most commonly reported infusion-related adverse events on this study included rigors in 89% of patients, drug-related fever in 83%, nausea in 47%, vomiting in 33%, and hypotension in 15%. Other frequently reported infusion-related events include, rash in 30% of patients, fatigue in 22%, urticaria in 22%, dyspnea in 17%, pruritus in 14%, headache in 13%, and diarrhea in 13%. Similar types of adverse events were reported on the supporting studies (see Table 2). Acute infusion-related events were most common during

the first week of therapy. In post-marketing reports, the following serious infusion-related events have been reported: syncope, pulmonary infiltrates, ARDS, respiratory arrest, cardiac arrhythmias, myocardial infarction and cardiac arrest. The cardiac adverse events have resulted in death in some cases. Antihistamines, acetaminophen, antiemetics, meperidine, and corticosteroids as well as incremental dose escalation were used to prevent or ameliorate infusion-related events. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Infections:

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

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

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

Hematologic Adverse Events:

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

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

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

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

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

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

	B-CLL STUDIES (N = 149)	
Adverse Event:	**ANY Grade (%)**	**Grade 3 or 4 (%)**
Body As A Whole		
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**	**--**
Cardiovascular Disorders, General		
Hypotension	**32**	**5**
Hypertension	**11**	**2**
Heart Rate & Rhythm Disorders		
Tachycardia, SVT	**11**	**3**
Central & Peripheral Nervous System Disorders		
Headache	**24**	**1**
Dysthesias	**15**	**--**
Dizziness	**12**	**1**
Tremor	**7**	**--**
Gastrointestinal Disorders		
Nausea	**54**	**2**
Vomiting	**41**	**4**
Diarrhea	**22**	**1**
Stomatitis, Ulcerative Stomatitis, Mucositis	**14**	**1**
Abdominal Pain	**11**	**2**

Adverse Event:	B-CLL STUDIES (N = 149)	
	ANY Grade (%)	Grade 3 or 4 (%)
Dyspepsia	10	--
Constipation	9	1
Hematologic Disorders		
WBC Disorders: Neutropenia	85	64
RBC Disorders: Anemia	80	38
Pancytopenia	5	3
Platelet, Bleeding & Clotting Disorders		
Thrombocytopenia	72	50
Purpura	8	--
Epistaxis	7	1
Musculoskeletal Disorders		
Myalgias	11	--
Psychiatric Disorders		
Insomnia	10	--
Depression	7	1
Somnolence	5	1
Resistance Mechanism Disorders		
Sepsis	15	10
Herpes Simplex	11	1
Moniliasis	8	1
Infection (other viral or unidentified)	7	1
Respiratory System Disorders		
Dyspnea	26	9
Cough	25	2
Bronchitis, Pneumonitis	21	13
Pneumonia	16	10
Pharyngitis	12	--
Bronchospasm	9	2
Rhinitis	7	--
Skin & Appendage Disorders		
Rash, Maculopapular Rash, Erythematous Rash	40	3
Urticaria	30	5
Pruritus	24	1
Sweating increased	19	1

Serious adverse events:

The following serious adverse events, defined as events which result in death, requiring or prolonging hospitalization, requiring medical intervention to prevent hospitalization, or malignancy, were reported in at least one patient treated on studies where Campath was used as a single agent (and are not reported in Table 2). These studies were conducted in patients with

258 lymphocytic leukemia and lymphoma (N = 745) and in patients with non-malignant diseases (N
259 =152) such as rheumatoid arthritis, solid organ transplant, or multiple sclerosis.

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

262 Cardiovascular Disorders: cardiac failure, cyanosis, atrial fibrillation, cardiac arrest, ventricular
263 arrhythmia, ventricular tachycardia, angina pectoris, coronary artery disorder, myocardial
264 infarction, pericarditis

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

267 Endocrine Disorders: hyperthyroidism

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

272 Hearing and Vestibular Disorders: decreased hearing

273 Metabolic and Nutritional Disorders: acidosis, aggravated diabetes mellitus, dehydration, fluid
274 overload, hyperglycemia, hyperkalemia, hypokalemia, hypoglycemia, hyponatremia, increased
275 alkaline phosphatase, respiratory alkalosis

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

278 Neoplasms: malignant lymphoma, malignant testicular neoplasm, prostatic cancer, plasma cell
279 dyscrasia, secondary leukemia, squamous cell carcinoma, transformation to aggressive
280 lymphoma, transformation to prolymphocytic leukemia

281 Platelet, Bleeding, and Clotting Disorders: coagulation disorder, disseminated intravascular
282 coagulation, hematoma, pulmonary embolism, thrombocythemia

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

284 White Cell and RES Disorders: agranulocytosis, aplasia, decreased haptoglobin,
285 lymphadenopathy, marrow depression

286 Red Blood Cell Disorders: hemolysis, hemolytic anemia, splenic infarction, splenomegaly

287 Reproductive System Disorders: cervical dysplasia

288 Resistance Mechanism Disorders: abscess, bacterial infection, *Herpes zoster* infection,
289 *Pneumocystis carinii* infection, otitis media, Tuberculosis infection, viral infection

290 Respiratory System Disorders: asthma, bronchitis, chronic obstructive pulmonary disease,
291 hemoptysis, hypoxia, pleural effusion, pleurisy, pneumothorax, pulmonary edema, pulmonary
292 fibrosis, pulmonary infiltration, respiratory depression, respiratory insufficiency, sinusitis,
293 stridor, throat tightness

294 Skin and Appendages Disorders: angioedema, bullous eruption, cellulitis, purpuric rash

295 Special Senses Disorders: taste loss

296 Urinary System Disorders: abnormal renal function, acute renal failure, anuria, facial edema,
297 hematuria, toxic nephropathy, ureteric obstruction, urinary retention, urinary tract infection

298 Vascular (Extracardiac) Disorders: cerebral hemorrhage, cerebrovascular disorder, deep vein
299 thrombosis, increased capillary fragility, intracranial hemorrhage, phlebitis, subarachnoid
300 hemorrhage, thrombophlebitis

301 Vision Disorders: endophthalmitis

302 **Post-marketing reports:**

303 Additional adverse reactions have been identified during post-marketing use of Campath.
304 Because these reactions are reported voluntarily from a population of uncertain size, it is not
305 always possible to reliably estimate their frequency or establish a causal relationship to
306 Campath exposure. Decisions to include these reactions in labeling are typically based on one
307 or more of the following factors: (1) seriousness of the reaction, (2) frequency of the reporting,
308 or (3) strength of causal connection to Campath.

309 The following serious adverse events were identified in post-marketing reports: tumor lysis
310 syndrome, Goodpasture's syndrome, Graves disease, Guillain-Barre syndrome, optic
311 neuropathy, and serum sickness.

312 **OVERDOSAGE**

313 Initial doses of Campath of greater than 3 mg are not well-tolerated. One patient who received
314 80 mg as an initial dose by IV infusion experienced acute bronchospasm, cough, and shortness
315 of breath, followed by anuria and death. A review of the case suggested that tumor lysis
316 syndrome may have played a role.

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

320 There is no known specific antidote for Campath overdosage. Treatment consists of drug
321 discontinuation and supportive therapy.

322 **DOSAGE AND ADMINISTRATION**

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

325 **Dosing Schedule and Administration:**

326 Campath therapy should be initiated at a dose of 3 mg administered as a 2 hour IV infusion
327 daily. (See ADVERSE EVENTS.) When the Campath 3 mg daily dose is tolerated (e.g.,
328 infusion-related toxicities are ≤ Grade 2), the daily dose should be escalated to 10 mg and
329 continued until tolerated. When the 10 mg dose is tolerated, the maintenance dose of Campath
330 30 mg may be initiated. The maintenance dose of Campath is 30 mg/day administered three
331 times per week on alternate days (i.e., Monday, Wednesday, and Friday) for up to 12 weeks. In

most patients, escalation to 30 mg can be accomplished in 3 - 7 days. **Dose escalation to the recommended maintenance dose of 30 mg administered three times per week is required. Single doses of Campath greater than 30 mg or cumulative weekly doses of greater than 90 mg should not be administered since higher doses are associated with an increased incidence of pancytopenia.** (See BOXED WARNING.) Campath should be administered intravenously only. The infusion should be administered over a 2 hour period. **DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.**

Recommended Concomitant Medications:

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

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

Dose Modification and Reinitiation of Therapy:

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

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

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

358 **Preparation and Administration:**

359 Parenteral drug products should be inspected for visible particulate matter and discoloration
360 prior to administration. If particulate matter is present or the solution is discolored, the vial
361 should not be used. **DO NOT SHAKE VIAL PRIOR TO USE.** As with all parenteral drug
362 products, aseptic technique should be used during the preparation and administration of
363 Campath. Withdraw the necessary amount of Campath from the vial into a syringe.

364 • To prepare the 3 mg dose, withdraw 0.1 mL into a 1 mL syringe calibrated in increments
365 of 0.1 mL.

366 • To prepare the 10 mg dose, withdraw 0.33 mL into a 1 mL syringe calibrated in
367 increments of 0.1 mL.

368 • To prepare the 30 mg dose, withdraw 1 mL in either a 1 mL or 3 mL syringe calibrated
369 in 0.1 mL increments.

370 **The vial contains no preservatives and is intended for single use only. DISCARD**
371 **VIAL including any unused portion after withdrawal of dose.**

372

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.

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.

Incompatibilities:

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

HOW SUPPLIED

Campath (Alemtuzumab) is supplied in single-use clear glass vials containing **30 mg of Alemtuzumab in 1 mL** of solution. Each carton contains three Campath vials (NDC 50419-357-03) or one Campath vial (NDC 50419-357-01).

Campath should be stored at 2-8°C (36-46°F). Do not freeze. If accidentally frozen, thaw at 2-8°C before administration. Protect from direct sunlight.

Rx only.

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

Other patents pending

Manufactured by: Genzyme Corporation, Cambridge, MA 02142

Distributed by: Berlex, Montville, NJ 07045

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