AUSTRALIAN PRODUCT INFORMATION – LEMTRADA® (ALEMTUZUMAB)

1 NAME OF THE MEDICINE

Alemtuzumab (rch)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1.0 mL of concentrate solution contains 10 mg Alemtuzumab (rch). Refer to Section 6.1 for list of excipients.

3 PHARMACEUTICAL FORM

Alemtuzumab (rch) is a recombinant DNA-derived humanised 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 with pH 7.0 - 7.4. It is intended for dilution prior to infusion.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

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 or more treatment courses.

Initial treatment of two courses

- First 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 first treatment course.

Additional as-needed treatment course(s)

- Additional treatment with a third or fourth course: 12mg/day on 3 consecutive days (36 mg total dose) administrated at least 12 months after the prior treatment course (see Section 5.1 Pharmacodynamic Properties - Clinical Trials).

Follow-up of patients

The therapy is recommended as an initial treatment of 2 courses with safety follow-up of patients from initiation of the first treatment course and until 48 months after the last infusion of the second treatment course. If an additional course is administered, continue safety follow-up until 48 months after the last infusion.

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 1000 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 Section 4.4 Special Warnings and Precautions for Use). 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 than 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 discoloured.

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.

Administer Lemtrada in a setting in which equipment and personnel are available to appropriately manage anaphylaxis, serious infusion reactions, myocardial ischaemia, myocardial infarction, and cerebrovascular adverse reactions.

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°C to 25°C) or for not more than 8 hours at refrigerated conditions (2°C 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.

4.3 CONTRAINDICATIONS

Lemtrada is contraindicated:

- Hypersensitivity or anaphylactic reactions to alemtuzumab, to murine proteins or to any of the excipients.
- Human Immunodeficiency Virus (HIV) infection.
- in patients with severe active infection
- in patients with uncontrolled hypertension
- in patients with a history of arterial dissection of the cervicocephalic arteries
- in patients with a history of stroke
- in patients with a history of angina pectoris or myocardial infarction
- in patients with known coagulopathy or on concomitant anti-coagulant therapy

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 Section 4.5 Interactions with Other Medicines and Other Forms of 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 follow up from treatment initiation until 48-months after the last infusion of the second Lemtrada treatment course. If an additional course is administered, continue safety follow-up until 48 months after the last infusion.

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 which may be serious and life threatening. Reported autoimmune conditions include thyroid disorders, immune thrombocytopenic purpura (ITP), or uncommonly, vasculitis, nephropathies (e.g., anti-glomerular basement membrane disease), autoimmune hepatitis (AIH), acquired haemophilia A, thrombotic thrombocytopenic purpura (TTP), and autoimmune encephalitis. In the post-marketing setting, patients developing multiple autoimmune disorders after Lemtrada treatment have been observed. Patients who develop autoimmunity should be assessed for other autoimmune mediated conditions. Patients and physicians should be made aware of the potential later onset of autoimmune disorders after the 48 months monitoring period.

Acquired haemophilia A

Cases of acquired haemophilia A (anti-factor VIII antibodies) have been reported in both clinical trial and post-marketing setting. Patients typically present with spontaneous subcutaneous haematomas and extensive bruising although haematuria, epistaxis, gastrointestinal or other types of bleeding may occur. A coagulopathy panel including aPTT must be obtained in all patients who present with such symptoms. Patients should be informed about the signs and symptoms of acquired haemophilia A and advised to seek immediate medical attention if any of these symptoms occur.

Immune Thrombocytopenic Purpura

Serious events of ITP have been observed in 12 (1%) of patients treated with alemtuzumab in controlled clinical trials in MS (corresponding to an annualised rate 0.0047 events/patient/year).

In a controlled clinical trial in patients with MS, 1 patient developed ITP that went unrecognised prior to the implementation of monthly blood monitoring requirements and died from intracerebral haemorrhage. An additional 12 serious events of ITP have been observed through up to 12 years follow up (cumulative annualised rate 0.0028 events/patient/year).

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.

Immune-Mediated Colitis

Immune-mediated colitis, which can present as a severe and acute-onset form of colitis, has been reported in patients receiving Lemtrada in the post-marketing setting. Some cases of colitis were serious, requiring hospitalisation. Systemic corticosteroids were required in some of these patients. The time from treatment initiation to onset of symptoms in these cases ranged from a few months to years. Monitor patients for immune-mediated colitis during and after Lemtrada treatment, and evaluate promptly if signs and symptoms that may indicate immune-mediated colitis, such as new or persistent diarrhoea or other gastrointestinal signs and symptoms, occur. It is unknown whether immune-mediated colitis in patients treated with Lemtrada is a monophasic disorder, or whether recurrent flares (as are seen in patients with inflammatory bowel disease) will occur.

Nephropathies

Nephropathies, including anti-glomerular basement membrane (anti-GBM) disease have been observed in 6 (0.4%) patients in clinical trials in MS through a median 6.1 years (maximum 12 years) of follow up 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. Anti-GBM disease may lead to renal failure requiring dialysis and/or transplantation if not treated rapidly and can be life-threatening if left untreated. The patient should be reminded to remain vigilant for symptoms they may experience and to seek immediate medical help if they have any concerns.

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

Endocrine disorders including autoimmune thyroid disorders have been observed in an estimated 36.8% of patients treated with alemtuzumab 12 mg in clinical trials in MS with a median of 6.1 years (maximum 12 years) of follow-up from the first alemtuzumab exposure.

Observed autoimmune thyroid disorders included hyperthyroidism or hypothyroidism. Most events were mild to moderate in severity. Serious endocrine events occurred in 4.4% of patients, with Graves' disease (also known as Basedow's disease), hyperthyroidism, hypothyroidism, autoimmune thyroiditis, and goitre 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 or in case of pregnancy.

Thyroid disease poses special risks in women who are pregnant (see Section 4.6 Fertility, Pregnancy and Lactation – Use in Pregnancy).

Cytopenias

Suspected autoimmune cytopenias such as neutropenia, haemolytic anaemia, 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.

Autoimmune Hepatitis (AIH)

Cases of autoimmune hepatitis (including fatal cases and cases requiring liver transplantation) causing clinically significant liver injury, including acute liver failure requiring transplant, has been reported in patients treated with Lemtrada in the postmarketing setting. If a patient develops clinical signs., including unexplained liver enzyme elevations or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine), promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment with Lemtrada, as appropriate. Liver function tests should be performed before initial treatment and at monthly intervals until at least 48 months after the last infusion. Patients should be informed about the risk of autoimmune hepatitis and related symptoms.

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 clinical trials in MS experienced mild to moderate IARs during and/or up to 24 hours after Lemtrada 12 mg administration. The incidence of IARs was higher in course 1 than in subsequent courses. Through all available follow-up, including patients who received additional treatment courses, the most common IARs included headache, rash, pyrexia, nausea, urticarial, pruritus, insomnia, chills, flushing, fatigue, dyspnoea, dysgeusia, chest discomfort, generalised rash, tachycardia, bradycardia, dyspepsia, dizziness, and pain. Serious reactions occurred in 3% of patients and included cases of headache, pyrexia, urticarial, tachycardia atrial fibrillation, nausea, chest discomfort, and hypotension. In addition, anaphylaxis has been reported rarely. During postmarketing use, serious, sometimes fatal and unpredictable adverse events from various organ systems have been reported. Cases of pulmonary alveolar haemorrhage, myocardial ischaemia, myocardial infarction, stroke (including ischemic and haemorrhagic stroke), cervicocephalic (e.g., vertebral, carotid) arterial dissection, and thrombocytopenia have been reported. Reactions may occur following any of the doses during the treatment course. In the majority of cases, time to onset was within 1-3 days of Lemtrada infusion. Patients should be informed about the signs and symptoms and advised to seek immediate medical attention if any of these symptoms occur.

Haemorrhagic stroke

In patients with available documentation, it was noted that there was increased blood pressure from baseline before the haemorrhage. There were no obvious risk factors in the majority of patients.

Myocardial ischemia and myocardial infarction

It was noted that in some of the patients, blood pressure and /or heart rate was temporarily abnormal during the infusion. There were no obvious risk factors in the majority of patients.

Dissection of the cervicocephalic arteries

Cases of cervicocephalic arterial dissections, including multiple dissections, have been reported both within the first days after the Lemtrada infusion or later on within the first month after the infusion.

Pulmonary alveolar haemorrhage

Reported cases of temporally associated events were not related to anti-GBM disease (Goodpasteur's syndrome).

Thrombocytopenia

Thrombocytopenia occurred within the first days after the Lemtrada infusion (unlike ITP). It was often self- limiting and relatively mild, although severity and outcome was unknown in many cases.

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. Observation for infusion reactions is recommended during and for at least 2 hours after each Lemtrada infusion. Physicians should alert patients that an IAR could occur within 48 hours of infusion. Monitor vital signs before the infusion and periodically during the infusion. Extended observation time should be considered, as appropriate. 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.

Infusion instructions to reduce serious reactions temporally associated with LEMTRADA infusion

- Pre-infusion evaluations:
  - Obtain a baseline ECG and vital signs, including heart rate and blood pressure measurement. Perform laboratory tests (complete blood count with differential, serum transaminases, serum creatinine, test of thyroid function and urinalysis with microscopy).
- During infusion:
  - Perform continuous/frequent (at least every hour) monitoring of heart rate, blood pressure and overall clinical status of the patients
  - In case of a severe adverse event:
    - Interrupt infusion
    - Medically evaluate the patient guided by the adverse event profile of Lemtrada prior to considering restarting therapy.
    - Provide appropriate treatment as needed.
  - Consider permanently discontinuing the Lemtrada infusion if the patient shows clinical symptoms suggesting development of a serious adverse event associated with the infusion (myocardial ischemia, haemorrhagic stroke, cervico-cephalic arterial dissection or pulmonary alveolar haemorrhage).
- Post-infusion:
  - Observation for infusion reactions is recommended for a minimum of 2 hours after Lemtrada infusion. Patients with clinical symptoms suggesting development of a serious adverse event temporarily associated with the infusion (myocardial ischemia, haemorrhagic stroke, cervico-cephalic arterial dissection or pulmonary alveolar haemorrhage) should be closely monitored until complete resolution of the symptoms. The observation time should be extended as appropriate. The patients should be educated on the potential for delayed onset of infusion associated reactions and instructed to report symptoms and seek appropriate medical care.

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.

The cumulative annualised rate of infection was 0.99 through a median of 6.1 years (maximum 12 years) of follow-up from the first Lemtrada exposure, as compared to 1.27 in controlled clinical trials.

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. Unless treated, listeria infection can lead to significant morbidity or mortality. 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 controlled 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.

Cytomegalovirus infections have been reported in Lemtrada-treated patients with concomitant corticosteroid use. Most cases occurred within 2 months of alemtuzumab dosing. In symptomatic patients, clinical assessment should be performed for CMV infection during and for at least two months following each Lemtrada treatment course.

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

Progressive Multifocal Leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised and that usually leads to death or severe disability. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

No case of PML has been reported in clinical studies of alemtuzumab in patients with multiple sclerosis. PML has been reported in the postmarketing setting in patients with other risk factors, specifically prior treatment with MS products associated with PML.

MRI findings may be apparent before clinical signs or symptoms. Cases of PML, diagnosed based on MRI findings and the detection of JCV DNA in the cerebrospinal fluid in the absence of clinical signs or symptoms specific to PML, have been reported in patients treated with other MS medications associated with PML. Many of these patients subsequently became symptomatic with PML. Therefore, monitoring with MRI, including prior to initiation of Lemtrada, for signs that may be consistent with PML may be useful, and any suspicious findings should lead to further investigation to allow for an early diagnosis of PML, if present. Following discontinuation of another MS medication associated with PML, lower PML-related mortality and morbidity have been reported in patients who were initially asymptomatic at diagnosis compared to patients who had characteristic clinical signs and symptoms at diagnosis. It is not known whether these differences are due to early detection and discontinuation of MS treatment or due to differences in disease in these patients.

Pneumonitis

Pneumonitis has been reported in Lemtrada treated patients. Most cases occurred within the first month after treatment with Lemtrada. Patients should be advised to report symptoms of pneumonitis, which may include shortness of breath, cough, wheezing, chest pain or tightness and haemoptysis.

Haemophagocytic lymphohistiocytosis (HLH)

During postmarketing use, HLH (including fatal cases) has been reported in patients treated with Lemtrada. HLH is a life-threatening syndrome of pathologic immune activation characterised by clinical signs and symptoms of extreme systemic inflammation. HLH is characterized by fever, hepatomegaly and cytopenias**.** It is associated with high mortality rates if not recognised early and treated. Symptoms have been reported to occur within a few months to four years following the initiation of treatment. Patients should be informed about symptoms of HLH and time to onset. Patients who develop early manifestations of pathologic immune activation should be evaluated immediately, and a diagnosis of HLH should be considered.

Adult Onset Still's Disease (AOSD)

During postmarketing use, AOSD has been reported in patients treated with Lemtrada. AOSD is a rare inflammatory condition that requires urgent evaluation and treatment. Patients with AOSD may have a combination of the following signs and symptoms: fever, arthritis, rash and leukocytosis in the absence of infections, malignancies and other rheumatic conditions. Consider interruption or discontinuation of treatment with Lemtrada if an alternate etiology for the signs or symptoms cannot be established.

Thrombotic Thrombocytopenic Purpura (TTP)

During postmarketing use, TTP, which can be fatal, has been reported in patients treated with Lemtrada. TTP is a serious condition that requires urgent evaluation and treatment. TTP may be characterized by thrombocytopenia, microangiopathic hemolytic anemia, neurological sequelae, fever and renal impairment. It is associated with high morbidity and mortality rates if not recognized and treated early.

Autoimmune Encephalitis

Cases of autoimmune encephalitis during postmarketing use have been reported in patients treated with Lemtrada. Autoimmune encephalitis is confirmed by the presence of neural autoantibodies as well as a variety of clinical manifestations like subacute onset of memory impairment, altered mental status, psychiatric symptoms, neurological findings and seizures.

Cervicocephalic Arterial Dissection and stroke

In the postmarketing setting, serious and life-threatening stroke (including ischaemic and haemorrhagic stroke) has been reported within one week of Lemtrada administration, with most cases occurring within 3 days of Lemtrada infusion. Cervicocephalic arterial dissections involving multiple arteries (e.g., vertebral, carotid) were reported in some cases.

Educate patients on the symptoms of stroke and cervicocephalic (e.g., carotid, vertebral) arterial dissection. Instruct patients to seek immediate medical attention if symptoms of stroke or cervicocephalic arterial dissection occur.

Acute Acalculous Cholecystitis

Lemtrada may increase the risk of acute acalculous cholecystitis. In controlled clinical studies, 0.2% of Lemtrada-treated MS patients developed acute acalculous cholecystitis, compared to 0% of patients treated with interferon beta 1a. During post-marketing use, additional cases of acute acalculous cholecystitis have been reported in Lemtrada-treated patients. Time to onset of symptoms ranged from less than 24 hours to 2 months after Lemtrada infusion. Typical risk or predisposing factors such as concurrent critical illness were often not reported. Abnormal ultrasound or computed tomography was used to support the diagnosis of acute acalculous cholecystitis in some cases. Most patients were treated conservatively with antibiotics and recovered without surgical intervention, whereas others underwent cholecystectomy.

Symptoms of acute acalculous cholecystitis include abdominal pain, abdominal tenderness, fever, nausea, and vomiting. Leukocytosis and abnormal liver enzymes are also commonly observed. Acute acalculous cholecystitis is a condition that may be associated with high morbidity and mortality rates if not diagnosed early and treated. If acute acalculous cholecystitis is suspected, evaluate and treat promptly.

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 annualised 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.

Clinical trial data to 6 years has not indicated an increased risk of malignancy greater than the general MS population is associated with use of Lemtrada. Regular routine surveillance for malignancies is recommended.

Vaccines

It is recommended that patients have completed local immunisation 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 immunisation 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 and serum transaminases (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.

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.

Use in renal and hepatic impairment

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

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.

Paediatric use

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

Effects on laboratory tests

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

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 foetus. 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 was 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 Section 4.4 Special Warnings and Precautions for Use – 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 foetus 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile in clinical studies

A total of 1,486 patients treated with Lemtrada (12 mg or 24 mg) constituted the safety population in a pooled analysis of MS clinical studies with a median follow-up of 6.1 years (maximum 12 years), resulting in 8,635 patient-years of safety follow-up.

The most important adverse reactions are autoimmunity (ITP, thyroid disorders, nephropathies, cytopenias), IARs, and infections (see Section 4.4 Special Warnings and Precautions for Use).

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

Tabulated list of adverse reactions

The tables below are based on pooled safety data on all alemtuzumab 12mg -treated patients during studies 1 and 2 (Table 1) and all available follow up in clinical trials (Table 2).

Study 1 and Study 2 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. Study 3 (CAMMS223) evaluated the safety and efficacy of Lemtrada in patients with RRMS over the course of 3 years.

Study 4 (CAMMS0309) was an open label uncontrolled extension study to evaluate the long term safety and efficacy (4 additional years) of Lemtrada in patients from Study 1 and 2.

Table 1 and Table 2 lists adverse reactions occurring in ≥ 5% of patients, listed by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT).

Table 1 - 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		

System Organ Class Preferred Term	Alemtuzumab 12 mg (N=811) %	IFNB-1a 44 µg (N=389) %
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		
Nausea	21.1	9.3
Diarrhoea	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
Dyspnoea	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 2 - Adverse Events in Study 1, 2, 3 and 4 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 System Disorders	Lymphopenia, leukopenia	Thrombocytopenia
Cardiac disorders	Tachycardia	
Endocrine disorders	Hyperthyroidism	Hypothyroidism, autoimmune thyroiditis
Gastrointestinal disorders	Nausea	Abdominal pain, vomiting, diarrhoea
General disorders and administration site conditions	Pyrexia, fatigue, chills	Chest discomfort, pain,
Infections and infestations	Urinary tract infection, upper respiratory tract infection	Oral herpes, herpes zoster
Nervous system disorders	Headache	Dizziness
Psychiatric disorders		Insomnia
Renal and urinary disorders		Proteinuria, haematuria

System Organ Class	Very Common (≥ 1/10)	Common (≥ 1/100 to < 1/10)
Respiratory, thoracic and mediastinal disorders		Dyspnoea
Skin and subcutaneous tissue disorders	Rash, urticaria, pruritus, rash generalised,	Erythema
Vascular disorders	Flushing	

Safety profile in long-term follow up

The type of adverse events including seriousness and severity observed in Lemtrada treatment groups through all available follow-up including patients who received additional treatment courses were similar to those in the active-controlled studies.

In patients continuing from controlled clinical studies and who did not receive any additional Lemtrada after the initial 2 treatment courses, the rate (events per person-year) of most adverse reactions was comparable to or reduced in years 3-6 as compared to years 1 and 2. The rate of thyroid adverse reactions was highest in year three and declined thereafter.

Post-Marketing Experience

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): (For additional information see Section 4.4 Special warnings and precautions for use).

Blood and lymphatic system disorders: Haemophagocytic lymphohistiocytosis, cases of severe (including fatal) neutropenia, acquired haemophilia A, thrombotic thrombocytopenic purpura (TTP).

Cardiac disorders: Myocardial infarction and myocardial ischaemia.

Gastrointestinal disorders: Immune-mediated colitis.

Hepatobiliary disorders: Cases of cholecystitis including acalculous cholecystitis and acute acalculous cholecystitis have been reported with Lemtrada. Autoimmune hepatitis, Hepatitis (associated with EBV infection).

Immune system disorder: Sarcoidosis.

Infections and Infestations: Cytomegalovirus infections have been reported in Lemtrada-treated patients with concomitant corticosteroid use, Epstein-Barr virus (EBV) infection

Musculoskeletal and connective tissue disorder**:** Adult Onset Still's Disease (AOSD) (see Section 4.4 Special warnings and precautions for use).

Nervous system disorders: Stroke, including haemorrhagic and ischaemic, and autoimmune encephalitis.

Respiratory, Thoracic and Mediastinal Disorders: Pulmonary alveolar haemorrhage.

Skin disorders: Vitiligo, Alopecia.

Vascular disorders: cervicocephalic arterial dissection (including cases with multiple arterial dissections).

Reporting Suspected Adverse Effects

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

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 Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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.

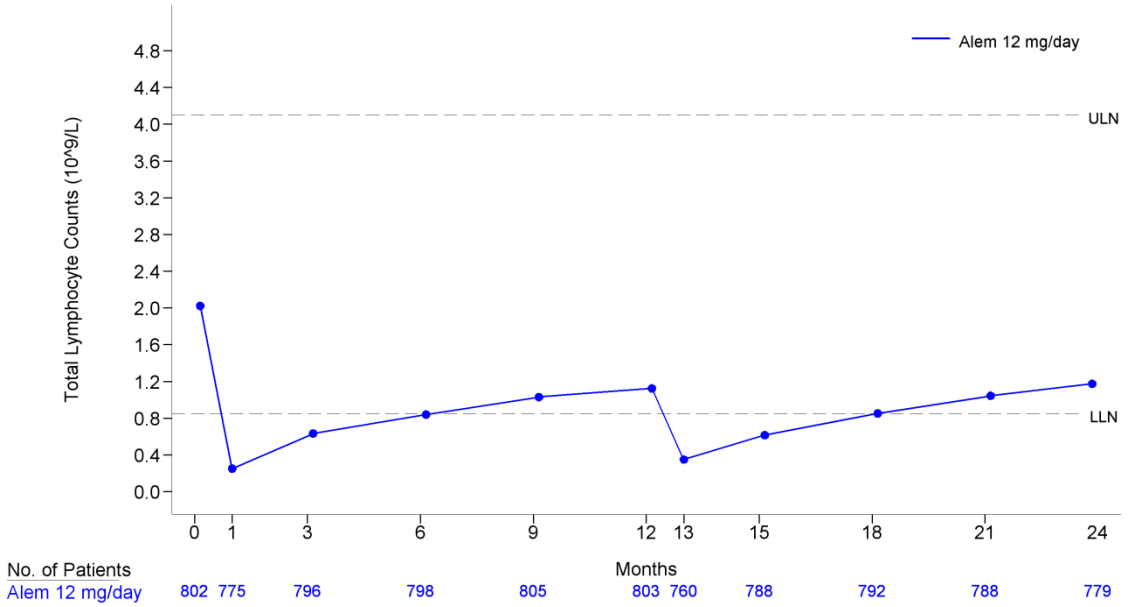
Alemtuzumab depletes circulating T and B lymphocytes after each treatment course with the lowest observed values occurring at the first post-treatment assessment, which was as early as

2 days after the end of the first treatment cycle in a Phase 2 study. Lymphocytes repopulate over time Figure 1. 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 1 - Total Lymphocyte Depletion and Repopulation Following Treatment with Alemtuzumab at Month 0 and Month 12 in CAMMS323 and CAMMS324



Clinical trials

The safety and efficacy of Lemtrada were evaluated in 3 randomised, rater-blinded, active-comparator clinical trials and one uncontrolled, rater-blinded extension study 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 confirmed disability worsening (CDW) [CDW is the currently preferred terminology during the study the endpoint was called sustained accumulation of disability or 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 3.

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 confirmed disability improvement (CDI) [CDI is the currently preferred terminology, during the study, CDI was referred to as “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 3.

Results are shown in Table 3 and Figure 2.

Table 3 - 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)

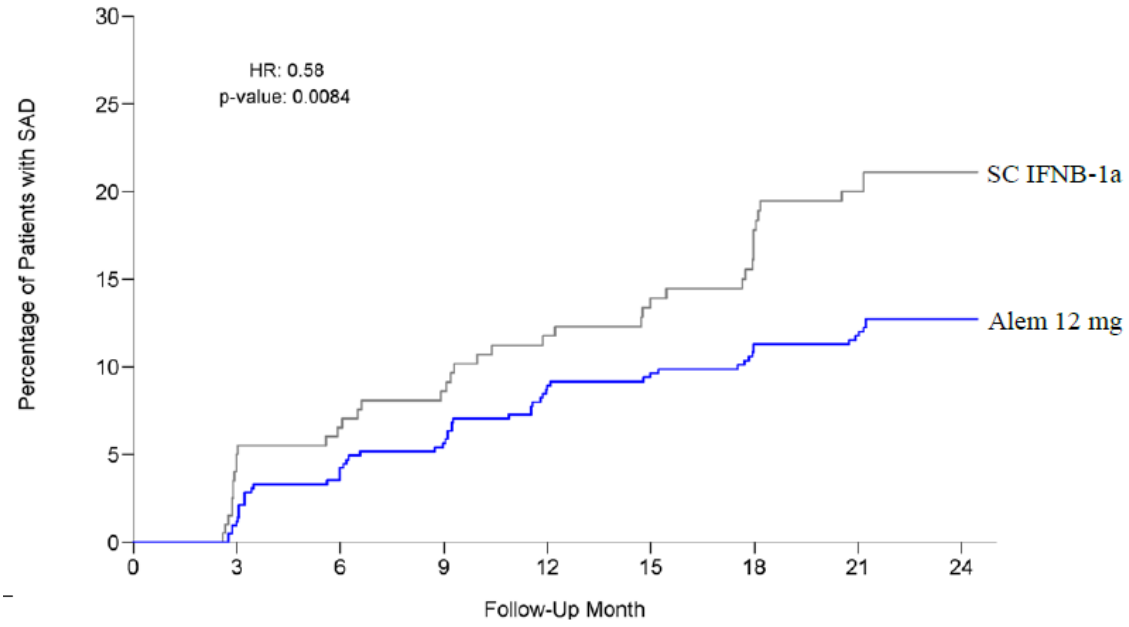
	Study 1 (CAMMS323)		Study 2 (CAMMS324)	
Endpoint	**Lemtrada (N=376)**	**SC IFNB-1a (N=187)**	**Lemtrada (N=426)**	**SC IFNB-1a (N=202)**
ARR (95% CI)	0.18 (0.13, 0.23)	0.39 (0.29, 0.53)	0.26 (0.21, 0.33)	0.52 (0.41, 0.66)
Rate ratio (95% CI)	0.45 (0.32, 0.63)		0.51 (0.39, 0.65)	
Risk reduction	54.88		49.40	
p-value	<0.0001		<0.0001	
Disability (CDW1 ≥ 6 months; co-primary endpoint)				
Estimate of patients with 6-month CDW (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[2] 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	
Confirmed disability improvement (CDI)				
Estimate of patients with 6-month CDI (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	

Endpoint	Study 1 (CAMMS323)		Study 2 (CAMMS324)	
	Lemtrada (N=376)	SC IFNB-1a (N=187)	Lemtrada (N=426)	SC IFNB-1a (N=202)

1-CDW was defined as an increase at least 1 point on the expanded disability status scale (EDSS) from the baselines EDSS score ≥ 1.0 (1.5 point increase for patients with baseline EDSS of 0) that was sustained from 6 months.

2-Mean change is presented for EDSS using mixed model for repeated measures. Median change is presented for MRI-T2 lesion volume and Brain Parenchymal Fraction.

Figure 2 - Time to 6-month Confirmed Disability Worsening in Study 2



Study 3 (Phase 2 study CAMMS223) evaluated the safety and efficacy of Lemtrada in patients with RRMS over the course of 3 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 CDW versus IFNB-1a.

Long term efficacy data

Study 4 provides efficacy data for up to 6 years from entry into studies 1 and 2. Of patients treated with Lemtrada 12 mg in studies 1 and 2, 91.8% entered Study 4.

In Study 4, 40% of the patients initially treated with Lemtrada 12 mg/day in Study 1 or 2 received additional courses upon documented evidence of MS disease activity (relapse and/or MRI) and the treating physician's decision to retreat. Relapse was defined as:

a) Have, within the previous year, experienced ≥1 protocol-defined relapse. Relapse was defined as new neurological symptoms or worsening of previous neurological symptoms with an objective change on neurological examination. Symptoms must be attributable to MS, last at least 48 hours, be present at normal body temperature, and be preceded by at least 1 month (30 days) of clinical stability.

b) Have, within the previous year or since their last on-study MRI, accumulated ≥2 unique lesions on brain or spinal cord MRIs comprised of any combination of the following:

- Gadolinium-enhancing lesion(s) (usually ≥ 3 mm in any dimension)
- New or enlarging MRI T2 lesions (usually ≥ 3 mm in any dimension, or ≥ 3 mm increase)

Additional course(s) of Lemtrada were administered at 12 mg/day for 3 consecutive days (36 mg total dose) at least 12 months after the prior treatment course.

377 patients received only 2 treatment courses of Lemtrada in prior studies and no further Lemtrada or other disease-modifying treatment in this extension study, having not met the criteria for relapse. In this 2-course subgroup 63/377 (16.7%) patients experienced CDW either in the 2 years of the initial study or in the 4 subsequent years compared with 110/321 (34.3%) patients who required additional treatment courses.

For patients who were retreated, the mean (SD) time to meeting retreatment criteria was 2.4(1.34) years prior to course 3 and 2.1(1.13) years prior to course 4.

Table 4 represents the key clinical and MRI outcome in Study 4 (year 0-6) for Lemtrada treated patients in Studies 1 and 2.

Table 4 - Overview of efficacy results after 1st and 2nd additional treatment (Course 3 and Course 4); retreatment subgroup; CAMMS323 and CAMMS324 pooled population

	1st additional treatment (Course 3) CAMMS323 and CAMMS324 pooled Retreatment subgroup (N=321)					2nd additional treatment (Course 4) CAMMS323 and CAMMS324 pooled Retreatment subgroup (N=120)				
		Year after 1st additional treatment					Year after 2nd additional treatment			
	Year prior to 1st additional treatment	1	2	3	4	Year prior to 2nd additional treatment	1	2	3	4
Relapse-related Endpoints										
Relapse rate										
n	321	321	275	155	8	120	119	87	43	16
Annualised relapse rate	0.79	0.18	0.29	0.30	0.13	0.83	0.25	0.39	0.18	0.50
95% CI	(0.73,0.87)	(0.14,0.24)	(0.23,0.38)	(0.21, 0.41)	(0.07, 0.26)	(0.73,0.95)	(0.17, 0.36)	(0.27, 0.57)	(0.08, 0.42)	(0.21, 1.19)
Disability-related endpoints										
Observed EDSS Scores										
n	307	269	168	83	39	114	90	40	16	2
Mean (SD)	2.89(1.514)	2.70(1.627)	2.65(1.623)	2.70(1.702)	2.50(1.740)	3.39(1.533)	2.97 (1.694)	3.20(1.825)	3.03(2.093)	5.00(3.536)
Imaging-Related Endpoints										
Patients without new and enlarging T2 lesions										
Number of patients (%)	155(49.2)	193(64.1)	130 (66.0)	68 (60.2)	42 (70.0)	59(50.4)	68 (64.2)	34 (63.0)	21 (72.4)	7 (77.8)
Patients without new Gadolinium enhancing lesions										
Number of patients (%)	213(67.8)	266(88.1)	160 (81.2)	95 (84.1)	53 (88.3)	78(66.7)	86 (81.1)	43 (79.6)	26 (89.7)	8. (88.9)
Brain atrophy										
n	314	298	196	116	63	116	104	55	31	9
Median BPF	0.811	0.809	0.807	0.810	0.808	0.809	0.805	0.800	0.806	0.807

EDSS = Expanded Disability Status Scale; SD = standard deviation

Additional as needed treatment

Relapse rate and MRI activity and mean EDSS score all improved in the year both following a third or fourth Lemtrada treatment course when compared with outcomes in the preceding year (Table 4).

These data demonstrate that patients with MS disease activity following a prior Lemtrada treatment course can achieve clinical improvement on clinical and MRI measures (reduced ARR, decreased lesions and stabilisation of disability) after additional Lemtrada treatment courses.

The benefits and risks of 5 or more treatment courses have not been fully established, but results suggest that the safety profile does not change with additional courses. If additional treatment courses are to be given they must be administered at least 12 months after the prior course.

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 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 90% 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. Through 2 treatment courses 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. High titre anti-alemtuzumab antibodies observed in some patients were associated with incomplete lymphocyte depletion following a third or fourth treatment course but there was no clear impact of anti-alemtuzumab antibodies on the clinical efficacy or safety profile of Lemtrada.

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.

5.2 PHARMACOKINETIC PROPERTIES

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.

5.3 PRECLINICAL SAFETY DATA

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

8.0 mg sodium chloride, 1.15 mg dibasic sodium phosphate heptahydrate, 0.2 mg potassium chloride, 0.2 mg monobasic potassium phosphate, 0.1 mg polysorbate 80, 0.0187 mg disodium edetate, 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

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

6.5 NATURE AND CONTENTS OF CONTAINER

Lemtrada is provided as a sterile, clear, colourless 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).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

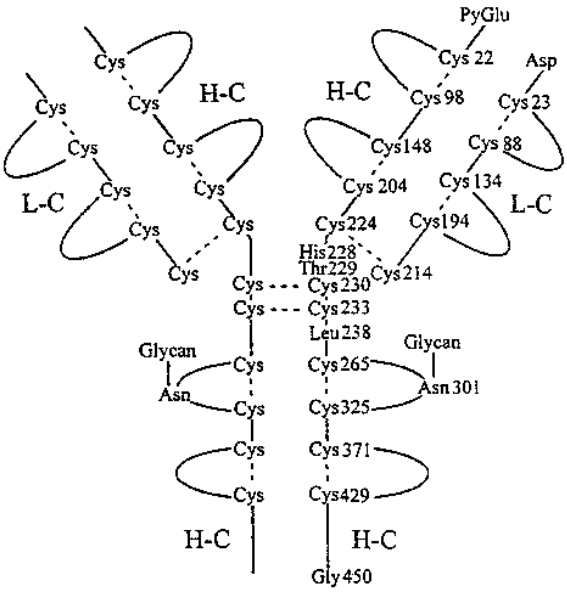
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

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 3 - Structural Formula



CAS number

Not Applicable.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8 SPONSOR

sanofi-aventis australia pty ltd
International Tower 3, Level 23
300 Barangaroo Avenue
Sydney NSW 2000
Freecall: 1800 818 806
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

18 December 2013

10 DATE OF REVISION

28 April 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Sponsor address updated