

Approved 9.19.2007

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

Indications and Usage: Previously untreated B-CLL patients (1) 9/2007

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/ μ L (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 ($\geq 10\%$): 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: 9/2007

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: CYTOPENIAS, INFUSION REACTIONS, and INFECTIONS

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Dosing Schedule and Administration
- 2.2 Recommended Concomitant Medications
- 2.3 Dose Modification
- 2.4 Preparation and Administration
- 2.5 Incompatibilities

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Cytopenias
- 5.2 Infusion Reactions
- 5.3 Immunosuppression/Infections
- 5.4 Laboratory Monitoring
- 5.5 Immunization

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Immunogenicity
- 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Previously Untreated B-CLL Patients
- 14.2 Previously Treated B-CLL Patients

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

1 **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)**].

2

3 **1 INDICATIONS AND USAGE**

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

6 **2 DOSAGE AND ADMINISTRATION**

7 **2.1 Dosing Schedule and Administration**

8 • Administer as an IV infusion over 2 hours. **Do not administer as intravenous push**
9 **or bolus.**

10 • Recommended Dosing Regimen

11 ○ Gradually escalate to the maximum recommended single dose of 30 mg.
12 Escalation is required at initiation of dosing or if dosing is held ≥ 7 days
13 during treatment. Escalation to 30 mg ordinarily can be accomplished in 3 - 7
14 days.

- 15 ○ Escalation Strategy:
- 16 ○ Administer 3 mg daily until infusion reactions are \leq grade 2 [*see*
- 17 *ADVERSE REACTIONS (6.1)*].
- 18 ○ Then administer 10 mg daily until infusion reactions are \leq 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 \geq 200 cells/ μ L, 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.
-

41
42

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

<u>Hematologic Values</u>	<u>Dose Modification*</u>
ANC < 250/ μ L and/or platelet count \leq 25,000/ μ L	
For first occurrence:	Withhold Campath therapy. Resume Campath at 30 mg when ANC \geq 500/ μ L and platelet count \geq 50,000/ μ L.
For second occurrence:	Withhold Campath therapy. Resume Campath at 10 mg when ANC \geq 500/ μ L and platelet count \geq 50,000/ μ L.
For third occurrence:	Discontinue Campath therapy.
\geq 50% decrease from baseline in patients initiating therapy with a baseline ANC \leq 250/ μ L and/or a baseline platelet count \leq 25,000/ μ L	
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.

43 *If the delay between dosing is \geq 7 days, initiate therapy at Campath 3 mg and escalate to 10 mg and then
44 to 30 mg as tolerated [see *DOSAGE AND ADMINISTRATION (2.1)*].
45

46 **2.4 Preparation and Administration**

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

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

- 52 • To prepare the 3 mg dose, withdraw 0.1 mL into a 1 mL syringe calibrated in
53 increments of 0.01 mL.
- 54 • To prepare the 10 mg dose, withdraw 0.33 mL into a 1 mL syringe calibrated in
55 increments of 0.01 mL.
- 56 • To prepare the 30 mg dose, withdraw 1 mL in either a 1 mL or 3 mL syringe
57 calibrated in 0.1 mL increments.

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

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

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

64 **2.5 Incompatibilities**

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

68 **3 DOSAGE FORMS AND STRENGTHS**

69 30 mg/1 mL single use vial

70 **4 CONTRAINDICATIONS**

71 None

72 **5 WARNINGS AND PRECAUTIONS**

73 **5.1 Cytopenias**

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

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

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

85 **5.2 Infusion Reactions**

86 Adverse reactions occurring during or shortly after Campath infusion include pyrexia,
87 chills/rigors, nausea, hypotension, urticaria, dyspnea, rash, emesis, and bronchospasm. In
88 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 ADMINISTRATION (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 severely lymphopenic patients to avoid
117 Graft versus Host Disease (GVHD), unless emergent circumstances dictate immediate
118 transfusion.¹

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

121 median was 183 cells/ μ L. In previously treated patients receiving Campath, the median
122 time to recovery of CD4+ counts to \geq 200 cells/ μ L was 2 months; however, full recovery
123 (to baseline) of CD4+ and CD8+ counts may take more than 12 months [see *BOXED*
124 *WARNING and ADVERSE REACTIONS (6)*].

125 **5.4 Laboratory Monitoring**

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

130 **5.5 Immunization**

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

135 **6 ADVERSE REACTIONS**

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

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

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

147 **6.1 Clinical Trials Experience**

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

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

155 *Lymphopenia:* Severe lymphopenia and a rapid and sustained decrease in lymphocyte
156 subsets occurred in previously untreated and previously treated patients following
157 administration of Campath. In previously untreated patients, the median CD4+ was 0
158 cells/ μ L at one month after treatment and 238 cells/ μ L [25-75% interquartile range 115
159 to 418 cells/ μ L at 6 months post-treatment [see *WARNINGS AND PRECAUTIONS*
160 (5.3)].

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

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

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

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

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

190 Other infections were reported in approximately 50% of patients across all studies. Grade
191 3 - 5 sepsis ranged from 3% to 10% across studies and was higher in previously treated
192 patients. Grade 3 - 4 febrile neutropenia ranged from 5 to 10% across studies and was
193 higher in previously treated patients. Infection-related fatalities occurred in 2% of
194 previously untreated patients and 16% of previously treated patients. There were 198
195 episodes of other infection in 109 previously untreated patients; 16% were bacterial, 7%
196 were fungal, 4% were other viral, and in 73%, the organism was not identified.

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

200 *Previously Untreated Patients*

201 Table 1 contains selected adverse reactions observed in 294 patients randomized (1:1) to
202 receive Campath or chlorambucil as first line therapy for B-CLL. Campath was
203 administered at a dose of 30 mg intravenously three times weekly for up to 12 weeks.
204 The median duration of therapy was 11.7 weeks with a median weekly dose of 82 mg
205 (25-75% interquartile range: 69 mg – 90 mg).

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

207 ¹Adverse reactions occurring at a higher relative frequency in the Campath arm

208 ²NCI CTC version 2.0 for adverse reactions; NCI CTCAE version 3.0 for laboratory values

209 ³CMV viremia (without evidence of symptoms) includes both cases of single PCR positive test results and of
 210 confirmed CMV viremia (≥ 2 occasions in consecutive samples 1 week apart). For the latter, ganciclovir (or
 211 equivalent) was initiated per protocol.

212 Previously Treated Patients

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

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

219 **6.2 Immunogenicity**

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

226 The incidence of antibody formation is highly dependent on the sensitivity and specificity
227 of the assay. Additionally, the observed incidence of antibody (including neutralizing
228 antibody) positivity in an assay may be influenced by several factors including assay
229 methodology, sample handling, timing of sample collection, concomitant medications,
230 and underlying disease. For these reasons, comparison of the incidence of antibodies to
231 Campath with the incidence of antibodies to other products may be misleading.

232 **6.3 Postmarketing Experience**

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

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

240 Infections: Epstein-Barr Virus (EBV), Progressive Multifocal Leukoencephalopathy
241 (PML).

242 Immune disorders: Goodpasture's syndrome, Graves' disease, aplastic anemia, Guillain
243 Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, serum
244 sickness.

245 Cardiovascular: cardiomyopathy, decreased ejection fraction (in patients previously
246 treated with cardiotoxic agents).

247 Metabolic: Tumor lysis syndrome

248 Neurologic: Optic neuropathy

249 **7 DRUG INTERACTIONS**

250 No formal drug interaction studies have been performed with Campath.

251 **8 USE IN SPECIFIC POPULATIONS**

252 **8.1 Pregnancy**

253 **Pregnancy Category C**

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

258 **8.3 Nursing Mothers**

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

265 **8.4 Pediatric Use**

266 Safety and effectiveness have not been established in pediatric patients.

267 **8.5 Geriatric Use**

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

274 **10 OVERDOSAGE**

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

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

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

284 **11 DESCRIPTION**

285 Campath (alemtuzumab) is a recombinant DNA-derived humanized monoclonal antibody
286 (Campath-1H) directed against the 21-28 kD cell surface glycoprotein, CD52. Campath-
287 1H is an IgG1 kappa antibody with human variable framework and constant regions, and
288 complementarity-determining regions from a murine (rat) monoclonal antibody
289 (Campath-1G). The Campath-1H antibody has an approximate molecular weight of 150
290 kD. Campath is produced in mammalian cell (Chinese hamster ovary) suspension culture
291 in a medium containing neomycin. Neomycin is not detectable in the final product.

292 Campath is a sterile, clear, colorless, isotonic solution (pH 6.8-7.4) for injection. Each
293 single use vial of Campath contains 30 mg alemtuzumab, 8.0 mg sodium chloride, 1.44
294 mg dibasic sodium phosphate, 0.2 mg potassium chloride, 0.2 mg monobasic potassium
295 phosphate, 0.1 mg polysorbate 80, and 0.0187 mg disodium edetate dihydrate. No
296 preservatives are added.

297 **12 CLINICAL PHARMACOLOGY**

298 **12.1 Mechanism of Action**

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

304 **12.3 Pharmacokinetics**

305 Campath pharmacokinetics were characterized in a study of 30 previously treated B-CLL
306 patients in whom Campath was administered at the recommended dose and schedule.
307 Campath pharmacokinetics displayed nonlinear elimination kinetics. After the last 30 mg
308 dose, the mean volume of distribution at steady-state was 0.18 L/kg (range 0.1 to 0.4
309 L/kg). Systemic clearance decreased with repeated administration due to decreased
310 receptor-mediated clearance (i.e., loss of CD52 receptors in the periphery). After 12
311 weeks of dosing, patients exhibited a seven-fold increase in mean AUC. Mean half-life
312 was 11 hours (range 2 to 32 hours) after the first 30 mg dose and was 6 days (range 1 to
313 14 days) after the last 30 mg dose.

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

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

321 **13 NONCLINICAL TOXICOLOGY**

322 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

323 No long-term studies in animals have been performed to establish the carcinogenic or
324 mutagenic potential of Campath, or to determine its effects on fertility in males or
325 females.

326 **14 CLINICAL STUDIES**

327 **14.1 Previously Untreated B-CLL Patients**

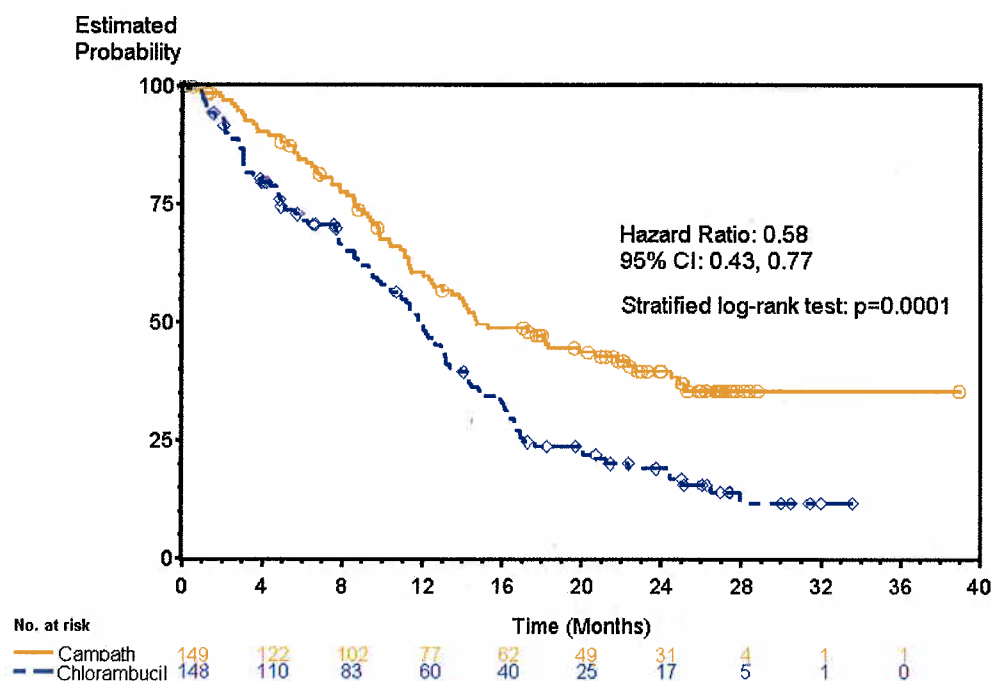
328 Campath was evaluated in an open-label, randomized (1:1) active-controlled study in
329 previously untreated patients with B-CLL, Rai Stage I-IV, with evidence of progressive
330 disease requiring therapy. Patients received either Campath 30 mg IV 3 times/week for a
331 maximum of 12 weeks or chlorambucil 40 mg/m² PO once every 28 days, for a maximum
332 of 12 cycles.

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

335 diameter ≥ 5 cm, 34% were Rai Stage III/IV, and 8% were treated in the U.S.
 336 Patients randomized to receive Campath experienced longer progression free survival
 337 (PFS) compared to those randomized to receive chlorambucil (median PFS 14.6 months
 338 vs. 11.7 months, respectively). The overall response rates were 83% and 55% ($p <$
 339 0.0001) and the complete response rates were 24% and 2% ($p < 0.0001$) for Campath and
 340 chlorambucil arms, respectively. The Kaplan-Meier curve for PFS is shown in **Figure 1**.

341 **Figure 1**

342 **Progression Free Survival in Previously Untreated B-CLL Patients¹**



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

345 **14.2 Previously Treated B-CLL Patients**

346 Campath was evaluated in three multicenter, open-label, single arm studies of 149
 347 patients with B-CLL previously treated with alkylating agents, fludarabine, or other
 348 chemotherapies. Patients were treated with the recommended dose of Campath, 30 mg
 349 intravenously, three times per week for up to 12 weeks. Partial response rates of 21 to
 350 31% and complete response rates of 0 to 2% were observed.

351 **15 REFERENCES**

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

354 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

360 **17 PATIENT COUNSELING INFORMATION**

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

364 *Infusion Reactions:* Advise patients of the signs and symptoms of infusion reactions and
365 of the need to take premedications as prescribed [see *WARNINGS AND PRECAUTIONS*
366 *(5.2)* and *OVERALL ADVERSE REACTIONS (6.1)*].

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

371 Advise patients that irradiation of blood products is required until adequate lymphocyte
372 recovery [see *WARNINGS AND PRECAUTIONS (5.3)*].

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

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

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

379 Manufactured by: Genzyme Corporation, Cambridge, MA 02142

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