SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

LEMTRADA 12 mg concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 12 mg alemtuzumab in 1.2 ml (10 mg/ml).

Alemtuzumab is a monoclonal antibody produced in mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium by recombinant DNA technology.

Excipients with known effect

This medicine contains less than 1 mmol potassium (39 mg) per infusion, i.e. it is essentially 'potassium- free'.

This medicine contains less than 1 mmol sodium (23 mg) per infusion, i.e. it is essentially 'sodium- free'.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

A clear, colourless to slightly yellow concentrate with pH 7.0 – 7.4.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

LEMTRADA is indicated as a single disease modifying therapy in adults with highly active relapsing remitting multiple sclerosis (RRMS) for the following patient groups:

- Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT) or
- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

4.2 Posology and method of administration

LEMTRADA treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with multiple sclerosis (MS) in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available.

Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.

Patients treated with LEMTRADA must be given the Patient Alert Card and Patient Guide and be informed about the risks of LEMTRADA (see also package leaflet).

Posology

The recommended dose of alemtuzumab is 12 mg/day administered by intravenous infusion for 2 initial treatment courses, with up to 2 additional treatment courses if needed.

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.

Up to two additional treatment courses, as needed, may be considered (see section 5.1):

- Third or fourth course: 12 mg/day on 3 consecutive days (36 mg total dose) administered at least 12 months after the prior treatment course (see section 4.1, 5.1).

Missed doses should not be given on the same day as a scheduled dose.

Follow-up of patients

The therapy is recommended as an initial treatment of 2 courses with up to 2 additional treatment courses if needed (see posology) with safety follow-up of patients from initiation of the first treatment course and for at least 48 months after the last infusion of the second treatment course. If an additional third or fourth course is administered, continue safety follow-up for at least 48 months after the last infusion (see section 4.4).

Pre-treatment

Patients should be pre-treated with corticosteroids immediately prior to LEMTRADA administration on each of the first 3 days of any treatment course. In clinical trials, patients were pre-treated with 1,000 mg methylprednisolone for 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). In clinical trials, patients were administered aciclovir 200 mg twice a day or equivalent.

Special populations

Elderly

Clinical studies did not include any patients aged over 61 years old. It has not been determined whether they respond differently than younger patients.

Renal or hepatic impairment

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

Paediatric population

The safety and efficacy of LEMTRADA in children with MS aged 0 to 18 years have not yet been established. There is no relevant use of alemtuzumab in children aged from birth to less than 10 years for the treatment of multiple sclerosis. No data are available.

Method of administration

LEMTRADA must be diluted before infusion. The diluted solution should be administered by intravenous infusion over a period of approximately 4 hours.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance, or to any of the excipients listed in section 6.1.

Human Immunodeficiency Virus (HIV) infection.

Patients with severe active infection until complete resolution.

Patients with uncontrolled hypertension.

Patients with a history of arterial dissection of the cervicocephalic arteries.

Patients with a history of stroke.

Patients with a history of angina pectoris or myocardial infarction.

Patients with known coagulopathy, on anti-platelet or anti-coagulant therapy.

Patients with other concomitant autoimmune diseases (besides MS).

4.4 Special warnings and precautions for use

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

Patients treated with LEMTRADA must be given the Package Leaflet, the Patient Alert 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 at least 48 months after the last infusion of the second LEMTRADA treatment course. If an additional course is administered, safety follow-up should be continued until at least 48 months after the last infusion.

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Autoimmunity
Treatment 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), nephropathies (e.g. anti-glomerular basement membrane disease), autoimmune hepatitis (AIH), acquired haemophilia A, thrombotic thrombocytopenic purpura, sarcoidosis, 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 (see section 4.3). 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 that present with such symptoms. In case of a prolonged aPTT patient should be referred to a haematologist. Educate patients on the signs and symptoms of acquired haemophilia A and to seek immediate medical attention, if any of these symptoms are observed.

Thrombotic Thrombocytopenic Purpura (TTP)
Development of TTP has been reported in patients treated with LEMTRADA during post-marketing use, including a fatal case. TTP is a serious condition that requires urgent evaluation and prompt treatment, and can develop several months after last LEMTRADA infusion. TTP may be characterized by thrombocytopenia, microangiopathic haemolytic anaemia, neurological symptoms, fever and renal impairment.

Autoimmune Encephalitis
Cases of autoimmune encephalitis have been reported in patients treated with LEMTRADA. Autoimmune encephalitis is characterized by subacute onset (with rapid progression over months) of memory impairment, altered mental status or psychiatric symptoms, generally in combination with new onset focal neurological findings and seizures. Patients with suspected autoimmune encephalitis should have neuroimaging (MRI), EEG, lumbar puncture and

serologic testing for appropriate biomarkers (e.g. neural autoantibodies) to confirm diagnosis and exclude alternative etiologies.

Immune Thrombocytopenic Purpura (ITP)
Serious events of ITP have been observed in 12 (1%) patients treated in controlled clinical trials in MS (corresponding to an annualised rate 4.7 events/1000 patient years). An additional 12 serious events of ITP have been observed through a median of 6.1 years (maximum 12 years) of follow-up (cumulative annualised rate of 2.8 events/1000 patient years). One patient developed ITP that went unrecognised prior to implementation of monthly blood monitoring requirements and died from intracerebral haemorrhage. In 79.5% of cases, ITP onset occurred within 4 years after first exposure. However, in some cases ITP developed years later. Symptoms of ITP could include (but are not limited to) easy bruising, petechiae, spontaneous mucocutaneous bleeding (e.g., epistaxis, haemoptysis), heavier than normal or irregular menstrual bleeding. Haemoptysis may also be indicative of anti-GBM disease (see below), and an appropriate differential diagnosis has to be undertaken. Remind the patient to remain vigilant for symptoms they may experience and to seek immediate medical help if they have any concerns.

Complete blood counts with differential should be obtained prior to initiation of treatment and at monthly intervals thereafter until at least 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 complete blood count should be obtained immediately.

If ITP onset is confirmed, appropriate medical intervention should be promptly initiated, including immediate 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.

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 the 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, haematuria, and/or proteinuria. While not observed in clinical trials, alveolar haemorrhage manifested as haemoptysis may occur with anti-GBM disease. Haemoptysis may also be indicative of ITP or acquired haemophilia A (see above), and an appropriate differential diagnosis has to be undertaken. The patient should be reminded to remain vigilant for symptoms they may experience and to seek immediate medical help if they have any concerns. 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.

Serum creatinine levels should be obtained prior to initiation of treatment and at monthly intervals thereafter until at least 48 months after the last infusion. Urinalysis with microscopy should be obtained prior to initiation and at monthly intervals thereafter until at least 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 immediate 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.

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. The incidence of thyroid events was higher in patients with a medical history of thyroid disorders both in the LEMTRADA and interferon beta 1a (IFNB-1a) treatment groups. 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 the post-marketing setting several patients who developed biopsy proven AIH had previously developed autoimmune thyroid disorders.

Thyroid function tests, such as thyroid stimulating hormone levels, should be obtained prior to initiation of treatment and every 3 months thereafter until 48 months following 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).

In clinical trials, 74% of patients with positive anti-thyroid peroxidase (anti-TPO) antibodies at baseline developed a thyroid event compared with 38% of patients with a baseline negative status. The vast majority (approximately 80%) of patients who presented with a thyroid event after treatment were anti-TPO antibody negative at baseline. Therefore, regardless of pretreatment anti-TPO antibody status patients may develop a thyroid adverse reaction and must have all tests periodically performed as described above.

Cytopenias
Suspected autoimmune cytopenias such as neutropenia, haemolytic anaemia and pancytopenia have been infrequently reported in clinical trials in MS.

Complete blood count results (see above under ITP) should be used to monitor for cytopenias, including neutropenia. If a cytopenia is confirmed, appropriate medical intervention should be promptly initiated, including referral to a specialist.

Autoimmune hepatitis and hepatic injury
Cases of autoimmune hepatitis (including fatal cases and cases requiring liver transplantation) and hepatic injury related to infections have been reported in patients treated with LEMTRADA (see section 4.3). 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, hepatic injury and related symptoms.

Haemophagocytic lymphohistiocytosis (HLH)
During post-marketing 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 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.

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 4.2).

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.

Adult Onset Still's Disease (AOSD)
During postmarketing use, Adult Onset Still's Disease (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.

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.

Haemorrhagic 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 haemorrhage.

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

Thrombocytopenia

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

Pericarditis
Rare cases of pericarditis, pericardial effusion and other pericardial events have been reported, both as part of acute infusion reaction and with later onset.

Pneumonitis
Pneumonitis has been reported in patients who received LEMTRADA infusions. 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.

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
    - 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, 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 temporally 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 (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.

Infections

Infections occurred in 71% of patients treated with LEMTRADA 12 mg as compared to 53% of patients treated with subcutaneous interferon beta-1a [IFNB 1a] (44mcg 3-times weekly) 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% 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 annualised 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.

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 and anogenital warts, has also been reported in patients treated with LEMTRADA 12 mg (2%). It is recommended that HPV screening be completed annually for female patients.

Cytomegalovirus infections (CMV) including cases of CMV reactivation have been reported in LEMTRADA-treated patients. Most cases occurred within 2 months of alemtuzumab dosing. Before initiation of therapy, evaluation of immune serostatus could be considered according to local guidelines.

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

Tuberculosis has been reported for patients treated with LEMTRADA and IFNB-1a in controlled clinical trials. Active and latent tuberculosis, including a few cases of disseminated tuberculosis, have been reported in 0.3% of the patients treated with LEMTRADA, most often in endemic regions. Before initiation of therapy, all patients must be evaluated for both active or inactive (“latent”) tuberculosis infection, according to local guidelines.

Listeriosis/*Listeria meningitis* has been reported in LEMTRADA treated patients, generally within one month of LEMTRADA infusion. To reduce the risk of infection, patients receiving LEMTRADA should avoid ingestion of uncooked or undercooked meats, soft cheeses and unpasteurized dairy products two weeks prior to, during, and for at least one month after LEMTRADA infusion.

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.

Initiation of treatment with LEMTRADA should be delayed in patients with severe active infection until resolution. Patients receiving LEMTRADA should be instructed to report symptoms of infections to a physician.

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. In clinical trials patients were administered cyclovir 200 mg twice a day or equivalent.

LEMTRADA has not been administered for treatment of MS concomitantly with or following 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 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.

Progressive Multifocal Leukoencephalopathy (PML)
Rare cases of PML (including fatal), have been reported in MS patients after treatment with alemtuzumab. Patients treated with alemtuzumab must be monitored for any signs that may be suggestive of PML. Risk factors of special importance include previous immunosuppressive treatment, in particular other MS treatments with known risk of causing PML.

MRI findings may be apparent before clinical signs or symptoms. Prior to initiation and readministration of alemtuzumab treatment, MRI scan should be made and evaluated for signs that are consistent with PML. Further evaluation, including cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments should be performed as appropriate. The physician should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive, neurological or psychiatric symptoms). Patients should also be advised to inform their relatives or caregivers about their treatment, since they may notice symptoms that the patient is not aware of. PML should be considered as a differential diagnosis in any MS patient taking alemtuzumab presenting with neurological symptoms and/or new brain lesions in MRI.

If a diagnosis of PML has been made, treatment with alemtuzumab should not be started or restarted.

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 IFNB-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. 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.

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. It is not currently known if LEMTRADA confers a higher risk for developing thyroid malignancies, since thyroid autoimmunity may itself be a risk factor for thyroid malignancies.

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 (see section 4.6).

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 LEMTRADA treatment has not been formally studied in controlled clinical trials in MS and 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 medicinal product, 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, treatment with LEMTRADA should be postponed for 6 weeks following vaccination.

Recommended laboratory tests for monitoring patients
Clinical examination and laboratory tests should be conducted at periodic intervals until at least 48 months following the last treatment course of LEMTRADA in order to monitor for early signs of autoimmune diseases:

- Complete blood count with differential, serum transaminases and serum creatinine levels (prior to treatment initiation and at monthly intervals thereafter).
- Urinalysis with microscopy (prior to treatment initiation and at monthly intervals thereafter)
- A test of thyroid function, such as thyroid stimulating hormone level (prior to treatment initiation and every 3 months thereafter).

Information from use of alemtuzumab prior to the marketing authorisation of LEMTRADA outside of company-sponsored studies
The following adverse reactions were identified prior to registration of LEMTRADA during use of alemtuzumab for the treatment of B-cell chronic lymphocytic leukaemia (B-CLL), as well as for the treatment of other disorders, generally at higher and more frequent doses (e.g. 30 mg) than that recommended in the treatment of MS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to alemtuzumab exposure.

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

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

Infections and infestations
Serious and sometimes fatal viral, bacterial, protozoan, and fungal infections, including those due to reactivation of latent infections, have been reported in

non-MS patients treated with alemtuzumab at higher and more frequent doses than used in MS.

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.

LEMTRADA contains sodium and potassium

This medicine contains less than 1 mmol potassium (39 mg) per infusion, i.e. it is essentially 'potassium- free'.
This medicine contains less than 1 mmol sodium (23 mg) per infusion, i.e. it is essentially 'sodium- free'.

4.5 Interaction with other medicinal products and other forms of interaction

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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Serum concentrations were low or undetectable within approximately 30 days following each treatment course. Therefore, women of childbearing potential have to use effective contraception when receiving a course of treatment with LEMTRADA and up to 4 months after each course of treatment.

Pregnancy

There is a limited amount of data from the use of alemtuzumab 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. Animal studies have shown reproductive toxicity (see section 5.3). It is not known whether alemtuzumab can cause foetal harm when administered to pregnant women or whether it can affect reproductive capacity.

Thyroid disease (see section 4.4 *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.

Breast-feeding

Alemtuzumab was detected in the milk and offspring of lactating female mice.

It is unknown whether alemtuzumab is excreted in human milk. A risk to the suckling newborn/infant cannot be excluded. Therefore, breast-feeding should be discontinued during each course of treatment with LEMTRADA and for 4 months following the last infusion of each treatment course. However, benefits of conferred immunity through breast-milk may outweigh the risks of potential exposure to alemtuzumab for the suckling newborn/infant.

Fertility

There are no adequate clinical safety data on the effect of LEMTRADA on fertility. In a sub-study in 13 male LEMTRADA-treated patients (treated with either 12 mg or 24 mg), there was no evidence of aspermia, azoospermia, consistently depressed sperm count, motility disorders or an increase in sperm morphological abnormalities.

CD52 is known to be present in human and rodent reproductive tissues. Animal data have shown effects on fertility in humanised mice (see section 5.3), however a potential impact on human fertility during the period of exposure is unknown based on the available data.

4.7 Effects on ability to drive and use machines

LEMTRADA has minor influence on the ability to drive and use machines. Most patients experience IARs which occur during or within 24 hours after treatment with LEMTRADA. Some of the IARs (e.g. dizziness) could temporarily impact the patient's ability to drive or use machines and caution should be exercised until these are resolved.

4.8 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. These are described in section 4.4.

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

Tabulated list of adverse reactions
The table below is based on the pooled safety data on all LEMTRADA 12 mg-treated patients during all available follow up in clinical trials. Adverse reactions are listed by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT). Frequencies are defined according to the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions have been presented in order of decreasing seriousness.

Table 1: Adverse reactions in study 1, 2, 3 and 4 observed in LEMTRADA 12 mg treated patients and post-marketing surveillance

System Organ Class	Very Common	Common	Uncommon	Rare	Not known
Infections and infestations	Upper respiratory tract infection, urinary tract infection, herpes virus infection,[1]	Herpes zoster infections[2], lower respiratory tract infections, gastroenteritis**,** oral candidiasis, vulvovaginal candidiasis, influenza, ear infection, pneumonia, vaginal infection, tooth infection	Onychomycosis, gingivitis, fungal skin infection, tonsillitis, acute sinusitis, cellulitis, tuberculosis, cytomegalovirus infection		Listeriosis/ listeria meningitis, Epstein-Bar virus (EBV) infection (including reactivation
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)		Skin papilloma			
Blood and lymphatic system disorders	Lymphopenia, leukopenia, including neutropenia	Lymphadenopathy, immune thrombocytopenic purpura, thrombocytopenia, anaemia haematocrit decreased, leukocytosis	Pancytopenia, haemolytic anaemia, acquired haemophilia A	Haemophagocytic lymphohistiocytosis (HLH), thrombotic thrombocytopenic purpura (TTP)	
Immune system disorders		Cytokine release syndrome*, hypersensitivity including anaphylaxis*	Sarcoidosis		
Endocrine disorders	Basedow's disease, hyperthyrodisim, hypothyroidism	Autoimmune thyroiditis including thyroiditis subacute, goitre, anti-thyroid antibody positive			
Metabolism and nutrition disorders			Decreased appetite		
Psychiatric disorders		Insomnia*, anxiety, depression			
Nervous system disorders	Headache*	MS relapse, dizziness*,	Sensory disturbance,		Haemorrhag stroke**,

		hypoaesthesia, paraesthesia, tremor, dysgeusia*, migraine*	hyperaesthesia, tension headache, autoimmune encephalitis		cervicocephic arterial dissection**
Eye disorders		Conjunctivitis, endocrine ophthalmopathy, vision blurred	Diplopia		
Ear and labyrinth disorders		Vertigo	Ear pain		
Cardiac disorders	Tachycardia*	Bradycardia*, palpitations*	Atrial fibrillation*		Myocardial ischaemia** myocardial infarction**
Vascular disorders	Flushing*	Hypotension*, hypertension*			
Respiratory, thoracic and mediastinal disorders		Dyspnoea*, cough, epistaxis, hiccups, oropharyngeal pain, asthma	Throat tightness*, throat irritation, pneumonitis		Pulmonary alveolar haemorrhag*
Gastrointestinal disorders	Nausea*	Abdominal pain, vomiting, diarrhoea dyspepsia*, stomatitis	Constipation, gastro-oesophageal reflux disease, gingival bleeding, dry mouth, dysphagia, gastrointestinal disorder, haematochezia		
Hepatobiliary disorders		Aspartate aminotransferase increased, alanine aminotransferase increase	Cholecystitis including acalculous cholecystitis and acute acalculous cholecystitis		Autoimmun hepatitis, Hepatitis (associated with EBV infection)
Skin and subcutaneous tissue disorders	Urticaria*, rash*, pruritus*, generalised rash*	Erythema*, ecchymosis, alopecia, hyperhidrosis, acne, skin lesion, dermatitis	Blister, night sweats, swelling face, eczema, vitiligo, alopecia areata		
Musculoskeletal and connective tissue disorders		Myalgia, muscle weakness, arthralgia, back pain, pain in extremity, muscle spasms, neck pain, musculoskeletal pain	Musculoskeletal stiffness, limb discomfort		Adult Onset Still's Disea (AOSD)

Renal and urinary disorders		Proteinuria, haematuria	Nephrolithiasis, ketonuria, nephropathies including anti-GBM disease		
Reproductive system and breast disorders		Menorrhagia, menstruation irregular	Cervical dysplasia, amenorrhoea		
General disorders and administration site conditions	Pyrexia*, fatigue*, chills*	Chest discomfort*, pain*, oedema peripheral, asthenia, influenza-like illness, malaise, infusion site pain			
Investigations		Blood creatinine increased	Weight decreased, weight increased, red blood cell count decreased, bacterial test positive, blood glucose increased, mean cell volume increase		
Injury, poisoning and procedural complications		Contusion, infusion related reaction			

[1] Herpes virus infections include PTs: Oral herpes, Herpes simplex, Genital herpes, Herpes virus infection, Genital herpes simplex, Herpes dermatitis, Ophthalmic herpes simplex, Herpes simplex serology positive.
[2] Herpes zoster infections include PTs: Herpes zoster, Herpes zoster cutaneous disseminated, Ophthalmic herpes zoster, Herpes ophthalmic, Herpes zoster infection neurological, Herpes zoster meningitis.

Description of selected adverse reactions

Terms marked with asterisk (*) in Table 1 include adverse reactions reported as Infusion Associated Reactions.

Terms marked with two asterisks (**) in Table 1 include adverse reactions observed in the post marketing setting which have occurred in the majority of cases with time to onset within 1-3 days of LEMTRADA infusion, following any of the doses during the treatment course.

Neutropenia

Cases of severe (including fatal) neutropenia have been reported within 2 months of LEMTRADA infusion.

Safety profile in long-term follow-up

The type of adverse reactions 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. The incidence of IARs was higher in course 1 than in subsequent courses.

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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In controlled clinical trials 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 alemtuzumab over dosage. Treatment consists of discontinuation of the medicinal product and supportive therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Monoclonal antibodies, ATC code: L04AG06

Mechanism of action
Alemtuzumab, is a recombinant DNA-derived humanised 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 complementary-determining regions from a murine (rat) monoclonal antibody. The antibody has an approximate molecular weight of 150 kD.

Alemtuzumab binds to CD52, a cell surface antigen present at high levels on T ($CD3^+$) and B ($CD19^+$) 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 LEMTRADA exerts its therapeutic effects in MS is not fully elucidated. However, research suggests immunomodulatory effects through the depletion and repopulation of lymphocytes, including:

- Alterations in the number, proportions, and properties of some lymphocyte subsets post-treatment
- Increased representation of regulatory T cell subsets
- Increased representation of memory T- and B-lymphocytes
- Transient effects on components of innate immunity (i.e., neutrophils, macrophages, NK cells)

The reduction in the level of circulating B and T cells by LEMTRADA and subsequent repopulation, may reduce the potential for relapse, which ultimately delays disease progression.

Pharmacodynamic effects

LEMTRADA depletes circulating T and B lymphocytes after each treatment course with the lowest observed values occurring 1 month after a course of treatment (the earliest post-treatment time point in phase 3 studies). Lymphocytes repopulate over time with B-cell recovery usually completed within 6 months. $CD3^+$ and $CD4^+$ 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 course.

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

Clinical efficacy and safety

The safety and efficacy of alemtuzumab in MS were evaluated in 3 randomised, rater-blinded, active-comparator clinical trials and 1 uncontrolled, rater-blinded extension study in patients with RRMS.

Study design/demographics for Studies 1, 2, 3 and 4 are shown in Table 2

Table 2: Study Design and Baseline Characteristics for Studies 1, 2, 3 and 4			
	Study 1	**Study 2**	**Study 3**
Study name	CAMMS323 (CARE-MS I)	CAMMS32400507 (CARE-MS II)	CAMMS223
Study design	Controlled, randomised, rater-blinded	Controlled, randomised, rater and dose-blinded	Controlled, randomised, rater-blinded
Disease history	Patients with active MS, defined as at least 2 relapses within the prior 2 years.		Patients with active MS, defined as at least 2 relapses within the prior 2 years and 1 or more contrast-enhancing lesions
Duration	2 years		3 years‡
Study population	Treatment-naïve patients	Patients with inadequate response to prior therapy*	Treatment- naïve patients
Baseline characteristics			
Mean Age (years)	33	35	32
Mean/Median Disease duration	2.0/1.6 years	4.5/3.8 years	1.5/1.3 years
Mean duration of prior MS therapy (≥1 drug used)	None	36 months	None
% receiving ≥2 prior MS therapies	Not applicable	28%	Not applicable
Mean EDSS score at baseline	2.0	2.7	1.9
	Study 4		
Study name	CAMMS03409		
Study design	Uncontrolled, rater-blinded extension study		
Study population	Patients who participated in CAMMS223, CAMMS323, or CAMMS32400507 (see baseline characteristics above)		
Duration of extension	4 years		

* Defined as patients having experienced at least 1 relapse during treatment with beta interferon or glatiramer acetate after having been on therapy with medicinal product for at least 6 months.

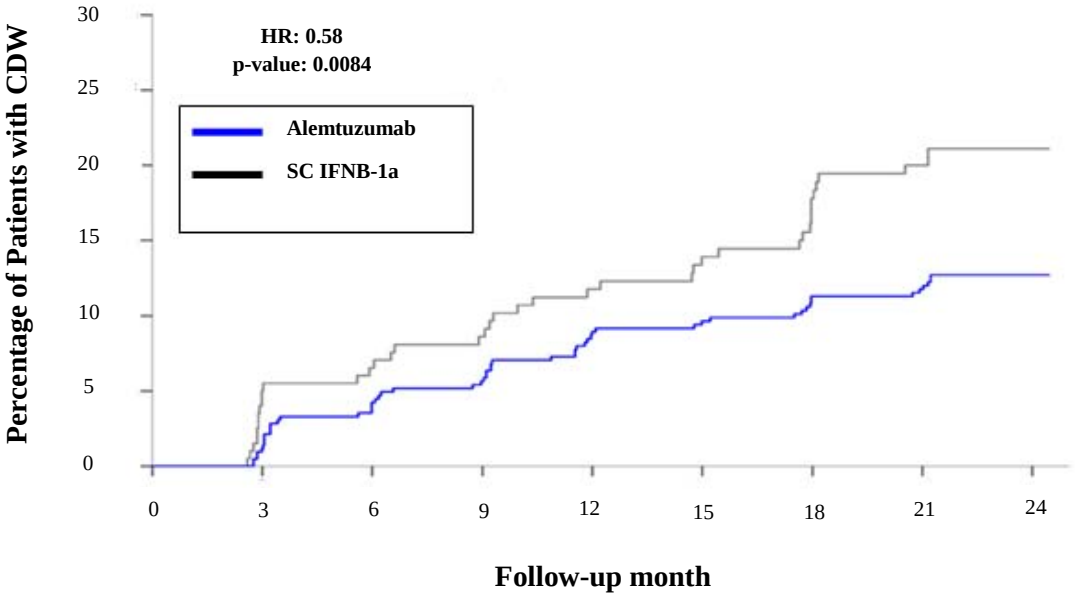
‡ Study primary endpoint was scored at 3 years. Additional follow-up provided data through a median of 4.8 years (maximum 6.7).

Results for Studies 1 and 2 are shown in Table 3.

Table 3: Key Clinical and MRI Endpoints from Studies 1 and 2				
	Study 1		**Study 2**	
Study name	CAMMS323 (CARE-MS I)		CAMMS32400507 (CARE-MS II)	
Clinical endpoints	**LEMTRADA 12 mg (N=376)**	**SC IFNB-1a (N=187)**	**LEMTRADA 12 mg (N=426)**	**SC IFNB-1a (N=202)**
Relapse Rate[1]				
Annualised Relapse rate (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	54.9 (p<0.0001)		49.4 (p<0.0001)	
Disability[1] (Confirmed Disability Worsening [CDW] [2]				
Patients with 6-month CDW (95% CI)	8.0% (5.7, 11.2)	11.1% (7.3, 16.7)	12.7% (9.9, 16.3)	21.1% (15.9, 27.7)
Hazard ratio (95% CI)	0.70 (0.40, 1.23) (p=0.22)		0.58 (0.38, 0.87) (p=0.0084)	
Patients who are relapse free at Year 2 (95% CI)	77.6% (72.9, 81.6) (p<0.0001)	58.7% (51.1, 65.5)	65.4% (60.6, 69.7) (p<0.0001)	46.7 (39.5, 53.5)
Change from Baseline in EDSS at Year 2[3] (95% CI)	-0.14 (-0.25, -0.02) (p=0.42)	-0.14 (-0.29, 0.01)	-0.17 (-0.29, -0.05) (p<0.0001)	0.24 (0.07, 0.41)
MRI Endpoints (0-2 years)				
Median % change in MRI-T2 lesion volume	-9.3 (-19.6, -0.2) (p=0.31)	-6.5 (-20.7, 2.5)	-1.3 (p=0.14)	-1.2
Patients with new or enlarging T2 lesions through Year 2	48.5% (p=0.035)	57.6%	46.2% (p<0.0001)	67.9%
Patients with Gadolinium enhancing lesions through Year 2	15.4% (p=0.001)	27.0%	18.5% (p<0.0001)	34.2%
Patients with new T1 hypointense lesions through Year 2	24.0% (p=0.055)	31.4%	19.9% (p<0.0001)	38.0%
Median % Change in Brain Parenchymal Fraction	-0.867 (p<0.0001)	-1.488	-0.615 (p=0.012)	-0.810

1 Co-primary endpoints: ARR & CDW. The study was declared successful if at least one of the two co-primary endpoint was met.
2 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.
3 Estimated using a mixed model for repeated measures.

Figure 1: Time to 6 Month Confirmed Disability Worsening in



Relapse severity
In alignment with the effect on relapse rate, supportive analyses from Study 1 (CAMMS323) showed that LEMTRADA 12 mg/day led to significantly fewer LEMTRADA -treated patients experiencing severe relapses (61% reduction, p=0.0056) and significantly fewer relapses that led to steroid treatment (58% reduction, p<0.0001) compared to IFNB-1a.

Supportive analyses from Study 2 (CAMMS32400507) showed that LEMTRADA 12 mg/day led to significantly fewer LEMTRADA -treated patients experiencing severe relapses (48% reduction, p=0.0121), and significantly fewer relapses that led to steroid treatment (56% reduction, p<0.0001) or to hospitalization (55% reduction, p=0.0045) compared to IFNB-1a.

Confirmed disability improvement (CDI)
Time to onset of CDI was defined as a decrease of at least one point on the EDSS from a baseline EDSS score ≥ 2 that was sustained for at least 6 months. CDI is a measure for sustained disability improvement. 29% of patients treated with LEMTRADA reached CDI in Study 2, while only 13% of subcutaneous IFNB-1a treated patiets reached this endpoint. The difference was statistically significant (p=0.0002).

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 for 5 days at month 0 and for 3 days at month 12 or subcutaneous IFNB-1a 44 µg (N=107) administered 3 times per week for 3 years. Forty-six patients received a third course of LEMTRADA treatment at 12 mg/day or 24 mg/day for 3 days at month 24.

At 3 years, LEMTRADA 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 subcutaneous IFNB-1a. LEMTRADA 12 mg/day led to significantly lower EDSS scores (improved compared to baseline) through 2 years of follow up, compared with IFNB-1a (p<0.0001).

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, was a Phase 3, multicenter, open-label, rater-blinded, efficacy and safety extension study for patients with RRMS who participated in Study 1, 2, or 3 (prior phase 3 and 2 studies) to assess long-term efficacy and safety of LEMTRADA. The study provides efficacy and safety through a median of 6 years from entry into Studies 1 and 2. Patients in the extension study (Study 4) were eligible to receive additional as-needed LEMTRADA treatment course(s) upon documentation of resumed disease activity, defined as the occurrence of ≥1 MS relapse and/or ≥2 new or enlarging brain or spinal lesions on magnetic resonance imaging (MRI). 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.

91.8% of the patients treated with LEMTRADA 12 mg in Studies 1 and 2 entered Study 4. 82.7% of these patients completed the study. Approximately half (51.2%) of patients initially treated with LEMTRADA 12 mg/day in Study 1 or 2 who enrolled in Study 4, received only the initial 2 courses of LEMTRADA and no other disease modifying treatment throughout 6 years of follow-up.

46.6% 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. No characteristics at study entry identified patients who would later receive one or more additional courses.

Through 6 years from initial LEMTRADA treatment, patients continuing in follow-up showed rates of MS relapse, brain lesion formation on MRI, and brain volume loss consistent with LEMTRADA's treatment effects during Studies 1 and 2 as well as predominantly stable or improved disability scores. Including follow-up in Study 4, patients originally treated with LEMTRADA in Studies 1 and 2, respectively, had ARRs 0.17 and 0.23, CDW was seen in 22.3% and 29.7%, while 32.7% and 42.5%

achieved CDI. In each year of Study 4, patients from both studies continued to show a low risk of forming new T2 (27.4% to 33.2%) or gadolinium-enhancing lesions (9.4% to 13.5%), and the median annual percent change in brain parenchymal fraction ranged from 0.19% to -0.09%.

Among patients who received one or two additional LEMTRADA treatment courses, improvements were seen in relapse rate, MRI activity and mean disability scores following a first or second LEMTRADA retreatment (Courses 3 and 4) when compared with outcomes in the preceding year. For these patients, the ARR declined from 0.79 in the year prior to Course 3 to 0.18 one year after, and the mean EDSS score from 2.89 to 2.69. The percentage of patients with new or enlarging T2 lesions declined from 50.8% the year prior to Course 3 to 35.9% one year after, and new gadolinium-enhancing lesions from 32.2% to 11.9%. Similar improvements in ARR, mean EDSS score, and T2 and gadolinium-enhancing lesions were seen after Course 4 when compared with the prior year. These improvements were subsequently maintained, but no firm conclusions can be made with regards to the longer-term efficacy (e.g. 3 and 4 years after additional treatment courses) because many patients completed the study before reaching these time points.

The benefits and risks of 5 or more treatment courses have not been established.

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 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 medicines, 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.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with alemtuzumab in children from birth to less than 10 years in treatment of multiple sclerosis (see section 4.2 for information on paediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with LEMTRADA in one or more subsets of the paediatric population in RRMS (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of alemtuzumab were evaluated in a total of 216 patients with RRMS who received intravenous 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 mean 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 4-5 days and was comparable between courses leading to low or undetectable serum concentrations within approximately 30 days following each treatment course.

Alemtuzumab is a protein for which the expected metabolic pathway is degradation to small peptides and individual amino acids by widely distributed proteolytic enzymes. Classical biotransformation studies have not been conducted.

Conclusions cannot be made with available data on the effect of race and gender on the pharmacokinetics of alemtuzumab. The pharmacokinetics of alemtuzumab in RRMS has not been studied in patients aged 55 years and older.

5.3 Preclinical safety data

Carcinogenesis and mutagenesis

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

Fertility and reproduction

Treatment with intravenous alemtuzumab at doses up to 10 mg/kg/day, administered for 5 consecutive days (AUC of 7.1 times the human exposure at the recommended daily dose) had no effect on fertility and reproductive performance in male huCD52 transgenic mice. The number of normal sperm was significantly reduced (<10%) relative to controls and the percent abnormal sperm (detached heads or no heads) were significantly increased (up to 3%). However, these changes did not affect fertility and were therefore considered to be non-adverse.

In female mice dosed with intravenous alemtuzumab up to 10 mg/kg/day (AUC of 4.7 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.

A reproductive toxicity study in pregnant mice exposed to intravenous doses of alemtuzumab up to 10 mg/kg/day (AUC 2.4 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 foetuses. There were no external, soft tissue, or skeletal malformations or variations observed at doses up to 10 mg/kg/day.

Placental transfer and potential pharmacologic activity of alemtuzumab were observed during gestation and following delivery in mice. In studies in mice, alterations in lymphocyte counts were observed in pups exposed to alemtuzumab during gestation at doses of 3 mg/kg/day for 5 consecutive days (AUC 0.6 times the human exposure at the recommended dose of 12 mg/day). Cognitive, physical, and sexual development of pups exposed to alemtuzumab during lactation were not affected at doses up to 10 mg/kg/day alemtuzumab.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate dihydrate (E339)

Disodium edetate dihydrate

Potassium chloride (E508)

Potassium dihydrogen phosphate (E340)

Polysorbate 80 (E433)

Sodium chloride

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Concentrate

4 years

Diluted solution
Chemical and physical in-use stability has been demonstrated for 8 hours at 2°C - 8°C.
From a microbiological point of view, it is recommended that the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 8 hours at 2°C - 8°C, under protection from light.

6.4 Special precautions for storage

Concentrate

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

LEMTRADA is supplied in a clear, 2 ml glass vial, with a butyl rubber stopper and aluminium seal with a plastic flip-off cap.

Pack size: carton with 1 vial.

6.6 Special precautions for disposal

The vial contents should be inspected for particulate matter and discoloration prior to administration. Do not use if particulate matter is present or the concentrate is discoloured.

Do not shake the vials prior to use.

For intravenous administration, withdraw 1.2 ml of LEMTRADA from the vial into a syringe using aseptic technique. Inject into 100 ml of sodium chloride 9 mg/ml (0.9%) solution for infusion or glucose (5%) solution for infusion. This medicinal product must not be diluted with other solvents. The bag should be inverted gently to mix the solution.

Care should be taken to ensure the sterility of the prepared solution. It is recommended that the diluted product be administered immediately. Each vial is intended for single use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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Trading as:
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8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

03/05/2024