HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Campath safely and effectively. See full prescribing information for Campath.

Campath® (alemtuzumab)
Injection for intravenous use
Initial U.S. Approval: 2001

WARNING: CYTOPENIAS, INFUSION REACTIONS, and INFECTIONS
See full prescribing information for complete boxed warning.
Serious, including fatal, cytopenias, infusion reactions and infections can occur (5.1 – 5.3).
- **Limit doses to 30 mg (single) and 90 mg (cumulative weekly); higher doses increase risk of pancytopenia (2.1).**
- **Escalate dose gradually and monitor patients during infusion. Withhold therapy for Grade 3 or 4 infusion reactions (5.2).**
- **Administer prophylaxis against *Pneumocystis jiroveci* pneumonia (PCP) and herpes virus infections (2.2, 5.3).**

----------RECENT MAJOR CHANGES----------
Warnings and Precautions (5.3) 3/2009

----------INDICATIONS AND USAGE----------
Campath is a CD52-directed cytolytic antibody indicated as a single agent for the treatment of B-cell chronic lymphocytic leukemia (B-CLL) (1).

----------DOSAGE AND ADMINISTRATION----------
- Administer as an IV infusion over 2 hours (2.1).
- Escalate to recommended dose of 30 mg/day three times per week for 12 weeks (2.1).
- Premedicate with oral antihistamine and acetaminophen prior to dosing (2.2).

----------DOSAGE FORMS AND STRENGTHS----------
30 mg/1 mL single use vial (3).

----------CONTRAINDICATIONS----------
None (4).

----------WARNINGS AND PRECAUTIONS----------
Cytopenias:
- Obtain complete blood counts (CBC) and platelet counts at weekly intervals during therapy and CD4 counts after therapy until recovery to ≥ 200 cells/µL (5.4).
- Discontinue for autoimmune or severe hematologic adverse reactions (5.1).

Infections:
- Campath induces severe and prolonged lymphopenia and increases risk of infection. If a serious infection occurs, withhold treatment until infection resolves (5.3).
- Do not administer live viral vaccines to patients who have recently received Campath (5.5).

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥ 10%): cytopenias, infusion reactions, cytomegalovirus (CMV) and other infections, nausea, emesis, diarrhea, and insomnia (6).

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals at 1-888-842-2937 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

See 17 for PATIENT COUNSELING INFORMATION

Revised: 3/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CYTOPENIAS, INFUSION REACTIONS, and INFECTIONS

Cytopenias: Serious, including fatal, pancytopenia/marrow hypoplasia, autoimmune idiopathic thrombocytopenia, and autoimmune hemolytic anemia can occur in patients receiving Campath. Single doses of Campath greater than 30 mg or cumulative doses greater than 90 mg per week increase the incidence of pancytopenia *[see WARNINGS AND PRECAUTIONS (5.1)]*.

Infusion Reactions: Campath administration can result in serious, including fatal, infusion reactions. Carefully monitor patients during infusions and withhold Campath for Grade 3 or 4 infusion reactions. Gradually escalate Campath to the recommended dose at the initiation of therapy and after interruption of therapy for 7 or more days *[see DOSAGE AND ADMINISTRATION (2) and WARNINGS AND PRECAUTIONS (5.2)]*.

Infections: Serious, including fatal, bacterial, viral, fungal, and protozoan infections can occur in patients receiving Campath. Administer prophylaxis against *Pneumocystis jiroveci* pneumonia (PCP) and herpes virus infections *[see DOSAGE AND ADMINISTRATION (2.2) and WARNINGS AND PRECAUTIONS (5.3)]*.

1 INDICATIONS AND USAGE

Campath is indicated as a single agent for the treatment of B-cell chronic lymphocytic leukemia (B-CLL).

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Schedule and Administration

- Administer as an IV infusion over 2 hours. **Do not administer as intravenous push or bolus.**
- Recommended Dosing Regimen
  - Gradually escalate to the maximum recommended single dose of 30 mg. Escalation is required at initiation of dosing or if dosing is held ≥ 7 days during treatment. Escalation to 30 mg ordinarily can be accomplished in 3 - 7 days.

15 ○ Escalation Strategy:

16 ○ Administer 3 mg daily until infusion reactions are ≤ grade 2 *[see*
17 *ADVERSE REACTIONS (6.1)]*.

18 ○ Then administer 10 mg daily until infusion reactions are ≤ grade 2.

19 ○ Then administer 30 mg/day three times per week on alternate days (e.g.,
20 Mon-Wed-Fri). The total duration of therapy, including dose escalation, is
21 12 weeks.

22 • **Single doses of greater than 30 mg or cumulative doses greater than 90 mg per**
23 **week increase the incidence of pancytopenia.**

24 **2.2 Recommended Concomitant Medications**

25 • Premedicate with diphenhydramine (50 mg) and acetaminophen (500-1000 mg) 30
26 minutes prior to first infusion and each dose escalation. Institute appropriate
27 medical management (e.g. steroids, epinephrine, meperidine) for infusion reactions
28 as needed *[see BOXED WARNING, WARNINGS AND PRECAUTIONS (5.2) and*
29 *ADVERSE REACTIONS (6.1)]*.

30 • Administer trimethoprim/sulfamethoxazole DS twice daily (BID) three times per
31 week (or equivalent) as *Pneumocystis jiroveci* pneumonia (PCP) prophylaxis.

32 • Administer famciclovir 250 mg BID or equivalent as herpetic prophylaxis.

33 Continue PCP and herpes viral prophylaxis for a minimum of 2 months after completion
34 of Campath or until the CD4+ count is ≥ 200 cells/μL, whichever occurs later *[see*
35 *BOXED WARNING and WARNINGS AND PRECAUTIONS (5.3)]*.

36 **2.3 Dose Modification**

37 • Withhold Campath during serious infection or other serious adverse reactions until
38 resolution.

39 • Discontinue Campath for autoimmune anemia or autoimmune thrombocytopenia.

40 • There are no dose modifications recommended for lymphopenia.

Dose Modification for Neutropenia or Thrombocytopenia
[see WARNINGS AND PRECAUTIONS (5.1)]

Hematologic Values	Dose Modification*
ANC < 250/µL and/or platelet count ≤25,000/µL	
For first occurrence:	Withhold Campath therapy. Resume Campath at 30 mg when ANC ≥ 500/µL and platelet count ≥ 50,000/µL.
For second occurrence:	Withhold Campath therapy. Resume Campath at 10 mg when ANC ≥ 500/µL and platelet count ≥ 50,000/µL.
For third occurrence:	Discontinue Campath therapy.
≥ 50% decrease from baseline in patients initiating therapy with a baseline ANC ≤ 250/µL and/or a baseline platelet count ≤ 25,000/µL	
For first occurrence:	Withhold Campath therapy. Resume Campath at 30 mg upon return to baseline value(s).
For second occurrence:	Withhold Campath therapy. Resume Campath at 10 mg upon return to baseline value(s).
For third occurrence:	Discontinue 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 *[see DOSAGE AND ADMINISTRATION (2.1)]*.

2.4 Preparation and Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter is present or the solution is discolored, the vial should not be used. **DO NOT SHAKE VIAL**.

Use aseptic technique during the preparation and administration of Campath. Withdraw the necessary amount of Campath from the vial into a syringe.

- To prepare the 3 mg dose, withdraw 0.1 mL into a 1 mL syringe calibrated in increments of 0.01 mL.
- To prepare the 10 mg dose, withdraw 0.33 mL into a 1 mL syringe calibrated in increments of 0.01 mL.
- To prepare the 30 mg dose, withdraw 1 mL in either a 1 mL or 3 mL syringe calibrated in 0.1 mL increments.

Inject syringe contents into 100 mL sterile 0.9% Sodium Chloride USP or 5% Dextrose in Water USP. **Gently invert the bag to mix the solution.** Discard syringe.

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

Use within 8 hours after dilution. Store diluted Campath at room temperature (15-30°C) or refrigerated (2-8°C). Protect from light.

2.5 Incompatibilities

Campath is compatible with polyvinylchloride (PVC) bags and PVC or polyethylene-lined PVC administration sets. Do not add or simultaneously infuse other drug substances through the same intravenous line.

3 DOSAGE FORMS AND STRENGTHS

30 mg/1 mL single use vial

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Cytopenias

Severe, including fatal, autoimmune anemia and thrombocytopenia, and prolonged myelosuppression have been reported in patients receiving Campath.

In addition, hemolytic anemia, pure red cell aplasia, bone marrow aplasia, and hypoplasia have been reported after treatment with Campath at the recommended dose. Single doses of Campath greater than 30 mg or cumulative doses greater than 90 mg per week increase the incidence of pancytopenia.

Withhold Campath for severe cytopenias (except lymphopenia). Discontinue for autoimmune cytopenias or recurrent/persistent severe cytopenias (except lymphopenia) *[see DOSAGE AND ADMINISTRATION (2.3)]*. No data exist on the safety of Campath resumption in patients with autoimmune cytopenias or marrow aplasia *[see ADVERSE REACTIONS (6.1)]*.

5.2 Infusion Reactions

Adverse reactions occurring during or shortly after Campath infusion include pyrexia, chills/rigors, nausea, hypotension, urticaria, dyspnea, rash, emesis, and bronchospasm. In clinical trials, the frequency of infusion reactions was highest in the first week of

89 treatment. Monitor for the signs and symptoms listed above and withhold infusion for
90 Grade 3 or 4 infusion reactions *[see ADVERSE REACTIONS (6.1)]*.

91 The following serious, including fatal, infusion reactions have been identified in post-
92 marketing reports: syncope, pulmonary infiltrates, acute respiratory distress syndrome
93 (ARDS), respiratory arrest, cardiac arrhythmias, myocardial infarction, acute cardiac
94 insufficiency, cardiac arrest, angioedema, and anaphylactoid shock.

95 Initiate Campath according to the recommended dose-escalation scheme [see *DOSAGE*
96 *AND ADMINSTRATION (2)*]. Premedicate patients with an antihistamine and
97 acetaminophen prior to dosing. Institute medical management (e.g., glucocorticoids,
98 epinephrine, meperidine) for infusion reactions as needed *[see DOSAGE AND*
99 *ADMINISTRATION (2.2)]*. If therapy is interrupted for 7 or more days, reinstitute
100 Campath with gradual dose escalation *[see DOSAGE AND ADMINISTRATION (2.3)* and
101 *ADVERSE REACTIONS (6)]*.

102 **5.3 Immunosuppression/Infections**

103 Campath treatment results in severe and prolonged lymphopenia with a concomitant
104 increased incidence of opportunistic infections *[see ADVERSE REACTIONS (6.1)]*.
105 Administer PCP and herpes viral prophylaxis during Campath therapy and for a
106 minimum of 2 months after completion of Campath or until the CD4+ count is ≥ 200
107 cells/μL, whichever occurs later *[see DOSAGE AND ADMINISTRATION (2.2)]*.
108 Prophylaxis does not eliminate these infections.

109 Routinely monitor patients for CMV infection during Campath treatment and for at least
110 2 months following completion of treatment. Withhold Campath for serious infections
111 and during antiviral treatment for CMV infection or confirmed CMV viremia (defined as
112 polymerase chain reaction (PCR) positive CMV in ≥ 2 consecutive samples obtained 1
113 week apart) *[see ADVERSE REACTIONS (6.1)]*. Initiate therapeutic ganciclovir (or
114 equivalent) for CMV infection or confirmed CMV viremia *[see DOSAGE AND*
115 *ADMINISTRATION (2.3)]*.

116 Administer only irradiated blood products to avoid transfusion associated Graft versus
117 Host Disease (TAGVHD), unless emergent circumstances dictate immediate transfusion.[1]

118 In patients receiving Campath as initial therapy, recovery of CD4+ counts to
119 ≥ 200 cells/μL occurred by 6 months post-treatment; however at 2 months post-treatment,
120 the median was 183 cells/μL. In previously treated patients receiving Campath, the

121 median time to recovery of CD4+ counts to ≥ 200 cells/μL was 2 months; however, full
122 recovery (to baseline) of CD4+ and CD8+ counts may take more than 12 months *[see*
123 *BOXED WARNING and ADVERSE REACTIONS (6)]*.

124 **5.4 Laboratory Monitoring**

125 Obtain complete blood counts (CBC) at weekly intervals during Campath therapy and
126 more frequently if worsening anemia, neutropenia, or thrombocytopenia occurs. Assess
127 CD4+ counts after treatment until recovery to ≥ 200 cells/μL *[see WARNINGS AND*
128 *PRECAUTIONS (5.3) and ADVERSE REACTIONS (6)]*.

129 **5.5 Immunization**

130 The safety of immunization with live viral vaccines following Campath therapy has not
131 been studied. Do not administer live viral vaccines to patients who have recently received
132 Campath. The ability to generate an immune response to any vaccine following Campath
133 therapy has not been studied.

134 **6 ADVERSE REACTIONS**

135 The following adverse reactions are discussed in greater detail in other sections of the
136 label:

137 - Cytopenias *[see WARNINGS AND PRECAUTIONS (5.1)]*
138 - Infusion Reactions *[see WARNINGS AND PRECAUTIONS (5.2)]*
139 - Immunosuppression/Infections *[see WARNINGS AND PRECAUTIONS (5.3)]*

140 The most common adverse reactions with Campath are: infusion reactions (pyrexia,
141 chills, hypotension, urticaria, nausea, rash, tachycardia, dyspnea), cytopenias
142 (neutropenia, lymphopenia, thrombocytopenia, anemia), infections (CMV viremia, CMV
143 infection, other infections), gastrointestinal symptoms (nausea, emesis, abdominal pain),
144 and neurological symptoms (insomnia, anxiety). The most common serious adverse
145 reactions are cytopenias, infusion reactions, and immunosuppression/infections.

146 **6.1 Clinical Trials Experience**

147 Because clinical trials are conducted under widely varying conditions, adverse reaction
148 rates observed in the clinical trials of a drug cannot be directly compared to rates in the
149 clinical trials of another drug and may not reflect the rates observed in practice.

The data below reflect exposure to Campath in 296 patients with CLL of whom 147 were previously untreated and 149 received at least 2 prior chemotherapy regimens. The median duration of exposure was 11.7 weeks for previously untreated patients and 8 weeks for previously treated patients.

Lymphopenia: Severe lymphopenia and a rapid and sustained decrease in lymphocyte subsets occurred in previously untreated and previously treated patients following administration of Campath. In previously untreated patients, the median CD4+ was 0 cells/μL at one month after treatment and 238 cells/μL [25-75% interquartile range 115 to 418 cells/μL at 6 months post-treatment *[see WARNINGS AND PRECAUTIONS (5.3)]*.

Neutropenia: In previously untreated patients, the incidence of Grade 3 or 4 neutropenia was 42% with a median time to onset of 31 days and a median duration of 37 days. In previously treated patients, the incidence of Grade 3 or 4 neutropenia was 64% with a median duration of 28 days. Ten percent of previously untreated patients and 17% of previously treated patients received granulocyte colony stimulating factors.

Anemia: In previously untreated patients, the incidence of Grade 3 or 4 anemia was 12% with a median time to onset of 31 days and a median duration of 8 days. In previously treated patients, the incidence of Grade 3 or 4 anemia was 38%. Seventeen percent of previously untreated patients and 66% of previously treated patients received either erythropoiesis stimulating agents, transfusions or both.

Thrombocytopenia: In previously untreated patients, the incidence of Grade 3 or 4 thrombocytopenia was 14% with a median time to onset of 9 days and a median duration of 14 days. In previously treated patients, the incidence of Grade 3 or 4 thrombocytopenia was 52% with a median duration of 21 days. Autoimmune thrombocytopenia was reported in 2% of previously treated patients with one fatality.

Infusion reactions: Infusion reactions, which included pyrexia, chills, hypotension, urticaria, and dyspnea, were common. Grade 3 and 4 pyrexia and/or chills occurred in approximately 10% of previously untreated patients and in approximately 35% of previously treated patients. The occurrence of infusion reactions was greatest during the initial week of treatment and decreased with subsequent doses of Campath. All patients were pretreated with antipyretics and antihistamines; additionally, 43% of previously untreated patients received glucocorticoid pre-treatment.

Infections: In the study of previously untreated patients, patients were tested weekly for CMV using a PCR assay from initiation through completion of therapy, and every 2 weeks for the first 2 months following therapy. CMV infection occurred in 16% (23/147) of previously untreated patients; approximately one-third of these infections were serious or life threatening. In studies of previously treated patients in which routine CMV surveillance was not required, CMV infection was documented in 6% (9/149) of patients; nearly all of these infections were serious or life threatening.

Other infections were reported in approximately 50% of patients across all studies. Grade 3 - 5 sepsis ranged from 3% to 10% across studies and was higher in previously treated patients. Grade 3 - 4 febrile neutropenia ranged from 5 to 10% across studies and was higher in previously treated patients. Infection-related fatalities occurred in 2% of previously untreated patients and 16% of previously treated patients. There were 198 episodes of other infection in 109 previously untreated patients; 16% were bacterial, 7% were fungal, 4% were other viral, and in 73%, the organism was not identified.

Cardiac: Cardiac dysrhythmias occurred in approximately 14% of previously untreated patients. The majority were tachycardias and were temporally associated with infusion; dysrhythmias were Grade 3 or 4 in 1% of patients.

Previously Untreated Patients

Table 1 contains selected adverse reactions observed in 294 patients randomized (1:1) to receive Campath or chlorambucil as first line therapy for B-CLL. Campath was administered at a dose of 30 mg intravenously three times weekly for up to 12 weeks. The median duration of therapy was 11.7 weeks with a median weekly dose of 82 mg (25-75% interquartile range: 69 mg – 90 mg).

205 **Table 1**

Per Patient Incidence of Selected[1] Adverse Reactions in Treatment Naive B-CLL Patients					
		Campath (n=147)		Chlorambucil (n=147)	
		All Grades[2] %	Grades 3-4 %	All Grades %	Grades 3-4 %
Blood and Lymphatic System Disorders	Lymphopenia	97	97	9	1
	Neutropenia	77	42	51	26
	Anemia	76	13	54	18
	Thrombocytopenia	71	13	70	14
General Disorders and Administration Site Conditions	Pyrexia	69	10	11	1
	Chills	53	3	1	0
Infections and Infestations	CMV viremia[3]	55	4	8	0
	CMV infection	16	5	0	0
	Other infections	74	21	65	10
Skin and Subcutaneous Tissue Disorders	Urticaria	16	2	1	0
	Rash	13	1	4	0
	Erythema	4	0	1	0
Vascular Disorders	Hypotension	16	1	0	0
	Hypertension	14	5	2	1
Nervous System Disorders	Headache	14	1	8	0
	Tremor	3	0	1	0
Respiratory, Thoracic and Mediastinal Disorders	Dyspnea	14	4	7	3
Gastrointestinal Disorders	Diarrhea	10	1	4	0
Psychiatric Disorders	Insomnia	10	0	3	0
	Anxiety	8	0	1	0
Cardiac Disorders	Tachycardia	10	0	1	0

206 [1]Adverse reactions occurring at a higher relative frequency in the Campath arm
207 [2]NCI CTC version 2.0 for adverse reactions; NCI CTCAE version 3.0 for laboratory values
208 [3]CMV viremia (without evidence of symptoms) includes both cases of single PCR positive test results and of
209 confirmed CMV viremia (≥ 2 occasions in consecutive samples 1 week apart). For the latter, ganciclovir (or
210 equivalent) was initiated per protocol.

211 *Previously Treated Patients*

212 Additional safety information was obtained from 3 single arm studies of 149 previously
213 treated patients with CLL administered 30 mg Campath intravenously three times weekly
214 for 4 to 12 weeks (median cumulative dose 673 mg [range 2 – 1106 mg]; median duration
215 of therapy 8.0 weeks). Adverse reactions in these studies not listed in Table 1 that

occurred at an incidence rate of > 5% were fatigue, nausea, emesis, musculoskeletal pain, anorexia, dysesthesia, mucositis, and bronchospasm.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Using an ELISA assay, anti-human antibodies (HAHA) were detected in 11 of 133 (8.3%) previously untreated patients. In addition, two patients were weakly positive for neutralizing activity. Limited data suggest that the anti-Campath antibodies did not adversely affect tumor response. Four of 211 (1.9%) previously-treated patients were found to have antibodies to Campath following treatment.

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, 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.

6.3 Postmarketing Experience

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

Fatal infusion reactions: *[see WARNINGS AND PRECAUTIONS (5.2)]*.

Cardiovascular: congestive heart failure, cardiomyopathy, decreased ejection fraction (some patients had been previously treated with cardiotoxic agents).

Immune disorders: Goodpasture's syndrome, Graves' disease, aplastic anemia, Guillain Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, serum sickness, fatal transfusion associated Graft versus Host Disease.

Infections: Epstein-Barr Virus (EBV) including EBV-associated lymphoproliferative disorder, progressive multifocal leukoencephalopathy (PML), re-activation of latent viruses.

Metabolic: tumor lysis syndrome

Neurologic: optic neuropathy

7 DRUG INTERACTIONS

No formal drug interaction studies have been performed with Campath.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with Campath. IgG antibodies, such as Campath, can cross the placental barrier. It is not known whether Campath can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Campath should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

Excretion of Campath in human breast milk has not been studied; it is not known whether this drug is excreted in human milk. IgG antibodies, such as Campath, can be excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Campath, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the elimination half-life of Campath and the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

8.5 Geriatric Use

Of 147 previously untreated B-CLL patients treated with Campath, 35% were ≥ age 65 and 4% were ≥ age 75. Of 149 previously treated patients with B-CLL, 44% were ≥ 65 years of age and 10% were ≥ 75 years of age. Clinical studies of Campath did not include sufficient number of subjects age 65 and over to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

10 OVERDOSAGE

Across all clinical experience, the reported maximum single dose received was 90 mg. Bone marrow aplasia, infections, or severe infusions reactions occurred in patients who received a dose higher than recommended.

One patient received an 80 mg dose by IV infusion and experienced acute bronchospasm, cough, and dyspnea, followed by anuria and death. Another patient received two 90 mg doses by IV infusion one day apart during the second week of treatment and experienced a rapid onset of bone marrow aplasia.

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

11 DESCRIPTION

Campath (alemtuzumab) is a recombinant DNA-derived humanized monoclonal antibody (Campath-1H) directed against the 21-28 kD cell surface glycoprotein, CD52. Campath-1H is an IgG1 kappa antibody 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 solution (pH 6.8-7.4) for injection. Each single use vial of Campath contains 30 mg alemtuzumab, 8.0 mg sodium chloride, 1.44 mg dibasic sodium phosphate, 0.2 mg potassium chloride, 0.2 mg monobasic potassium phosphate, 0.1 mg polysorbate 80, and 0.0187 mg disodium edetate dihydrate. No preservatives are added.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Campath binds to CD52, an antigen present on the surface of B and T lymphocytes, a majority of monocytes, macrophages, NK cells, and a subpopulation of granulocytes. A proportion of bone marrow cells, including some $CD34^+$ cells, express variable levels of CD52. The proposed mechanism of action is antibody-dependent cellular-mediated lysis following cell surface binding of Campath to the leukemic cells.

12.3 Pharmacokinetics

Campath pharmacokinetics were characterized in a study of 30 previously treated B-CLL patients in whom Campath was administered at the recommended dose and schedule. Campath pharmacokinetics displayed nonlinear elimination kinetics. After the last 30 mg dose, the mean volume of distribution at steady-state was 0.18 L/kg (range 0.1 to 0.4 L/kg). Systemic clearance decreased with repeated administration due to decreased receptor-mediated clearance (i.e., loss of CD52 receptors in the periphery). After 12 weeks of dosing, patients exhibited a seven-fold increase in mean AUC. Mean half-life was 11 hours (range 2 to 32 hours) after the first 30 mg dose and was 6 days (range 1 to 14 days) after the last 30 mg dose.

Comparisons of AUC in patients ≥ 65 years (n=6) versus patients < 65 years (n=15) suggested that no dose adjustments are necessary for age. Comparisons of AUC in female patients (n=4) versus male patients (n=17) suggested that no dose adjustments are necessary for gender.

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

13 NONCLINICAL TOXICOLOGY

13.1 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.

14 CLINICAL STUDIES

14.1 Previously Untreated B-CLL Patients

Campath was evaluated in an open-label, randomized (1:1) active-controlled study in previously untreated patients with B-CLL, Rai Stage I-IV, with evidence of progressive disease requiring therapy. Patients received either Campath 30 mg IV 3 times/week for a maximum of 12 weeks or chlorambucil 40 mg/m^2 PO once every 28 days, for a maximum of 12 cycles.

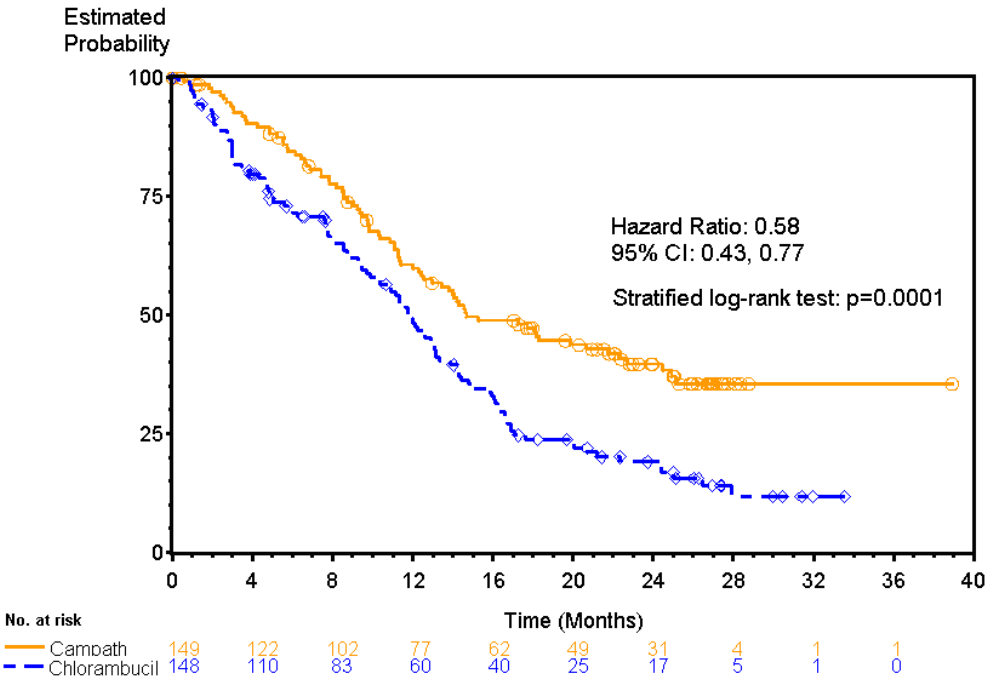
Of the 297 patients randomized, the median age was 60 years, 72% were male, 99% were Caucasian, 96% had a WHO performance status 0-1, 23% had maximum lymph node

diameter ≥ 5cm, 34% were Rai Stage III/IV, and 8% were treated in the U.S.

Patients randomized to receive Campath experienced longer progression free survival (PFS) compared to those randomized to receive chlorambucil (median PFS 14.6 months vs. 11.7 months, respectively). The overall response rates were 83% and 55% ($p < 0.0001$) and the complete response rates were 24% and 2% ($p < 0.0001$) for Campath and chlorambucil arms, respectively. The Kaplan-Meier curve for PFS is shown in Figure 1.

Figure 1

Progression Free Survival in Previously Untreated B-CLL Patients[1]



[1] Log-rank test adjusted for Rai Stage (I-II vs. III-IV).

14.2 Previously Treated B-CLL Patients

Campath was evaluated in three multicenter, open-label, single arm studies of 149 patients with B-CLL previously treated with alkylating agents, fludarabine, or other chemotherapies. Patients were treated with the recommended dose of Campath, 30 mg intravenously, three times per week for up to 12 weeks. Partial response rates of 21 to 31% and complete response rates of 0 to 2% were observed.

15 REFERENCES

[1] American Association of Blood Banks, America's Blood Centers, American Red Cross. Circular of Information for the Use of Human Blood and Blood Components. July 2002.

16 HOW SUPPLIED/STORAGE AND HANDLING

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).

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

17 PATIENT COUNSELING INFORMATION

Cytopenias: Advise patients to report any signs or symptoms such as bleeding, easy bruising, petechiae or purpura, pallor, weakness or fatigue *[see WARNINGS AND PRECAUTIONS (5.1)* and *ADVERSE REACTIONS (6.1)]*.

Infusion Reactions: Advise patients of the signs and symptoms of infusion reactions and of the need to take premedications as prescribed *[see WARNINGS AND PRECAUTIONS (5.2) and OVERALL ADVERSE REACTIONS (6.1)]*.

Infections: Advise patients to immediately report symptoms of infection (e.g. pyrexia) and to take prophylactic anti-infectives for PCP (trimethoprim/sulfamethoxazole DS or equivalent) and for herpes virus (famciclovir or equivalent) as prescribed *[see WARNINGS AND PRECAUTIONS (5.3) and ADVERSE REACTIONS (6.1)]*.

Advise patients that irradiation of blood products is required *[see WARNINGS AND PRECAUTIONS (5.3)]*.

Advise patients that they should not be immunized with live viral vaccines if they have recently been treated with Campath *[see WARNINGS AND PRECAUTIONS (5.5)]*.

Advise male and female patients with reproductive potential to use effective contraceptive methods during treatment and for a minimum of 6 months following Campath therapy *[see NONCLINICAL TOXICOLOGY (13.1)]*.

U.S. Patents: 5,846,534; 6,569,430

Manufactured by: Genzyme Corporation, Cambridge, MA 02142

Distributed by: Bayer HealthCare Pharmaceuticals Inc., Wayne, NJ 07470