

## Data Sheet

# MabCampath®

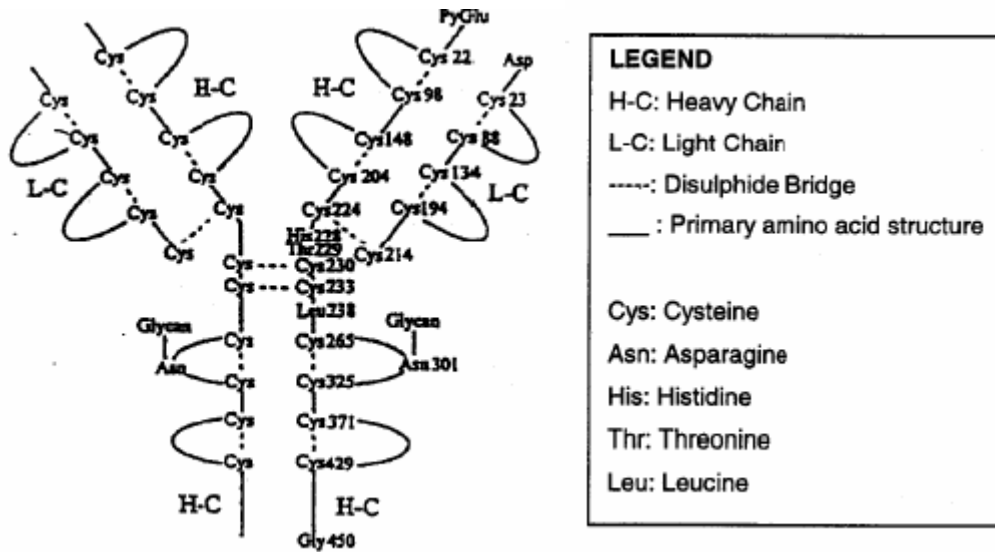
Concentrated Solution for Infusion

Alemtuzumab 30 mg/mL

## Name of the Medicine

MabCampath contains the monoclonal antibody alemtuzumab as the active ingredient.

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 below). 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.



## Description

Each vial contains 30 mg alemtuzumab as a concentrated solution for infusion.

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.

**Excipients**

Disodium edentate

Polysorbate 80

Phosphate buffered saline consisting of: Potassium chloride, monobasic potassium phosphate, sodium chloride, sodium phosphate – dibasic, water for injections.

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**Pharmacology**

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**Pharmacodynamics**

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.

**Pharmacokinetics**

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.

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**Clinical Trials**

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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:

<b>Efficacy Parameters</b>	<b>Study 1</b>	<b>Study 2</b>	<b>Study 3</b>
Number of patients	93	32	24
Diagnostic group	B-CLL patients who had received an	B-CLL patients who had failed to respond	B-CLL (plus a PLL) patients who had

alkylating agent and had failed fludarabine	or relapsed following treatment with conventional chemotherapy		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
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

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## Indications

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MabCampath is indicated for the third line treatment of patients with chronic lymphocytic leukaemia (CLL) who have been treated with alkylating agents and who have failed to

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achieve a complete or partial response or achieved only short remission (less than 6 months) following fludarabine phosphate therapy.

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## Contraindications

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- 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

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## Precautions

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### 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 Dosage and Administration).

Patients may have allergic or hypersensitivity reactions to MabCampath and to murine or chimeric monoclonal antibodies. 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, rigors, fever, shortness of breath, chills and rashes. 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 reinstated with gradual dose escalation.

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.

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. The recommended premedication is hydrocortisone 100 - 200 mg, or equivalent, which may be reduced 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.

## 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

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weeks 8 - 12 during treatment and continue to recover for several months following the discontinuation of treatment. The median time to reach a level of 200 cells/ $\mu$ L is 2 months following last infusion with MabCampath but may take 6 months or longer 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 carinii* 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 carinii* pneumonia (PCP) and an effective oral anti - herpes agent, such as famciclovir 500 mg twice daily) should be initiated while on therapy and continued following the completion of treatment with MabCampath until the CD4+ count has recovered to 200 cells/ $\mu$ L or greater. If CD4 counts are not obtainable, then patients should remain on anti-infective prophylaxis for 4 months.

## Graft versus Host Disease (GVHD)

Because of the potential for GVHD in severely lymphopenic patients, blood products should be irradiated prior to use until lymphopenia has resolved, and particularly until the T-cells are adequately repopulated to at least 200 cells/ $\mu$ L or greater.

## Haematological 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 30 mg or cumulative doses greater than 90 mg per week should not be administered because these doses are associated with a higher incidence of pancytopenia.

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 discontinued until the event resolves. MabCampath treatment may be reinstated following resolution of the haematological toxicity (see Dosage and Administration). MabCampath should be permanently discontinued if MabCampath related 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.

## Paediatric Use

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

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## 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 Dosage and Administration).

## 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. Based on preclinical immunohistochemical assays with MabCampath, the possibility of male reproductive tract toxicity cannot be ruled out, although this has not been observed in clinical trials.

## 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 Use in Pregnancy and Use in 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.

## Carcinogenicity and Genotoxicity

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

## Interactions with Other Medicines

No formal 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.

## 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.

## Adverse Effects

More than 80% patients may be expected to experience adverse reactions; the most commonly reported reactions usually occur during the first week of therapy.

The frequencies of the adverse reactions by system organ classes and in descending order of severity in the table below are based on clinical trial data in the B-CLL study population (n = 149). The frequencies are defined according to CIOMS III and V:

Very common ≥ 1/10  
 Common ≥ 1/100 to < 1/10  
 Uncommon ≥ 1/1000 to < 1/100

Body System	Adverse Reactions and Infections		
Very Common	Common		Uncommon
General disorders and administration site conditions	Rigors Fever Fatigue Sweating increased	Pain Chest Pain Asthenia Malaise Influenza-like symptoms Oedema Oedema mouth Mucositis Temperature change sensation Injection site reaction	Pulmonary oedema Peripheral oedema Periorbital oedema Injection site bruising Injection site dermatitis Injection site pain
Cardiac disorders	Tachycardia Palpitation		Cardiac arrest Myocardial infarction Atrial fibrillation Supraventricular tachycardia ECG abnormal Arrhythmia Bradycardia
Vascular disorders	Hypotension	Hypertension Vasospasm Flushing	Syncope Peripheral ischemia
Nervous system disorders	Headache	Taste loss Tremor Hypoesthesia Dizziness Hyperkinesia Paraesthesia Vertigo	Abnormal gait Dystonia Hyperaesthesia Taste perversion Neuropathy
Eye disorders	Conjunctivitis		Endophthalmitis
Ear and laby-	Deafness		

rinth disorders		Tinnitus	
Gastrointestinal disorders	Vomiting Nausea Diarrhoea	Gastro-intestinal haemorrhage Stomatitis Constipation Dyspepsia Stomatitis ulcerative Flatulence Abdominal pain	Gastroenteritis Gingivitis Eructation Hiccup Dry mouth Mucosal ulceration Tongue ulceration
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Lymphoma like disorder	
Blood and lymphatic system disorders	Granulocytopenia Thrombocytopenia Anaemia	Neutropenic fever Pancytopenia Leukopenia Lymphopenia Purpura	Bone marrow aplasia Haptoglobin decreased Disseminated intravascular coagulation Haemolytic anaemia Marrow depression Epistaxis Gingival bleeding
Immune system disorders		Allergic reaction	
Metabolism and nutritional disorders	Anorexia	Hyponatraemia Dehydration Weight decrease Hypocalcaemia Thirst	Diabetes mellitus aggravated Hypokalaemia
Musculo-skeletal and connective tissue disorders	Skeletal pain Arthralgia Myalgia Back pain	Leg pain Hypertonia	
Psychiatric disorders	Confusion Anxiety Somnolence Depression Insomnia	Nervousness Abnormal thinking Depersonalisation Impotence Personality disorder	
Hepatobiliary disorders		Hepatic function abnormal	

Infections and infestations	Sepsis Pneumonia Herpes simplex	Cytomegalovirus infection <i>Pneumocystis carinii</i> infection Pneumonitis Moniliasis Herpes zoster Sinusitis Bronchitis Upper respiratory tract	Viral infection Bacterial infection Laryngitis Rhinitis Fungal dermatitis Onychomycosis
infection Pharyngitis Urinary tract infection Infection Fungal infection Abscess			
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Bronchospasm Coughing Hypoxia Haemoptysis	Stridor Pulmonary infiltration Respiratory disorder Breath sounds decreased Tightness of the throat Pleural effusion
Skin and subcutaneous tissue disorders	Urticaria Rash Pruritus	Rash erythematous Bullous eruption	Rash maculo-papular Skin disorder
Renal and urinary disorders	Renal function abnormal Polyuria Haematuria Urinary incontinence Urine flow decreased		

### Post Marketing Data

The reactions presented in this section were identified mainly from post marketing experience. The frequencies are based upon reporting rates:

- Very common ≥ 1/10
- Common ≥ 1/100 to < 1/10
- Uncommon ≥ 1/1000 to < 1/100
- Rare ≥ 1/10,000 to < 1/1000
- Very rare < 1/10000

**General**

*Very common:* Fever, rigors, fatigue, Herpes simplex

*Common:* cytomegalovirus, moniliasis, *Herpes zoster*, adenovirus, parainfluenza, fungal infections

*Uncommon:* hepatitis B, tuberculosis, atypical mycobacteriosis, nocardiosis, *Toxoplasma gondii*

**Cardiovascular:**

*Very common:* hypotension

*Uncommon:* syncope, arrhythmia, acute cardiac insufficiency, myocardial infarction, cardiac arrest, congestive heart failure, cardiomyopathy,

**Respiratory**

*Very common:* dyspnoea, pneumonia

*Common:* bronchospasm, hypoxia, *Pneumocystis carinii* pneumonia, *Aspergillus* pneumonia

*Uncommon:* pulmonary infiltrates, acute respiratory distress syndrome, respiratory arrest

**Immunological**

*Very common:* Profound lymphocyte depletion

*Common:* Coomb's Test Positive

*Uncommon:* autoimmune haemolytic anaemia, autoimmune thrombocytopenia, aplastic anaemia, Guillian Barre Syndrome and its chronic form, chronic inflammatory demyelinating polyradiculoneuropathy

*Rare:* anaphylactic shock, angioedema

**Haematological**

*Very common:* neutropenia, thrombocytopenia

*Common:* pancytopenia

**Neurological**

*Very common:* headache

*Uncommon:* rhinocerebral mucormycosis

*Rare:* progressive multifocal leukoencephalopathy, intracranial haemorrhage

**Gastrointestinal**

*Very common:* nausea, vomiting, diarrhoea

**Metabolic and Nutritional**

*Rare:* tumour lysis syndrome

## **Skin**

*Very common:* rash, urticaria, pruritis

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## **Dosage and Administration**

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

The 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 premedicated with an appropriate antihistamine and analgesic prior to the first dose at each escalation and prior to subsequent infusions, as clinically indicated (see Precautions).

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

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 Precautions).

The majority of major responses to MabCampath have been achieved with treatment duration of 4 – 12 weeks. 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 discontinued until the event resolves. It is recommended that MabCampath should be discontinued in patients whose platelet count falls to < 25,000/ $\mu$ L or whose absolute neutrophil count (ANC) drops to < 250/ $\mu$ L. MabCampath may be reinstated after the infection or toxicity has resolved. The following table outlines the recommended procedure for dose modification following the occurrence of haematological toxicity while on therapy:

Haematological Toxicity (platelets < 25,000/ $\mu$ L and/or ANC < 250/ $\mu$ L)	Reinstitution of MabCampath
First occurrence	After resolution, reinstitute at 30 mg*
Second occurrence	After resolution, reinstitute at 10 mg*
Third occurrence	Permanent discontinuation

\*if therapy has been withheld for more than 7 days, MabCampath must be reinstated by gradual dose escalation.

### Patients with Renal or Hepatic Impairment

No studies have been conducted.

### Elderly (over 65 years of age)

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

### Instructions for Use and 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 should not be used.

Product is for single use in one patient only. Discard any residue.

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.

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

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

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

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.

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

There are no known incompatibilities with other medicinal products.

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## Overdosage

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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 overdosage. Treatment consists of discontinuation of MabCampath and supportive therapy.

In cases of overdose, it is advisable to contact the National Poisons Information Centre (0800 POISON or 0800 764 766) for recommendations on the management and treatment of overdosage.

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## Presentations and Storage Conditions

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

Pack size: 3 vials.

### **Storage**

Store 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.

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## Medicine Classification

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Prescription Medicine

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## Name and Address

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**Date of Preparation**

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