PRODUCT INFORMATION

LEMTRADA®

NAME OF MEDICINE

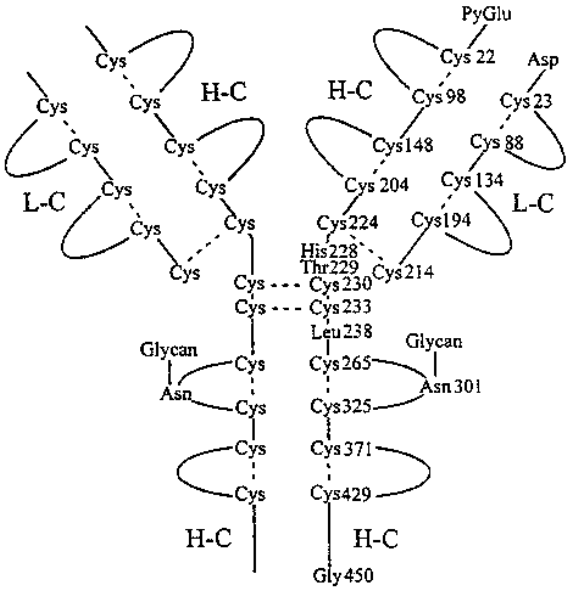
AUSTRALIAN APPROVED NAME

Alemtuzumab (rch)

CHEMICAL STRUCTURE

Alemtuzumab (rch) is a Y-shaped molecule consisting of two 24-kilodalton (kD) light polypeptide chains (L-C) and two 49-kD heavy polypeptide chains (H-C) linked together by 2 interdisulfide (L-C)-(H-C) bridges and two interdisulfide (H-C)-(H-C) bridges. Each molecule also contains a total of 12 intrachain disulfide bridges and an asparagine residue in each heavy chain that is amenable to glycosylation.

Figure 1 - Structural Formula



CAS REGISTRY NUMBER

Not Applicable

DESCRIPTION

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, colorless to slightly yellow, injection concentrate with pH 7.0 - 7.4. It is intended for dilution prior to infusion.

Each 1.0 mL of concentrate solution contains 10 mg Alemtuzumab (rch) and the following excipients: 8.0 mg sodium chloride, 1.15 mg sodium phosphate-monobasic , 0.2 mg potassium chloride, 0.2 mg potassium phosphate-monobasic , 0.1 mg polysorbate 80, 0.0187 mg disodium edetate, and water for injection.

PHARMACOLOGY

PHARMACODYNAMICS

Mechanism of Action

Alemtuzumab binds to CD52, a cell surface antigen present at high levels on T and B lymphocytes, and at lower levels on natural killer cells, monocytes, and macrophages, There is little or no CD52 detected on neutrophils, plasma cells, or bone marrow stem cells. Alemtuzumab acts through antibody-dependent cellular cytolysis and complement-mediated lysis following cell surface binding to T and B lymphocytes.

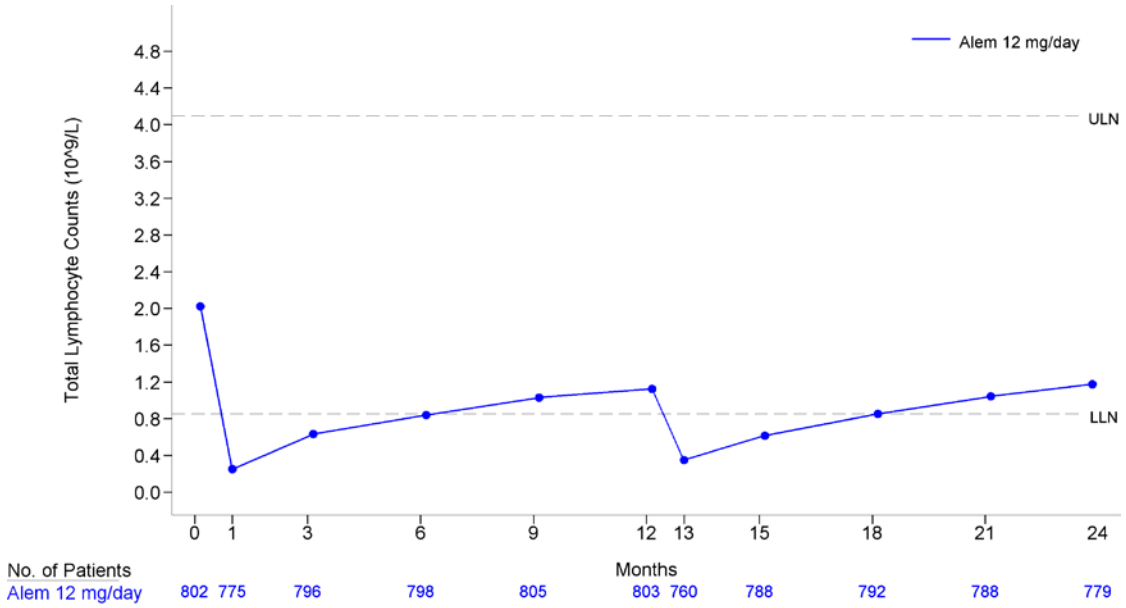
The mechanism by which alemtuzumab exerts its therapeutic effects in MS is unknown, but may involve immunomodulation through the depletion and repopulation of lymphocytes. Research suggests that the potential immunomodulatory effects in MS may include alterations in the number, proportions, and properties of some lymphocyte subsets post-treatment.

Alemtuzumab depletes circulating T and B lymphocytes after each treatment course with the lowest observed values occurring at the first post-treatment assessment, which was as early as 2 days after the end of the first treatment cycle in a Phase 2 study. Lymphocytes repopulate over time Figure 2. B cells recover to normal within 6 months for >90% of patients.
T lymphocyte counts rise more slowly towards normal, and 10-70% (depending on cell type) return to baseline by 12 months post-treatment. Approximately 40% of patients had total lymphocyte counts reaching the lower limit of normal (LLN) by 6 months after each treatment course, and approximately 80% of patients had total lymphocyte counts reaching the LLN by 12

months after each treatment course.

Neutrophils, monocytes, eosinophils, basophils, and natural killer cells are only transiently affected by alemtuzumab.

Figure 2 - Total Lymphocyte Depletion and Repopulation Following Treatment with Alemtuzumab at Month 0 and Month 12 in CAMMS323 and CAMMS324



PHARMACOKINETICS

The pharmacokinetics of alemtuzumab were evaluated in a total of 216 patients with RRMS who received IV infusions of either 12 mg/day or 24 mg/day for 5 consecutive days (Course 1), followed by 3 consecutive days 12 months following the initial treatment course (Course 2). Serum concentrations increased with each consecutive dose within a treatment course, with the highest observed concentrations occurring following the last infusion of a treatment course. Administration of 12 mg/day resulted in a C_{max} of 3014 ng/mL on Day 5 of the initial treatment course, and 2276 ng/mL on Day 3 of the second treatment course. The alpha half-life approximated 2 days and was comparable between courses leading to low or undetectable serum concentrations within approximately 30 days following each treatment course.

The population pharmacokinetics of alemtuzumab were best described by a linear, 2-compartment model. Systemic clearance decreased with lymphocyte count due to loss of CD52 antigen in the periphery; however, the decrease from Course 1 to Course 2 was less than 20%. The central volume of distribution was proportional to body weight, and approximated extracellular fluid volume (14.1 L), suggesting that Lemtrada is largely confined to the blood and interstitial space.

Special Populations

No effect of age, race, or gender on the pharmacokinetics of Lemtrada was observed.

Hepatic Impairment

Lemtrada has not been studied in patients with hepatic impairment.

Renal Impairment

Lemtrada has not been studied in patients with renal impairment.

CLINICAL TRIALS

The safety and efficacy of Lemtrada were evaluated in 3 randomised, rater-blinded, active-comparator trials in patients with MS.

Studies 1 and 2 (CAMMS323 and CAMMS324) enrolled patients with active MS who had experienced at least 2 clinical episodes during the prior 2 years. Neurological examinations were performed every 12 weeks and at times of suspected relapse. MRI evaluations were performed annually. Patients were followed for 2 years. In both studies, patients were randomised to receive Lemtrada 12 mg/day IV infusion administered once per day on 5 days at Month 0 and on 3 days at Month 12 (the 12 mg group) or interferon beta-1a (IFNB-1a) 44 µg SC injection administered 3 times per week. Study 2 also included an exploratory dose arm for Lemtrada 24 mg/day administered once per day on 5 days at Month 0 and on 3 days at Month 12 (the 24 mg group). The primary outcome measures for Studies 1 and 2 were the annualised relapse rate (ARR) over 2 years and the time to onset of sustained accumulation of disability (SAD), defined as an increase of at least 1 point on the expanded disability status scale (EDSS) from a baseline EDSS score ≥ 1.0 (1.5 point increase for patients with baseline EDSS of 0) that was sustained for 6 months.

Study 1 (CAMMS323) included patients with RRMS with an EDSS from 0-3.0 with N=376 in the Lemtrada 12 mg group and N=187 in the IFNB-1a group. Mean age was 33 years, mean disease duration was 2 years and mean EDSS score was 2.0 at baseline. Patients had not received prior therapy for MS at study entry.

The ARR was significantly reduced by 55% in patients treated with Lemtrada as compared to SC IFNB-1a at 2 years. There was no statistically significant difference between the treatment groups in the 6-month sustained accumulation of disability; at 2 years 8% of Lemtrada-treated patients had a sustained increase in EDSS score as compared to 11% of IFNB-1a patients
Results are shown in Table 1.

Study 2 (CAMMS324) included patients with RRMS with an EDSS from 0-5 with N=426 in the Lemtrada 12 mg group and N=202 in the IFNB-1a group. Mean age was 35 years, mean disease duration was 4.5 years, and mean EDSS score was 2.7 at baseline. Prior to enrolling, patients experienced at least 1 relapse during treatment with beta interferon or glatiramer acetate after having been on therapy with drug for at least 6 months. At baseline, the mean duration of

exposure to prior MS therapies (≥1 drug used) was 35 months in the Lemtrada 12 mg group; 29% had received ≥2 prior MS therapies.

The RR was significantly reduced by 49% in patients in the Lemtrada 12 mg group as compared to SC IFNB-1a over 2 years. In addition, treatment with Lemtrada significantly reduced by 42% the risk of 6-month SAD versus SC IFNB-1a over 2 years; 13% of Lemtrada-treated patients had a sustained increase in EDSS score as compared to 21% of IFNB-1a patients (absolute difference 8.42%). The mean EDSS score in patients treated with Lemtrada was significantly reduced over 2 years, (indicating improvement), compared to the mean EDSS score from baseline for patients treated with SC IFNB-1a Compared with IFNB-1a-treated patients, Lemtrada-treated patients were 2.6 times more likely to achieve a sustained reduction in disability. The secondary variable percent change from baseline in MRI-T2-hyperintense lesion volume at Year 2 showed no significant different between treatments. Effects on tertiary MRI measures are shown in Table 1 Results are shown in Table 1 and Figure 3.

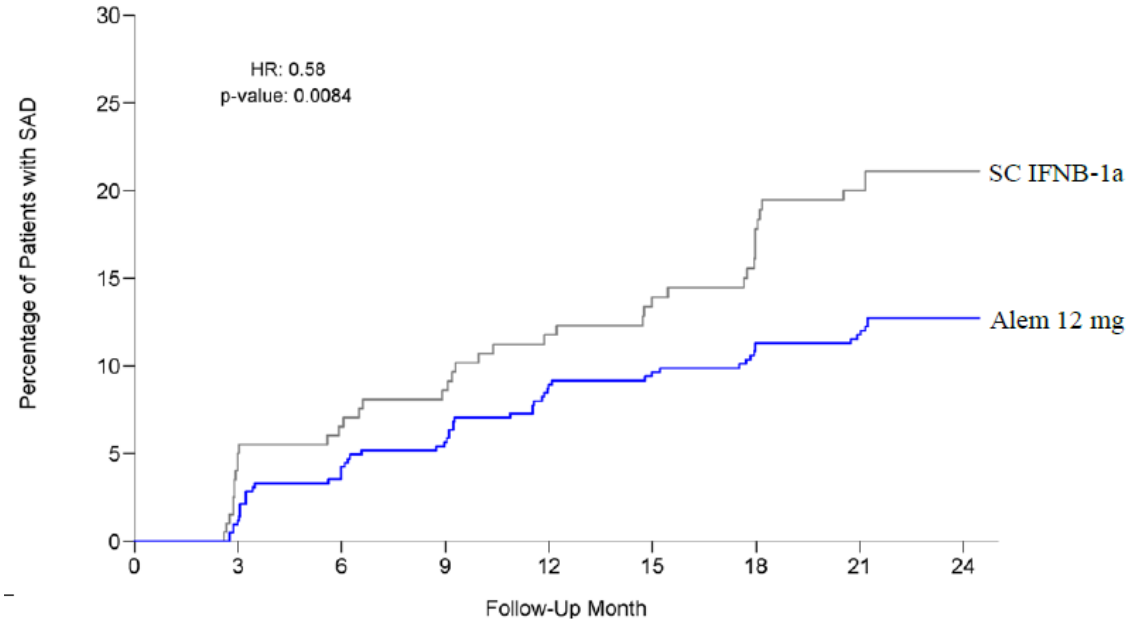
Table 1 - Key Clinical and MRI Endpoints form Study 1 and Study 2

	Study 1 (CAMMS323)		Study 2 (CAMMS324)	
Endpoint	Lemtrada (N=376)	SC IFNB-1a (N=187)	Lemtrada (N=426)	SC IFNB-1a (N=202)
Clinical Endpoints				
Relapse Rate (co-primary endpoint)				
Patients with event (number of events)	82 (119)	75 (122)	147 (236)	104 (201)
ARR (95% CI)	0.18 (0.13, 0.23)	0.39 (0.29, 0.53)	0.26 (0.21, 0.33)	0.52 (0.41, 0.66)
Rate ratio (95% CI)	0.45 (0.32, 0.63)		0.51 (0.39, 0.65)	
Risk reduction	54.88		49.40	
p-value	<0.0001		<0.0001	
Disability (SAD ≥6 months; co-primary endpoint)				
Estimate of patients with 6-month SAD (95% CI)	8.00 (5.66, 11.24)	11.12 (7.32, 16.71)	12.71 (9.89, 16.27)	21.13 (15.95, 27.68)
Hazard ratio (95% CI)	0.70 (0.40, 1.23)		0.58 (0.38, 0.87)	
p-value	0.2173		0.0084	
Patients who are relapse free at Year 2 (%)				
Estimate (95% CI)	77.59 (72.87, 81.60)	58.69 (51.12, 65.50)	65.38 (60.65, 69.70)	46.70 (39.53, 53.54)
p-value	<0.0001		<0.0001	
Change from baseline in EDSS at Year 2				
Estimate (95% CI)	-0.14 (-0.25, -0.02)	-0.14 (-0.29, 0.01)	-0.17 (-0.29, -0.05)	0.24 (0.07, 0.41)
p-value	0.4188		<0.0001	
Sustained reduction in disability (SRD)				

	Study 1 (CAMMS323)		Study 2 (CAMMS324)	
Endpoint	Lemtrada (N=376)	SC IFNB-1a (N=187)	Lemtrada (N=426)	SC IFNB-1a (N=202)
Estimate of patients with 6-month SRD (95% CI)			28.82 (24.18, 34.13)	12.93 (8.34, 19.77)
Hazard ratio (95% CI)			2.57 (1.57, 4.20)	
p-value			0.0002	
MRI Endpoints				
Change in MRI-T2 lesion volume from baseline to Year 2 (%)	-9.3	-6.5	-1.27	-1.23
p-value	0.3080		0.1371	
Patients with new or enlarging T2 lesions through Year 2 (%)	48.5	57.6	46.2	67.9
p-value	0.0352		<0.0001	
Patients with Gadolinium enhancing lesions through Year 2 (%)	15.4	27.0	18.5	34.2
p-value	0.0008		<0.0001	
Patients with new T1 hypointense lesions through Year 2 (%)	24.0	31.4	19.9	38.0
p-value	0.0545		<0.0001	
Change in Brain Parenchymal Fraction from baseline to Year 2 (%)	-0.867	-1.488	-0.615	-0.810
p-value	<0.0001		0.0121	

Mean change is presented for EDSS. Median change is presented for MRI-T2 lesion volume and Brain Parenchymal Fraction.

Figure 3 - Time to 6-month Sustained Accumulation of Disability in Study 2



No. at Risk									
SC IFNB-1a	202	200	184	175	167	162	155	145	131
Alem 12 mg/day	426	426	412	404	392	384	380	375	354

Study 3 (phase 2 study CAMMS223) evaluated the safety and efficacy of Lemtrada in patients with RRMS over the course of 5 years. Patients had an EDSS from 0-3.0, at least 2 clinical episodes of MS in the prior 2 years, and ≥1 gadolinium-enhancing lesion at study entry. Patients had not received prior therapy for MS. Patients were treated with Lemtrada 12 mg/day (N=108) or 24 mg/day (N=108) administered once per day on 5 days at Month 0 and on 3 days at Month 12 or SC IFNB-1a 44 µg (N=107) administered 3 times per week for 3 years. Twenty-four patients received a third course of Lemtrada treatment at 12 mg/day for 3 days at Month 24.

At 3 years, the ARR was significantly reduced by 70% in patients in the Lemtrada 12 mg group who had received 2 courses of therapy as compared to SC IFNB-1a. In addition, treatment with Lemtrada significantly reduced by 70% the risk of 6-month SAD versus IFNB-1a.

The benefits and risks of >2 treatment courses of Lemtrada have not been fully established, but results suggest that the safety profile does not appear to change with additional courses.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Data reflect the percentage of patients whose test results were considered positive for antibodies to alemtuzumab using an enzyme-linked immunosorbent assay (ELISA) and confirmed by a competitive binding assay. Positive samples were further evaluated for evidence of *in vitro* inhibition using a flow cytometry assay. Patients in controlled clinical trials in MS had serum samples collected 1, 3, and 12 months after each treatment course for determination of anti-alemtuzumab antibodies. Approximately 85% of patients receiving Lemtrada tested positive for anti-alemtuzumab antibodies during the study, with 92% of these patients testing positive also for antibodies that inhibited alemtuzumab binding *in vitro*. Patients who developed anti-alemtuzumab antibodies did so by 15 months from initial exposure. There was no association of the presence of anti-alemtuzumab or inhibitory anti-alemtuzumab antibodies with a reduction in efficacy, change in pharmacodynamics, or the occurrence of adverse reactions, including infusion associated reactions.

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

INDICATIONS

Lemtrada is indicated for the treatment of relapsing forms of multiple sclerosis (MS) for patients with active disease defined by clinical or imaging features to slow the accumulation of physical disability and reduce the frequency of clinical relapses.

CONTRAINDICATIONS

Lemtrada is contraindicated:

- Hypersensitivity or anaphylactic reactions to alemtuzumab, to murine proteins or to any of the excipients.
- Human Immunodeficiency Virus (HIV) infection.

PRECAUTIONS

Lemtrada is not recommended for patients with inactive disease or those stable on current therapy.

Lemtrada has not been administered for treatment of MS concomitantly with other disease modifying MS therapies. As with other immunomodulating therapies, potential combined effects on the patient's immune system should be taken into account when considering administration of

Lemtrada (see DRUG INTERACTIONS). There are limited data for use of other disease modifying therapies after Lemtrada.

Patients treated with Lemtrada must be given the Consumer Medicines Information, the Patient Wallet Card and the Patient Guide. Before treatment, patients must be informed about the risks and benefits, and the need to commit to 48-months of follow-up after the last infusion of Lemtrada.

Remind the patient to remain vigilant for symptoms they may experience and to seek immediate medical help if they have any concerns.

Autoimmunity

Treatment with Lemtrada may result in the formation of autoantibodies and increase the risk of autoimmune mediated conditions including immune thrombocytopenic purpura (ITP), thyroid disorders or, uncommonly, nephropathies (e.g., anti-glomerular basement membrane disease).

Immune Thrombocytopenic Purpura

Serious events of ITP have been observed in approximately 1% of patients treated with alemtuzumab in controlled clinical trials in MS. In a controlled clinical trial in patients with MS, 1 patient developed ITP that went unrecognized prior to the implementation of monthly blood monitoring requirements and died from intracerebral hemorrhage. ITP onset has generally occurred between 14 and 36 months after first alemtuzumab exposure (range 3.7 to 40.7 months).

Full blood counts (FBC) with differential should be obtained prior to initiation of treatment and at monthly intervals thereafter until 48 months after the last infusion. After this period of time, testing should be performed based on clinical findings suggestive of ITP. If ITP is suspected a FBC should be obtained immediately.

If ITP onset is confirmed, appropriate medical intervention should be promptly initiated, including referral to a specialist. Data from clinical trials in MS has shown that adherence to the blood monitoring requirements and education relative to signs and symptoms of ITP has led to early detection and treatment of ITP with most cases responding to first-line medical therapy.

The potential risk associated with retreatment with alemtuzumab following the occurrence of ITP is unknown.

Nephropathies

Nephropathies, including anti-glomerular basement membrane (anti-GBM) disease have been observed in 0.3% of patients in clinical trials in MS and generally occurred within 39 months following last administration of alemtuzumab. In clinical trials, there were 2 cases of anti-GBM disease. Both cases were serious, were identified early through clinical and laboratory monitoring, and had a positive outcome after treatment.

Clinical manifestations of nephropathy may include elevation in serum creatinine, haematuria, and/or proteinuria. While not observed in clinical trials, alveolar haemorrhage manifested as haemoptysis may occur as a component of anti-GBM disease.

Serum creatinine levels and urinalysis with cell counts should be obtained prior to initiation of treatment and at monthly intervals thereafter until 48 months after the last infusion. The observation of clinically significant changes from baseline in serum creatinine, unexplained haematuria, and/or proteinuria, should prompt further evaluation for nephropathies, including referral to a specialist. Early detection and treatment of nephropathies may decrease the risk of poor outcomes. After this period of time, testing should be performed based on clinical findings suggestive of nephropathies.

The potential risk associated with retreatment with alemtuzumab following the occurrence of nephropathies is unknown.

Thyroid Disorders

Autoimmune thyroid disorders have been observed in an estimated 36% of patients treated with alemtuzumab 12 mg in clinical trials in MS through 4 years following first alemtuzumab exposure.

Observed autoimmune thyroid disorders included hyperthyroidism or hypothyroidism. Most events were mild to moderate in severity. Serious events occurred in <1% of patients, with only Graves'disease (also known as Basedow's disease), hyperthyroidism, and hypothyroidism occurring in more than 1 patient. Most thyroid events were managed with conventional medical therapy however some patients required surgical intervention.

Thyroid function tests, such as thyroid stimulating hormone (TSH) levels, should be obtained prior to initiation of treatment and every 3 months thereafter until 48 months after the last infusion. After this period of time testing should be performed based on clinical findings suggestive of thyroid dysfunction.

Thyroid disease poses special risks in women who are pregnant (see USE IN PREGNANCY).

Cytopenias

Suspected autoimmune cytopenias such as neutropenia, hemolytic anemia, and pancytopenia have been reported uncommonly in patients in clinical trials in MS. Neutropenia was commonly reported in both treatment groups in clinical trials (IFNB-1a 4.0% vs. 1.8% Lemtrada 12mg). FBC results should be used to monitor for cytopenias. If a cytopenia is confirmed, appropriate medical intervention should be promptly initiated, including referral to a specialist.

Infusion Associated Reactions

In clinical trials, infusion associated reactions (IARs) were defined as any adverse event occurring during or within 24 hours of Lemtrada infusion. Most patients treated with Lemtrada in controlled

clinical trials in MS experienced mild to moderate IARs during and/or up to 24 hours after Lemtrada 12 mg administration, which often included headache, rash, pyrexia, nausea, urticaria, pruritus, insomnia, chills, flushing, fatigue, dyspnoea, dysgeusia, chest discomfort, generalized rash, tachycardia, bradycardia, dyspepsia, dizziness, and pain. Serious reactions occurred in 3% of patients including cases of pyrexia, urticaria, atrial fibrillation, nausea, chest discomfort, and hypotension. In addition, anaphylaxis has been reported rarely.

It is recommended that patients be premedicated with corticosteroids immediately prior to the initiation of the Lemtrada infusion on the first 3 days of any treatment course to ameliorate the effects of infusion reactions. In clinical trials patients were pretreated with 1,000 mg of methylprednisolone on the first 3 days of each Lemtrada treatment course. Pretreatment with antihistamines and/or antipyretics prior to Lemtrada administration may also be considered. Most patients in controlled clinical trials received antihistamines and/or antipyretics before at least 1 Lemtrada infusion. IARs may occur in patients despite pretreatment. Physicians should be aware of the patient's cardiac history as infusion-associated reactions can include cardiac symptoms such as tachycardia. Observation for infusion reactions is recommended during and for 2 hours after each Lemtrada infusion. If an IAR occurs, provide the appropriate symptomatic treatment, as needed. If the infusion is not well tolerated, the infusion duration may be extended. If severe infusion reactions occur, immediate discontinuation of the IV infusion should be considered.

Within the clinical trials, anaphylaxis or serious reactions that necessitated treatment discontinuation were very rare. Facilities for the management of anaphylaxis or serious reactions should be available.

Infections

Infections occurred in 71% of patients treated with alemtuzumab 12 mg as compared to 53% of patients treated with Rebif (interferon beta-1a [IFNB-1a]) in controlled clinical trials in MS up to 2 years in duration and were predominantly mild to moderate in severity. Infections that occurred more often in alemtuzumab-treated patients than IFNB-1a patients included nasopharyngitis, urinary tract infection, upper respiratory tract infection, sinusitis, oral herpes, influenza, and bronchitis. Serious infections occurred in 2.7% of patients treated with alemtuzumab as compared to 1.0% of patients treated with IFNB-1a in controlled clinical trials in MS. Serious infections in the alemtuzumab group included: appendicitis, gastroenteritis, pneumonia, herpes zoster, and tooth infection. Infections were generally of typical duration and resolved following conventional medical treatment.

Serious varicella zoster virus infections, including primary varicella and varicella zoster re-activation, have occurred more often in patients treated with alemtuzumab 12 mg (0.4%) in clinical trials as compared to IFNB-1a (0%).

Cervical human papilloma virus (HPV) infection, including cervical dysplasia, has also been reported in patients treated with alemtuzumab 12 mg (2%). It is recommended that HPV screening, such as a cervical smear, be completed annually for female patients.

Tuberculosis has been reported for patients treated with alemtuzumab and IFNB-1a in controlled clinical trials. Active and latent tuberculosis have been reported in 0.3% of the patients treated

with alemtuzumab, most often in endemic regions. Tuberculosis screening should be done according to local guidelines prior to initiation of alemtuzumab.

Listeria meningitis has been reported in Lemtrada-treated patients. Cases of listeria meningitis occurred within 1 month of alemtuzumab dosing. The duration of increased risk for listeria meningitis is unclear. Patients should avoid or adequately heat foods that are potential sources of *Listeria monocytogenes*.

Superficial fungal infections, especially oral and vaginal candidiasis, occurred more commonly in alemtuzumab-treated patients (12%) than in patients treated with IFNB-1a (3%) in clinical trials in MS.

Physicians should consider delaying initiation of Lemtrada administration in patients with active infection until the infection is fully controlled.

Prophylaxis with an oral anti-herpes agent should be initiated starting on the first day of Lemtrada treatment and continuing for a minimum of 1 month following each course of treatment.

Lemtrada has not been administered for treatment of MS concomitantly with antineoplastic or immunosuppressive therapies. As with other immunomodulating therapies, potential combined effects on the patient's immune system should be taken into account when considering administration of Lemtrada. Concomitant use of Lemtrada with any of these therapies could increase the risk of immunosuppression.

No data are available on the association of alemtuzumab with Hepatitis B virus (HBV) or Hepatitis C virus (HCV) reactivation as patients with evidence of active or chronic infections were excluded from clinical trials. Screening patients at high risk of HBV and/or HCV infection before initiation of Lemtrada should be considered and caution should be exercised in prescribing Lemtrada to patients identified as carriers of HBV and/or HCV as these patients may be at risk of irreversible liver damage relative to a potential virus reactivation as a consequence of their pre-existing status.

Malignancy

As with other immunomodulatory therapies, caution should be exercised in initiating Lemtrada therapy in patients with pre-existing and/or an on-going malignancy.

In clinical trials of up to 24 months duration no increase in the incidence of malignancy was seen in patients given alemtuzumab compared with interferon β-1a. Additionally, over all available follow-up for alemtuzumab treated patients (up to 9 years) the annualized rate of malignancy was within the range of the background population. The most common malignancies reported in patients given alemtuzumab were thyroid cancer (5 patients), breast cancer (5 patients) and basal cell carcinoma (4 patients), which are among the most frequent cancers reported for white, young adults.

There is limited information on the safety of Lemtrada beyond two years. Observation over longer treatment periods is required before any effect of Lemtrada on malignancies can be excluded.

Vaccines

It is recommended that patients have completed local immunization requirements at least 6 weeks prior to treatment with Lemtrada. The ability to generate an immune response to any vaccine following Lemtrada treatment has not been studied.

The safety of immunization with live viral vaccines following a course of alemtuzumab treatment has not been formally studied in controlled clinical trials in MS. Live vaccines should not be administered to MS patients who have recently received a course of Lemtrada.

Varicella zoster virus antibody testing/vaccination

As for any immune modulating drug, before initiating a course of Lemtrada treatment, patients without a history of chickenpox or without vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV. VZV vaccination of antibody-negative patients should be considered prior to treatment initiation with Lemtrada. To allow for the full effect of the VZV vaccination to occur, postpone treatment with Lemtrada for 6 weeks following vaccination.

Recommended Laboratory Tests for Monitoring Patients

Laboratory tests should be conducted at periodic intervals for 48 months following the last treatment course of Lemtrada in order to monitor for early signs of autoimmune disease:

- FBC with differential (prior to treatment initiation and at monthly intervals thereafter)
- Serum creatinine levels (prior to treatment initiation and at monthly intervals thereafter)
- Urinalysis with urine cell counts (prior to treatment initiation and at monthly intervals thereafter)
- A test of thyroid function, such as TSH level (prior to treatment initiation and every 3 months thereafter)

Information from the post-marketing use of alemtuzumab in B-cell chronic lymphocytic leukaemia and other disorders

Alemtuzumab (also known commercially as MabCampath®) was first approved in 2006 for use in B-CLL. The following adverse reactions were identified during post-approval use of alemtuzumab for the treatment of B-cell chronic lymphocytic leukaemia (B-CLL), as well as for the treatment of other disorders, generally at higher and more frequent doses (e.g. 30 mg) than that recommended in the treatment of MS. 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.

Autoimmune Disease

Autoimmune events reported in alemtuzumab-treated patients include neutropenia, haemolytic anaemia (including a fatal case), acquired haemophilia, anti-GBM disease, and thyroid disease. Serious and sometimes fatal autoimmune phenomena including autoimmune haemolytic anaemia, autoimmune thrombocytopenia, aplastic anaemia, Guillain-Barré syndrome, and chronic inflammatory demyelinating polyradiculoneuropathy have been reported in alemtuzumab-treated non-MS patients. A positive Coombs test has been reported in an alemtuzumab-treated oncology patient. A fatal event of transfusion associated graft versus host disease has been reported in an alemtuzumab-treated oncology patient.

Infusion-associated Reactions

Serious and sometimes fatal IARs including bronchospasm, hypoxia, syncope, pulmonary infiltrates, acute respiratory distress syndrome , respiratory arrest, myocardial infarction, arrhythmias, acute cardiac insufficiency, and cardiac arrest have been observed in non-MS patients treated with alemtuzumab at higher and more frequent doses than used in MS. Severe anaphylaxis and other hypersensitivity reactions, including anaphylactic shock and angioedema have also been reported.

Infections and Infestations

Serious and sometimes fatal viral, bacterial, protozoan, and fungal infections, including those due to reactivation of latent infections, have been reported in non-MS patients treated with alemtuzumab at higher and more frequent doses than used in MS. Progressive multifocal leukoencephalopathy (PML) has been reported in patients with B-CLL with or without treatment with alemtuzumab. The frequency of PML in B-CLL patients treated with alemtuzumab is no greater than the background frequency.

Blood and Lymphatic System Disorders

Severe bleeding reactions have been reported in non-MS patients.

Cardiac Disorders

Congestive heart failure, cardiomyopathy, and decreased ejection fraction have been reported in alemtuzumab-treated non-MS patients previously treated with potentially cardiotoxic agents.

Epstein-Barr Virus-associated Lymphoproliferative Disorders

Epstein-Barr Virus-associated lymphoproliferative disorders have been observed outside company-sponsored studies.

Effects on Ability to Drive and Handle Heavy Machinery

No studies of the effect of Lemtrada on the ability to drive and handle machines have been performed.

Renal and Hepatic Impairment

Lemtrada has not been studied in patients with renal or hepatic impairment.

Effects on Fertility

In male transgenic mice, intravenous administration of alemtuzumab at doses of 3 and up to 10 mg/kg/day for 5 consecutive days (respective plasma AUC exposure 4 and 12 times clinical exposure at the MRHD) had no effect on fertility or reproductive performance. Effects on sperm were observed, with a significant increase in abnormal (detached head/no head) sperm; (respective incidences of 11%, 15%, 17% in control 3 and 10 mg/kg dose groups; a no-effect dose was not determined. The clinical significance of these effects is unknown.

In female transgenic mice treated intravenously with alemtuzumab for 5 consecutive days, the numbers of corpora lutea and implantation sites were significantly reduced at 10 mg/kg/day (plasma AUC 8 times clinical exposure at the MRHD); the no-effect dose was 3 mg/kg/day (3 times clinical exposure). Other mating and fertility parameters were unaffected at these doses.

Use in pregnancy (Category B3)

There are no adequate and well-controlled studies of Lemtrada in pregnant women. Lemtrada should be administered during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Human IgG is known to cross the placental barrier; alemtuzumab may cross the placental barrier as well and thus potentially pose a risk to the fetus. It is not known whether Lemtrada can cause foetal harm when administered to pregnant women or whether it can affect reproductive capacity. Alemtuzumab crosses the placenta in transgenic mice. Intravenous administration of alemtuzumab to pregnant mice during late organogenesis at a dose of 10 mg/kg/day for 5 consecutive days (plasma AUC exposure 4 times clinical exposure at the MRHD) was associated with an increased number of dams with all conceptuses dead or resorbed, along with a concomitant reduction in the number of dams with viable foetuses. There were no external, soft tissue or skeletal malformations or variations. There was evidence for reductions in lymphocytic counts and altered lymphocyte subpopulations in offspring at 3 weeks postpartum was observed following alemtuzumab treatment of mice during early or late gestation at doses of 3 mg/kg/day or greater for 5 consecutive days (plasma AUC similar to clinical exposure at the MRHD); a no-effect dose was not determined. The relevance to humans of reproductive toxicity findings in transgenic mice is unknown.

Women of child bearing potential should use effective contraceptive measures when receiving a course of treatment with Lemtrada and for 4 months following that course of treatment.

Thyroid disease (see *Thyroid Disorders*) poses special risks in women who are pregnant. Without treatment of hypothyroidism during pregnancy, there is an increased risk for miscarriage and foetal effects such as mental retardation and dwarfism. In mothers with Graves' disease, maternal thyroid stimulating hormone receptor antibodies can be transferred to a developing fetus and can cause transient neonatal Graves' disease.

Use in Lactation

It is not known whether alemtuzumab is excreted in human milk. Because immunoglobulins are excreted in milk, caution should be exercised when alemtuzumab is administered to a nursing woman. Breast feeding should be discontinued during each course of treatment with alemtuzumab and for 4 months following the last infusion of each treatment course.

Alemtuzumab was detected in the milk and offspring of lactating female transgenic mice administered intravenous alemtuzumab 10 mg/kg/day for 5 consecutive days postpartum. There was evidence for reductions in lymphocytic counts, along with a reduced IgM antibody response in offspring at about 9 weeks postpartum following this treatment; a no-effect dose was not determined. Cognitive, physical, and sexual development of pups exposed to alemtuzumab during lactation were not affected. The relevance to humans of reproductive toxicity findings in transgenic mice is unknown.

Paediatric use

The safety and efficacy of alemtuzumab in MS patients below the age of 18 years of age has not yet been established.

Use in the elderly

Clinical studies of Lemtrada did not include sufficient numbers of patients aged 55 and over to determine whether they respond differently than younger patients.

Genotoxicity

There have been no studies to assess the mutagenic potential of alemtuzumab.

Carcinogenicity

There have been no studies to assess the carcinogenic potential of alemtuzumab.

Effect on laboratory tests

It is not known whether alemtuzumab interferes with any routine clinical laboratory tests.

INTERACTIONS WITH OTHER MEDICINES

No formal drug interaction studies have been conducted with alemtuzumab using the recommended dose in patients with MS. In a controlled clinical trial in MS, patients recently treated with beta interferon and glatiramer acetate were required to discontinue treatment 28-days before initiating treatment with Lemtrada.

Lemtrada is administered parenterally, therefore interactions with food and drink are unlikely.

In the absence of compatibility studies, alemtuzumab should not be mixed with other medicinal products. Do not add or simultaneously infuse other medicinal products through the same intravenous line.

ADVERSE EFFECTS

Summary of the safety profile

A total of 1485 patients with relapsing remitting MS (RRMS) treated with Lemtrada (12 mg or 24 mg) constituted the safety population in a pooled analysis of controlled clinical studies resulting in 4262 patient-years of safety follow-up and a median follow-up of 33 months.

The most important adverse reactions are autoimmunity (ITP, thyroid disorders, nephropathies, cytopenias), IARs, and infections (See PRECAUTIONS).

The most common adverse reactions with alemtuzumab (in ≥20% of patients) are rash, headache, and pyrexia.

Tabulated list of adverse reactions

The table below is based on pooled safety data from Study 1 and Study 2 which were 2-year active-controlled trials in MS patients treated with alemtuzumab 12 mg/day on 5 consecutive days at study entry and on 3 consecutive days at Study Month 12, or subcutaneous (SC) IFNB-1a 44 µg 3 times per week. Adverse reactions occurring in ≥5% of patients are listed by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT).

Table 2 - Adverse Events in Study 1 and Study 2 Reported for Alemtuzumab 12 mg Treated Patients (occurring in ≥5% of patients)

System Organ Class **Preferred Term**	**Alemtuzumab 12 mg (N=811)** **%**	**IFNB-1a 44 µg (N=389)** **%**
Nervous system disorders		
Headache	51.8	22.6
Multiple sclerosis relapse	27.5	44.2
Paraesthesia	10.1	8.5
Dizziness	10.0	4.9
Dysgeusia	8.4	6.9
Hypoaesthesia	7.8	9.0
Skin and subcutaneous tissue disorders		
Rash	45.3	5.1
Urticaria	15.7	1.8
Pruritus	14.5	2.1
Rash generalised	7.5	1.0
Erythema	5.3	2.3
Infections and infestations		
Nasopharyngitis	24.9	18.8
Urinary tract infection	19.4	8.0
Upper respiratory tract infection	15.8	12.9
Sinusitis	10.9	7.5
Oral herpes	9.2	1.5
Influenza	8.5	5.7
Bronchitis	7.0	3.6
General disorders and administration site conditions		
Pyrexia	28.9	9.3
Fatigue	18.4	12.6
Chills	9.0	3.1
Chest discomfort	7.2	1.8
Pain	7.2	3.3
Influenza like illness	6.2	27.2
Oedema peripheral	5.4	2.3
Musculoskeletal and connective tissue disorders		
Back pain	12.3	8.0
Pain in extremity	12.3	9.0
Arthralgia	12.1	9.0
Muscular weakness	7.2	6.4
Myalgia	6.4	5.1
Muscle spasms	5.9	5.4
Gastrointestinal disorders		

System Organ Class Preferred Term	Alemtuzumab 12 mg (N=811) %	IFNB-1a 44 µg (N=389) %
Nausea	21.1	9.3
Diarrhea	11.6	5.9
Vomiting	10.0	3.3
Dyspepsia	8.0	4.4
Abdominal pain	5.5	3.1
Psychiatric disorders		
Insomnia	15.5	15.2
Depression	7.0	10.0
Anxiety	6.8	6.2
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain	11.0	5.4
Cough	9.1	4.1
Dyspnea	8.5	1.3
Vascular disorders		
Flushing	9.6	4.4
Injury, poisoning and procedural complications		
Contusion	10.9	6.7
Investigations		
CD4 lymphocytes decreased	6.0	1.5
CD8 lymphocytes decreased	6.0	2.3
Cardiac disorders		
Tachycardia	7.8	1.0
Blood and lymphatic system disorders		
Lymphopenia	6.0	3.1

Table 3 - Adverse Events in Study 1 and 2 Observed in ≥5% of Lemtrada 12 mg Treated Patients in CIOMS format

System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)
Blood and lymphatic disorders		Lymphopenia
Cardiac disorders		Tachycardia
Gastrointestinal disorders	Nausea, diarrhoea, vomiting	Dyspepsia, abdominal pain
General disorders and administration site conditions	Pyrexia, Fatigue	Chills, chest discomfort, pain, influenza like illness, oedema peripheral
Infections and infestations	Nasopharyngitis, urinary tract infection, upper respiratory tract infection, sinusitis	Oral herpes, influenza, bronchitis,
Injury, poisoning and procedural complications	Contusion	
Investigations		CD4 lymphocytes decreased,

		CD8 lymphocytes decreased
Musculoskeletal and connective tissue disorders	Back pain, pain in extremity, arthralgia	Muscular weakness, myalgia, muscle spasms
Nervous system disorders	Headache, MS relapse, paraesthesia, dizziness	Dysgeusia, hypoaesthesia
Psychiatric disorders	Insomnia	Depression, anxiety,
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	Cough, dyspnoea
Skin and subcutaneous tissue disorders	Rash, uticaria, pruritus	Rash generalized, erythema
Vascular disorders		Flushing

DOSAGE AND ADMINISTRATION

Dosage

Lemtrada treatment should be initiated and supervised by a neurologist. Specialists and equipment required for the timely diagnosis and management of serious adverse reactions, especially autoimmune conditions and infections, should be available.

Facilities for the management of hypersensitivity and/or anaphylactic reactions should be available.

Patients treated with Lemtrada must be given the Patient Wallet Card and Patient Guide and be informed about the risks of Lemtrada.

The recommended dose of Lemtrada is 12 mg/day administered by IV infusion for 2 treatment courses.

- Initial treatment course: 12 mg/day on 5 consecutive days (60 mg total dose)
- Second treatment course: 12 mg/day on 3 consecutive days (36 mg total dose) administered 12 months after the initial treatment course.

Recommended concomitant medication

Patients should be premedicated with corticosteroids immediately prior to Lemtrada administration on the first 3 days of any treatment course. In clinical trials, patients were pretreated with 1,000 mg methylprednisolone on the first 3 days of each Lemtrada treatment course. Pretreatment with antihistamines and/or antipyretics prior to Lemtrada administration may also be considered.

Oral prophylaxis for herpes infection should be administered to all patients starting on the first day of each treatment course and continuing for a minimum of 1 month following treatment with Lemtrada (see also under ‘Infections’ in PRECAUTIONS). In clinical trials, patients were administered aciclovir 200 mg BID or equivalent.

Patients with renal or hepatic impairment

Lemtrada has not been studied in patients with renal or hepatic impairment.

Elderly population

Clinical studies of Lemtrada did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently that younger patients.

Paediatric population

The safety and efficacy of alemtuzumab in MS patients below the age of 18 years of age has not yet been established.

Administration

Lemtrada should be administered by IV infusion over a period of approximately 4 hours.

Lemtrada vials should be inspected for particulate matter and discoloration prior to administration. Do not use if particulate matter is present or the solution is discolored.

For IV administration, withdraw 1.2 mL of Lemtrada from the vial and inject into 100 mL sterile 0.9% sodium chloride. or 5% dextrose/glucose in water. Gently invert the bag to mix the solution.

Lemtrada contains no antimicrobial preservatives and therefore care should be taken to ensure the sterility of the prepared solution. Product is for single use in one patient only.

To reduce microbiological hazard, use as soon as practical after preparation. Lemtrada diluted product may be stored for not more than 6 hours at room temperature (15° to 25°C) or for not more than 8 hours at refrigerated conditions (2° to 8°C). Protect from light. Partially used, unused, or damaged drug vials should be disposed of in accordance with local requirements.

There are no known incompatibilities between Lemtrada and PVC infusion bags, or PVC or polyethylene-lined PVC administration sets or low protein binding filters.

OVERDOSAGE

Two MS patients accidentally received up to 60 mg Lemtrada (i.e., total dose for initial treatment course) in a single infusion and experienced serious reactions (headache, rash, and either hypotension or sinus tachycardia). Doses of Lemtrada greater than those tested in clinical studies may increase the intensity and/or duration of infusion-associated adverse reactions or its immune effects.

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

For information on the management of overdose, contact the Poison Information Centre on 131126.

PRESENTATION AND STORAGE CONDITIONS

Lemtrada is provided as a sterile, clear, colorless to slightly yellow concentrate solution for infusion with pH 7.0-7.4, containing no antimicrobial preservatives. It is supplied in a clear, single use, 2 mL glass vial, with a latex-free stopper. Each 2 mL Lemtrada vial is filled to deliver 1.2 mL of 10 mg/mL solution (12 mg alemtuzumab).

Lemtrada vials should be stored at 2° to 8°C. Do not freeze or shake. Protect from light.

NAME AND ADDRESS OF THE SPONSOR

sanofi-aventis pty ltd
12-24 Talavera Road
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

Schedule 4 (Prescription Only Medicine)

DATE OF FIRST INCLUSION IN THE ARTG

18 December 2013.

DATE OF MOST RECENT AMENDMENT

03 December 2015.