ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MabCampath 10 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains 10 mg of alemtuzumab.
Each ampoule contains 30 mg of alemtuzumab.

Alemtuzumab is a genetically engineered humanised IgG1 kappa monoclonal antibody specific for a 21-28 kD lymphocyte cell surface glycoprotein (CD52). The antibody is produced in mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Colourless to slightly yellow concentrate.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MabCampath is indicated for the treatment of patients with B-cell chronic lymphocytic leukaemia (B-CLL) for whom fludarabine combination chemotherapy is not appropriate.

4.2 Posology and method of administration

MabCampath should be administered under the supervision of a physician experienced in the use of cancer therapy.

Posology

During the first week of treatment, MabCampath should be administered in escalating doses: 3 mg on day 1, 10 mg on day 2 and 30 mg on day 3 assuming that each dose is well tolerated. Thereafter, the recommended dose is 30 mg daily administered 3 times weekly on alternate days up to a maximum of 12 weeks.

In most patients, dose escalation to 30 mg can be accomplished in 3-7 days. However, if acute moderate to severe adverse reactions such as hypotension, rigors, fever, shortness of breath, chills, rashes and bronchospasm (some of which may be due to cytokine release) occur at either the 3 mg or 10 mg dose levels, then those doses should be repeated daily until they are well tolerated before further dose escalation is attempted (see section 4.4).

Median duration of treatment was 11.7 weeks for first-line patients and 9.0 weeks for previously treated patients.

Once a patient meets all laboratory and clinical criteria for a complete response, MabCampath should be discontinued and the patient monitored. If a patient improves (i.e. achieves a partial response or stable disease) and then reaches a plateau without further improvement for 4 weeks or more, then MabCampath should be discontinued and the patient monitored. Therapy should be discontinued if there is evidence of disease progression.

Concomitant medicinal products

Premedications

Patients should be premedicated with oral or intravenous steroids, an appropriate antihistamine and analgesic 30-60 minutes prior to each MabCampath infusion during dose escalation and as clinically indicated thereafter (see section 4.4).

Prophylactic antibiotics

Antibiotics and antivirals should be administered routinely to all patients throughout and following treatment (see section 4.4).

Dose modification guidelines

There are no dose modifications recommended for severe lymphopenia given the mechanism of action of MabCampath.

In the event of serious infection or severe haematological toxicity MabCampath should be interrupted until the event resolves. It is recommended that MabCampath should be interrupted in patients whose platelet count falls to < 25,000/μl or whose absolute neutrophil count (ANC) drops to < 250/μl. MabCampath may be reinstituted after the infection or toxicity has resolved. MabCampath should be permanently discontinued if autoimmune anaemia or autoimmune thrombocytopenia appears. The following table outlines the recommended procedure for dose modification following the occurrence of haematological toxicity while on therapy:

Haematologic values	**Dose modification***
ANC < 250/µl and/or platelet count ≤25,000/µl	
For first occurrence	Withhold MabCampath therapy. Resume MabCampath at 30 mg when ANC ≥ 500/µl and platelet count ≥ 50,000/µl.
For second occurrence	Withhold MabCampath therapy. Resume MabCampath at 10 mg when ANC ≥ 500/µl and platelet count ≥ 50,000/µl.
For third occurrence	Discontinue MabCampath 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 MabCampath therapy. Resume MabCampath at 30 mg upon return to baseline value(s).
For second occurrence	Withhold MabCampath therapy. Resume MabCampath at 10 mg upon return to baseline value(s).
For third occurrence	Discontinue MabCampath therapy.

*If the delay between dosing is ≥ 7 days, initiate therapy at MabCampath 3 mg and escalate to 10 mg and then to 30 mg as tolerated

Special populations

Elderly (over 65 years of age)

Recommendations are as stated above for adults. Patients should be monitored carefully (see section 4.4).

Patients with renal or hepatic impairment

No studies have been conducted.

Paediatric population

The safety and efficacy of MabCampath in children aged less than 17 years of age have not been established. No data are available.

Method of administration

The MabCampath solution must be prepared according to the instructions provided in section 6.6. All doses should be administered by intravenous infusion over approximately 2 hours.

4.3 Contraindications

- Hypersensitivity to alemtuzumab, to murine proteins or to any of the excipients.
- Active systemic infections.
- HIV.
- Active second malignancies.
- Pregnancy.

4.4 Special warnings and precautions for use

Acute adverse reactions, which may occur during initial dose escalation and some of which may be due to the release of cytokines, include hypotension, chills/rigors, fever, shortness of breath and rashes. Additional reactions include nausea, urticaria, vomiting, fatigue, dyspnoea, headache, pruritus, diarrhoea and bronchospasm. The frequency of infusion reactions was highest in the first week of therapy, and declined in the second or third week of treatment, in patients treated with MabCampath both as first line therapy and in previously treated patients.

If these events are moderate to severe, then dosing should continue at the same level prior to each dose escalation, with appropriate premedication, until each dose is well tolerated. If therapy is withheld for more than 7 days, MabCampath should be reinstituted with gradual dose escalation.

Transient hypotension has occurred in patients receiving MabCampath. Caution should be used in treating patients with ischaemic heart disease, angina and/or in patients receiving an antihypertensive medicinal product. Myocardial infarction and cardiac arrest have been observed in association with MabCampath infusion in this patient population.

Assessment and ongoing monitoring of cardiac function (e.g. echocardiography, heart rate and body weight) should be considered in patients previously treated with potentially cardiotoxic agents.

It is recommended that patients be premedicated with oral or intravenous steroids 30 - 60 minutes prior to each MabCampath infusion during dose escalation and as clinically indicated. Steroids may be discontinued as appropriate, once dose escalation has been achieved. In addition, an oral antihistamine, e.g. diphenhydramine 50 mg, and an analgesic, e.g. paracetamol 500 mg, may be given. In the event that acute infusion reactions persist, the infusion time may be extended up to 8 hours from the time of reconstitution of MabCampath in solution for infusion.

Profound lymphocyte depletion, an expected pharmacological effect of MabCampath, inevitably occurs and may be prolonged. CD4 and CD8 T-cell counts begin to rise from weeks 8-12 during treatment and continue to recover for several months following the discontinuation of treatment. In patients receiving MabCampath as first line therapy, the recovery of CD4+ counts to ≥200 cells/µl occurred by 6 months post-treatment, however, at 2 months post-treatment the median was 183 cells/µl. In previously treated patients receiving MabCampath, the median time to reach a level of 200 cells/µl is 2 months following last infusion with MabCampath but may take more than 12 months to approximate pretreatment levels. This may predispose patients to opportunistic infections. It is highly recommended that anti-infective prophylaxis (e.g. trimethoprim/sulfamethoxazole 1 tablet twice daily, 3 times weekly, or other prophylaxis against *Pneumocystis jiroveci* pneumonia (PCP) and an effective oral anti-herpes agent, such as famciclovir, 250 mg twice daily) should be initiated while on therapy and for a minimum of 2 months following completion of treatment with MabCampath or until the CD4+ count has recovered to 200 cells/µl or greater, whichever is the later.

The potential for an increased risk of infection-related complications may exist following treatment with multiple chemotherapeutic or biological agents.

Because of the potential for Transfusion Associated Graft Versus Host Disease (TAGVHD) it is recommended that patients who have been treated with MabCampath receive irradiated blood products.

Asymptomatic laboratory positive Cytomegalovirus (CMV) viraemia should not necessarily be considered a serious infection requiring interruption of therapy. Ongoing clinical assessment should be performed for symptomatic CMV infection during MabCampath treatment and for at least 2 months following completion of treatment.

Transient grade 3 or 4 neutropenia occurs very commonly by weeks 5-8 following initiation of treatment. Transient grade 3 or 4 thrombocytopenia occurs very commonly during the first 2 weeks of therapy and then begins to improve in most patients. Therefore, haematological monitoring of patients

is indicated. If a severe haematological toxicity develops, MabCampath treatment should be interrupted until the event resolves. Treatment may be reinstituted following resolution of the haematological toxicity (see section 4.2). MabCampath should be permanently discontinued if autoimmune anaemia or autoimmune thrombocytopenia appears.

Complete blood counts and platelet counts should be obtained at regular intervals during MabCampath therapy and more frequently in patients who develop cytopenias.

It is not proposed that regular and systematic monitoring of CD52 expression should be carried out as routine clinical practice. However, if retreatment is considered, it may be prudent to confirm the presence of CD52 expression. In data available from first line patients treated with MabCampath, loss of CD52 expression was not observed around the time of disease progression or death.

Patients may have allergic or hypersensitivity reactions to MabCampath and to murine or chimeric monoclonal antibodies.

Medicinal products for the treatment of hypersensitivity reactions, as well as preparedness to institute emergency measures in the event of reaction during administration is necessary (see section 4.2).

Males and females of childbearing potential should use effective contraceptive measures during treatment and for 6 months following MabCampath therapy (see sections 4.6 and 5.3).

No studies have been conducted which specifically address the effect of age on MabCampath disposition and toxicity. In general, older patients (over 65 years of age) tolerate cytotoxic therapy less well than younger individuals. Since CLL occurs commonly in this older age group, these patients should be monitored carefully (see section 4.2). In the studies in first line and previously treated patients no substantial differences in safety and efficacy related to age were observed; however the sizes of the databases are limited.

4.5 Interaction with other medicinal products and other forms of interaction

Although no formal drug interaction studies have been performed with MabCampath, there are no known clinically significant interactions of MabCampath with other medicinal products. Because MabCampath is a recombinant humanized protein, a P450 mediated drug-drug interaction would not be expected. However, it is recommended that MabCampath should not be given within 3 weeks of other chemotherapeutic agents.

Although it has not been studied, it is recommended that patients should not receive live viral vaccines in, at least, the 12 months following MabCampath therapy. The ability to generate a primary or anamnestic humoral response to any vaccine has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

MabCampath is contraindicated during pregnancy. Human IgG is known to cross the placental barrier; MabCampath may cross the placental barrier as well and thus potentially cause foetal B and T cell lymphocyte depletion. Animal reproduction studies have not been conducted with MabCampath. It is not known if MabCampath can cause foetal harm when administered to a pregnant woman.

Males and females of childbearing capacity should use effective contraceptive measures during treatment and for 6 months following MabCampath therapy (see section 5.3).

Lactation

It is not known whether MabCampath is excreted in human milk. If treatment is needed, breast-feeding should be discontinued during treatment and for at least 4 weeks following MabCampath therapy.

Fertility

There are no definitive studies of MabCampath which assess its impact on fertility. It is not known if MabCampath can affect human reproductive capacity (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, caution should be exercised as confusion and somnolence have been reported.

4.8 Undesirable effects

The tables below report adverse reactions by MedDRA system organ classes (MedDRA SOCs). The frequencies are based on clinical trial data.
The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

The frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000). No information is available for events that occur at lower frequency, due to the size of the population studied; n=147 for first line treated patients and n=149 for previously treated patients.

The most frequent adverse reactions with MabCampath are: infusion reactions (pyrexia, chills, hypotension, urticaria, nausea, rash, tachycardia, dyspnoea), cytopenias (neutropenia, lymphopenia, thrombocytopenia, anaemia), infections (CMV viraemia, CMV infection, other infections), gastrointestinal symptoms (nausea, emesis, abdominal pain), and neurological symptoms (insomnia, anxiety). The most frequent serious adverse reactions are cytopenias, infusion reactions, and immunosuppression/infections.

Undesirable effects in first line patients

Safety data in first-line B-CLL patients are based on adverse reactions that occurred on study in 147 patients enrolled in a randomized, controlled study of MabCampath as a single agent administered at a dose of 30 mg intravenously three times weekly for up to 12 weeks, inclusive of dose escalation period. Approximately 97% of first-line patients experienced adverse reactions; the most commonly reported reactions in first line patients usually occurred in the first week of therapy.

Within each frequency grouping, undesirable effects observed during treatment or within 30 days following the completion of treatment with MabCampath are presented in order of decreasing seriousness.

System organ class	Very common	Common	Uncommon
Infections and infestations	Cytomegalovirus viraemia Cytomegalovirus infection	Pneumonia Bronchitis Pharyngitis Oral candidiasis	Sepsis Staphylococcal bacteraemia Tuberculosis Bronchopneumonia Herpes ophthalmicus Beta haemolytic streptococcal infection Candidiasis Genital candidiasis Urinary tract infection Cystitis Body tinea Nasopharyngitis Rhinitis
Blood and lymphatic system disorder		Febrile neutropenia Neutropenia Leukopenia Thrombocytopenia Anaemia	Agranulocytosis Lymphopenia Lymphadenopathy Epistaxis
Immune system disorders			Anaphylactic reaction Hypersensitivity
Metabolism and nutrition disorders		Weight decreased	Tumour lysis syndrome Hyperglycaemia Protein total decreased Anorexia
Psychiatric disorders		Anxiety	
Nervous system disorders		Syncope Dizziness Tremor Paraesthesia Hypoesthesia Headache	Vertigo
Eye disorders			Conjunctivitis
Cardiac disorders		Cyanosis Bradycardia Tachycardia Sinus tachycardia	Cardiac arrest Myocardial infarction Angina pectoris Atrial fibrillation Arrhythmia supraventricular Sinus bradycardia Supraventricular extrasystoles
Vascular disorders	Hypotension	Hypertension	Orthostatic hypotension Hot flush Flushing
Respiratory, thoracic and mediastinal disorders		Bronchospasm Dyspnoea	Hypoxia Pleural effusion Dysphonia Rhinorrhoea

System organ class	Very common	Common	Uncommon
Gastrointestinal disorders	Nausea	Vomiting Abdominal pain	Ileus Oral discomfort Stomach discomfort Diarrhoea
Skin and subcutaneous tissue disorders	Urticaria Rash	Dermatitis allergic Pruritus Hyperhidrosis Erythema	Rash pruritic Rash macular Rash erythematous Dermatitis
Musculoskeletal and connective tissue disorders		Myalgia Musculoskeletal pain Back pain	Bone pain Arthralgia Musculoskeletal chest pain Muscle spasms
Renal and urinary disorders			Urine output decreased Dysuria
General disorders and administration site conditions	Fever Chills	Fatigue Asthenia	Mucosal inflammation Infusion site erythema Localised oedema Infusion site oedema Malaise

Acute infusion reactions including fever, chills, nausea, vomiting, hypotension, fatigue, rash, urticaria, dyspnoea, headache, pruritus and diarrhoea have been reported. The majority of these reactions are mild to moderate in severity. Acute infusion reactions usually occur during the first week of therapy and substantially decline thereafter. Grade 3 or 4 infusion reactions are uncommon after the first week of therapy.

Undesirable effects in previously treated patients

Safety data in previously treated B-CLL patients are based on 149 patients enrolled in single-arm studies of MabCampath (Studies 1, 2, and 3). More than 80% of previously treated patients may be expected to experience adverse reactions; the most commonly reported reactions usually occur during the first week of therapy.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	Very common	Common	Uncommon
Infections and infestations	Sepsis Pneumonia Herpes simplex	Cytomegalovirus infection Pneumocystis jiroveci infection Pneumonitis Fungal infection Candidiasis Herpes zoster Abscess Urinary tract infection Sinusitis Bronchitis Upper respiratory tract infection Pharyngitis Infection	Bacterial infection Viral infection Fungal dermatitis Laryngitis Rhinitis Onychomycosis
Neoplasms, benign, malignant and unspecified (incl. cysts and polyps)			Lymphoma – like disorder
Blood and lymphatic system disorder	Granulocytopenia Thrombocytopenia Anaemia	Febrile neutropenia Pancytopenia Leukopenia Lymphopenia Purpura	Aplasia bone marrow Disseminated intravascular coagulation Haemolytic anaemia, Decreased haptoglobin Bone marrow depression Epistaxis Gingival bleeding Haematology test abnormal
Immune system disorders			Allergic reaction
			Severe anaphylactic and other hypersensitivity reactions
Metabolism and nutrition disorders	Anorexia	Hyponatraemia Hypocalcaemia Weight decrease Dehydration Thirst	Hypokalaemia Diabetes mellitus aggravated
Psychiatric disorders		Confusion Anxiety Depression Somnolence Insomnia	Depersonalisation Personality disorder Abnormal thinking Impotence Nervousness

Nervous system disorders	Headache	Vertigo Dizziness Tremor Paresthesia Hypoesthesia Hyperkinesia Taste loss	Syncope Abnormal gait Dystonia Hyperesthesia Neuropathy Taste perversion
Eye disorders		Conjunctivitis	Endophthalmitis
Ear and labyrinth disorders			Deafness Tinnitus
Cardiac disorders		Palpitation Tachycardia	Cardiac arrest Myocardial infarction Atrial fibrillation Supraventricular tachycardia Arrhythmia Bradycardia Abnormal ECG
Vascular disorders	Hypotension	Hypertension Vasospasm Flushing	Peripheral ischaemia
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Hypoxia Haemoptysis Bronchospasm Coughing	Stridor Throat tightness Pulmonary infiltration Pleural effusion Breath sounds decreased Respiratory disorder
Gastrointestinal disorders	Vomiting Nausea Diarrhoea	Gastrointestinal haemorrhage Ulcerative stomatitis Stomatitis Abdominal pain Dyspepsia Constipation Flatulence	Gastroenteritis Tongue ulceration Gingivitis Hiccup Eructation Dry mouth
Hepatobiliary disorders		Hepatic function abnormal	
Skin and subcutaneous tissue disorders	Pruritus Urticaria Rash Hyperhidrosis	Bullous eruption Erythematous rash	Maculo-papular rash Skin disorder
Musculoskeletal and connective tissue disorders		Arthralgia Myalgia Skeletal pain Back pain	Leg pain Hypertonia
Renal and urinary disorders			Haematuria Urinary incontinence Urine flow decreased Polyuria Renal function abnormal

General disorders and administration site conditions	Chills Fever Fatigue	Chest pain Influenza-like symptoms Mucositis Oedema mouth Oedema Asthenia Malaise Temperature change sensation Infusion site reaction Pain	Pulmonary oedema Peripheral oedema Periorbital oedema Mucosal ulceration Infusion site bruising Infusion site dermatitis Infusion site pain

Undesirable effects observed during post-marketing surveillance

Infusion reactions: Serious and sometimes fatal reactions, including bronchospasm, hypoxia, syncope, pulmonary infiltrates, acute respiratory distress syndrome (ARDS), respiratory arrest, myocardial infarction, arrhythmias, acute cardiac insufficiency and cardiac arrest have been observed. Severe anaphylactic and other hypersensitivity reactions, including anaphylactic shock and angioedema, have been reported following MabCampath administration. These symptoms can be ameliorated or avoided if premedication and dose escalation are utilised (see section 4.4).

Infections and infestations: Serious and sometimes fatal viral (e.g. adenovirus, parainfluenza, hepatitis B, progressive multifocal leukoencephalopathy (PML)), bacterial (including tuberculosis and atypical mycobacterioses, nocardiosis), protozoan (e.g. toxoplasma gondii), and fungal (e.g. rhinocerebral mucormycosis) infections, including those due to reactivation of latent infections have occurred during post-marketing surveillance. The recommended anti-infective prophylaxis treatment appears to be effective in reducing the risk of PCP and herpes infections (see section 4.4).

EBV-associated lymphoproliferative disorders, in some cases fatal, have been reported.

Blood and lymphatic system disorders: Severe bleeding reactions have been reported.

Immune system disorders: Serious and sometimes fatal autoimmune phenomena including autoimmune haemolytic anaemia, autoimmune thrombocytopenia, aplastic anaemia, Guillain Barré syndrome and its chronic form, chronic inflammatory demyelinating polyradiculoneuropathy have been reported. A positive Coombs test has also been observed. Fatal Transfusion Associated Graft Versus Host Disease (TAGVHD) has also been reported.

Metabolism and nutritional disorders: Tumour lysis syndrome with fatal outcome has been reported.

Nervous system disorders: Intracranial haemorrhage has occurred with fatal outcome, in patients with thrombocytopenia.

Cardiac disorders: Congestive heart failure, cardiomyopathy, and decreased ejection fraction have been reported in patients previously treated with potentially cardiotoxic agents.

4.9 Overdose

Patients have received repeated unit doses of up to 240 mg of MabCampath. The frequency of grade 3 or 4 adverse events, such as fever, hypotension and anaemia, may be higher in these patients. There is no known specific antidote for MabCampath. Treatment consists of discontinuation of MabCampath and supportive therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC04.

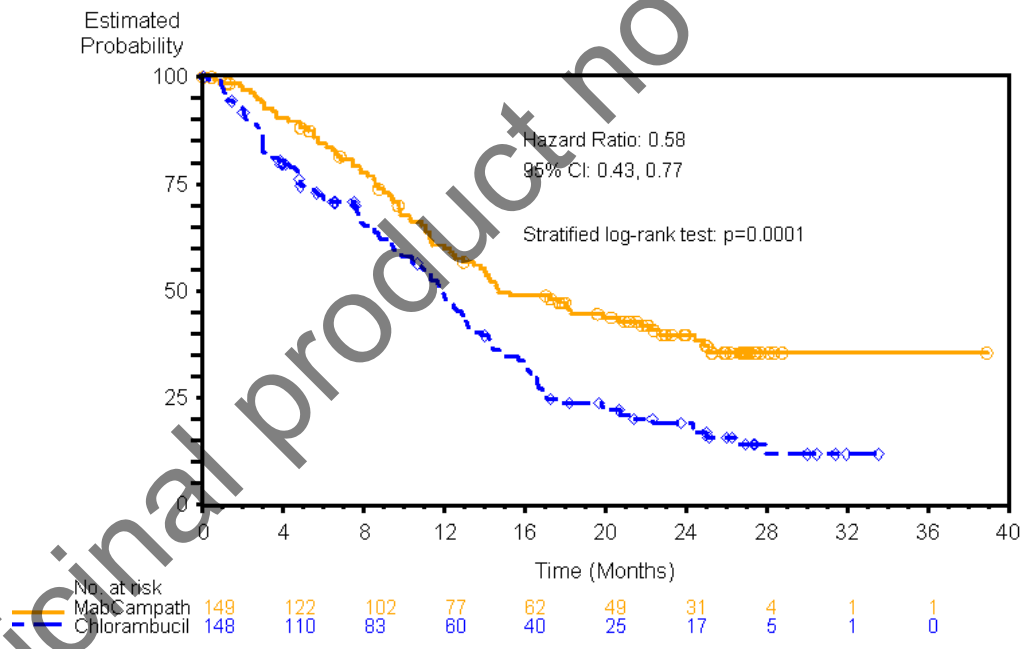
Alemtuzumab is a genetically engineered humanised IgG1 kappa monoclonal antibody specific for a 21-28 kD lymphocyte cell surface glycoprotein (CD52) expressed primarily on the surface of normal and malignant peripheral blood B and T cell lymphocytes. Alemtuzumab was generated by the insertion of six complementarity-determining regions from an IgG2a rat monoclonal antibody into a human IgG1 immunoglobulin molecule.

Alemtuzumab causes the lysis of lymphocytes by binding to CD52, a highly expressed, non-modulating antigen which is present on the surface of essentially all B and T cell lymphocytes as well as monocytes, thymocytes and macrophages. The antibody mediates the lysis of lymphocytes via complement fixation and antibody-dependent cell mediated cytotoxicity. The antigen has been found on a small percentage (< 5%) of granulocytes, but not on erythrocytes or platelets. Alemtuzumab does not appear to damage haematopoietic stem cells or progenitor cells.

First line B-CLL patients

The safety and efficacy of MabCampath were evaluated in a Phase 3, open-label, randomized comparative trial of first line (previously untreated) Rai stage I-IV B-CLL patients requiring therapy (Study 4). MabCampath was shown to be superior to chlorambucil as measured by the primary endpoint progression free survival (PFS) (see Figure 1).

Figure 1: Progression free survival in first line study (by treatment group)



The secondary objectives included complete response (CR) and overall response (CR or partial response) rates using the 1996 NCIWG criteria, the duration of response, time to alternative treatment and safety of the two treatment arms.

Summary of first-line patient population and outcomes

	Independent review of response rate and duration		
	MabCampath n=149	**Chlorambucil n=148**	**P value**
Median Age (Years)	59	60	Not Applicable
Rai Stage III/IV Disease	33.6%	33.1%	Not Applicable
Overall Response Rate	83.2%	55.4%	<0.0001*
Complete Response	24.2%	2.0%	<0.0001*
MRD negative****	7.4%	0.0%	0.0008*
Partial Response	59.1%	53.4%	Not Applicable
Duration of Response, CR or PR (Months)** **K-M median (95% Confidence Interval)**	N=124 16.2 (11.5, 23.0)	N=82 12.7 (10.2, 14.3)	Not Applicable
Time to Alternative Treatment (Months) **K-M median (95% Confidence Interval)**	23.3 (20.7, 31.0)	14.7 (12.6, 16.8)	0.0001***

*Pearson chi-square test or Exact test
** Duration of best response
*** log-rank test stratified by Rai group (Stage I-II vs III-IV)
**** by 4-colour flow

Cytogenetic analyses in first line B-CLL patients:

The cytogenetic profile of B-CLL has been increasingly recognized as providing important prognostic information and may predict response to certain therapies. Of the first-line patients (n=282) in whom baseline cytogenetic (FISH) data were available in Study 4, chromosomal aberrations were detected in 82%, while normal karyotype was detected in 18%. Chromosomal aberrations were categorized according to Döhner's hierarchical model. In first line patients, treated with either MabCampath or chlorambucil, there were 21 patients with the 17p deletion, 54 patients with 11q deletion, 34 patients with trisomy 12, 51 patients with normal karyotype and 67 patients with sole 13q deletion.

ORR was superior in patients with any 11q deletion (87% v 29%; p<0.0001) or sole deletion 13q (91% v 62%; p=0.0087) treated with MabCampath compared to chlorambucil. A trend toward improved ORR was observed in patients with 17p deletion treated with MabCampath (64% v 20%; p=0.0805). Complete remissions were also superior in patients with sole 13q deletion treated with MabCampath (27% v 0%; p=0.0009). Median PFS was superior in patients with sole 13q deletion treated with MabCampath (24.4 v 13.0 months; p=0.0170 stratified by Rai Stage). A trend towards improved PFS was observed in patients with 17p deletion, trisomy 12 and normal karyotype, which did not reach significance due to small sample size.

Assessment of CMV by PCR:

In the randomized controlled trial in first line patients (Study 4), patients in the MabCampath arm were tested weekly for CMV using a PCR (polymerase chain reaction) assay from initiation through completion of therapy, and every 2 weeks for the first 2 months following therapy. In this study, asymptomatic positive PCR only for CMV was reported in 77/147 (52.4%) of MabCampath-treated patients; symptomatic CMV infection was reported less commonly in 23/147 MabCampath treated patients (16%). In the MabCampath arm 36/77 (46.8%) of patients with asymptomatic PCR positive CMV received antiviral therapy and 47/77 (61%) of these patients had MabCampath therapy interrupted. The presence of asymptomatic positive PCR for CMV or symptomatic PCR positive

CMV infection during treatment with MabCampath had no measurable impact on progression free survival (PFS).

Previously treated B-CLL patients:

Determination of the efficacy of MabCampath is based on overall response and survival rates. Data available from three uncontrolled B-CLL studies are summarised in the following table:

Efficacy parameters	Study 1	Study 2	Study 3
Number of Patients	93	32	24
Diagnostic Group	B-CLL pts who had received an alkylating agent and had failed fludarabine	B-CLL pts who had failed to respond or relapsed following treatment with conventional chemotherapy	B-CLL (plus a PLL) pts who had failed to respond or relapsed following treatment with fludarabine
Median Age (years)	66	57	62
Disease Characteristics (%)			
Rai Stage III/IV	76	72	71
B Symptoms	42	31	21
Prior Therapies (%):			
Alkylating Agents	100	100	92
Fludarabine	100	34	100
Number of Prior Regimens (range)	3 (2-7)	3 (1-10)	3 (1-8)
Initial Dosing Regimen	Gradual escalation from 3 to 10 to 30 mg	Gradual escalation from 10 to 30 mg	Gradual escalation from 10 to 30 mg
Final Dosing Regimen	30 mg iv 3 x weekly	30 mg iv 3 x weekly	30 mg iv 3 x weekly
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)
Survival (months):			
(95% Confidence Interval)			
All patients	16 (12-22)	26 (12-44)	28 (7-33)
Responders	33 (26-NR)	44 (28-NR)	36 (19-NR)

NR = not reached

5.2 Pharmacokinetic properties

Pharmacokinetics were characterised in MabCampath-naive patients with B-cell chronic lymphocytic leukaemia (B-CLL) who had failed previous therapy with purine analogues. MabCampath was administered as a 2 hour intravenous infusion, at the recommended dosing schedule, starting at 3 mg and increasing to 30 mg, 3 times weekly, for up to 12 weeks. MabCampath pharmacokinetics followed a 2-compartment model and displayed non-linear elimination kinetics. After the last 30 mg dose, the median volume of distribution at steady-state was 0.15 l/kg (range: 0.1-0.4 l/kg), indicating that distribution was primarily to the extracellular fluid and plasma compartments. Systemic clearance decreased with repeated administration due to decreased receptor-mediated clearance (i.e. loss of CD52 receptors in the periphery). With repeated administration and consequent plasma concentration accumulation, the rate of elimination approached zero-order kinetics. As such, half-life was 8 hours (range: 2-32 hours) after the first 30 mg dose and was 6 days (range: 1-14 days) after the last 30 mg

dose. Steady-state concentrations were reached after about 6 weeks of dosing. No apparent difference in pharmacokinetics between males and females was observed nor was any apparent age effect observed.

5.3 Preclinical safety data

Preclinical evaluation of alemtuzumab in animals has been limited to the cynomolgus monkey because of the lack of expression of the CD52 antigen on non-primate species.

Lymphocytopenia was the most common treatment-related effect in this species. A slight cumulative effect on the degree of lymphocyte depletion was seen in repeated dose studies compared to single dose studies. Lymphocyte depletion was rapidly reversible after cessation of dosing. Reversible neutropenia was seen following daily intravenous or subcutaneous dosing for 30 days, but not following single doses or daily dosing for 14 days. Histopathology results from bone marrow samples revealed no remarkable changes attributable to treatment. Single intravenous doses of 10 and 30 mg/kg produced moderate to severe dose related hypotension accompanied by a slight tachycardia.

MabCampath Fab binding was observed in lymphoid tissues and the mononuclear phagocyte system. Significant Fab binding was also observed in the male reproductive tract (epididymis, sperm, seminal vesicle) and the skin.

No other findings, in the above toxicity studies, provide information of significant relevance to clinical use.

No short or long term animal studies have been conducted with MabCampath to assess carcinogenic and mutagenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate
Polysorbate 80
Potassium chloride
Potassium dihydrogen phosphate
Sodium chloride
Dibasic sodium phosphate
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

There are no known incompatibilities with other medicinal products. However, other medicinal products should not be added to the MabCampath infusion or simultaneously infused through the same intravenous line.

6.3 Shelf life

Unopen ampoule: 3 years.

Reconstituted solution: MabCampath contains no antimicrobial preservative. MabCampath should be used within 8 hours after dilution. Solutions may be stored at 15°C-30°C or refrigerated. This can only be accepted if preparation of the solution takes place under strictly aseptic conditions and the solution is protected from light.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).
Do not freeze.
Store in the original package in order to protect from light.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Clear Type I glass ampoule, containing 3 ml of concentrate.
Pack size: carton of 3 ampoules.

6.6 Special precautions for disposal and other handling

The ampoule contents should be inspected for particulate matter and discolouration prior to administration. If particulate matter is present or the concentrate is coloured, then the ampoule should not be used.

MabCampath contains no antimicrobial preservatives, therefore, it is recommended that MabCampath should be prepared for intravenous infusion using aseptic techniques and that the diluted solution for infusion should be administered within 8 hours after preparation and protected from light. The required amount of the ampoule contents should be added, via a sterile, low-protein binding, non-fibre 5 µm filter, to 100 ml of sodium chloride 9 mg/ml (0.9%) solution for infusion or glucose (5%) solution for infusion. The bag should be inverted gently to mix the solution. Care should be taken to ensure the sterility of the prepared solution particularly as it contains no antimicrobial preservatives.

Other medicinal products should not be added to the MabCampath infusion solution or simultaneously infused through the same intravenous line (see section 4.5).

Caution should be exercised in the handling and preparation of the MabCampath solution. The use of latex gloves and safety glasses is recommended to avoid exposure in case of breakage of the ampoule or other accidental spillage. Women who are pregnant or trying to become pregnant should not handle MabCampath.

Procedures for proper handling and disposal should be observed. Any spillage or waste material should be disposed of by incineration.

7. MARKETING AUTHORISATION HOLDER

Genzyme Europe BV
Gooimeer 10
1411 DD Naarden
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/193/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06/07/2001
Date of latest renewal: 10/07/2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency: http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

MabCampath 30 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains 30 mg of alemtuzumab.
Each vial contains 30 mg of alemtuzumab.

Alemtuzumab is a genetically engineered humanised IgG1 kappa monoclonal antibody specific for a 21-28 kD lymphocyte cell surface glycoprotein (CD52). The antibody is produced in mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Colourless to slightly yellow concentrate.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MabCampath is indicated for the treatment of patients with B-cell chronic lymphocytic leukaemia (B-CLL) for whom fludarabine combination chemotherapy is not appropriate.

4.2 Posology and method of administration

MabCampath should be administered under the supervision of a physician experienced in the use of cancer therapy.

Posology

During the first week of treatment, MabCampath should be administered in escalating doses: 3 mg on day 1, 10 mg on day 2 and 30 mg on day 3 assuming that each dose is well tolerated. Thereafter, the recommended dose is 30 mg daily administered 3 times weekly on alternate days up to a maximum of 12 weeks.

In most patients, dose escalation to 30 mg can be accomplished in 3-7 days. However, if acute moderate to severe adverse reactions such as hypotension, rigors, fever, shortness of breath, chills, rashes and bronchospasm (some of which may be due to cytokine release) occur at either the 3 mg or 10 mg dose levels, then those doses should be repeated daily until they are well tolerated before further dose escalation is attempted (see section 4.4).

Median duration of treatment was 11.7 weeks for first-line patients and 9.0 weeks for previously treated patients.

Once a patient meets all laboratory and clinical criteria for a complete response, MabCampath should be discontinued and the patient monitored. If a patient improves (i.e. achieves a partial response or stable disease) and then reaches a plateau without further improvement for 4 weeks or more, then MabCampath should be discontinued and the patient monitored. Therapy should be discontinued if there is evidence of disease progression.

Concomitant medicinal products

Premedications

Patients should be premedicated with oral or intravenous steroids, an appropriate antihistamine and analgesic 30-60 minutes prior to each MabCampath infusion during dose escalation and as clinically indicated thereafter (see section 4.4).

Prophylactic antibiotics

Antibiotics and antivirals should be administered routinely to all patients throughout and following treatment (see section 4.4).

Dose modification guidelines

There are no dose modifications recommended for severe lymphopenia given the mechanism of action of MabCampath.

In the event of serious infection or severe haematological toxicity MabCampath should be interrupted until the event resolves. It is recommended that MabCampath should be interrupted in patients whose platelet count falls to < 25,000/μl or whose absolute neutrophil count (ANC) drops to < 250/μl. MabCampath may be reinstituted after the infection or toxicity has resolved. MabCampath should be permanently discontinued if autoimmune anaemia or autoimmune thrombocytopenia appears. The following table outlines the recommended procedure for dose modification following the occurrence of haematological toxicity while on therapy:

Haematologic values	Dose modification*
ANC < 250/µl and/or platelet count ≤25,000/µl	
For first occurrence	Withhold MabCampath therapy. Resume MabCampath at 30 mg when ANC ≥ 500/µl and platelet count ≥ 50,000/µl.
For second occurrence	Withhold MabCampath therapy. Resume MabCampath at 10 mg when ANC ≥ 500/µl and platelet count ≥ 50,000/µl.
For third occurrence	Discontinue MabCampath 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 MabCampath therapy. Resume MabCampath at 30 mg upon return to baseline value(s).
For second occurrence	Withhold MabCampath therapy. Resume MabCampath at 10 mg upon return to baseline value(s).
For third occurrence	Discontinue MabCampath therapy.

*If the delay between dosing is ≥ 7 days, initiate therapy at MabCampath 3 mg and escalate to 10 mg and then to 30 mg as tolerated

Special populations

Elderly (over 65 years of age)

Recommendations are as stated above for adults. Patients should be monitored carefully (see section 4.4).

Patients with renal or hepatic impairment

No studies have been conducted.

Paediatric population

The safety and efficacy of MabCampath in children aged less than 17 years of age have not been established. No data are available.

Method of administration

The MabCampath solution must be prepared according to the instructions provided in section 6.6. All doses should be administered by intravenous infusion over approximately 2 hours.

4.3 Contraindications

- Hypersensitivity to alemtuzumab, to murine proteins or to any of the excipients.
- Active systemic infections.
- HIV.
- Active second malignancies.
- Pregnancy.

4.4 Special warnings and precautions for use

Acute adverse reactions, which may occur during initial dose escalation and some of which may be due to the release of cytokines, include hypotension, chills/rigors, fever, shortness of breath and rashes. Additional reactions include nausea, urticaria, vomiting, fatigue, dyspnoea, headache, pruritus, diarrhoea and bronchospasm. The frequency of infusion reactions was highest in the first week of therapy, and declined in the second or third week of treatment, in patients treated with MabCampath both as first line therapy and in previously treated patients.

If these events are moderate to severe, then dosing should continue at the same level prior to each dose escalation, with appropriate premedication, until each dose is well tolerated. If therapy is withheld for more than 7 days, MabCampath should be reinstituted with gradual dose escalation.

Transient hypotension has occurred in patients receiving MabCampath. Caution should be used in treating patients with ischaemic heart disease, angina and/or in patients receiving an antihypertensive medicinal product. Myocardial infarction and cardiac arrest have been observed in association with MabCampath infusion in this patient population.

Assessment and ongoing monitoring of cardiac function (e.g. echocardiography, heart rate and body weight) should be considered in patients previously treated with potentially cardiotoxic agents.

It is recommended that patients be premedicated with oral or intravenous steroids 30 - 60 minutes prior to each MabCampath infusion during dose escalation and as clinically indicated. Steroids may be discontinued as appropriate, once dose escalation has been achieved. In addition, an oral antihistamine, e.g. diphenhydramine 50 mg, and an analgesic, e.g. paracetamol 500 mg, may be given. In the event that acute infusion reactions persist, the infusion time may be extended up to 8 hours from the time of reconstitution of MabCampath in solution for infusion.

Profound lymphocyte depletion, an expected pharmacological effect of MabCampath, inevitably occurs and may be prolonged. CD4 and CD8 T-cell counts begin to rise from weeks 8-12 during treatment and continue to recover for several months following the discontinuation of treatment. In patients receiving MabCampath as first line therapy, the recovery of CD4+ counts to ≥200 cells/µl occurred by 6 months post-treatment, however, at 2 months post-treatment the median was 183 cells/µl. In previously treated patients receiving MabCampath, the median time to reach a level of 200 cells/µl is 2 months following last infusion with MabCampath but may take more than 12 months to approximate pretreatment levels. This may predispose patients to opportunistic infections. It is highly recommended that anti-infective prophylaxis (e.g. trimethoprim/sulfamethoxazole 1 tablet twice daily, 3 times weekly, or other prophylaxis against *Pneumocystis jiroveci* pneumonia (PCP) and an effective oral anti-herpes agent, such as famciclovir, 250 mg twice daily) should be initiated while on therapy and for a minimum of 2 months following completion of treatment with MabCampath or until the CD4+ count has recovered to 200 cells/µl or greater, whichever is the later.

The potential for an increased risk of infection-related complications may exist following treatment with multiple chemotherapeutic or biological agents.

Because of the potential for Transfusion Associated Graft Versus Host Disease (TAGVHD) it is recommended that patients who have been treated with MabCampath receive irradiated blood products.

Asymptomatic laboratory positive Cytomegalovirus (CMV) viraemia should not necessarily be considered a serious infection requiring interruption of therapy. Ongoing clinical assessment should be performed for symptomatic CMV infection during MabCampath treatment and for at least 2 months following completion of treatment.

Transient grade 3 or 4 neutropenia occurs very commonly by weeks 5-8 following initiation of treatment. Transient grade 3 or 4 thrombocytopenia occurs very commonly during the first 2 weeks of therapy and then begins to improve in most patients. Therefore, haematological monitoring of patients is indicated. If a severe haematological toxicity develops, MabCampath treatment should be

interrupted until the event resolves. Treatment may be reinstituted following resolution of the haematological toxicity (see section 4.2). MabCampath should be permanently discontinued if autoimmune anaemia or autoimmune thrombocytopenia appears.

Complete blood counts and platelet counts should be obtained at regular intervals during MabCampath therapy and more frequently in patients who develop cytopenias.

It is not proposed that regular and systematic monitoring of CD52 expression should be carried out as routine clinical practice. However, if retreatment is considered, it may be prudent to confirm the presence of CD52 expression. In data available from first line patients treated with MabCampath, loss of CD52 expression was not observed around the time of disease progression or death.

Patients may have allergic or hypersensitivity reactions to MabCampath and to murine or chimeric monoclonal antibodies.

Medicinal products for the treatment of hypersensitivity reactions, as well as preparedness to institute emergency measures in the event of reaction during administration is necessary (see section 4.2).

Males and females of childbearing potential should use effective contraceptive measures during treatment and for 6 months following MabCampath therapy (see sections 4.6 and 5.3).

No studies have been conducted which specifically address the effect of age on MabCampath disposition and toxicity. In general, older patients (over 65 years of age) tolerate cytotoxic therapy less well than younger individuals. Since CLL occurs commonly in this older age group, these patients should be monitored carefully (see section 4.2). In the studies in first line and previously treated patients no substantial differences in safety and efficacy related to age were observed; however the sizes of the databases are limited.

4.5 Interaction with other medicinal products and other forms of interaction

Although no formal drug interaction studies have been performed with MabCampath, there are no known clinically significant interactions of MabCampath with other medicinal products. Because MabCampath is a recombinant humanized protein, a P450 mediated drug-drug interaction would not be expected. However, it is recommended that MabCampath should not be given within 3 weeks of other chemotherapeutic agents.

Although it has not been studied, it is recommended that patients should not receive live viral vaccines in, at least, the 12 months following MabCampath therapy. The ability to generate a primary or anamnestic humoral response to any vaccine has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

MabCampath is contraindicated during pregnancy. Human IgG is known to cross the placental barrier; MabCampath may cross the placental barrier as well and thus potentially cause foetal B and T cell lymphocyte depletion. Animal reproduction studies have not been conducted with MabCampath. It is not known if MabCampath can cause foetal harm when administered to a pregnant woman.

Males and females of childbearing capacity should use effective contraceptive measures during treatment and for 6 months following MabCampath therapy (see section 5.3).

Lactation

It is not known whether MabCampath is excreted in human milk. If treatment is needed, breast-feeding should be discontinued during treatment and for at least 4 weeks following MabCampath therapy.

Fertility

There are no definitive studies of MabCampath which assess its impact on fertility. It is not known if MabCampath can affect human reproductive capacity (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, caution should be exercised as confusion and somnolence have been reported.

4.8 Undesirable effects

The tables below report adverse reactions by MedDRA system organ classes (MedDRA SOCs). The frequencies are based on clinical trial data.
The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

The frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000). No information is available for events that occur at lower frequency, due to the size of the population studied; n=147 for first line treated patients and n=149 for previously treated patients.

The most frequent adverse reactions with MabCampath are: infusion reactions (pyrexia, chills, hypotension, urticaria, nausea, rash, tachycardia, dyspnoea), cytopenias (neutropenia, lymphopenia, thrombocytopenia, anaemia), infections (CMV viraemia, CMV infection, other infections), gastrointestinal symptoms (nausea, emesis, abdominal pain), and neurological symptoms (insomnia, anxiety). The most frequent serious adverse reactions are cytopenias, infusion reactions, and immunosuppression/infections.

Undesirable effects in first line patients

Safety data in first-line B-CLL patients are based on adverse reactions that occurred on study in 147 patients enrolled in a randomized, controlled study of MabCampath as a single agent administered at a dose of 30 mg intravenously three times weekly for up to 12 weeks, inclusive of dose escalation period. Approximately 97% of first-line patients experienced adverse reactions; the most commonly reported reactions in first line patients usually occurred in the first week of therapy.

Within each frequency grouping, undesirable effects observed during treatment or within 30 days following the completion of treatment with MabCampath are presented in order of decreasing seriousness.

System organ class	Very common	Common	Uncommon
Infections and infestations	Cytomegalovirus viraemia Cytomegalovirus infection	Pneumonia Bronchitis Pharyngitis Oral candidiasis	Sepsis Staphylococcal bacteraemia Tuberculosis Bronchopneumonia Herpes ophthalmicus Beta haemolytic streptococcal infection Candidiasis Genital candidiasis Urinary tract infection Cystitis Body tinea Nasopharyngitis Rhinitis
Blood and lymphatic system disorder		Febrile neutropenia Neutropenia Leukopenia Thrombocytopenia Anaemia	Agranulocytosis Lymphopenia Lymphadenopathy Epistaxis
Immune system disorders			Anaphylactic reaction Hypersensitivity
Metabolism and nutrition disorders		Weight decreased	Tumour lysis syndrome Hyperglycaemia Protein total decreased Anorexia
Psychiatric disorders		Anxiety	
Nervous system disorders		Syncope Dizziness Tremor Paraesthesia Hypoesthesia Headache	Vertigo
Eye disorders			Conjunctivitis
Cardiac disorders		Cyanosis Bradycardia Tachycardia Sinus tachycardia	Cardiac arrest Myocardial infarction Angina pectoris Atrial fibrillation Arrhythmia supraventricular Sinus bradycardia Supraventricular extrasystoles
Vascular disorders	Hypotension	Hypertension	Orthostatic hypotension Hot flush Flushing
Respiratory, thoracic and mediastinal disorders		Bronchospasm Dyspnoea	Hypoxia Pleural effusion Dysphonia Rhinorrhoea

System organ class	Very common	Common	Uncommon
Gastrointestinal disorders	Nausea	Vomiting Abdominal pain	Ileus Oral discomfort Stomach discomfort Diarrhoea
Skin and subcutaneous tissue disorders	Urticaria Rash	Dermatitis allergic Pruritus Hyperhidrosis Erythema	Rash pruritic Rash macular Rash erythematous Dermatitis
Musculoskeletal and connective tissue disorders		Myalgia Musculoskeletal pain Back pain	Bone pain Arthralgia Musculoskeletal chest pain Muscle spasms
Renal and urinary disorders			Urine output decreased Dysuria
General disorders and administration site conditions	Fever Chills	Fatigue Asthenia	Mucosal inflammation Infusion site erythema Localised oedema Infusion site oedema Malaise

Acute infusion reactions including fever, chills, nausea, vomiting, hypotension, fatigue, rash, urticaria, dyspnoea, headache, pruritus and diarrhoea have been reported. The majority of these reactions are mild to moderate in severity. Acute infusion reactions usually occur during the first week of therapy and substantially decline thereafter. Grade 3 or 4 infusion reactions are uncommon after the first week of therapy.

Undesirable effects in previously treated patients

Safety data in previously treated B-CLL patients are based on 149 patients enrolled in single-arm studies of MabCampath (Studies 1, 2, and 3). More than 80% of previously treated patients may be expected to experience adverse reactions; the most commonly reported reactions usually occur during the first week of therapy.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	Very common	Common	Uncommon
Infections and infestations	Sepsis Pneumonia Herpes simplex	Cytomegalovirus infection Pneumocystis jiroveci infection Pneumonitis Fungal infection Candidiasis Herpes zoster Abscess Urinary tract infection Sinusitis Bronchitis Upper respiratory tract infection Pharyngitis Infection	Bacterial infection Viral infection Fungal dermatitis Laryngitis Rhinitis Onychomycosis
Neoplasms, benign, malignant and unspecified (incl. cysts and polyps)			Lymphoma – like disorder
Blood and lymphatic system disorder	Granulocytopenia Thrombocytopenia Anaemia	Febrile neutropenia Pancytopenia Leukopenia Lymphopenia Purpura	Aplasia bone marrow Disseminated intravascular coagulation Haemolytic anaemia, Decreased haptoglobin Bone marrow depression Epistaxis Gingival bleeding Haematology test abnormal
Immune system disorders			Allergic reaction
			Severe anaphylactic and other hypersensitivity reactions
Metabolism and nutrition disorders	Anorexia	Hyponatraemia Hypocalcaemia Weight decrease Dehydration Thirst	Hypokalaemia Diabetes mellitus aggravated
Psychiatric disorders		Confusion Anxiety Depression Somnolence Insomnia	Depersonalisation Personality disorder Abnormal thinking Impotence Nervousness

Nervous system disorders	Headache	Vertigo Dizziness Tremor Paresthesia Hypoesthesia Hyperkinesia Taste loss	Syncope Abnormal gait Dystonia Hyperesthesia Neuropathy Taste perversion
Eye disorders		Conjunctivitis	Endophthalmitis
Ear and labyrinth disorders			Deafness Tinnitus
Cardiac disorders		Palpitation Tachycardia	Cardiac arrest Myocardial infarction Atrial fibrillation Supraventricular tachycardia Arrhythmia Bradycardia Abnormal ECG
Vascular disorders	Hypotension	Hypertension Vasospasm Flushing	Peripheral ischaemia
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Hypoxia Haemoptysis Bronchospasm Coughing	Stridor Throat tightness Pulmonary infiltration Pleural effusion Breath sounds decreased Respiratory disorder
Gastrointestinal disorders	Vomiting Nausea Diarrhoea	Gastrointestinal haemorrhage Ulcerative stomatitis Stomatitis Abdominal pain Dyspepsia Constipation Flatulence	Gastroenteritis Tongue ulceration Gingivitis Hiccup Eructation Dry mouth
Hepatobiliary disorders		Hepatic function abnormal	
Skin and subcutaneous tissue disorders	Pruritus Urticaria Rash Hyperhidrosis	Bullous eruption Erythematous rash	Maculo-papular rash Skin disorder
Musculoskeletal and connective tissue disorders		Arthralgia Myalgia Skeletal pain Back pain	Leg pain Hypertonia
Renal and urinary disorders			Haematuria Urinary incontinence Urine flow decreased Polyuria Renal function abnormal

General disorders and administration site conditions	Chills Fever Fatigue	Chest pain Influenza-like symptoms Mucositis Oedema mouth Oedema Asthenia Malaise Temperature change sensation Infusion site reaction Pain	Pulmonary oedema Peripheral oedema Periorbital oedema Mucosal ulceration Infusion site bruising Infusion site dermatitis Infusion site pain

Undesirable effects observed during post-marketing surveillance

Infusion reactions: Serious and sometimes fatal reactions, including bronchospasm, hypoxia, syncope, pulmonary infiltrates, acute respiratory distress syndrome (ARDS), respiratory arrest, myocardial infarction, arrhythmias, acute cardiac insufficiency and cardiac arrest have been observed. Severe anaphylactic and other hypersensitivity reactions, including anaphylactic shock and angioedema, have been reported following MabCampath administration. These symptoms can be ameliorated or avoided if premedication and dose escalation are utilised (see section 4.4).

Infections and infestations: Serious and sometimes fatal viral (e.g. adenovirus, parainfluenza, hepatitis B, progressive multifocal leukoencephalopathy (PML)), bacterial (including tuberculosis and atypical mycobacterioses, nocardiosis), protozoan (e.g. toxoplasma gondii), and fungal (e.g. rhinocerebral mucormycosis) infections, including those due to reactivation of latent infections have occurred during post-marketing surveillance. The recommended anti-infective prophylaxis treatment appears to be effective in reducing the risk of PCP and herpes infections (see section 4.4).

EBV-associated lymphoproliferative disorders, in some cases fatal, have been reported.

Blood and lymphatic system disorders: Severe bleeding reactions have been reported.

Immune system disorders: Serious and sometimes fatal autoimmune phenomena including autoimmune haemolytic anaemia, autoimmune thrombocytopenia, aplastic anaemia, Guillain Barré syndrome and its chronic form, chronic inflammatory demyelinating polyradiculoneuropathy have been reported. A positive Coombs test has also been observed. Fatal Transfusion Associated Graft Versus Host Disease (TAGVHD) has also been reported.

Metabolism and nutritional disorders: Tumour lysis syndrome with fatal outcome has been reported.

Nervous system disorders: Intracranial haemorrhage has occurred with fatal outcome, in patients with thrombocytopenia.

Cardiac disorders: Congestive heart failure, cardiomyopathy, and decreased ejection fraction have been reported in patients previously treated with potentially cardiotoxic agents.

4.9 Overdose

Patients have received repeated unit doses of up to 240 mg of MabCampath. The frequency of grade 3 or 4 adverse events, such as fever, hypotension and anaemia, may be higher in these patients. There is no known specific antidote for MabCampath. Treatment consists of discontinuation of MabCampath and supportive therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC04.

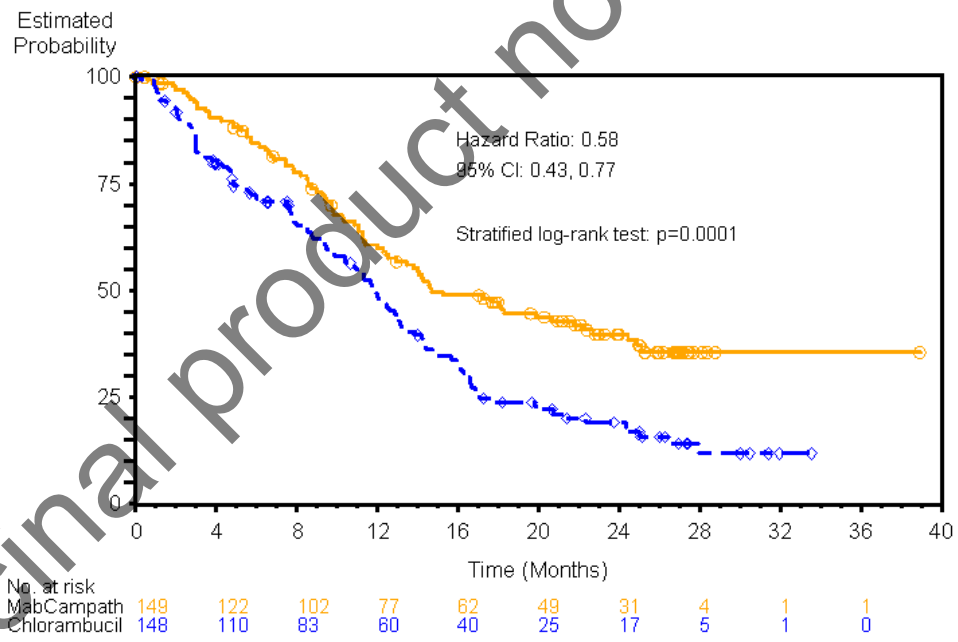
Alemtuzumab is a genetically engineered humanised IgG1 kappa monoclonal antibody specific for a 21-28 kD lymphocyte cell surface glycoprotein (CD52) expressed primarily on the surface of normal and malignant peripheral blood B and T cell lymphocytes. Alemtuzumab was generated by the insertion of six complementarity-determining regions from an IgG2a rat monoclonal antibody into a human IgG1 immunoglobulin molecule.

Alemtuzumab causes the lysis of lymphocytes by binding to CD52, a highly expressed, non-modulating antigen which is present on the surface of essentially all B and T cell lymphocytes as well as monocytes, thymocytes and macrophages. The antibody mediates the lysis of lymphocytes via complement fixation and antibody-dependent cell mediated cytotoxicity. The antigen has been found on a small percentage (< 5%) of granulocytes, but not on erythrocytes or platelets. Alemtuzumab does not appear to damage haematopoietic stem cells or progenitor cells.

First line B-CLL patients

The safety and efficacy of MabCampath were evaluated in a Phase 3, open-label, randomized comparative trial of first line (previously untreated) Rai stage I-IV B-CLL patients requiring therapy (Study 4). MabCampath was shown to be superior to chlorambucil as measured by the primary endpoint progression free survival (PFS) (see Figure 1).

Figure 1: Progression free survival in first line study (by treatment group)



The secondary objectives included complete response (CR) and overall response (CR or partial response) rates using the 1996 NCIWG criteria, the duration of response, time to alternative treatment and safety of the two treatment arms.

Summary of first-line patient population and outcomes

	Independent review of response rate and duration		
	MabCampath n=149	**Chlorambucil n=148**	**P value**
Median Age (Years)	59	60	Not Applicable
Rai Stage III/IV Disease	33.6%	33.1%	Not Applicable
Overall Response Rate	83.2%	55.4%	<0.0001*
Complete Response	24.2%	2.0%	<0.0001*
MRD negative****	7.4%	0.0%	0.0008*
Partial Response	59.1%	53.4%	Not Applicable
Duration of Response, CR or PR (Months)** **K-M median (95% Confidence Interval)**	N=124 16.2 (11.5, 23.0)	N=82 12.7 (10.2, 14.3)	Not Applicable
Time to Alternative Treatment (Months) **K-M median (95% Confidence Interval)**	23.3 (20.7, 31.0)	14.7 (12.6, 16.8)	0.0001***

*Pearson chi-square test or Exact test
** Duration of best response
*** log-rank test stratified by Rai group (Stage I-II vs III-IV)
**** by 4-colour flow

Cytogenetic Analyses in first line B-CLL patients:

The cytogenetic profile of B-CLL has been increasingly recognized as providing important prognostic information and may predict response to certain therapies. Of the first-line patients (n=282) in whom baseline cytogenetic (FISH) data were available in Study 4, chromosomal aberrations were detected in 82%, while normal karyotype was detected in 18%. Chromosomal aberrations were categorized according to Döhner's hierarchical model. In first line patients, treated with either MabCampath or chlorambucil, there were 21 patients with the 17p deletion, 54 patients with 11q deletion, 34 patients with trisomy 12, 51 patients with normal karyotype and 67 patients with sole 13q deletion.

ORR was superior in patients with any 11q deletion (87% v 29%; p<0.0001) or sole deletion 13q (91% v 62%; p=0.0087) treated with MabCampath compared to chlorambucil. A trend toward improved ORR was observed in patients with 17p deletion treated with MabCampath (64% v 20%; p=0.0805). Complete remissions were also superior in patients with sole 13q deletion treated with MabCampath (27% v 0%; p=0.0009). Median PFS was superior in patients with sole 13q deletion treated with MabCampath (24.4 v 13.0 months; p=0.0170 stratified by Rai Stage). A trend towards improved PFS was observed in patients with 17p deletion, trisomy 12 and normal karyotype, which did not reach significance due to small sample size.

Assessment of CMV by PCR:

In the randomized controlled trial in first line patients (Study 4), patients in the MabCampath arm were tested weekly for CMV using a PCR (polymerase chain reaction) assay from initiation through completion of therapy, and every 2 weeks for the first 2 months following therapy. In this study, asymptomatic positive PCR only for CMV was reported in 77/147 (52.4%) of MabCampath-treated patients; symptomatic CMV infection was reported less commonly in 23/147 MabCampath treated patients (16%). In the MabCampath arm 36/77 (46.8%) of patients with asymptomatic PCR positive CMV received antiviral therapy and 47/77 (61%) of these patients had MabCampath therapy interrupted. The presence of asymptomatic positive PCR for CMV or symptomatic PCR positive

CMV infection during treatment with MabCampath had no measurable impact on progression free survival (PFS).

Previously treated B-CLL patients:

Determination of the efficacy of MabCampath is based on overall response and survival rates. Data available from three uncontrolled B-CLL studies are summarised in the following table:

Efficacy parameters	Study 1	Study 2	Study 3
Number of Patients	93	32	24
Diagnostic Group	B-CLL pts who had received an alkylating agent and had failed fludarabine	B-CLL pts who had failed to respond or relapsed following treatment with conventional chemotherapy	B-CLL (plus a PLL) pts who had failed to respond or relapsed following treatment with fludarabine
Median Age (years)	66	57	62
Disease Characteristics (%)			
Rai Stage III/IV	76	72	71
B Symptoms	42	31	21
Prior Therapies (%):			
Alkylating Agents	100	100	92
Fludarabine	100	34	100
Number of Prior Regimens (range)	3 (2-7)	3 (1-10)	3 (1-8)
Initial Dosing Regimen	Gradual escalation from 3 to 10 to 30 mg	Gradual escalation from 10 to 30 mg	Gradual escalation from 10 to 30 mg
Final Dosing Regimen	30 mg iv 3 x weekly	30 mg iv 3 x weekly	30 mg iv 3 x weekly
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)
Survival (months):			
(95% Confidence Interval)			
All patients	16 (12-22)	26 (12-44)	28 (7-33)
Responders	33 (26-NR)	44 (28-NR)	36 (19-NR)

NR = not reached

5.2 Pharmacokinetic properties

Pharmacokinetics were characterised in MabCampath-naive patients with B-cell chronic lymphocytic leukaemia (B-CLL) who had failed previous therapy with purine analogues. MabCampath was administered as a 2 hour intravenous infusion, at the recommended dosing schedule, starting at 3 mg and increasing to 30 mg, 3 times weekly, for up to 12 weeks. MabCampath pharmacokinetics followed a 2-compartment model and displayed non-linear elimination kinetics. After the last 30 mg dose, the median volume of distribution at steady-state was 0.15 l/kg (range: 0.1-0.4 l/kg), indicating that distribution was primarily to the extracellular fluid and plasma compartments. Systemic clearance decreased with repeated administration due to decreased receptor-mediated clearance (i.e. loss of CD52 receptors in the periphery). With repeated administration and consequent plasma concentration accumulation, the rate of elimination approached zero-order kinetics. As such, half-life was 8 hours (range: 2-32 hours) after the first 30 mg dose and was 6 days (range: 1-14 days) after the last 30 mg

dose. Steady-state concentrations were reached after about 6 weeks of dosing. No apparent difference in pharmacokinetics between males and females was observed nor was any apparent age effect observed.

5.3 Preclinical safety data

Preclinical evaluation of alemtuzumab in animals has been limited to the cynomolgus monkey because of the lack of expression of the CD52 antigen on non-primate species.

Lymphocytopenia was the most common treatment-related effect in this species. A slight cumulative effect on the degree of lymphocyte depletion was seen in repeated dose studies compared to single dose studies. Lymphocyte depletion was rapidly reversible after cessation of dosing. Reversible neutropenia was seen following daily intravenous or subcutaneous dosing for 30 days, but not following single doses or daily dosing for 14 days. Histopathology results from bone marrow samples revealed no remarkable changes attributable to treatment. Single intravenous doses of 10 and 30 mg/kg produced moderate to severe dose related hypotension accompanied by a slight tachycardia.

MabCampath Fab binding was observed in lymphoid tissues and the mononuclear phagocyte system. Significant Fab binding was also observed in the male reproductive tract (epididymis, sperm, seminal vesicle) and the skin.

No other findings, in the above toxicity studies, provide information of significant relevance to clinical use.

No short or long term animal studies have been conducted with MabCampath to assess carcinogenic and mutagenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate
Polysorbate 80
Potassium chloride
Potassium dihydrogen phosphate
Sodium chloride
Dibasic sodium phosphate
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

There are no known incompatibilities with other medicinal products. However, other medicinal products should not be added to the MabCampath infusion or simultaneously infused through the same intravenous line.

6.3 Shelf life

Unopen vial: 3 years.

Reconstituted solution: MabCampath contains no antimicrobial preservative. MabCampath should be used within 8 hours after dilution. Solutions may be stored at 15°C-30°C or refrigerated. This can only be accepted if preparation of the solution takes place under strictly aseptic conditions and the solution is protected from light.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).
Do not freeze.
Store in the original package in order to protect from light.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Clear type I glass vial, closed with a rubber stopper, containing 1 ml of concentrate.

Pack size: carton of 3 vials.

6.6 Special precautions for disposal and other handling

The vial contents should be inspected for particulate matter and discolouration prior to administration. If particulate matter is present or the concentrate is coloured, then the vial should not be used.

MabCampath contains no antimicrobial preservatives, therefore, it is recommended that MabCampath should be prepared for intravenous infusion using aseptic techniques and that the diluted solution for infusion should be administered within 8 hours after preparation and protected from light. The required amount of the vial contents should be added to 100 ml of sodium chloride 9 mg/ml (0.9%) solution for infusion or glucose (5%) solution for infusion. The bag should be inverted gently to mix the solution. Care should be taken to ensure the sterility of the prepared solution particularly as it contains no antimicrobial preservatives.

Other medicinal products should not be added to the MabCampath infusion solution or simultaneously infused through the same intravenous line (see section 4.5).

Caution should be exercised in the handling and preparation of the MabCampath solution. The use of latex gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage. Women who are pregnant or trying to become pregnant should not handle MabCampath.

Procedures for proper handling and disposal should be observed. Any spillage or waste material should be disposed of by incineration.

7. MARKETING AUTHORISATION HOLDER

Genzyme Europe BV
Gooimeer 10
1411 DD Naarden
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/193/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06/07/2001
Date of latest renewal: 10/07/2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency: http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Boehringer Ingelheim Pharma GmbH & Co. KG
Birkendorfer Strasse 65
D-88397 Biberach an der Riss
Deutschland

Genzyme Flanders bvba
Cipalstraat 8
2440 Geel
Belgium

Name and address of the manufacturer responsible for batch release

Genzyme Ltd.
37 Hollands Road
Haverhill, Suffolk CB9 8PU
United Kingdom

Genzyme Ireland Limited.
IDA Industrial Park
Old Kilmeaden Road
Waterford
Ireland

Bayer Schering Pharma AG
Müllerstrasse 178
D-13342 Berlin
Deutschland

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex 1: Summary of Product Characteristics, section 4.2).

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

The MAH shall agree the details of an educational brochure with the National Competent Authorities.

The MAH shall ensure that all doctors who prescribe MabCampath are provided with a healthcare professional information pack containing the following:

- Educational brochure
- Summary of Product Characteristics (SPC) and Package Leaflet and Labelling

Key elements to be included in the educational brochure

- The risk of opportunistic infections, in particular CMV viraemia
- Recommendation to avoid vaccination with live vaccines for at least 12 months following MabCampath therapy
- The risk of infusion reactions
    - Need for premedication
    - That treatment for hypersensitivity reactions, including measures for resuscitation should be available during administration
    - That the risk of infusion reactions is highest in first week of therapy
    - That if the reaction is moderate or severe dosing should continue at the same level (ie no dose escalation) until each dose is well tolerated
    - That if therapy is withheld for more than 7 days then MabCampath should be reinstituted with gradual dose escalation

- **OTHER CONDITIONS**

The MAH will continue to submit yearly PSURs, unless otherwise specified by the CHMP.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 3.3 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMA

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

MabCampath 10 mg/ml concentrate for solution for infusion
Alemtuzumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains 10 mg of alemtuzumab.
Each ampoule contains 30 mg of alemtuzumab.

3. LIST OF EXCIPIENTS

Other ingredients:
Disodium edetate, polysorbate 80, potassium chloride, potassium dihydrogen phosphate, sodium chloride, dibasic sodium phosphate, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
3 x 3 ml ampoules
30 mg/3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Read the leaflet for the shelf life of the reconstituted product.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C-8°C).
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any spillage or waste material should be disposed of by incineration.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:
Genzyme Europe BV, Gooimeer 10, 1411 DD Naarden, Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/193/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

AMPOULE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

MabCampath 10 mg/ml concentrate for solution for infusion
Alemtuzumab
Intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

30 mg/3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

MabCampath 30 mg/ml concentrate for solution for infusion
Alemtuzumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains 30 mg of alemtuzumab.
Each vial contains 30 mg of alemtuzumab.

3. LIST OF EXCIPIENTS

Other ingredients:
Disodium edetate, polysorbate 80, potassium chloride, potassium dihydrogen phosphate, sodium chloride, dibasic sodium phosphate, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
3 x 1 ml vials
30 mg/ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Read the leaflet for the shelf life of the reconstituted product.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C-8°C).
Do not freeze.
Store in the original package in order to protect from light,.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any spillage or waste material should be disposed of by incineration.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:
Genzyme Europe BV, Gooimeer 10, 1411 DD Naarden, Netherlands

12. MARKETING AUTHORISATION NUMBER (S)

EU/1/01/193/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

MabCampath 30 mg/ml concentrate for solution for infusion
Alemtuzumab
Intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

30 mg/ml

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

MabCampath 10 mg/ml concentrate for solution for infusion
Alemtuzumab

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT MABCAMPATH IS AND WHAT IT IS USED FOR

MabCampath is used to treat patients with chronic lymphocytic leukaemia (CLL), a cancer of the lymphocytes (a type of white blood cell). It is used in patients for whom treatment combinations including fludarabine (another medicine used in leukaemia) are not appropriate.

The active substance in MabCampath, alemtuzumab, is a monoclonal antibody. A monoclonal antibody is an antibody (a type of protein) that has been designed to recognise and bind to a specific structure (called an antigen) that is found in certain cells in the body. In CLL, too many lymphocytes are produced. Alemtuzumab has been designed to bind to a glycoprotein (a protein that is coated with sugar molecules) that is found on the surface of lymphocytes. As a result of this binding, the lymphocytes die, and this helps to control the CLL.

2. BEFORE YOU USE MABCAMPATH

Do not use MabCampath if you:

- are allergic to alemtuzumab or to proteins of a similar origin or to any of the other ingredients of MabCampath (see section 6 “Further Information”). Your doctor will inform you accordingly
- have an infection
- have HIV
- have an active second malignancy
- are pregnant (see also “Pregnancy”).

Take special care with MabCampath:

When you **first receive** MabCampath, you may experience side effects soon after the first infusions (see section 4 “Possible side effects”). These effects will gradually reduce as treatment is continued.

You may also be given

- **steroids, antihistamines or analgesics** (treatment for fever) to help reduce some of the side effects.

The dosage of MabCampath will not be increased until the effects are reduced.

MabCampath treatment may reduce your natural resistance to infections

- **antibiotics** and **antivirals** may be given to provide you with extra protection.

You will be examined for symptoms of a certain type of viral infection called *CMV (cytomegalovirus)* during your MabCampath therapy and for at least 2 months afterwards.

Your doctor will monitor you carefully if you

- have **heart disease or chest pains** and/or you are receiving treatment to reduce **high blood pressure,** as MabCampath may make these conditions worse.
  Patients with these conditions may be at higher risk of a heart attack.

- have been treated in the past with **chemotherapies** or **general medications** that have a high risk of causing heart damage, your doctor may wish to monitor your cardiac function (ECG, heart rate, body weight) while receiving MabCampath.

- have other side effects, most often blood disorders from taking MabCampath.
  Your doctor will be monitoring the effects of treatment and your progress carefully by examining you and by taking blood samples for analysis on a regular basis.

- are over 65 years of age as you may be more intolerant to the medicine than other patients.

You may experience an **allergic or hypersensitivity reaction** to MabCampath solution, especially against the protein contained in it, while the infusion is given to you. Your doctor will treat you for this, if this happens.

Because of the potential for a fatal reaction to **transfusion** of any blood products following treatment with MabCampath, it is recommended that you speak to your doctor regarding the **irradiation of blood products** prior to receiving the transfusion. You should inform your doctor if you experience any unusual symptoms after a transfusion.

MabCampath is not recommended in children below 17 years of age or in patients who have kidney or liver disorders.

Taking other medicines

You should inform your doctor if you are taking or have recently taken any other medicines, even those not prescribed.

In particular, you should **not** be given MabCampath within 3 weeks of taking any **other anti-cancer agents**.

Also, you should not be vaccinated with live viral vaccines during treatment and for at least 12 months after you have finished your treatment. Speak to your doctor before receiving any vaccinations.

Pregnancy

MabCampath must not be administered to patients who are pregnant, therefore if you:

- are pregnant or you think you may be pregnant, you should tell your doctor immediately.
- are a woman of childbearing potential or a fertile man, then you should use effective contraceptive methods before you start treatment, during treatment and for 6 months after treatment.

Breast-feeding

You should stop breast-feeding when you start your treatment and you should not begin breast-feeding again until at least 4 weeks after you have finished your treatment and you have consulted your doctor on the matter.

Driving or using machines

No studies of the effects of MabCampath on the ability to drive and use machines have been performed. However you should be cautious as confusion and sleepiness have been seen. You should ask your doctor for advice.

3. HOW TO USE MABCAMPATH

MabCampath is administered into one of your veins via a drip (see also 'information intended for medical or healthcare professionals').

Each time you are given MabCampath, it will take about 2 hours for all the solution to enter your blood.

MabCampath treatment may continue for up to **12 weeks** depending on your progress.

During the first week, your doctor will increase the dose of MabCampath slowly to reduce the possibility of you having side effects and to allow your body to tolerate MabCampath better.

If you experience early side effects the initial smaller doses may be repeated until the effects go away or reduce. The doctor will carefully monitor you and decide what are the appropriate amounts of MabCampath to give you during your whole treatment period.

If more MabCampath is given than recommended

Your doctor will treat you, as appropriate, if you have any side effects.

4. POSSIBLE SIDE EFFECTS

Like all medicines, MabCampath can cause side effects, although not everybody gets them.

Your doctor may give you other medicines or change your dose to help reduce any side effects (see section 2 "*Take Special care*").

Serious side effects, including difficulty in breathing, inflammation of the lungs, extreme shortness of breath, fainting, heart attack, low red blood cell and low blood platelet levels, infections, bleeding in the brain (intracranial haemorrhage) have occurred with fatal outcome. Diseases related to an overactive immune system where your immune system attacks your own body can lead to low red blood cells, low blood platelets and/or low white blood cells, and nerve disorders, and these can also be fatal. **Tell your doctor immediately if you experience any of these side effects.**

In addition, testing indicating the presence of antibodies that may destroy red blood cells (Coombs test) has been reported.

Very common side effects (seen in at least 1 in every 10 patients treated in clinical trials):

Usually one or more of these effects happen during the first week after the start of treatment:

- fever, shivering/chills, sweating, nausea (feeling sick), vomiting, low blood pressure, low white/red blood cell levels, infections including pneumonia and blood poisoning, irritation and/or blistering of the mouth region, low blood platelet levels, tiredness, rash, itching, red raised lesions on the skin, shortness of breath, headache, diarrhoea and loss of appetite.

They are usually only mild or moderate problems and they gradually diminish during the course of treatment.

Common side effects (affects 1 to 10 patients in every 100 patients treated in clinical trials):

- high blood pressure, fast or slow heart rate, feeling your heart racing, blood vessel spasm
- becoming red in the face, bruising of the skin
- taste changes
- decreased sense of touch
- dizziness, sensation of spinning, fainting, shaking or trembling movements, feeling restless
- eye inflammation (e.g. conjunctivitis)
- pins and needles or burning sensation of the skin
- abnormal liver function, constipation, indigestion, passing abdominal gas
- inflammation, irritation and/or tightness of the lungs, throat and/or sinuses, too little oxygen reaching the body organs, coughing, coughing up of blood
- abdominal bleeding (e.g. in the stomach and intestine)
- injection site reactions including redness, swelling, pain, bruising, inflammation
- generally feeling unwell, weakness, pain in various parts of the body (muscle, back, chest, bones, joints, stomach and intestine)
- weight loss, dehydration, thirst, swelling of the lower legs, temperature change sensation, low calcium or sodium blood levels
- flu-like symptoms
- abscess, skin redness or allergic skin reaction, blistering of the skin
- confusion, anxiety, depression, sleeplessness

Uncommon side effects (affects 1 to 10 patients in every 1,000 patients treated in clinical trials):

- bone marrow disorders
- heart disorders (heart stopping, heart attack, heart congestion, irregular heart rate)
- blood disorders (abnormal clotting, decreased protein, low potassium levels)
- high blood sugar, worsening diabetes
- bleeding and inflammation of the gums, blisters on the tongue, nosebleeds
- fluid in the lungs, difficulty breathing, harsh sound when breathing, runny nose, abnormal findings in the lungs, lymph gland disorders
- nervousness, abnormal thinking
- swelling around the eye
- ringing sound in the ears, deafness
- hiccups, burping
- hoarseness
- abnormal kidney function
- paralysis of the small bowel
- impotence
- unsteadiness, increased muscle tone
- unusual increased or altered sensitivity to touch
- abnormal sensation/feeling or movement

- pain when urinating, decreases in urine flow, increased frequency in urination, blood in urine, incontinence
- tumour lysis syndrome (a metabolic disorder, which may begin with pains in the side and blood in the urine)

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or your pharmacist.

5. HOW TO STORE MABCAMPATH

Keep out of the reach and sight of children.

Do not use MabCampath after the expiry date (EXP) which is stated on the outer carton and the ampoule label. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C-8°C).

Do not freeze.

Store in the original packaging in order to protect from light.

MabCampath should be used within 8 hours after dilution. During that time the solution may be stored at 15°C-30°C or refrigerated.

Do not use MabCampath if you notice any signs of particulate matter or discolouration prior to administration.

Medicines should not be disposed of via wastewater or household waste. Your healthcare professional will dispose of medicines no longer required. These measures will help protect the environment.

6. FURTHER INFORMATION

What MabCampath contains

The **active** substance is alemtuzumab.
One ml contains 10 mg of alemtuzumab. Each ampoule contains 30 mg of alemtuzumab.

The **other** ingredients are disodium edetate, polysorbate 80, potassium chloride, potassium dihydrogen phosphate, sodium chloride, dibasic sodium phosphate and water for injections.

What MabCampath looks like and contents of the pack

MabCampath is a concentrate for solution for infusion that comes in a glass ampoule.

Each pack of MabCampath contains 3 ampoules.

Marketing Authorisation Holder

Genzyme Europe BV, Gooimeer 10, 1411 DD Naarden, Netherlands

Manufacturer

Genzyme Ltd., 37 Hollands Road, Haverhill, Suffolk CB9 8PU, United Kingdom

Genzyme Ireland Limited., IDA Industrial Park, Old Kilmeaden Road, Waterford, Ireland

Bayer Schering Pharma AG, Müllerstrasse 178, D-13342 Berlin, Germany.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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United Kingdom/Ireland
Genzyme Therapeutics Ltd. (United Kingdom),
Tel: +44 1865 405200

This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for medical or healthcare professionals only:

During the first week, 3 mg of MabCampath is given on Day 1, then 10 mg on Day 2 and then 30 mg on Day 3, depending on tolerability. MabCampath will be given at 30 mg three times per calendar week on alternate days, for up to 12 weeks.

The ampoule contents should be inspected for particulate matter and discolouration prior to administration. If particulate matter is present or the solution is coloured, then the ampoule should not be used.

MabCampath contains no antimicrobial preservatives, therefore, it is recommended that MabCampath should be prepared for intravenous infusion using aseptic techniques and that the diluted solution for infusion should be administered within 8 hours after preparation and protected from light. The required amount of the ampoule contents should be added, via a sterile, low-protein binding, non-fibre 5 µm filter, to 100 ml of sodium chloride 9 mg/ml (0.9%) solution for infusion or glucose (5%) solution for infusion. The bag should be inverted gently to mix the solution. Care should be taken to ensure the sterility of the prepared solution particularly as it contains no antimicrobial preservatives.

Other medicinal products should not be added to the MabCampath infusion solution or simultaneously infused though the same intravenous line.

Caution should be exercised in the handling and preparation of the MabCampath solution. The use of latex gloves and safety glasses is recommended to avoid exposure in case of breakage of the ampoule or other accidental spillage. Women who are pregnant or trying to become pregnant should not handle MabCampath.

Procedures for proper handling and disposal should be observed. Any spillage or waste material should be disposed of by incineration.

PACKAGE LEAFLET: INFORMATION FOR THE USER

MabCampath 30 mg/ml concentrate for solution for infusion
Alemtuzumab

Read all of this leaflet carefully before you start using this medicine

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT MABCAMPATH IS AND WHAT IT IS USED FOR

MabCampath is used to treat patients with chronic lymphocytic leukaemia (CLL), a cancer of the lymphocytes (a type of white blood cell). It is used in patients for whom treatment combinations including fludarabine (another medicine used in leukaemia) are not appropriate.

The active substance in MabCampath, alemtuzumab, is a monoclonal antibody. A monoclonal antibody is an antibody (a type of protein) that has been designed to recognise and bind to a specific structure (called an antigen) that is found in certain cells in the body. In CLL, too many lymphocytes are produced. Alemtuzumab has been designed to bind to a glycoprotein (a protein that is coated with sugar molecules) that is found on the surface of lymphocytes. As a result of this binding, the lymphocytes die, and this helps to control the CLL.

2. BEFORE YOU USE MABCAMPATH

Do not use MabCampath if you:

- are allergic to alemtuzumab or to proteins of a similar origin or to any of the other ingredients of MabCampath (see section 6 “Further Information”). Your doctor will inform you accordingly
- have an infection
- have HIV
- have an active second malignancy
- are pregnant (see also “Pregnancy”).

Take special care with MabCampath:

When you **first receive** MabCampath, you may experience side effects soon after the first infusions (see section 4 “Possible side effects”). These effects will gradually reduce as treatment is continued.

You may also be given

- **steroids, antihistamines or analgesics** (treatment for fever) to help reduce some of the side effects.

The dosage of MabCampath will not be increased until the effects are reduced.

MabCampath treatment may reduce your natural resistance to infections

- **antibiotics** and **antivirals** may be given to provide you with extra protection.

You will be examined for symptoms of a certain type of viral infection called *CMV (cytomegalovirus)* during your MabCampath therapy and for at least 2 months afterwards.

Your doctor will monitor you carefully if you

- have **heart disease or chest pains** and/or you are receiving treatment to reduce **high blood pressure,** as MabCampath may make these conditions worse.
  Patients with these conditions may be at higher risk of a heart attack.

- have been treated in the past with **chemotherapies** or **general medications** that have a high risk of causing heart damage, your doctor may wish to monitor your cardiac function (ECG, heart rate, body weight) while receiving MabCampath.

- have other side effects, most often blood disorders from taking MabCampath.
  Your doctor will be monitoring the effects of treatment and your progress carefully by examining you and by taking blood samples for analysis on a regular basis.

- are over 65 years of age as you may be more intolerant to the medicine than other patients.

You may experience an **allergic or hypersensitivity reaction** to MabCampath solution, especially against the protein contained in it, while the infusion is given to you. Your doctor will treat you for this, if this happens.

Because of the potential for a fatal reaction to **transfusion** of any blood products following treatment with MabCampath, it is recommended that you speak to your doctor regarding the **irradiation of blood products** prior to receiving the transfusion. You should inform your doctor if you experience any unusual symptoms after a transfusion.

MabCampath is not recommended in children below 17 years of age or in patients who have kidney or liver disorders.

Taking other medicines

You should inform your doctor if you are taking or have recently taken any other medicines, even those not prescribed.

In particular, you should **not** be given MabCampath within 3 weeks of taking any **other anti-cancer agents**.

Also, you should not be vaccinated with live viral vaccines during treatment and for at least 12 months after you have finished your treatment. Speak to your doctor before receiving any vaccinations.

Pregnancy

MabCampath must not be administered to patients who are pregnant, therefore if you:

- are pregnant or you think you may be pregnant, you should tell your doctor immediately.

- are a woman of childbearing potential or a fertile man, then you should use effective contraceptive methods before you start treatment, during treatment and for 6 months after treatment.

Breast-feeding

You should stop breast-feeding when you start your treatment and you should not begin breast-feeding again until at least 4 weeks after you have finished your treatment and you have consulted your doctor on the matter.

Driving or using machines

No studies of the effects of MabCampath on the ability to drive and use machines have been performed. However you should be cautious as confusion and sleepiness have been seen. You should ask your doctor for advice.

3. HOW TO USE MABCAMPATH

MabCampath is administered into one of your veins via a drip (see also 'information intended for medical or healthcare professionals').

Each time you are given MabCampath, it will take about 2 hours for all the solution to enter your blood.

MabCampath treatment may continue for up to **12 weeks** depending on your progress.

During the first week, your doctor will increase the dose of MabCampath slowly to reduce the possibility of you having side effects and to allow your body to tolerate MabCampath better.

If you experience early side effects the initial smaller doses may be repeated until the effects go away or reduce. The doctor will carefully monitor you and decide what are the appropriate amounts of MabCampath to give you during your whole treatment period.

If more MabCampath is given than recommended

Your doctor will treat you, as appropriate, if you have any side effects.

4. POSSIBLE SIDE EFFECTS

Like all medicines, MabCampath can cause side effects, although not everybody gets them.

Your doctor may give you other medicines or change your dose to help reduce any side effects (see section 2 "*Take Special care*").

Serious side effects, including difficulty in breathing, inflammation of the lungs, extreme shortness of breath, fainting, heart attack, low red blood cell and low blood platelet levels, infections, bleeding in the brain (intracranial haemorrhage) have occurred with fatal outcome. Diseases related to an overactive immune system where your immune system attacks your own body can lead to low red blood cells, low blood platelets and/or low white blood cells, and nerve disorders, and these can also be fatal. **Tell your doctor immediately if you experience any of these side effects.**

In addition, testing indicating the presence of antibodies that may destroy red blood cells (Coombs test) has been reported.

Very common side effects (seen in at least 1 in every 10 patients treated in clinical trials):

Usually one or more of these effects happen during the first week after the start of treatment:

- fever, shivering/chills, sweating, nausea (feeling sick), vomiting, low blood pressure, low white/red blood cell levels, infections including pneumonia and blood poisoning, irritation and/or blistering of the mouth region, low blood platelet levels, tiredness, rash, itching, red raised lesions on the skin, shortness of breath, headache, diarrhoea and loss of appetite.

They are usually only mild or moderate problems and they gradually diminish during the course of treatment.

Common side effects (affects 1 to 10 patients in every 100 patients treated in clinical trials):

- high blood pressure, fast or slow heart rate, feeling your heart racing, blood vessel spasm
- becoming red in the face, bruising of the skin
- taste changes
- decreased sense of touch
- dizziness, sensation of spinning, fainting, shaking or trembling movements, feeling restless
- eye inflammation (e.g. conjunctivitis)
- pins and needles or burning sensation of the skin
- abnormal liver function, constipation, indigestion, passing abdominal gas
- inflammation, irritation and/or tightness of the lungs, throat and/or sinuses, too little oxygen reaching the body organs, coughing, coughing up of blood
- abdominal bleeding (e.g. in the stomach and intestine)
- injection site reactions including redness, swelling, pain, bruising, inflammation
- generally feeling unwell, weakness, pain in various parts of the body (muscle, back, chest, bones, joints, stomach and intestine)
- weight loss, dehydration, thirst, swelling of the lower legs, temperature change sensation, low calcium or sodium blood levels
- flu-like symptoms
- abscess, skin redness or allergic skin reaction, blistering of the skin
- confusion, anxiety, depression, sleeplessness

Uncommon side effects (affects 1 to 10 in every patients in 1,000 patients treated in clinical trials):

- bone marrow disorders
- heart disorders (heart stopping, heart attack, heart congestion, irregular heart rate)
- blood disorders (abnormal clotting, decreased protein, low potassium levels)
- high blood sugar, worsening diabetes
- bleeding and inflammation of the gums, blisters on the tongue, nosebleeds
- fluid in the lungs, difficulty breathing, harsh sound when breathing, runny nose, abnormal findings in the lungs, lymph gland disorders
- nervousness, abnormal thinking
- swelling around the eye
- ringing sound in the ears, deafness
- hiccups, burping
- hoarseness
- abnormal kidney function
- paralysis of the small bowel
- impotence
- unsteadiness, increased muscle tone
- unusual increased or altered sensitivity to touch’
- abnormal sensation/feeling or movement
- pain when urinating, decreases in urine flow, increased frequency in urination, blood in urine, incontinence

- tumour lysis syndrome (a metabolic disorder, which may begin with pains in the side and blood in the urine)

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or your pharmacist.

5. HOW TO STORE MABCAMPATH

Keep out of the reach and sight of children.

Do not use MabCampath after the expiry date (EXP) which is stated on the outer carton and the vial label. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C-8°C).

Do not freeze.

Store in the original packaging in order to protect from light.

MabCampath should be used within 8 hours after dilution. During that time the solution may be stored at 15°C-30°C or refrigerated.

Do not use MabCampath if you notice any signs of particulate matter or discolouration prior to administration.

Medicines should not be disposed of via wastewater or household waste. Your healthcare professional will dispose of medicines no longer required. These measures will help protect the environment.

6. FURTHER INFORMATION

What MabCampath contains

The **active** substance is alemtuzumab.
One ml contains 30 mg of alemtuzumab. Each vial contains 30 mg of alemtuzumab.

The **other** ingredients are disodium edetate, polysorbate 80, potassium chloride, potassium dihydrogen phosphate, sodium chloride, dibasic sodium phosphate and water for injections.

What MabCampath looks like and contents of the pack

MabCampath is a concentrate for solution for infusion that comes in a glass vial.

Each pack of MabCampath contains 3 vials.

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This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for medical or healthcare professionals only:

During the first week, 3 mg of MabCampath is given on Day 1, then 10 mg on Day 2 and then 30 mg on Day 3, depending on tolerability. MabCampath will be given at 30 mg three times per calendar week on alternate days, for up to 12 weeks.

The vial contents should be inspected for particulate matter and discolouration prior to administration. If particulate matter is present or the solution is coloured, then the vial should not be used.

MabCampath contains no antimicrobial preservatives, therefore, it is recommended that MabCampath should be prepared for intravenous infusion using aseptic techniques and that the diluted solution for infusion should be administered within 8 hours after preparation and protected from light. The required amount of the vial contents should be added to 100 ml of sodium chloride 9 mg/ml (0.9%) solution for infusion or glucose (5%) solution for infusion. The bag should be inverted gently to mix the solution. Care should be taken to ensure the sterility of the prepared solution particularly as it contains no antimicrobial preservatives.

Other medicinal products should not be added to the MabCampath infusion solution or simultaneously infused though the same intravenous line.

Caution should be exercised in the handling and preparation of the MabCampath solution. The use of latex gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage. Women who are pregnant or trying to become pregnant should not handle MabCampath.

Procedures for proper handling and disposal should be observed. Any spillage or waste material should be disposed of by incineration.