For the use only of a Registered Medical Practitioner or Hospital or a Laboratory
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Alemtuzumab **12mg/1.2 ml**

Concentrate for solution for infusion

Lemtrada®

DESCRIPTION

Proprietary Name: Lemtrada®
Generic or Official Name: Alemtuzumab

Structural formula: Alemtuzumab 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.

Alemtuzumab is a recombinant DNA-derived humanized monoclonal antibody directed against the 21-28 kD cell surface glycoprotein, CD52. Alemtuzumab is an IgG1 kappa antibody with human variable framework and constant regions, and complementarity-determining regions from a murine (rat) monoclonal antibody. The antibody has an approximate molecular weight of 150 kD. Alemtuzumab is produced in mammalian cell (Chinese hamster ovary) suspension culture in a nutrient medium Alemtuzumab is a sterile, clear, colorless to slightly yellow, concentrate solution (pH 7.0 7.4) for infusion

THERAPEUTIC OR PHARMACOLOGICAL CLASS

Monoclonal antibody
ATC code: L04AA34

PHARMACEUTICAL FORM(S)

Concentrate for solution for infusion. Each 2 mL LEMTRADA vial is filled to deliver 1.2 mL of 10mg/mL solution (12 mg alemtuzumab)

COMPOSITION

Active ingredient: Each single-use LEMTRADA vial contains 12 mg alemtuzumab in 1.2 mL (10 mg/mL).

Excipients: Each 1.0 mL of concentrate solution contains 10 mg alemtuzumab, 8.0 mg sodium chloride, 1.15 mg dibasic sodium phosphate, 0.2 mg potassium chloride, 0.2 mg potassium dihydrogen phosphate, 0.1 mg polysorbate 80, 0.0187 mg disodium edetate dihydrate, and water for injection.

NATURE AND CONTENTS OF CONTAINER

Alemtuzumab 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 filled in a clear, single use, 2 mL glass vial, with a latex-free stopper

INDICATIONS

LEMTRADA is indicated for the treatment of patients with an aggressive form of Relapsing Remitting Multiple Sclerosis (RRMS) in whom there has been a failure of one first line disease modifying therapy

DOSAGE AND ADMINISTRATION

GENERAL

The recommended dose of LEMTRADA is 12 mg/day administered by IV infusion for 2 or more treatment courses. Initial treatment of 2 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 courses:

- 12 mg/day on 3 consecutive days (36 mg total dose) administered at least 12 months after the prior treatment course

LEMTRADA should be administered by IV infusion over a period of approximately 4 hours. 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. Each vial is intended for single use only.

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

Recommended Concomitant Medications

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. In clinical trials, patients were administered acyclovir 200 mg BID or equivalent

Useful Laboratory Tests for Monitoring Patients

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

- CBC 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)

SPECIAL POPULATIONS

Pediatric patients
The safety and efficacy of LEMTRADA in pediatric MS patients below the age of 18 years of age have not been established

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

Hepatic impairment
LEMTRADA has not been studied in patients with hepatic impairment.

Renal impairment
LEMTRADA has not been studied in patients with renal impairment

ADMINISTRATION

Route of administration: Intravenous (IV) infusion.

CONTRAINDICATIONS

LEMTRADA is contraindicated:

- in patients with known Type 1 hypersensitivity or anaphylactic reactions to the active substance or any of the excipients
- in patients who are infected with Human Immunodeficiency Virus (HIV)
- 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

WARNINGS AND PRECAUTIONS FOR USE

Before treatment, patients must receive educational information and 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, rarely, nephropathies (e.g., anti-glomerular basement membrane disease), autoimmune hepatitis (AIH), acquired hemophilia A, and thrombotic thrombocytopenic purpura (TTP). 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 hemophilia A
Cases of acquired hemophilia A (anti-factor VIII antibodies) have been reported in both clinical trial and post-marketing setting. Patients typically present with spontaneous subcutaneous hematomas and extensive bruising although hematuria, 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 hemophilia 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%) patients treated with LEMTRADA in controlled clinical trials in MS (corresponding to an annualized rate 0.0047 events/patient/year).

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. An additional

12 serious events of ITP have been observed through a median of 6.1 years (maximum 12 years) of follow-up (cumulative annualized rate 0.0028 events/patient/year).

ITP onset has generally occurred between 14 and 36 months after first LEMTRADA exposure.

Complete blood counts (CBC) with differential should be obtained prior to initiation of treatment and at monthly intervals thereafter until 48 months after the last infusion. If ITP is suspected a CBC 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 LEMTRADA following the occurrence of ITP is unknown.

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 of 6.1 years (maximum 12 years) of follow-up and generally occurred within 39 months following last administration of LEMTRADA. 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, hematuria, and/or proteinuria. While not observed in clinical trials, alveolar hemorrhage manifested as hemoptysis 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 hematuria, 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. The potential risk associated with retreatment with LEMTRADA following the occurrence of nephropathies is unknown.

Thyroid Disorders
Thyroid endocrine disorders including autoimmune thyroid disorders have been observed in 36.8% of patients treated with LEMTRADA 12 mg in clinical trials in MS with a median of 6.1 years (maximum 12 years) of follow-up from the first LEMTRADA 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 Basedow's disease (also known as Graves' 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. In clinical trials, patients who developed thyroid adverse events were permitted to receive re-treatment with LEMTRADA. Approximately 5 %of patients from the total study population developed a thyroid adverse event during the year following the initial treatment course of alemtuzumab and were re-treated. The majority of those patients did not experience a worsening in severity of thyroid disorders. Thyroid function tests (TFTs), 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 Pregnancy).

Cytopenias
Suspected autoimmune cytopenias such as neutropenia, hemolytic anemia, and pancytopenia have been infrequently reported in patients in clinical trials in MS. CBC 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 (IARs)
In clinical trials, infusion associated reactions (IARs) were defined as any adverse event occurring during or within 24 hours of LEMTRADA infusion. The majority of these may be due to cytokine release during 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, urticaria, 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, urticaria, tachycardia, atrial fibrillation, nausea, chest discomfort, and hypotension. Clinical manifestations of anaphylaxis may appear similar to clinical manifestations of infusion associated reactions, but would tend to be more severe or potentially life-threatening. Reactions attributed to anaphylaxis have been reported rarely in contrast to infusion associated reactions. It is recommended that patients be premedicated to ameliorate the effects of infusion reactions (see section DOSAGE AND ADMINISTRATION).

Most patients in controlled clinical trials received antihistamines and/or antipyretics before at least one LEMTRADA infusion. IARs may occur in patients despite pretreatment. Observation for infusion reactions is recommended during and for at least 2 hours after LEMTRADA infusion. Extended observation time (hospitalization) should be considered, as appropriate. If severe infusion reactions occur, the intravenous infusion should be discontinued immediately. Resources for the management of anaphylaxis or serious reactions (see below) should be available.

Other serious reactions temporally associated with LEMTRADA infusion
During post-marketing use, rare, serious, sometimes fatal and unpredictable adverse events from various organ systems have been reported. In the majority of cases time to onset was within 1-3 days of the LEMTRADA infusion. Reactions have occurred following any of the doses and also after course number 2. Patients should be informed about the signs and symptoms and on the time to onset of the events. Patients should be advised to seek immediate medical attention if any of these symptoms occur and be informed on the potential for delayed onset.

Hemorrhagic stroke
Several of the patient reported were below 50 years of age and had no history of hypertension, bleeding disorders or concomitant anticoagulants or platelet inhibitors. In some patients there was increased blood pressure from baseline before the hemorrhage.

Myocardial ischemia and myocardial infarction
Several of the patients reported were below 40 years of age and had no risk factors for ischemic heart disease. It was noted that in some of the patients, blood pressure and /or heart rate was temporarily abnormal during the infusion.

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 hemorrhage

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

Thrombocytopenia
Thrombocytopenia occurred within the first days after the 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. Resources 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 urine analysis with microscopy).
- During infusion:
  - Perform continuous/frequent (at least every hour) monitoring of heart rate, blood pressure and overall clinical status of the patients
    - Discontinue the infusion
      - In case of a severe adverse event
      - If the patient shows clinical symptoms suggesting development of a serious adverse event associated with the infusion (myocardial ischemia, hemorrhagic stroke, cervico-cephalic arterial dissection or pulmonary alveolar hemorrhage
- 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 temporally associated with the infusion (myocardial ischemia, hemorrhagic stroke, cervico-cephalic arterial dissection or pulmonary alveolar hemorrhage) should be closely monitored until complete resolution of the symptoms. The observation time should be extended (hospitalisation) 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.
  - Platelet count should be obtained immediately after infusion on Days 3 and 5 of the first infusion course, as well as immediately after infusion on Day 3 of any subsequent course. Clinically significant thrombocytopenia needs to be followed until resolution. Referral to a haematologist for management should be considered.

Hemophagocytic 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 characterized 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 recognized and treated early. 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.

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.

Infections
Infections occurred in 71% of patients treated with LEMTRADA 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 LEMTRADA-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 LEMTRADA as compared to 1.0% of patients treated with IFNB-1a in controlled clinical trials in MS. Serious infections in the LEMTRADA group included: appendicitis, gastroenteritis, pneumonia, herpes zoster, and tooth infection. Infections were generally of typical duration and resolved following conventional medical treatment.

The cumulative annualized rate of infections 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.

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.

Serious varicella zoster virus infections, including primary varicella and varicella zoster re activation, have occurred more often in patients treated with LEMTRADA 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 LEMTRADA 12 mg (2%). It is recommended that HPV screening be completed annually for female patients.

Tuberculosis has been reported for patients treated with LEMTRADA and IFNB-1a in controlled clinical trials. Active and latent tuberculosis have been reported in 0.3% of the patients treated with LEMTRADA, most often in endemic regions. Tuberculosis screening should be done according to local guidelines prior to initiation of LEMTRADA.

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

Listeria meningitis has been reported in LEMTRADA -treated patients. The duration of increased risk for listeria meningitis is unclear, although cases of listeria meningitis generally occurred within 1 month of alemtuzumab dosing. 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.

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 the treatment of MS concomitantly with antineoplastic or immunosuppressive therapies. Concomitant use of LEMTRADA with any of these therapies could increase the risk of immunosuppression.

No data are available on the association of LEMTRADA 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

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 hemoptysis.

Stroke and Cervicocephalic Arterial Dissection
Stroke:
In the postmarketing setting, serious and life-threatening stroke (including ischemic and hemorrhagic stroke) has been reported with some cases occurring as early as within 3 days of LEMTRADA administration.

Cervicocephalic Arterial Dissection:
In the postmarketing setting, cases of cervicocephalic (e.g., vertebral, carotid) arterial dissection have been reported within 3 days of LEMTRADA administration.

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 postmarketing 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. 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. 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

Contraception
Placental transfer and potential pharmacologic activity of LEMTRADA were observed in mice during gestation and following delivery. Women of childbearing potential should use effective contraceptive measures during treatment and for 4 months following a course of LEMTRADA treatment.

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 LEMTRADA 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.

INTERACTIONS

Drug/Drug
No formal drug interaction studies have been conducted with LEMTRADA 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.

Drug/Food
LEMTRADA is administered parenterally, therefore interactions with food and drink are unlikely.

PREGNANCY

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 fetus.

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 alemtuzumab can cause fetal harm when administered to pregnant women or whether it can affect reproductive capacity.

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 Warnings and Precautions for Use) poses special risks in women who are pregnant. Without treatment of hypothyroidism during pregnancy, there is an increased risk for miscarriage and fetal 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.

LACTATION

LEMTRADA was detected in the milk and offspring of lactating female mice administered 10 mg/kg LEMTRADA for 5 consecutive days postpartum.

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

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS

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

ADVERSE REACTIONS
The following CIOMS frequency rating is used, when applicable:
Very common ≥ 10%; Common ≥ 1 and < 10%; Uncommon ≥ 0.1 and < 1%;
Rare ≥ 0.01 and < 0.1%; Very rare < 0.01%; Not known (cannot be estimated from available data).

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. Study 1 and Study 2 were 2-year active-controlled trials in RRMS patients treated with LEMTRADA 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 (CAMMS03409) was an uncontrolled extension study to evaluate the long term safety and efficacy (4 additional years) of LEMTRADA in patients from Studies 1, 2, or 3. **As the number of courses increases, data from fewer patients and shorter-term follow-up are available.** Table 1 lists adverse reactions occurring in ≥5% of LEMTRADA-treated patients (12 mg/day) through complete follow-up by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT).

Table 1 - Adverse Reactions in Study 1, 2, 3, and 4 Observed in ≥ 5% of LEMTRADA 12 mg Treated Patients

System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)
Blood and lymphatic 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, hematuria
Respiratory, thoracic and mediastinal disorders		Dyspnoea

Skin and subcutaneous tissue disorders	Rash, urticaria, pruritus, rash generalized	Erythema
Vascular disorders	Flushing	

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.

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 LEMTRADA binding in vitro. Patients who developed anti-alemtuzumab antibodies did so by 15 months of initial exposure. Through 2 treatment courses, there was no apparent 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 titer 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 antibodies 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.

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.

Post Marketing Experience with LEMTRADA
The following adverse reactions were identified during post-approval use of alemtuzumab for the treatment of relapsing forms of multiple sclerosis (MS)

Nervous System Disorders: Stroke, including hemorrhagic and ischemic stroke, and cervicocephalic arterial dissection (see WARNINGS & PRECAUTIONS FOR USE)

Gastrointestinal System Disorders: Cases of cholecystitis including acalculous cholecystitis and acute acalculous cholecystitis have been reported with LEMTRADA (see WARNINGS & PRECAUTIONS FOR USE)

Infections and Infestations: Cytomegalovirus infections have been reported in LEMTRADA- treated patients with concomitant corticosteroid use, Epstein-Barr virus (EBV) infection (see WARNINGS & PRECAUTIONS FOR USE)

Respiratory, Thoracic and Mediastinal Disorders: Pulmonary alveolar hemorrhage (see WARNINGS & PRECAUTIONS FOR USE).

Blood and lymphatic system disorders: Cases of severe (including fatal) neutropenia, acquired hemophilia A, thrombotic thrombocytopenic purpura (TTP) (see WARNINGS & PRECAUTIONS FOR USE).

Cardiac disorders: Myocardial ischemia and Myocardial infarction (see WARNINGS & PRECAUTIONS FOR USE).

Hepatobiliary Disorders: Autoimmune hepatitis, Hepatitis (associated with EBV infection) (see WARNINGS & PRECAUTIONS FOR USE).

Immune System Disorders: Hemophagocytic lymphohistiocytosis (see WARNINGS & PRECAUTIONS FOR USE), Sarcoidosis

Post Marketing Experience with Campath /MabCampath[63]
Alemtuzumab (also known commercially as Campath and MabCampath) was first approved in 2001 for use in B-CLL. The following adverse reactions were identified during post-approval use of alemtuzumab for the treatment of 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 (>12 mg/day).

Autoimmune Disease
Autoimmune events reported in alemtuzumab-treated patients include neutropenia, hemolytic anemia (including a fatal case), acquired hemophilia, anti-GBM disease, and thyroid disease. Serious and sometimes fatal autoimmune phenomena including autoimmune hemolytic anemia, autoimmune thrombocytopenia, aplastic anemia, 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 in postmarketing experience.

OVERDOSE

SIGNS AND SYMPTOMS
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.

MANAGEMENT

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

INTERFERENCES WITH LABORATORY AND DIAGNOSTIC TEST

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

ABUSE AND DEPENDENCE

There have been no reports of patient abuse of, or dependence on, LEMTRADA.

PHARMACODYNAMICS

MODE OF ACTION/PHARMACODYNAMIC CHARACTERISTICS

Mechanism of action
LEMTRADA 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. LEMTRADA acts through antibody-dependent cellular cytolysis and complement-mediated lysis following cell surface binding to T and B lymphocytes.

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

Pharmacodynamics
LEMTRADA depletes circulating T and B lymphocytes after each treatment course with the lowest observed values occurring 1 month after a course of treatment. Lymphocytes repopulate over time with B cell recovery usually completed within 6 months. T lymphocyte counts rise more slowly towards normal, but generally do not 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 LEMTRADA.

Fertility in Males
Data in a small number (N = 13) of male patients in two clinical trials suggest that alemtuzumab treatment does not have an adverse impact on sperm quality, quantity, or motility

CLINICAL EFFICACY/CLINICAL STUDIES

The safety and efficacy of LEMTRADA were evaluated in 3 randomized, rater-blinded, active-comparator clinical trials and one uncontrolled, rater-blinded extension study in patients with MS.

Studies 1 and 2 (CAMMS32400507 and CAMMS323) enrolled patients with 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 randomized 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 IFNB-1a 44 μg SC injection administered 3 times per week. Study 1 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 annualized relapse rate (ARR) over 2 years and the time to onset of confirmed disability worsening (CDW), 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 score of 0) that was sustained for 6 months.

Study 1 (CAMMS32400507) 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 12mg group, 29% had received ≥2 prior MS therapies

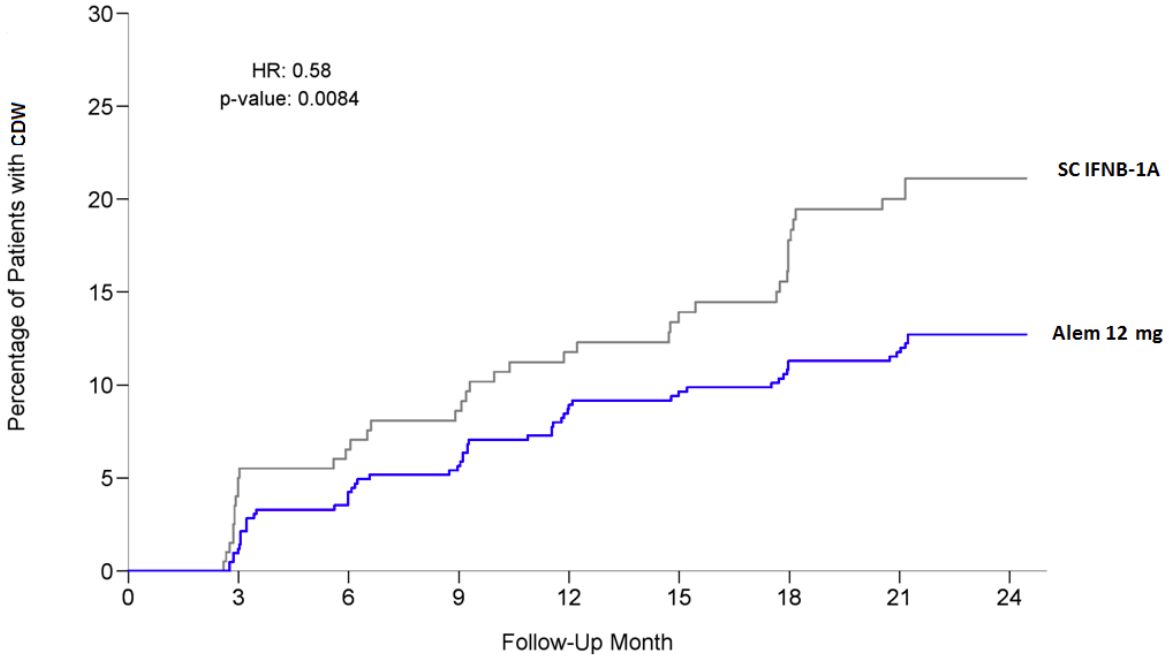
The ARR was significantly reduced by 49% in patients in the LEMTRADA 12 mg group as compared to SC IFNB-1a over 2 years. In addition, treatment with LEMTRADA significantly reduced by 42% the risk of 6-month CDW versus SC IFNB-1a over 2 years. Key secondary endpoints included the change in EDSS score from baseline and MRI parameters. The mean EDSS score in patients treated with LEMTRADA was significantly reduced over 2 years, indicating an improvement in disability score, while the mean EDSS score for patients treated with SC IFNB-1a was significantly increased from baseline.
Compared with IFNB-1a-treated patients, LEMTRADA -treated patients were 2.6 times more likely to achieve a confirmed disability improvement. Treatment effects on clinical endpoints were supported by significant effects on MRI measures of inflammation and disease progression, including brain volume.

Results are shown in Table 2 and Figure 1.
Table 2: Key Clinical and MRI Endpoints from Study

Endpoint	**LEMTRADA (N=426)**	**SC IFNB-1a (N=202)**
Clinical Endpoints		
Relapse Rate (co-primary endpoint) ARR (95% CI) Rate ratio (95% CI) p-value	 0.26 (0.21, 0.33) 0.51 (0.39, 0.65) <0.0001	 0.52 (0.41, 0.66)
Disability (CDW ≥6 months; co-primary endpoint) Estimate of patients with 6-month CDW (95% CI) Hazard ratio (95% CI) p-value	 12.71 (9.89, 16.27) 0.58 (0.38, 0.87) 0.0084	 21.13 (15.95, 27.68)
Proportion of patients who are relapse free at Year 2 (%) Estimate (95% CI) p-value	 65.38 (60.65, 69.70) <0.0001	 46.70 (39.53, 53.54)
Change from baseline in EDSS at Year 2 (95% CI) p-value	-0.17 (-0.29, -0.05) <0.0001	0.24 (0.07, 0.41)
Confirmed disability improvement (CDI) Estimate of patients with 6-month CDI (95% CI) Hazard ratio (95% CI) p-value	 28.82 (24.18, 34.13) 2.57 (1.57, 4.20) 0.0002	 12.93 (8.34, 19.77)

MRI Endpoints		
Change in MRI-T2 lesion volume from baseline to Year 2 (%) p-value	-1.27 0.1371	-1.23
Patients with new or enlarging T2 lesions through Year 2 (%) p-value	46.2 <0.0001	67.9
Patients with Gadolinium enhancing lesions through Year 2 (%) p-value	18.5 <0.0001	34.2
Patients with new T1 hypointense lesions through Year 2 (%) p-value	19.9 <0.0001	38.0
Change in Brain Parenchymal Fraction from baseline to Year 2 (%) p-value	-0.615 0.0121	-0.810
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. CDW was defined as an increase of at least 1 point on the expanded disability status scale (EDSS) from a baselines EDSS score ≥ 1.0 (1.5 point increase for patients with baseline EDSS of 0) that was sustained for 6 months		

Figure 1 - Time to 6-month Confirmed Disability Worsening in Study 1



Study 2 (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 CDW; 8% of LEMTRADA treated patients had a sustained increase in EDSS score as compared to 11% of IFNB-1a patients. Treatment effects on clinical endpoints were supported by significant effects on MRI measures of inflammation and disease progression, including brain volume. Results are shown in Table 3

Table 3:- Key Clinical and MRI Endpoints from study 2

Endpoint	**LEMTRADA (N=376)**	**SC IFNB-1a (N=187)**
Clinical Endpoints		
Relapse Rate (co-primary endpoint) ARR (95% CI) Rate ratio (95% CI) p-value	 0.18 (0.13, 0.23) 0.45 (0.32, 0.63) <0.0001	0.39 (0.29, 0.53)
Disability (CDW ≥6 months; co-primary endpoint) Estimate of patients with 6-month CDW (95% CI) Hazard ratio (95% CI) p-value	 8.00 (5.66, 11.24) 0.70 (0.40, 1.23) 0.2173	11.12 (7.32, 16.71)

Proportion of patients who are relapse free at Year 2 (%) Estimate (95% CI) p-value	 77.59 (72.87, 81.60) <0.0001	 58.69 (51.12, 65.50)
Change from baseline in EDSS at Year 2 (95% CI) p-value	 -0.14 (-0.25, -0.02) 0.4188	 -0.14 (-0.29, 0.01)
MRI Endpoints		
Change in MRI-T2 lesion volume from baseline to Year 2 (%) p-value	 -9.3 (-19.6, -0.2) 0.3080	 -6.5 (-20.7, 2.5)
Patients with new or enlarging T2 lesions through Year 2 (%) p-value	 48.5 0.0352	 57.6
Patients with Gadolinium enhancing lesions through Year 2 (%) p-value	 15.4 0.0008	 27.0
Patients with new T1 hypointense lesions through Year 2 (%) p-value	 24.0 0.0545	 31.4
Change in Brain Parenchymal Fraction from baseline to Year 2 (%) p-value	 -0.867 <0.0001	 -1.488
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. CDW was defined as an increase of at least 1 point on the expanded disability status scale (EDSS) from a baselines EDSS score ≥ 1.0 (1.5 point increase for patients with baseline EDSS of 0) that was sustained for 6 months		

Study 3 (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 were treated with LEMTRADA 12 mg/day (N=108) or 24 mg/day (N=108) administered once per day for 5 days at Month 0 and for 3 days at Month 12 or SC IFNB 1a 44 μg (N=107) administered 3 times per week for 3 years.
Forty-six patients received a planned third course of LEMTRADA treatment at 12 mg/day or 24/mg day on 3 days at Month 24.

At 3 years, LEMTRADA 12 mg reduced the risk of 6 month CDW by 76% (hazard ratio 0.24 [95% CI: 0.110, 0.545], p<0.0006) and reduced the ARR by 67% (rate ratio 0.33 [95% CI: 0.196, 0.552], p<0.0001) as compared to SC IFNB-1a.

In the subgroup of RRMS patients with 2 or more relapses in the prior year and at least 1 Gd-enhanced T1 lesion at baseline, the annualised relapse rate was 0.26 (95% CI: 0.20, 0.34) in the Lemtrada treated group (n = 205) and 0.51 (95% CI: 0.40, 0.64) in the IFNB-1a group (n = 102) (p<0.0001). This analysis includes data from Phase 3 studies only (CAMMS324 and CAMMS323) due to differences in the MRI acquisition algorithms between the Phase 2 and Phase 3 studies. These results were obtained from a post hoc analysis and should be interpreted cautiously.

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.

Table 4 presents the key clinical and MRI outcomes in Study 4 for LEMTRADA 12 mg patients from Studies 1 and 2.

Table 4- Key clinical and MRI Endpoints from Data in Study 4 for LEMTRADA 12 mg patients from Studies 1 and 2

	Study 1 patients in Study 4	**Study 2 patients in Study 4**
Clinical endpoints		
Annualized Relapse rate (ARR) Range, individual years 3-6	0.12 – 0.19	0.16 – 0.24
Patients who are relapse free Range, individual years 3-6	83.2% - 88.3%	78.9% - 86.1. %
Disability (Confirmed Disability Worsening [CDW] [1] Patients with 6-month CDW, cumulative years 0-6 (95% CI)	22.3% (18.3%, 27.1%)	29.7% (25.4%, 34.5%)
Change from Baseline in EDSS [2] Range, individual years 3-6	-0.08 – 0.09	-0.02 – 0.18
MRI Endpoints		
Patients with new or enlarging T2 lesions, % Range, individual years 3-6	27.4% -33.2%	29.8% -33.0%

Patients with new gadolinium enhancing lesions, % Range, individual years 3-6	9.4% -13.3%	10.0% - 13.5%
Median annual % change in MRI-T2 lesion volume Range, individual years 3-6	-0.7% – 1.5%	-0.6% – 0.5%
Median annual % change in brain parenchymal fraction Range, individual years 3-6	-0.19% – -0.17%	-0.19% – -0.09%

1. CDW was 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.
2. Estimated using mixed model for repeated measures

The ARR of patients originally treated with LEMTRADA remained low throughout Study (Table 4), with a high percentage of patients relapse-free in each year of follow-up. Most patients never experienced confirmed disability worsening. Mean disability scores were stable or improved in most years. Through 6 years from first LEMTRADA treatment, 32.7% and 42.5% of patients from Studies 1 and 2, respectively, reached CDI.

Patients also continued to show a low risk of forming new T2 lesions or gadolinium enhancing lesions in each year of follow-up. The T2 lesion volume remained lower throughout the follow-up period than prior to initial LEMTRADA treatment (median percent change at Year 6, -8.5 and -0.1 for Study 1 and 2 populations, respectively), with only small changes from year to year. The median annual percent change (reduction) in brain parenchymal fraction was lower during the extension period than in the prior studies. Approximately half (51.2%) of patients initially treated with LEMTRADA 12 mg/day in Study 1 or 2 who enrolled in Study 4 had received only the initial 2 courses of LEMTRADA and no other disease modifying treatment throughout 6 years of follow-up.

These results demonstrate durable efficacy of LEMTRADA on reducing the risk of MS relapse, suppressing the formation of new MS lesions, slowing brain volume loss (atrophy) and disability worsening in the absence of continuous treatment.

Additional as-needed treatment

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. 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. Efficacy results in these patients, by treatment course, are presented in Table 5.

Table 5 - Key Efficacy Endpoints, Before and After an Additional Treatment Course in Study 4 for Patients Who First Received LEMTRADA 12 mg in Studies 1 & 2 (Pooled Population)

	Course 3 **(N=321)**	**Course 4** **(N=120)**

Mean time to meeting retreatment criteria, in years from last prior course (SD)	2.4 (1.34)		2.1 (1.13)	
Clinical endpoints	**Year Prior to Course 3**	**Year After Course 3**	**Year Prior to Course 4**	**Year After Course 4**
Relapse Rate Annualized Relapse rate (ARR) (95% CI)	0.79 (0.73, 0.87)	0.18 (0.14, 0.24)	0.83 (0.73,0.95)	0.25 (0.17, 0.36)
Observed EDSS Scores: Mean (SD)	2.89 (1.514)	2.69 (1.628)	3.39 (1.533)	2.97 (1.694)
MRI Endpoints				
Patients with gadolinium enhancing lesions	32.2%	11.9%	33.3%	18.9%
Patients with new or enlarging T2 lesions	50.8%	35.9%	49.6%	35.8%

Relapse rate, 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 5).

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 stabilization 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.

PHARMACOKINETICS

The pharmacokinetics of LEMTRADA were evaluated in a total of 216 patients with RRMS who received IV infusions of either 12 mg/day or 24 mg/day on 5 consecutive days, followed by 3 consecutive days 12 months following the initial treatment course. 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 Cmax 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 LEMTRADA 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. No effect of age, race, or gender on the pharmacokinetics of LEMTRADA was observed.

NON-CLINICAL SAFETY DATA

CARCINOGENICITY

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

MUTAGENICITY

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

TERATOGENICITY

A reproductive toxicity study in pregnant mice exposed to IV doses of LEMTRADA up to 10 mg/kg/day (AUC 4.1 times the human exposure at the recommended dose of 12 mg/day) for 5 consecutive days during gestation resulted in significant increases in the number of dams with all conceptuses dead or resorbed, along with a concomitant reduction in the number of dams with viable fetuses. There were no external, soft tissue, or skeletal malformations or variations observed at doses up to 10 mg/kg/day.

During pre-natal/postnatal development studies in pregnant huCD52 transgenic mice given LEMTRADA at doses of 3 or 10 mg/kg/day IV (AUC 1 to 4 times the human exposure at the recommended dose of 12 mg/day), there were no statistically significant or biologically important differences in the values for learning, motor activity, or on the mating and fertility parameters evaluated in the F1 generation male and female mice. Exposure to alemtuzumab during the gestation and lactation periods resulted in altered lymphocyte numbers and subpopulations in F1 male and female mice, as well as reduced IgM and/or IgG responses in F1 pups but a majority of the pups did mount antibody responses to antigen challenge. The toxicologic significance of these findings and how they relate to immune system development in humans is uncertain.

IMPAIRMENT OF FERTILITY

Treatment with LEMTRADA IV at doses up to 10 mg/kg/day, administered for 5 consecutive days (AUC of 11.8 times the human exposure at the recommended daily dose) had no effect on fertility and reproductive performance in male mice.

In female mice dosed with LEMTRADA up to 10 mg/kg/day IV (AUC of 7.9 times the human exposure at the recommended daily dose) for 5 consecutive days prior to cohabitation with wild-type male mice, the average number of corpora lutea and implantation sites per mouse were significantly reduced as compared to vehicle treated animals. Reduced gestational weight gain relative to the vehicle controls was observed in pregnant mice dosed with 10 mg/kg/day. No other mating and fertility parameters were affected by doses of LEMTRADA as high as 10 mg/kg/day.

LACTATION STUDIES

Concentrations of alemtuzumab in the milk of F0 generation mice dosed for 5 consecutive days at 10 mg/kg/day were approximately 8990 ng/mL on postpartum Day 13. Serum concentrations in F0 and F1 generation mice dosed for 5 consecutive days at 10 mg/kg/day were approximately 44 100 ng/mL and 66 500 ng/mL, respectively on postpartum Day 13. Therefore, serum levels of alemtuzumab were similar in lactating mice and offspring on postpartum Day 13 and were associated with evidence of pharmacological activity (decrease in lymphocyte counts) in the offspring

INCOMPATIBILITIES / COMPATIBILITIES

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.
This medicinal product should not be diluted with solvents other than those mentioned in Section (Dosage and Administration) and Section (Preparation and Handling).
There are no known incompatibilities between alemtuzumab and PVC infusion bags, or PVC or polyethylene-lined PVC administration sets or low protein binding filters.

STORAGE CONDITIONS AND SHELF-LIFE

Vials
Alemtuzumab vials should be stored at 2° to 8°C (36° to 46°F). Do not freeze or shake. Protect from light.

Infusion solution
Alemtuzumab diluted product may be stored at room temperature (15° to 25°C) or refrigerated conditions (2° to 8°C). The alemtuzumab diluted product must be prepared using aseptic technique. The alemtuzumab diluted product should be used within 8 hours after dilution. Protect from light. Partially used, unused, or damaged drug vials should be disposed according to institutional policies.

Shelf Life:
Alemtuzumab vials: 3 years
The diluted product should be used within 8 hours after dilution.

PREPARATION AND HANDLING

Alemtuzumab 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. Do not freeze or shake vials prior to use. Protect from light.
For IV administration, withdraw 1.2 mL of alemtuzumab from the vial into a syringe using aseptic technique. 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. Each vial is intended for single use only. Alemtuzumab is supplied as a sterile preservative-free concentrate for solution for infusion.

PATIENT INFORMATION

Inflammation of the gallbladder

LEMTRADA may increase your chance of getting inflammation of the gallbladder. This may be a serious medical condition that can be life threatening. You should report to your doctor if you have symptoms such as stomach pain or discomfort, fever, nausea or vomiting

Stroke and tears in arteries that supply blood to the brain
Some people have had serious or life-threatening strokes or tears in arteries that supply blood to the brain within 3 days of receiving LEMTRADA. Get help right away if you have any of the following symptoms: drooping of parts of your face, sudden severe headache, weakness on one side, difficulty with speech, neck pain.

Infusion reactions
Most patients treated with LEMTRADA will experience side-effects at the time of the infusion or within 24 hours after the infusion. There have also been reports of rare but serious infusion reactions, including bleeding in the lung, chest tightness/pain or discomfort, heart attack, and stroke or tears in blood vessels supplying the brain, which should be reported to your doctor. To try to reduce infusion reactions, your doctor will give you other medicine(s). Reactions may occur following any of the doses during the treatment course. In the majority of cases reactions occurred within 1-3 days of the infusion. Your doctor will monitor vital signs, including blood pressure, before and during the infusion. Get help right away if you have any of the following symptoms: trouble breathing, chest pain, facial drooping, sudden severe headache, weakness on one side of the body, difficulty with speech, or neck pain.

Hemophagocytic lymphohistiocytosis
Treatment with LEMTRADA may increase the risk of excessive activation of white blood cells (cells that fight infections) associated with inflammation (hemophagocytic lymphohistiocytosis), which can be fatal if not diagnosed and treated early. If you experience symptoms such as fever, swollen glands, bruising, or skin rash, contact your doctor immediately.

Acquired hemophilia A
Uncommonly, patients developed a bleeding disorder caused by antibodies that work against factor VIII (a protein needed for normal clotting of blood), called Acquired hemophilia A after receiving LEMTRADA. This condition must be diagnosed and treated immediately. Symptoms of acquired hemophilia A are spontaneous bruising, nose bleeds, painful or swollen joints, other types of bleeding, or bleeding from a cut that may take longer than usual to stop.

Liver inflammation
Some patients have developed liver inflammation after receiving LEMTRADA. Liver inflammation can be diagnosed from the blood tests that you will be having regularly after LEMTRADA treatment. If you develop nausea, vomiting, abdominal pain, fatigue, loss of appetite, yellow skin or eyes and/or dark urine, or bleeding or bruising more easily than normal, report this to your doctor.

Progressive multifocal leukoencephalopathy (PML)
Advise patients that progressive multifocal leukoencephalopathy (PML) has been reported with use of LEMTRADA. PML is characterized by a progression of adverse neurological symptoms and usually leads to death or severe disability over weeks or months.

PML has been reported in the postmarketing setting in patients with other risk factors, specifically prior treatment with MS products associated with PML.

Instruct the patient of the importance of contacting their doctor if they develop any symptoms suggestive of PML. 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.

Epstein-Barr virus (EBV)
Patients treated with LEMTRADA have had infections due to a virus called Epstein-Barr virus (EBV), including cases with severe and sometimes fatal liver inflammation. Tell your doctor right away if you have symptoms of infection such as fever, swollen glands, or fatigue.

Sarcoidosis
An immune disorder that can cause inflammation of one or more organs including lungs, lymph nodes, skin or cardiac (sarcoidosis).

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