AUSTRALIAN PRODUCT INFORMATION SHEET – MABCAMPATH (ALEMTUZUMAB)

1 NAME OF THE MEDICINE

Alemtuzumab (rch)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 30 mg/mL alemtuzumab as a concentrated solution for infusion. See Section 6.1 for list of excipients.

3 PHARMACEUTICAL FORM

Alemtuzumab (rch) is a recombinant DNA-derived humanized monoclonal antibody directed against the 21-28 kD cell surface glycoprotein, CD52. Alemtuzumab (rch) is an IgG1 kappa antibody with human variable framework and constant regions, and complementarity-determining regions from a murine monoclonal antibody. The antibody has an approximate molecular weight of 150 kD. Alemtuzumab (rch) is produced in mammalian cell (Chinese hamster ovary) suspension culture in a nutrient medium.

Alemtuzumab (rch) is a sterile, clear, colourless to slightly yellow, injection concentrate. It is intended for dilution prior to infusion.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

MabCampath is indicated for the treatment of patients with B - cell chronic lymphocytic leukaemia (B - CLL).

4.2 DOSE AND METHOD OF ADMINISTRATION

General considerations

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

Medications for the treatment of hypersensitivity reactions as well as preparedness for institution of emergency measures is necessary.

MabCampath solution must be prepared according to the instructions provided under ‘Instructions for use and handling and disposal’. All doses should be administered by intravenous infusion over approximately 2 hours.

Patients should be pre-medicated with an appropriate antihistamine and analgesic prior to the first dose at each escalation and prior to subsequent infusions, as clinically indicated (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Antibiotics and antivirals should be administered routinely to all patients throughout and following treatment (see Section 4.4- SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Dose

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 due to cytokine release (hypotension, rigors, fever, shortness of breath, chills, rashes and bronchospasm) 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- SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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.

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	
First occurrence	Withhold MabCampath therapy. Resume MabCampath at 30 mg when ANC ≥500/µL and platelet count ≥50,000/µL.
Second occurrence	Withhold MabCampath therapy. Resume MabCampath at 10 mg when ANC ≥500µL and platelet count ≥50,000/µL.
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	
First occurrence	Withhold MabCampath therapy. Resume MabCampath at 30 mg upon return to baseline value(s).
Second occurrence	Withhold MabCampath therapy. Resume MabCampath at 10 mg upon return to baseline value(s).
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.

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

Instructions for reconstitution, handling and disposal

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 must not be used.

MabCampath contains no antimicrobial preservatives, therefore, it is recommended that it should be prepared using aseptic techniques and that the diluted solution for infusion should be administered within 8 hours after preparation. The required amount of the vial contents should be added to 100 mL of 0.9% sodium chloride solution or 5% glucose solution. The bag should be inverted gently to mix the solution.

This medicinal product should not be reconstituted with solvents other than those mentioned above.

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

Women who are pregnant or planning pregnancy should not handle MabCampath.

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.

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

Patients with renal impairment

No studies have been conducted in patients with renal impairment.

Patients with hepatic impairment

No studies have been conducted in patients with hepatic impairment.

Elderly patients (over 65 years of age)

Recommendations are as stated above for adults. Patients should be monitored carefully (see Section 4.4- SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.3 CONTRAINDICATIONS

MabCampath is contraindicated in:

- Hypersensitivity or anaphylactic reactions to alemtuzumab, to murine proteins or to any of the excipients.
- In patients with active systemic infections.
- In patients infected with HIV.
- In patients with active secondary malignancies.
- Pregnancy.
- Breast-feeding

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Infusion-related reactions

MabCampath can result in serious, and in some instances fatal, infusion reactions. Patients should be carefully monitored during infusions and MabCampath discontinued if indicated. Gradual escalation to the recommended maintenance dose is required at the initiation of therapy and after interruption of therapy for 7 or more days (see Section 4.2-DOSE AND METHOD OF ADMINISTRATION).

Patients may have allergic or hypersensitivity reactions to MabCampath and to murine or chimeric monoclonal antibodies (see Section 4.3-CONTRAINDICATIONS). If any of these occur medications for the treatment of hypersensitivity reactions as well as preparedness for institution of emergency measures is necessary.

Acute adverse reactions, which may occur during initial dose escalation 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 acute infusion-related 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. Grade 3 or 4 (according to Common Terminology Criteria for Adverse Events-CTCAE) infusion-related reactions are uncommon after the first week of therapy.

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.

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 50mg, and an analgesic, e.g. paracetamol 500mg, 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.

Transient hypotension has occurred in patients receiving MabCampath. Careful monitoring of blood pressure and hypotensive symptoms is recommended especially in patients with ischaemic heart disease, angina and/or in patients receiving antihypertensive medication. 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.

Therapy should be discontinued if there is evidence of disease progression. (see Section 4.2 - DOSE AND METHOD OF ADMINISTRATION)

Immunosuppression

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 median time to 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.

Serious, sometimes fatal bacterial, viral, fungal and protozoan infections have been reported in patients receiving MabCampath therapy. Prophylaxis directed against Pneumocystis jirovecii pneumonia and herpes virus infections has been shown to decrease, but not to eliminate, the occurrence of these 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 jirovecii pneumonia (PCP) and an effective oral anti - herpes agent, such as famciclovir 500 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.

Because of the potential of Transfusion associated Graft versus Host Disease (TAGVHD), it is recommended that patients who have been treated with MabCampath should receive irradiated blood products.

Asymptomatic laboratory positive cytomegalovirus (CMV) 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.

Epstein-Barr virus (EBV) infection, including severe and sometimes fatal EBV associated hepatitis, has been reported in MabCampath-treated patients.

Haemophagocytic lymphohistiocytosis (HLH)

During post-marketing use, HLH has been reported in patients treated with MabCampath. HLH is a life-threatening syndrome of pathologic immune activation characterized by clinical signs and symptoms of extreme systemic inflammation. It is associated with high mortality rates if not recognized early and treated. Symptoms have been reported to occur within a few months following the initiation of treatment, commonly observed in association with infections. Patients who develop early manifestations of pathologic immune activation should be evaluated immediately, and a diagnosis of HLH should be considered.

Haemotological toxicity

Serious and, in rare instances fatal, pancytopenia, autoimmune idiopathic thrombocytopenia and autoimmune haemolytic anaemia have occurred in patients receiving MabCampath. Single doses of MabCampath greater than 30mg or cumulative doses greater than 90mg per week should not be administered because these doses are associated with a higher incidence of pancytopenia.

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. MabCampath treatment may be reinstituted following resolution of the haematological toxicity (see Section 4.2- DOSE AND METHOD OF ADMINISTRATION). 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.

CD52 expression

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 patients in both treatment arms of the first line study, loss of CD52 expression was not observed around the time of progression or death.

Use in hepatic impairment

No studies have been conducted in patients with hepatic impairment.

Use in renal impairment

No studies have been conducted in patients with renal impairment.

Use in the elderly

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- DOSE AND METHOD OF ADMINISTRATION). 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.

Paediatric use

No studies have been conducted to investigate the safety and efficacy of MabCampath in children.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No formal drug interaction studies have been performed with MabCampath. There are no known clinically significant interactions of MabCampath with other medicinal products. 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

Effects on fertility

The potential effects on fertility have not been investigated in animal studies. CD52 is expressed on sperm and epithelial cells of the epididymis and seminal vesicle. It is not known whether MabCampath can affect the reproductive capacity of men or women.

Use in pregnancy (Category B2)

MabCampath is contraindicated during pregnancy. Human IgG is known to cross the placental barrier; MabCampath is likely to 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. Males and females of childbearing potential should use effective contraceptive measures during treatment and for 6 months following MabCampath therapy (see Section 4.6- FERTILITY, PREGNANCY AND LACTATION).

Use in lactation

MabCampath is contraindicated during breast - feeding. It is not known whether MabCampath is excreted in human milk. Breast - feeding should be discontinued during treatment and for at least 4 weeks following MabCampath therapy. No studies have been performed in lactating animals.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The frequencies of the adverse reactions by system organ classes and in descending order of severity in the tables below are based on clinical trial data.

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.

System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Infections and infestations	Sepsis Pneumonia Herpes simplex	Cytomegalovirus infection Pneumocystis jirovecii infection Pneomonitis 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 disorders	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
Metabolism and nutritional 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

System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Nervous system disorders	Headache	Vertigo Dizziness Tremor Paraesthesia Hypoaesthesia Hyperkinesia Taste loss	Syncope Abnormal gait Dystonia Hyperaesthesia Neutropathy 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 ischemia
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	Gastro-intestinal 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 Hyperhydrosis	Bullous eruption Erythematous rash	Maculo-papular rash Skin disorder
Musculo-skeletal and connective tissue disorders		Arthralgia Myalgia Skeletal pain Back pain	Leg pain Hypertonia

System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
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

The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

Undesirable effects in first line patients

Safety data in first - line B-CLL patients are based on 147 patients enrolled in a randomised, 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 during the first week of therapy.

n (≥System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Infections and infestations	Cytomegalovirus infection Cytomegalovirus viremia	Pneumonia Bronchitis Pharyngitis Oral candidiasis	Sepsis Staphylococcal bacteraemia Tuberculosis Bronchopneumonia Herpes ophthalmicus Beta haemolytic streptococcal infections Candidiasis Genital candidiasis Urinary tract infection Cystitis Body tinea Nasopharyngitis Rhinitis
Blood and lymphatic system disorder		Febrile neutropenia Neutropenia Leukopoenia Thrombocytopenia Anaemia	Agranulocytosis Lymphopenia Lymphadenopathy Epistaxis
Immune system disorders			Anaphylactic reaction Hypersensitivity
Metabolic and nutrition disorders		Weight decreased	Tumour lysis syndrome Hyperglycaemia Protein total,decreased Anorexia
Psychiatric disorders		Anxiety	
Nervous system disorders		Syncope Dizziness Tremor Paresthesia 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

n (≥System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Vascular disorders	Hypotension	Hypertension	Orthostatic hypotension Hot flush Flushing
Respiratory, thoracic and mediastinal disorders		Bronchospasm Dyspnoea	Hypoxia Pleural effusion Dysphonia Rhinorrhoea
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

The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

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 according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE version 3.0) infusion reactions are uncommon after the first week of therapy.

Post marketing Data

The reactions presented in this section were identified mainly from post marketing experience in previously treated patients. As these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to MabCampath exposure. Decisions to include these reactions in labelling are typically based on one or more of the following factors: (1) seriousness of the

reaction, (2) reported frequency of the reaction, or (3) strength of causal connection to MabCampath. Events previously identified in clinical studies are not listed in this section.

Blood and lymphatic system disorders

Severe bleeding reactions have been reported.

Cardiac Disorders

Cardiomyopathy, congestive heart failure and decreased ejection fraction have been reported in patients previously treated with potentially cardiotoxic agents.

Hepatobiliary Disorders

Hepatitis (associated with EBV infection) has been reported.

Immune system disorders

Serious and sometimes fatal autoimmune phenomena including autoimmune haemolytic anaemia, autoimmune thrombocytopenia, aplastic anaemia, Graves' disease, Guillian Barre syndrome and its chronic form, chronic inflammatory demyelinating polyradiculoneuropathy, serum sickness have been reported. A positive Coomb's test has also been observed. Fatal Transfusion associated Graft versus Host Disease has also been reported. Haemophagocytic lymphohistiocytosis (HLH)

Infusion reactions

Serious and sometimes fatal reactions including bronchospasm, hypoxia, syncope, pulmonary infiltrates, 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 - SPECIAL WARNINGS AND PRECAUTIONS FOR USE, and Section 4.2 -DOSE AND METHOD OF ADMINISTRATION).

Infections and infestations

Serious and sometimes fatal viral (e.g. adenovirus, parainfluenza, hepatitis B, progressive multifocal leukoencephalopathy [PML], bacterial (including tuberculosis and atypical mycobacteriosis, nocardiosis), protozoan (e.g. toxoplasma gondii) and fungal (e.g. rhinocerebral mucormycosis) infections, including those due to reactivation of latent infections, have been observed during post - marketing surveillance. The recommended anti-infective prophylaxis appears to be effective in reducing the risk of Pneumocystis jirovecii pneumonia (PCP) and herpes infections (see Section 4.4 - SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Epstein-Barr virus (EBV) infection and Epstein Barr Virus (EBV)-associated lymphoproliferative disorder has been reported.

Metabolism and nutrition disorders

Tumour lysis syndrome with fatal outcome has been reported.

Nervous system disorders

Intracranial haemorrhage has occurred with fatal outcome, in patients with thrombocytopenia. Stroke, including haemorrhagic and ischaemic stroke

Renal and Urinary Disorders

Glomerulonephritis

Post Marketing Experience with LEMTRADA

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to alemtuzumab exposure.

The following adverse reactions were identified during post-approval use of alemtuzumab for the treatment of relapsing forms of multiple sclerosis (MS):

Nervous System Disorders: Stroke, including haemorrhagic and ischaemic stroke, cervicocephalic arterial dissection, and autoimmune encephalitis.

Endocrine Disorders: Hypothyroidism, hyperthyroidism, and thyroiditis

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Alemtuzumab is a genetically engineered humanised IgG1 kappa monoclonal antibody specific for a 21-28 kD lymphocyte cell surface glycoprotein, (CD52) antigen. It was

generated by the insertion of six complementary-determining regions from an IgG2a rat monoclonal antibody into a human IgG1 immunoglobulin molecule.

Alemtuzumab causes the lysis of lymphocytes by binding to CD52 antigen, which is expressed on the surface of essentially all B and T lymphocytes (benign and malignant) as well as monocytes, thymocytes and macrophages, sperm and epithelial cells of epididymis and seminal vesicle. The antigen has also been found on a small percentage (<5%) of granulocytes, but not on erythrocytes or platelets.

The antibody mediates the lysis of lymphocytes via complement fixation and antibody-dependent cell mediated cytotoxicity. Alemtuzumab does not appear to damage haematopoietic stem cells or progenitor cells.

Clinical trials

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 patients who had received an alkylating agent and had failed fludarabine	B-CLL patients who had failed to respond or relapsed following treatment with conventional chemotherapy	B-CLL (plus a PLL) patients who had failed to respond or relapsed following treatment with fludarabine
Median age (years)	66	57	62
Disease characteristics (%) Rai stage III/IV B symptoms	76 42	72 31	71 21
Prior therapies (%) Alkylating agents fludarabine	100 100	100 34	92 100
Number of prior regimens (range)	3 (2-7)	3 (1-10)	3 (1-8)
Initial dosing regimen	Gradual escalation from 3 to 10 to 30mg	Gradual escalation from 10 to 30mg	Gradual escalation from 10 to 30mg
Final dosing regimen	30mg iv 3 x weekly	30mg iv 3 x weekly	30mg iv 3 x weekly

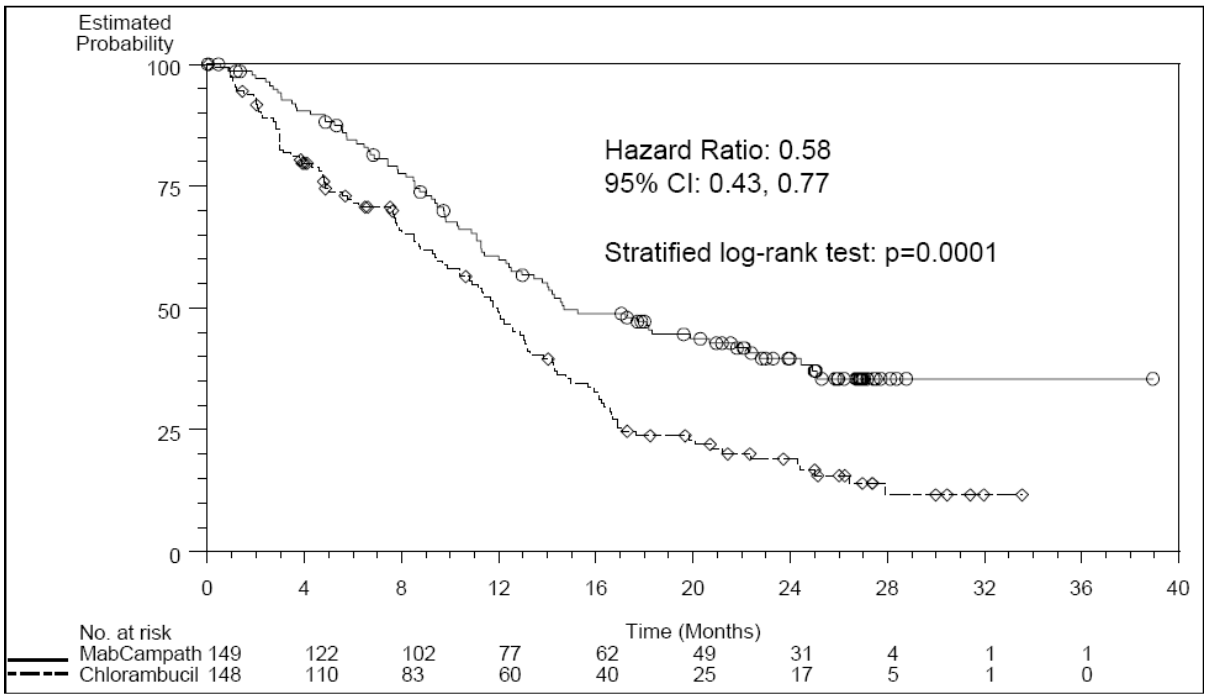
Efficacy parameters	Study 1	Study 2	Study 3
Overall response rate (%) (95% CI) Complete response Partial response	33 (23-43) 2 31	21 (8-33) 0 21	29 (11-47) 0 29
Median duration of response (months) (95% CI)	7 (5-8)	7 (5-23)	11 (6-19)
Median time to response (months) (95% CI)	2 (1-2)	4 (1-5)	4 (2-4)
Progression free survival (months) (95% CI)	4 (3-5)	5 (3-7)	7 (3-9)
Survival (months): (95% CI) All patients Responders	16 (12-22) 33 (26-NR)	26 (12-44) 44 (28-NR)	28 (7-33) 36 (19-NR)

NR= not reached

First Line B-CLL Patients

The safety and efficacy of MabCampath were evaluated in a Phase 3, open-label, randomised 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 (PR)) 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 (Study 4)

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 (ORR)	83.2%	55.4%	<0.0001*
Complete Response (CR)	24.2%	2.0%	<0.0001*
Minimal Residual Disease (MRD) negative****	7.4%	0.0%	0.0008*
Partial Response (PR)	59.1%	53.4%	Not Applicable
Duration of Response, CR or PR (Months) Kaplan-Meier 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) Kaplan-Meier 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

There are no data on the safety and efficacy of retreatment with alemtuzumab in patients who received the drug as first - line therapy.

Cytogenetic Analyses in First Line B-CLL Patients

The cytogenetic profile of B-CLL has been increasingly recognised 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 17 p deletion, 54 patients with 11 q deletion, 34 patients with trisomy 12, 51 patients with normal karyotype and 67 patients with sole 13q deletion.

Overall Response Rate (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 cytomegalovirus (CMV) by PCR

In the randomised 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).

5.2 PHARMACOKINETIC PROPERTIES

Pharmacokinetics were characterised in alemtuzumab-naive patients with B-cell chronic lymphocytic leukaemia (B-CLL) who had failed previous therapy with purine analogues.

Alemtuzumab was administered as a 2 hour intravenous infusion, at the recommended dosing schedule, starting at 3mg and increasing to 30mg, 3 times weekly, for up to 12 weeks. Alemtuzumab pharmacokinetics followed a 2 compartment model and displayed non linear elimination kinetics. After the last 30mg 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 30mg dose and was 6 days (range 1-14 days) after the last 30mg 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

Genotoxicity

No in vitro or animal studies have been conducted with MabCampath to assess the mutagenic potential.

Carcinogenicity

No in vitro or animal studies have been conducted with MabCampath to assess the carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

0.0187 mg disodium edetate, 0.1 mg polysorbate 80, 0.2 mg potassium chloride, 0.2 mg monobasic potassium phosphate, 8 mg sodium chloride, 1.15 mg dibasic sodium phosphate heptahydrate, and water for injections

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

MabCampath vials should be stored at 2 – 8 °C (in a refrigerator).

Do not freeze. Protect from light.

Reconstituted solution: MabCampath contains no antimicrobial preservative. To reduce microbiological hazard, use as soon as practicable after reconstitution / preparation. If storage is necessary, hold at 2°C to 8°C for not more than 8 hours. This can only be accepted if preparation of the solution takes place under strictly aseptic conditions and the solution is protected from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Vials of 2 mL, clear, glass type I, containing 1 mL colourless to slightly yellow concentrate.

Pack size: 3 vials.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

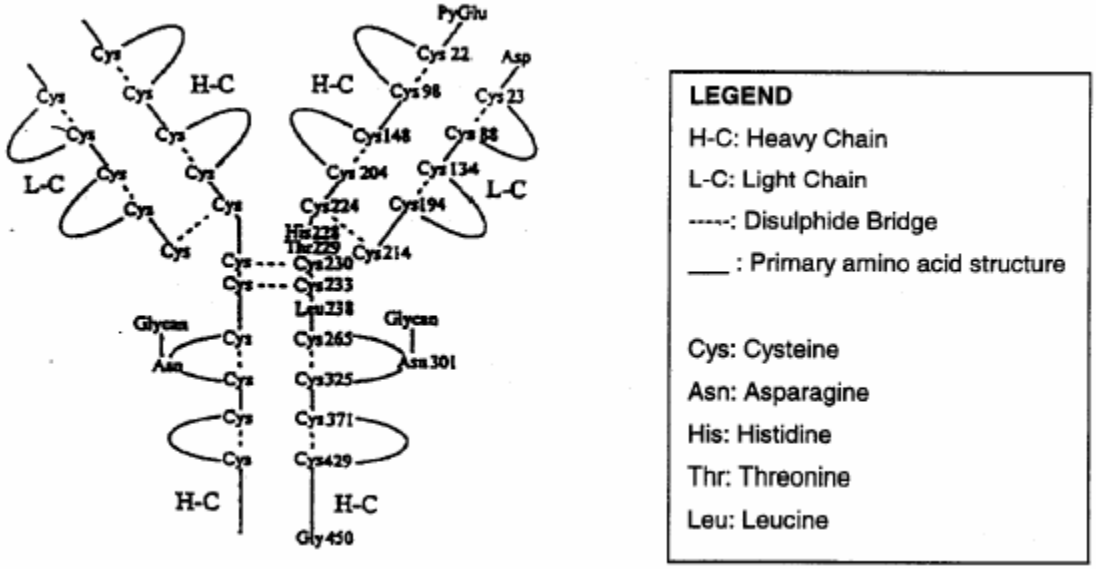
Chemical structure

The alemtuzumab molecule consists of two ~ 24 kD small polypeptide chains (light chains, 214 amino acids) and two larger ~ 49 kD polypeptide chains (heavy chains, 450 amino acids) linked together by two inter (light chain - heavy chain) disulphide bridges and two inter (heavy chain - heavy chain) disulphide bridges to form a Y-shaped molecule, typical for immunoglobulins of the IgG1 subclass (see Figure 2).

Each molecule also contains a total of 12 intra-chain disulphide bridges and an asparagine residue (301) in each heavy chain which is glycosylated.

The structure is provided below:

Figure 2 - Structure of alemtuzumab



CAS number

Not applicable

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8 SPONSOR

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park NSW 2113
Freecall: 1800 818 806
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

10 May 2006

10 DATE OF REVISION

12 December 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.8, 4.9	New Zealand details removed
8	Sponsor details reformatted