

ANNEX I

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.

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 for adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features (see sections 4.4 and 5.1).

4.2 Posology and method of administration

LEMTRADA treatment should be initiated and supervised by a neurologist experienced in the treatment of patients with MS. Specialists and equipment required for the timely diagnosis and management of the most frequent adverse reactions, especially autoimmune conditions and infections, should be available.

Resources for the management of 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 LEMTRADA is 12 mg/day administered by intravenous infusion for 2 treatment courses.

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

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

Follow-up of patients

The therapy is recommended as 2 treatment courses (see posology) with safety follow-up of patients from initiation of treatment and until 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.

Additionally, 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.

Elderly

Clinical studies did not include any patients aged over 55 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.

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 48-months of follow-up after the last infusion of LEMTRADA.

Autoimmunity

Treatment may result in the formation of autoantibodies and increase the risk of autoimmune mediated conditions including immune thrombocytopenic purpura (ITP), thyroid disorders or, rarely, nephropathies (e.g. anti-glomerular basement membrane disease). Caution should be exercised in patients with previous autoimmune conditions other than MS, although available data suggests there is no worsening of pre-existing autoimmune conditions after alemtuzumab treatment.

Immune Thrombocytopenic Purpura (ITP)

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

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 0.3% of patients in clinical trials in MS 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 (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 48 months after the last infusion. Urinalysis with microscopy should be obtained prior to initiation and at monthly intervals thereafter until 48 months after the last infusion. The observation of clinically significant changes from baseline in serum creatinine, unexplained haematuria, and/or proteinuria, should prompt further evaluation for nephropathies including 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.

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

Thyroid disorders

Autoimmune thyroid disorders have been observed in an estimated 36% of patients treated with LEMTRADA 12 mg in clinical trials in MS through 48 months following 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. In patients with ongoing thyroid disorder

LEMTRADA should be administered if the potential benefit justifies the potential risks. Observed autoimmune thyroid disorders included hyperthyroidism or hypothyroidism. Most events were mild to moderate in severity. Prior to authorisation, serious events occurred in <1% of patients, with only Basedow's disease (also known as Graves' disease), hyperthyroidism, and hypothyroidism occurring in more than 1 patient. Most thyroid events were managed with conventional medical therapy however some patients required surgical intervention. In clinical trials, patients who developed thyroid events were permitted to receive re-treatment with LEMTRADA. Although experience is limited, patients who were re-treated generally did not experience a worsening in severity of thyroid disorders. Further treatment with LEMTRADA should be considered on an individual basis taking into account the clinical condition of the respective patient.

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.

Thyroid disease poses special risks in women who are pregnant (see section 4.6).

In clinical trials, a patient's anti-thyroid peroxidase (anti-TPO) antibody status prior to treatment was not indicative for the development of a thyroid related adverse event. Half the patients who tested positive at baseline, and a quarter of patients who tested negative at baseline for anti-TPO antibodies developed a thyroid event. 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. If a cytopenia is confirmed, appropriate medical intervention should be promptly initiated, including referral to a specialist.

Infusion-associated Reactions (IARs)

In controlled 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 controlled clinical trials in MS experienced mild to moderate IARs during and/or up to 24 hours after LEMTRADA 12 mg administration, which often included headache, rash, pyrexia, nausea, urticaria, pruritus, insomnia, chills, flushing, fatigue, dyspnoea, dysgeusia, chest discomfort, generalised rash, tachycardia, bradycardia, dyspepsia, dizziness, and pain. Serious reactions occurred in 3% of patients including cases of pyrexia, urticaria, atrial fibrillation, nausea, chest discomfort, and hypotension. 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 2 hours after LEMTRADA infusion. If an IAR occurs, provide the appropriate symptomatic treatment, as needed. If the infusion is not well tolerated, the infusion duration may be extended. If severe infusion reactions occur, immediate discontinuation of the intravenous infusion should be considered. Within the clinical trials, anaphylaxis or serious reactions that necessitated treatment discontinuation were very rare.

Physicians should be aware of the patient's cardiac history as infusion-associated reactions can include cardiac symptoms such as tachycardia.

Resources for the management of anaphylaxis or serious reactions should be available.

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.

Serious varicella zoster virus infections, including primary varicella and varicella zoster re-activation, have occurred more often in patients treated with LEMTRADA 12 mg (0.3%) 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. 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 this risk, patients receiving LEMTRADA should avoid ingestion of uncooked or undercooked meats, soft cheeses and unpasteurized dairy products for at least one month after LEMTRADA treatment.

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.

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. In clinical trials patients were administered aciclovir 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.

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 alemtuzumab

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

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

- Complete blood count with differential (prior to treatment initiation and at monthly intervals thereafter)
- Serum creatinine levels (prior to treatment initiation and at monthly intervals thereafter)
- Urinalysis with 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)

After this period of time, any clinical findings suggestive of nephropathies or thyroid dysfunction will require further testing.

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. Progressive multifocal leukoencephalopathy (PML) has been reported in patients with B-CLL with or without treatment with alemtuzumab. The frequency of PML in B-CLL patients treated with alemtuzumab is no greater than the background frequency.

Blood and lymphatic system disorders

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

Cardiac disorders

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

Epstein-Barr Virus-associated lymphoproliferative disorders

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

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 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.

Pregnancy

There is a limited amount of data from the use of LEMTRADA in pregnant women. LEMTRADA should be administered during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Human IgG is known to cross the placental barrier; alemtuzumab may cross the placental barrier as well and thus potentially pose a risk to the foetus. 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 breastfed child 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 breastfed child.

Fertility

There are no adequate clinical safety data on the effect of LEMTRADA on fertility. In a sub-study in 13 male alemtuzumab-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

No studies on the effects of LEMTRADA on the ability to drive and use machines have been performed.

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

A total of 1,188 patients with relapsing remitting MS (RRMS) treated with LEMTRADA (12 mg or 24 mg) constituted the safety population in a pooled analysis of controlled clinical studies resulting in 2,363 patient-years of safety follow-up and a median follow-up of 24 months.

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 $\geq 20\%$ of patients) are rash, headache, pyrexia, and respiratory tract infections.

Tabulated list of adverse reactions

The table below is based on the pooled safety data up to 24 months from RRMS patients treated with LEMTRADA 12 mg/day for 5 consecutive days at study entry and for 3 consecutive days at Study Month 12. Adverse reactions occurring in $\geq 0.5\%$ of patients 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$). Within each frequency grouping, adverse reactions have been presented in order of decreasing seriousness.

Table 1: Adverse reactions in study 1, 2, and 3 observed in $\geq 0.5\%$ of LEMTRADA 12 mg treated patients

System Organ Class	Very Common	Common	Uncommon
Infections and infestations	Upper respiratory tract infection, urinary tract infection	Lower respiratory tract infections, herpes zoster, gastroenteritis, oral herpes, oral candidiasis, vulvovaginal candidiasis, influenza, ear infection	Tooth infection, genital herpes, onychomycosis
Blood and lymphatic system disorders	Lymphopenia, leukopenia	Lymphadenopathy	Immune thrombocytopenic purpura, thrombocytopenia, haemoglobin decreased, haematocrit decreased
Immune system disorders		Cytokine release syndrome	
Endocrine disorders		Basedow's disease, hyperthyroidism, autoimmune thyroiditis, hypothyroidism, goitre, anti-thyroid antibody positive	
Psychiatric disorders		Insomnia*, anxiety	Depression
Nervous system disorders	Headache*	MS relapse, dizziness*, hypoaesthesia, paraesthesia, tremor, dysgeusia*	Sensory disturbance, hyperaesthesia
Eye disorders		Vision blurred	Conjunctivitis
Ear and labyrinth disorders		Vertigo	
Cardiac disorders		Tachycardia*, bradycardia*, palpitations	
Vascular disorders	Flushing*	Hypotension*, hypertension	
Respiratory, thoracic and mediastinal disorders		Dyspnoea*, cough, epistaxis, oropharyngeal pain	Throat tightness, hiccups, throat irritation,
Gastrointestinal disorders	Nausea*	Abdominal pain, vomiting, diarrhoea, dyspepsia*, stomatitis	Constipation, gastro-oesophageal reflux disease, gingival bleeding, dysphagia
Hepatobiliary disorders			Aspartate aminotransferase increased
Skin and subcutaneous tissue disorders	Urticaria*, rash*, pruritus*	Generalised rash*, erythema, ecchymosis, alopecia, hyperhidrosis, acne	Blister, night sweats
Musculoskeletal and connective tissue disorders		Myalgia, muscle weakness, arthralgia, back pain, pain in	

		extremity, muscle spasms, neck pain	
Renal and urinary disorders		Proteinuria, haematuria	
Reproductive system and breast disorders		Menorrhagia, irregular menstruation	Cervical dysplasia, amenorrhoea
General disorders and administration site conditions	Pyrexia*, fatigue*	Chest discomfort*, chills*, pain*, oedema peripheral, asthenia, influenza-like illness, malaise, infusion site pain	
Investigations			Weight decreased
Injury, poisoning and procedural complications		Contusion	

Description of selected adverse reactions

Terms marked with asterisk (*) in Table 1 include adverse reactions reported as Infusion Associated Reactions. IAR's also include atrial fibrillation and anaphylaxis which occur beneath the 0.5% cut for related events (see section 4.4).

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 national reporting system listed in Appendix V.

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: Selective immunosuppressants, ATC code: L04AA34.

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 cytotoxicity 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 LEMTRADA were evaluated in 3 randomised, rater-blinded, active-comparator clinical trials in patients with RRMS.

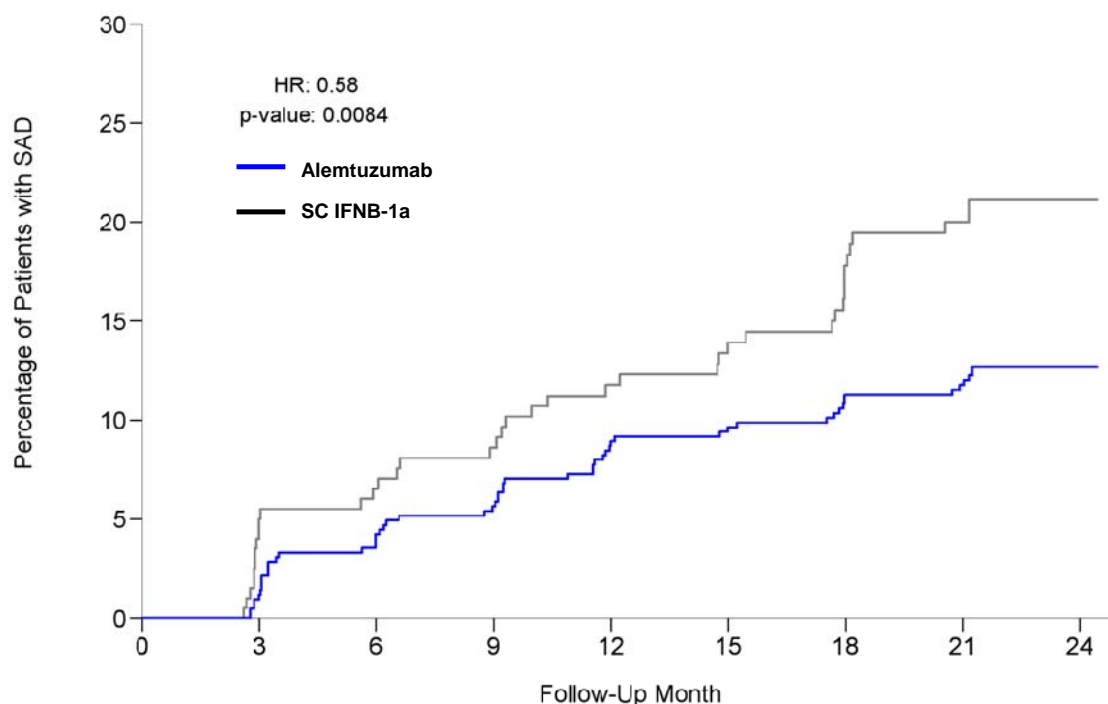
For studies 1 and 2, Study design/demographics and results are shown in Table 2 and Table 3 respectively.

Table 2: Study Design and Baseline Characteristics for Studies 1 and 2		
	Study 1	Study 2
Study name	CAMMS323 (CARE-MS I)	CAMMS32400507 (CARE-MS II)
Study design		
Disease history	Patients with active MS, defined as at least 2 relapses within the prior 2 years.	
Follow-up	2 years	
Study population	Treatment-naïve patients	Patients with inadequate response to prior therapy*
Baseline characteristics		
Mean Age (years)	33	35
Mean/Median Disease duration	2.0/1.6 years	4.5/3.8 years
Mean duration of prior MS therapy (≥1 drug used)	None	36 months
% receiving ≥2 prior MS therapies	Not applicable	28%
Mean EDSS score at baseline	2.0	2.7

* 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.

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) Risk reduction	0.45 (0.32, 0.63) 54.9 (p<0.0001)		0.51 (0.39, 0.65) 49.4 (p<0.0001)	
Disability ² (Sustained Accumulation of Disability [SAD] ≥6 months ¹)				
Patients with 6-month SAD (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, 81.60) (p<0.0001)	58.7% (51.1, 65.50)	65.4% (60.6, 69.7) (p<0.0001)	46.7 (39.5, 53.5)
Change from Baseline in EDSS at Year 2 Estimate (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
<p>1 Co-primary endpoints: ARR & SAD. The study was declared successful if at least one of the two co-primary endpoint was met.</p> <p>2 Time to onset of SAD 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.</p>				

Figure 1: Time to 6-month Sustained Accumulation of Disability in Study 2



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.

Sustained reduction of disability (SRD)

Time to onset of SRD 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. SRD is a measure for sustained disability improvement. 29% of patients treated with LEMTRADA reached SRD in study 2, while only 13% of subcutaneous IFNB-1a treated patients 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 5 years. Patients had an EDSS from 0-3.0, at least 2 clinical episodes of MS in the prior 2 years, and ≥ 1 gadolinium-enhancing lesion at study entry. Patients had not received prior therapy for MS. Patients were treated with LEMTRADA 12 mg/day ($N=108$) or 24 mg/day ($N=108$) administered once per day 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 SAD 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. Alemtuzumab 12 mg/day led to significantly lower EDSS scores (improved compared to baseline) through 2 years of follow up, compared with IFNB-1a ($p < 0.0001$).

At 5 years, LEMTRADA reduced the risk of SAD by 69% (hazard ratio 0.31 [95% CI: 0.161, 0.598], $p = 0.0005$) and reduced the ARR by 66% (rate ratio 0.34 [95% CI: 0.202, 0.569], $p < 0.0001$) as compared to subcutaneous IFNB-1a.

In open-label follow-up of LEMTRADA clinical trials, some patients received additional “as needed” treatment with LEMTRADA upon documented evidence of resumed MS disease activity. The 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. The benefits and risks of >2 treatment courses have not been fully established, but results suggest that the safety profile does not appear to change with additional courses. If additional treatment courses are to be given they must be administered at least 12 months after the prior course.

Immunogenicity

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

The incidence of 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.

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 LEMTRADA were evaluated in a total of 216 patients with RRMS who received intravenous infusions of either 12 mg/day or 24 mg/day for 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 LEMTRADA. The pharmacokinetics of LEMTRADA 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 fetuses. 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

3 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 and other handling

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.

LEMTRADA contains no antimicrobial preservatives and, therefore, 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

Genzyme Therapeutics Ltd
4620 Kingsgate
Cascade Way
Oxford Business Park South
Oxford
OX4 2SU
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/869/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 September 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER OF THE BIOLOGICAL ACTIVE
SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR
BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND
USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE
MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE
SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Boehringer Ingelheim Pharma GmbH & Co. KG
Birkendorfer Straße 65
88397 Biberach an der Riss
GERMANY

Name and address of the manufacturer(s) responsible for batch release

Genzyme Limited
37 Hollands Road
Haverhill
Suffolk
CB9 8PU
United Kingdom

Genzyme Ireland Limited
IDA Industrial Park
Old Kilmeaden Road
Waterford
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Prior to launch in each Member State the Marketing Authorisation Holder (MAH) shall agree an educational programme for Health Care Professionals (HCP) and patients with the National Competent Authority.

The MAH shall ensure that, following agreement with the National Competent Authorities in each Member State where LEMTRADA is marketed, at launch and after launch, all physicians who intend to prescribe LEMTRADA are provided with an updated physician educational pack containing the following elements:

- The Summary of Product Characteristics
- HCP guide
- Prescriber checklist
- Patient guide
- Patient alert card

The HCP guide shall contain the following key messages:

1. A description of the risks associated with the use of LEMTRADA namely:
 - Immune Thrombocytopenic Purpura (ITP)
 - Nephropathies including anti-Glomerular Basement Membrane (anti-GBM) disease
 - Thyroid disorders
2. Recommendations on how to mitigate these risks through appropriate patient counselling, monitoring and management.
3. A “Frequently asked questions” section

The prescriber checklist shall contain the following key messages:

1. Lists of tests to be conducted for the initial screening of the patient
2. Vaccination course to be completed 6 weeks before treatment
3. Premedication, general health, and pregnancy and contraception checks immediately before treatment
4. Monitoring activities during treatment and for 4 years after last treatment
5. A specific reference to the fact that the patient has been informed and understands the risks of serious autoimmune disorders, infections and malignancies, and the measures to minimize them

The patient guide shall contain the following key messages:

1. A description of the risks associated with the use of LEMTRADA namely:
 - Immune Thrombocytopenic Purpura (ITP)
 - Nephropathies, including anti-Glomerular Basement Membrane (anti-GBM) disease

- Thyroid disorders
 - Serious infections
2. A description of the sign and symptoms of autoimmune risks
 3. A description of the best course of action if sign and symptoms of those risks present themselves (e.g. How to reach your doctors)
 4. Recommendations for the planning of the monitoring schedule

The **patient alert card** shall contain the following key messages:

1. A warning message for HCPs treating the patient at any time, including in conditions of emergency, that the patient has been treated with LEMTRADA
2. That LEMTRADA treatment may increase the risk of:
 - Immune Thrombocytopenic Purpura (ITP)
 - Nephropathies, including anti-Glomerular Basement Membrane (anti-GBM) disease
 - Thyroid disorders
 - Serious infections
3. Contact details of the prescriber of LEMTRADA

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON/PACK OF 1 VIAL

1. NAME OF THE MEDICINAL PRODUCT

LEMTRADA 12 mg concentrate for solution for infusion
alemtuzumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

E339, disodium edetate dihydrate, E508, E340, E433, sodium chloride, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

1 vial

12 mg/1.2 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Intravenous use.

Administer within 8 hours after dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

Store in a refrigerator.

Do not freeze or shake.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Genzyme Therapeutics Ltd
4620 Kingsgate
Cascade Way
Oxford Business Park South
Oxford
OX4 2SU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/869/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

<Justification for not including Braille accepted>

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL/VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

LEMTRADA 12 mg sterile concentrate
alemtuzumab
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.2 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

LEMTRADA 12 mg concentrate for solution for infusion alemtuzumab

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are administered this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side-effects talk to your doctor. This includes any possible side-effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What LEMTRADA is and what it is used for
2. What you need to know before you are administered LEMTRADA
3. How LEMTRADA will be administered
4. Possible side effects
5. How to store LEMTRADA
6. Contents of the pack and other information

1. What LEMTRADA is and what it is used for

LEMTRADA contains the active substance alemtuzumab, which is used to treat a form of multiple sclerosis (MS) in adults, called relapsing remitting MS (RRMS). LEMTRADA does not cure MS, but it can reduce the number of MS relapses. It can also help to slow down or reverse some of the signs and symptoms of MS. In clinical studies, patients treated with LEMTRADA had fewer relapses and were less likely to experience worsening of their disability compared to patients treated with a beta-interferon injected multiple times per week.

What is multiple sclerosis?

MS is an autoimmune disease that affects the central nervous system (brain and spinal cord). In MS your immune system mistakenly attacks the protective layer (myelin) around the nerve fibres, causing inflammation. When the inflammation causes symptoms this is often called an “attack” or a “relapse”. In RRMS patients experience relapses followed by periods of recovery.

The symptoms you experience are determined by which part of your central nervous system is affected. The damage done to your nerves during this inflammation may be reversible, but as your disease progresses the damage may accumulate and become permanent.

How LEMTRADA works

LEMTRADA adjusts your immune system to limit its attacks on your nervous system.

2. What you need to know before you are administered LEMTRADA

Do NOT use LEMTRADA if you are:

- allergic to alemtuzumab or any of the other ingredients of this medicine (listed in section 6)
- infected with human immunodeficiency virus (HIV).

Warnings and precautions

Talk to your doctor before LEMTRADA is given. After having a course of treatment with LEMTRADA you may be at greater risk of developing other autoimmune conditions, or experiencing serious infections. It is important you understand these risks and how to monitor for them. You will be given a Patient Alert Card and a Patient Guide with further information. It is important that you keep the Patient Alert Card with you during treatment and for 4 years after your last infusion with LEMTRADA, because side effects may occur many years after treatment. When you have medical treatment, even if it is not for your MS, show the Patient Alert Card to the doctor.

Your doctor will perform blood tests before you start treatment with LEMTRADA. These tests are done to see whether you may take LEMTRADA. Your doctor will also want to make sure that you do not have certain medical conditions or disorders before you start your treatment with LEMTRADA.

• **Autoimmune conditions**

Treatment with LEMTRADA may increase the risk for autoimmune conditions. These are conditions in which your immune system mistakenly attacks your body. Information about some specific conditions that have been seen in MS patients who have been treated with LEMTRADA is provided below.

The autoimmune conditions can occur many years after treatment with LEMTRADA. Therefore, regular blood and urine tests are needed until 4 years after your last infusion. Testing is needed even if you are feeling well and your MS symptoms are under control. In addition, there are certain signs and symptoms that you should look out for yourself. Details about the signs and symptoms, testing, and actions you need to take are described in section 4 – *autoimmune conditions*.

More helpful information about these autoimmune conditions (and the testing for them) can be found in the **LEMTRADA Patient Guide**.

○ **Immune Thrombocytopenic Purpura (ITP)**

Uncommonly, patients have developed a **bleeding disorder** caused by a low level of blood platelets, called immune thrombocytopenic purpura (ITP). This must be diagnosed and treated early, as otherwise the effects can be **serious or even fatal**. Signs and symptoms of ITP are described in section 4.

○ **Kidney disease (such as anti-GBM disease)**

Rarely, patients have experienced autoimmune related problems with their **kidneys**, such as anti-glomerular basement membrane disease (anti-GBM disease). Signs and symptoms of kidney disease are described in section 4. If untreated it can cause kidney failure requiring dialysis or transplantation, and may lead to death.

○ **Thyroid disorders**

Very commonly, patients have experienced an autoimmune disorder of the **thyroid gland** affecting its ability to make or control hormones that are important for your metabolism.

LEMTRADA may cause different types of thyroid disorders, including:

- **Over-active thyroid gland** (hyperthyroidism) when the thyroid produces too much hormone
- **Under-active thyroid gland** (hypothyroidism) when the thyroid does not produce enough hormone.

Signs and symptoms of thyroid disorders are described in section 4.

If you develop a thyroid disorder, in most cases you will need to be treated for the rest of your life with medicines to control your thyroid disorder, and in some cases your thyroid gland may have to be removed.

It is very important that you are properly treated for a thyroid disorder, especially if you become pregnant after using LEMTRADA. Having an untreated thyroid disorder could harm your unborn baby, or harm your baby after birth.

- **Other autoimmune conditions**

Rarely, patients have experienced autoimmune conditions involving **red blood cells or white blood cells**. These can be diagnosed from the blood tests that you will be having regularly after LEMTRADA treatment. If you develop one of these conditions your doctor will tell you, and take appropriate measures to treat it.

- **Infusion reactions**

Most patients treated with LEMTRADA will experience side-effects at the time of the infusion or within 24 hours after the infusion. To try to reduce infusion reactions, your doctor will give you other medicine(s) (see section 4 – *infusion reactions*).

- **Infections**

Patients treated with LEMTRADA are at a higher risk of getting a **serious infection** (see section 4 – *infections*). In general, the infections can be treated with standard medicines.

In order to reduce the chance of getting an infection, your doctor will check if other medicines you are taking might be affecting your immune system. Therefore, **it is important to tell your doctor about all medicines you are taking**.

Also, if you are suffering from an infection before the start of your LEMTRADA treatment, **your doctor will consider delaying the treatment until the infection is under control or resolved**.

Patients treated with Lemtrada are at a higher risk of developing herpes infection (e.g. **a cold sore**). In general, once a patient has had a herpes infection, they have an increased risk of developing another one. It is also possible to develop a herpes infection for the first time. It is recommended that your doctor prescribes a medicine to reduce the chance of developing a herpes infection, which should be taken on the days that you receive LEMTRADA treatment, and for one month following the treatment.

In addition, infections which can result in **abnormalities of the cervix** (the neck of the womb) are possible. Therefore, it is recommended that all female patients have an annual screening performed, such as a cervical smear. Your doctor will explain to you what tests you will need.

Patients treated with LEMTRADA are also at a higher risk of developing listeriosis/*Listeria meningitis*. To reduce this risk, you should avoid ingestion of uncooked or undercooked meats, soft cheeses and unpasteurized dairy products for at least one month after LEMTRADA treatment.

If you live in a region where **tuberculosis** infections are common, you may be at greater risk of infection with tuberculosis. Screening for tuberculosis will be arranged by your doctor.

If you are a carrier of **hepatitis B or hepatitis C infection** (these affect the liver), extra caution is needed before you receive LEMTRADA treatment as it is unknown if treatment could lead to activation of the hepatitis infection which could subsequently damage your liver.

- **Previously diagnosed cancer**

If you have been diagnosed with cancer in the past, please inform your doctor about it.

- **Vaccines**

It is not known if LEMTRADA affects your response to a vaccine. If you have not completed the standard required vaccinations, your doctor will consider whether you should have them before your LEMTRADA treatment. In particular, your doctor will consider vaccinating you against chickenpox if you have never had it. Any vaccination will need to be given to you at least 6 weeks before starting a LEMTRADA treatment course.

You must NOT receive certain types of vaccines (**live viral vaccines**) if you have recently received LEMTRADA.

Children and adolescents

LEMTRADA is not intended to be used in children and adolescents below 18 years old as it has not been studied in MS patients below 18 years old.

Other medicines and LEMTRADA

Tell your doctor or pharmacist if you are taking, have recently taken, or are planning to take any other medicines (including any vaccinations or herbal medicines).

Besides LEMTRADA, there are other treatments (including those for MS, or to treat other conditions) which could affect your immune system and so could affect your ability to fight infections. If you are using such a medicine, your doctor may ask you to stop this medicine before starting treatment with LEMTRADA.

Pregnancy

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before being given this medicine.

Women who are able to conceive should use effective contraceptive methods during each treatment course with LEMTRADA and for 4 months after each course of treatment.

If you become pregnant after treatment with LEMTRADA and experience a thyroid disorder during pregnancy, extra caution is needed. Thyroid disorders could be harmful to the baby (see section 2 *Warnings and precautions – autoimmune conditions*).

Breast-feeding

It is unknown if LEMTRADA can be transferred to a baby through breast milk, but there is a possibility that it could be. It is recommended that you do not breast-feed during each course of treatment with LEMTRADA and for 4 months after each treatment course. However, there may be benefits of breast milk (which can help protect a baby from infections), so talk to your doctor if you are planning to breast-feed your baby. They will advise you what is right for you and your baby.

Fertility

During your treatment course and for 4 months afterwards, you may have LEMTRADA in your body. It is not known if LEMTRADA will have an effect on fertility during this period. Talk to your doctor if you are thinking about trying to become pregnant.

Driving and using machines

Many patients experience side effects at the time of the infusion or within 24 hours after the infusion with LEMTRADA, and some of these, for example dizziness, could make it unsafe to drive or use machines. If affected, stop these activities until you feel better.

LEMTRADA contains potassium and sodium

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

This medicinal product contains less than 1 mmol **sodium** (23 mg) per infusion, i.e. it is essentially ‘sodium-free’.

3. How LEMTRADA will be administered

Your doctor will explain to you how LEMTRADA will be given. Ask your doctor if you have any questions.

For the first treatment course you will receive one infusion per day for 5 days (course 1).

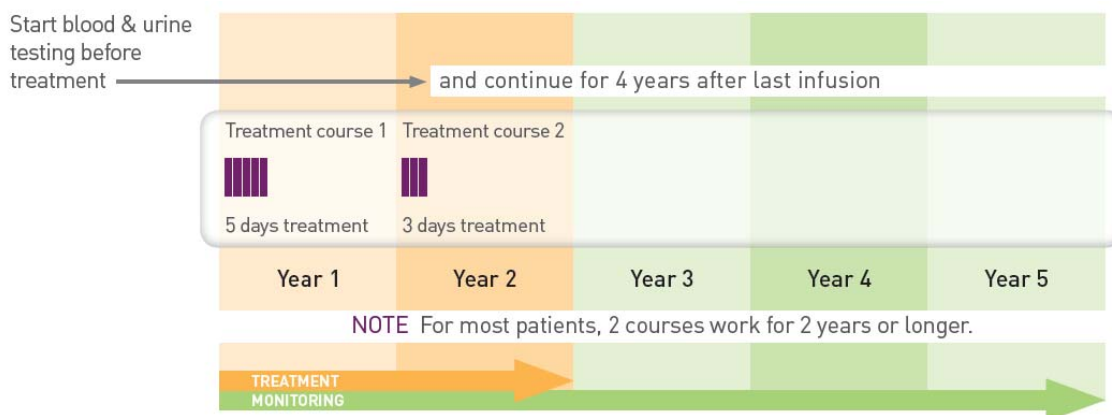
One year later you will receive one infusion per day for 3 days (course 2).

There is no LEMTRADA treatment between the two courses.

The maximum daily dose is one infusion.

LEMTRADA will be given to you as an infusion into a vein. Each infusion will take approximately 4 hours. For most patients 2 treatment courses reduces MS activity for 2 years. Monitoring for side effects and regular testing must continue for 4 years after the last infusion.

To help you better understand the duration of the effects of treatment and the length of required follow-up, please refer to the diagram below.



Follow-up after treatment with LEMTRADA

Once you have received LEMTRADA, you will need to undergo regular tests to ensure that any potential side effects can be diagnosed and treated promptly. These tests must continue until 4 years after your last infusion and are described in-section 4 *most important side-effects*.

If you are given more LEMTRADA than you should receive

Patients who were accidentally given too much LEMTRADA in one infusion have experienced serious reactions, such as headache, rash, low blood pressure or increased heart rate. Doses higher than the recommended dose may result in more serious or longer lasting infusion reactions (see section 4) or a stronger effect on the immune system. The treatment consists of stopping LEMTRADA administration and treating the symptoms.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, LEMTRADA can cause side effects, although not everybody gets them.

The **most important side effects** are the **autoimmune conditions** described in section 2 which include:

- **ITP (bleeding disorders)**, (uncommon – may affect up to 1 in 100 people): may show as small scattered red, pink or purple spots on your skin; easy bruising; bleeding from a cut that is harder to stop; heavier, longer or more frequent menstrual periods than normal; bleeding between menstrual periods; bleeding from your gums or nose that is new or takes longer than usual to stop; or coughing up blood.
- **kidney disorders**, (rare – may affect up to 1 in 1,000 people): may show as blood in the urine (your urine may be red or tea-coloured), or as swelling in your legs or feet. It can also lead to damage of your lungs, which can result in coughing up blood.

If you notice any of these signs or symptoms for bleeding or kidney disorders, call your doctor immediately to report the symptoms. If you cannot reach your doctor, you must seek immediate medical attention.

- **thyroid disorders** (very common – may affect more than 1 in 10 people): may show as excessive sweating; unexplained weight-loss or gain; eye swelling; nervousness; fast heartbeat; feeling cold; worsening tiredness; or newly occurring constipation.
- **red and white blood cells disorders** (rare – may affect up to 1 in 1,000 people): diagnosed from your blood tests.

All of these serious side effects can start many years after you have received LEMTRADA. **If you notice any of these signs or symptoms, call your doctor right away to report them.** You will also have regular blood and urine tests to ensure that if you develop any of these conditions, they **are treated promptly.**

Summary of tests you will have for autoimmune conditions:

Test	When?	For how long?
Blood test (to diagnose all important serious side effects listed above)	Before treatment starts and every month after treatment	Until 4 years after your last LEMTRADA infusion
Urine test (additional test to diagnose kidney disorders)	Before treatment starts and every month after treatment	Until 4 years after your last LEMTRADA infusion

After this time, if you have symptoms of ITP, kidney or thyroid disorders, your doctor will perform more tests. You should also continue looking for signs and symptoms of side effects beyond four years as detailed in your patient guide, and you should continue carrying the Patient Alert Card with you.

Another side effect is an **increased risk of infections** (see below for information on how often patients experience infections). In most cases, these are mild but **serious infections** can occur.

Tell your doctor right away if you have any of these signs of infection

- fever and/or chills
- swollen glands

To help reduce the risk of some infections your doctor may consider giving you vaccination against chickenpox and/or other vaccinations that they think are necessary for you (see section 2: *What you need to know before you are administered LEMTRADA - Vaccines*). Your doctor can also prescribe a medicine for cold sores (see section 2: *What you need to know before you are administered LEMTRADA – Infections*).

The **most frequent side effects** are **infusion reactions** (see below for information on how often patients experience these), which can happen at the time of the infusion or within 24 hours after the infusion. In most cases these are mild but some serious reactions are possible. Occasionally allergic reactions could occur.

To try to reduce infusion reactions, your doctor will give you medication (corticosteroids) before each of the first 3 infusions of a LEMTRADA course. Other treatments to limit these reactions can also be given before the infusion or when you experience symptoms. In addition, you will be monitored during the infusion and for 2 hours after the infusion has been completed. In case of serious reactions, the infusion may be slowed down or even stopped.

Please refer to the **LEMTRADA Patient Guide** for more information about these events.

These are the **side effects** that you may experience

Very common side effects (may affect more than 1 in 10 people):

- **Infusion reactions** that can happen at the time of the infusion or within 24 hours after the infusion: headache, rash, fever, feeling sick, hives, itching, reddening of the face and neck, feeling tired
- **Infections:** airway infections such as colds and sinus infections, cystitis
- Decrease in white blood cell numbers (lymphocytes)

Common side effects (may affect up to 1 in 10 people):

- **Infusion reactions** that can happen at the time of the infusion or within 24 hours after the infusion: changes in heart rate, indigestion, chills, chest discomfort, pain, dizziness, altered taste, difficulty sleeping, difficulty breathing or shortness of breath, rash over your body, low blood pressure
- **Infections:** cough, ear infection, flu-like illness, bronchitis, pneumonia, oral thrush or vaginal thrush, shingles, chickenpox, cold sore, swollen or enlarged glands
- pain at the site of the infusion, pain in the back, the neck, or in arms or legs, muscle pain, muscle spasms, joint pain, painful mouth or throat
- inflammation of the mouth/gums/tongue
- general discomfort, weakness, vomiting, diarrhoea, abdominal pain, gastric flu
- heartburn
- abnormalities that can be found during examinations: blood or protein in urine, decreased heart rate, irregular or abnormal heart beat, high blood pressure
- MS relapse
- trembling, loss of sensation, burning or prickling sensation
- over-active or under-active thyroid gland, or goitre (swelling of the thyroid gland in the neck)
- swelling of arms and/or legs
- vision problems
- feelings of anxiety
- abnormally heavy, prolonged or irregular menstruation
- acne, redness of the skin, excessive sweating
- nose bleeds, bruises
- hair loss

Uncommon side effects (may affect up to 1 in 100 people)

- **Infections:** genital herpes, eye infection, tooth infection
- problems with blood clotting, anaemia
- athlete's foot
- abnormal vaginal smear
- depression
- increased sensation
- difficulty swallowing
- hiccups
- decreased weight
- constipation
- bleeding of gums
- abnormal liver test
- blisters

Show the Patient Alert Card and this package leaflet to any doctor involved with your treatment, not only to your neurologist.

You will also find this information in the Patient Alert Card and Patient Guide that you have been given by your doctor.

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store LEMTRADA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton and the vial label after EXP. The expiry date refers to the last day of the month.

Store in a refrigerator (2°C-8°C).

Do not freeze.

Store in the original package to protect from light.

It is recommended that the product is used immediately after dilution, due to a possible risk for microbial contamination. If it is 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 to 8°C, under protection from light.

Do not use this medicine if you notice particles in the liquid and/or the liquid in the vial is discoloured.

Do not throw away any medicines via wastewater in order to help protect the environment.

6. Contents of the pack and other information

What LEMTRADA contains

The **active substance** is alemtuzumab.

Each vial contains 12 mg alemtuzumab in 1.2 ml.

The **other ingredients** are:

- disodium phosphate dihydrate (E339)
- disodium edetate dihydrate
- potassium chloride (E508)
- potassium dihydrogen phosphate (E340)
- polysorbate 80 (E433)
- sodium chloride
- water for injections

What LEMTRADA looks like and contents of the pack

LEMTRADA is a clear, colourless to slightly yellow concentrate for solution for infusion (sterile concentrate) that comes in a glass vial with stopper.

There is 1 vial in each carton.

Marketing Authorisation Holder

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Manufacturer

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in**Other sources of information**

To assist in the education of patients regarding potential side-effects and instructions on what to do in case of certain side-effects, the following risk minimisation materials are available:

- 1 Patient Alert Card: For the patient to present to other healthcare providers to alert them to the use of LEMTRADA in this patient
- 2 Patient Guide: For further information on autoimmune reactions, infections and other information.

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:**Information on risk minimisation – autoimmune conditions**

- It is extremely important that your patient understands the commitment to having periodic testing performed (for 4 years after last infusion) even if they are asymptomatic and their MS disease is well controlled.
- Together with your patient you need to plan and manage their periodic monitoring.
- If non-compliant, patients may need further counseling to highlight the risks of missing scheduled monitoring tests.
- You should monitor their test results and remain vigilant for symptoms of adverse events.
- Review the LEMTRADA Patient Guide and Package Leaflet with your patient. Remind the patient to remain vigilant for symptoms related to autoimmune conditions, and to seek medical help if they have any concerns.

Educational Materials for Healthcare Providers are also available:

- LEMTRADA Health Care Professional Guide
- LEMTRADA Training Module
- LEMTRADA Prescriber's Check-list

Read the summary of product characteristics (available at the EMA website mentioned above) for more information.

Information on preparing to administer LEMTRADA and patient monitoring

- Patients should be premedicated with corticosteroids immediately prior to LEMTRADA infusion for the first 3 days on any treatment course. Pretreatment with antihistamines and/or antipyretics prior to LEMTRADA administration may also be considered.
- An oral anti-herpes agent should be administered to all patients during and for 1 month following treatment. In clinical trials, patients were administered aciclovir 200 mg twice a day or equivalent.
- Complete baseline tests and screening as described in SmPC section 4.
- The vial contents should be inspected for particulate matter and discolouration prior to administration. Do not use if particulate matter is present or the concentrate is discoloured. **DO NOT SHAKE VIALS PRIOR TO USE.**
- Use aseptic techniques to withdraw 1.2 ml of LEMTRADA from the vial and inject into 100 ml of sodium chloride 9 mg/ml (0.9%) solution for infusion or glucose (5%) solution for infusion. The bag should be inverted gently to mix the solution. Care should be taken to ensure the sterility of the prepared solution particularly as it contains no preservatives.
- Administer LEMTRADA infusion solution via intravenous administration over approximately 4 hours.
- Other medicinal products should not be added to the LEMTRADA infusion solution or simultaneously infused through the same intravenous line.
- It is recommended that the product is used immediately after dilution, due to a possible risk for microbial contamination. If it is 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 to 8°C, under protection from light.
- Procedures for proper handling and disposal should be observed. Any spillage or waste material should be disposed of in accordance with local requirements.
- After each infusion, the patient should be observed for 2 hours for infusion associated reactions. Symptomatic treatment can be initiated if needed – see SmPC. Continue to test the patient every month for autoimmune conditions, until 4 years after last infusion. See LEMTRADA Health Care Professional Guide for more information, or read the summary of product characteristics available at the EMA website mentioned above.

Annex IV

Scientific conclusions and grounds for the variation to the terms of the marketing authorisation

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for alemtuzumab, the scientific conclusions of CHMP are as follows:

Listeriosis/Listeria meningitis

Medicines that have a modulating effect on the immune system as Lemtrada might be associated with an increased risk of opportunistic infections. A total of 5 case reports all originating from the EU were identified. One alemtuzumab -treated MS clinical trial patient, enrolled in study CAMMS223, developed listeria meningitis and four spontaneous post-marketing cases of either systemic listeriosis or *Listeria monocytogenes* meningitis.

Bradycardia as an infusion related adverse reaction

Seventy-one cases (in 55 patients) of bradycardia (two of which were assessed as serious, the remainder as non-serious) were reported in clinical trials. A total of 1,505 alemtuzumab patients were exposed in these trials. In addition, thirty-nine cases of bradycardia (eight of which were assessed as serious, the remainder as non-serious) were reported from alemtuzumab post-marketing reports as of 01 May 2015. Each of the ten serious cases involving bradycardia occurred in the context of infusion- associated reactions.

Therefore, in view of the data presented in the reviewed PSUR, the PRAC considered that changes to the product information of medicinal products containing alemtuzumab were warranted. The section 4.4 of the summary of product characteristics and the relevant sections of the package leaflet were updated.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation

On the basis of the scientific conclusions for alemtuzumab the CHMP is of the opinion that the benefit-risk balance of the medicinal product containing alemtuzumab is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation should be varied.