PRACTICAL INFORMATION ON PRESCRIBING LEMTRADA▼ (ALEMTUZUMAB)

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This is a promotional material for healthcare professionals.
For full prescribing details please refer to the SmPC and risk minimisation materials.
Prescribing information (PI) and adverse event reporting can be accessed from every page.

**Adverse events should be reported. Reporting forms and information can be found at:
In the UK: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.**

**Adverse events should also be reported to the Sanofi Drug Safety department on Tel: 0800 0902314.
Alternatively, send via email to UK-drugsafety@sanofi.com.**

**In Ireland: www.hpra.ie; email: medsafety@hpra.ie. Adverse events should also be reported to Sanofi Ireland Ltd.
Tel: 01 403 5600. Alternatively, send via email to IEPharmacovigilance@sanofi.com.**

**▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information.
You can help by reporting any side effects that you may get.**

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PRACTICAL INFORMATION GUIDE

LEMTRADA® alemtuzumab 12mg IV

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Indication

LEMTRADA is indicated as a single disease modifying therapy (DMT) in adults with highly active relapsing-remitting multiple sclerosis (RRMS) for the following patient groups:[1]

- Patients with highly active disease despite a full and adequate course of treatment with at least one DMT

Or,

- Patients with rapidly evolving severe (RES) relapsing-remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI

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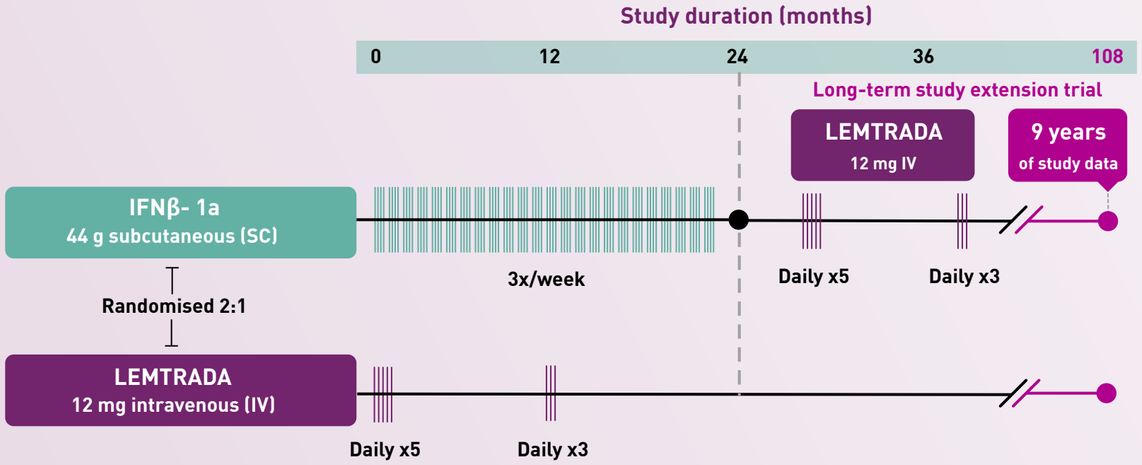
Study design

CARE-MS II Study Design:[2–4]



- Co-primary endpoints: Annualised relapse rate (ARR) and time to 6-month sustained accumulation of disability (SAD)[5]
- All co-primary endpoints in the CARE-MS II study were met[5]

Key inclusion criteria:[2]

- ≥1 relapses during treatment with IFNβ or glatiramer acetate (after receiving that therapy for at least 6 months)
  - Prior treatment with other disease-modifying therapies was also permitted
- Active MS: ≥2 relapses in last 2 years; ≥1 relapse in last year
- Extended Disability Status Scale (EDSS) score ≤5.0
- Disease onset <10 years

Endpoint definitions:[2]

- **SAD:** Increase of ≥1.0 EDSS point for ≥6 months (or ≥1.5 points if baseline EDSS = 0)
- **Sustained reduction in disability (SRD):** Decrease of ≥1.0 EDSS point for ≥6 months (in subset of patients with baseline EDSS ≥2)
- **MRI activity-free:** absence of new gadolinium-enhancing lesion or new or enlarging T2 hyperintense lesion
- **MS disease activity-free:** no relapse, no SAD, no new gadolinium-enhancing lesions or new/enlarging T2 hyperintense lesions

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Clinical profile

What is the efficacy in a highly-active 2nd line population?

In a subset of CARE-MS II patients, with highly active disease, the efficacy of alemtuzumab 12 mg (n=101 [23.7%] of overall population) was compared with those receiving SC IFNβ-1a (n=42 [20.8% of overall population]).[2,3]

Annualised relapse rate over 9 years[2,3,6]

LEMTRADA REDUCED THE ARR BY 51% COMPARED TO SC IFNβ-1A AT 2 YEARS[2,3]

7.4% OF LEMTRADA-TREATED PATIENTS VS. **17.5%** OF IFNβ-1A PATIENTS HAD SAD AFTER 2 YEARS.[2]

EDSS scores over 9 years[6]

65% OF LEMTRADA PATIENTS REMAINED STABLE OR IMPROVED DISABILITY OVER 9 YEARS.[6]

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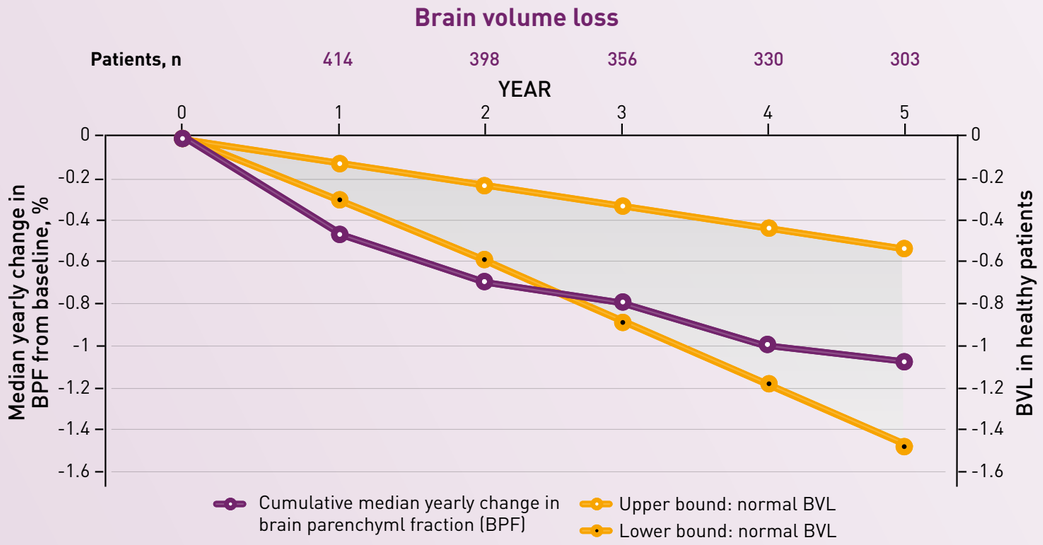
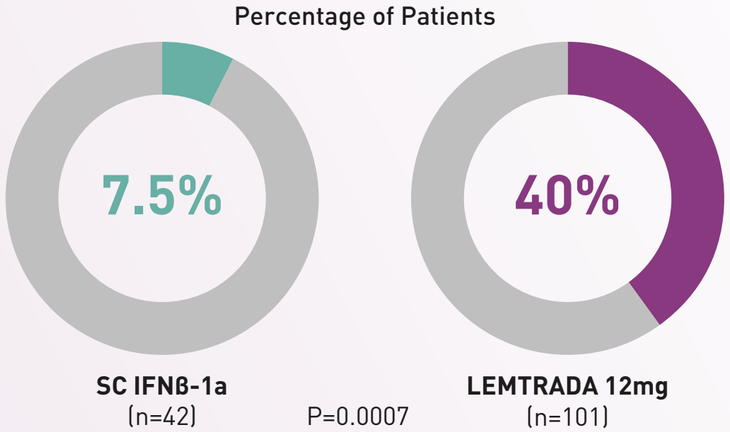
LEMTRADA can help normalise the rate of brain volume loss (BVL) to the range of healthy individuals[7–9]



THE EFFECTIVENESS OF LEMTRADA IN THE HIGHLY ACTIVE COHORT WAS COMPARABLE TO THAT SEEN IN THE OVERALL CARE-MS II POPULATION.[2]

MRI activity-free status over 2 years[2]



24.2% OF LEMTRADA-TREATED PATIENTS REMAINED MS DISEASE ACTIVITY-FREE AT TWO YEARS (P=0.0002).[2]

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What adverse events have been observed in trials and post-marketing surveillance?

The most important adverse reactions are:[1]

- Infusion-associated reactions (IARs)
- Infections
- Autoimmunity (immune thrombocytopenic purpura (ITP) thyroid disorders, nephropathies, cytopenias)

The most common adverse reactions with LEMTRADA (in ≥20% of patients) were:

- Rash
- Headache
- Pyrexia
- Respiratory tract infections

The table presented on the following pages is based on the pooled safety data from patients treated with LEMTRADA 12 mg in clinical trials where follow-up is available.[1] Within each system class, adverse events have been reported by decreasing seriousness.

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System Organ Class	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)	Not known (cannot be estimated from the available data)
Infections and infestations[1]	Upper respiratory tract infection, urinary tract infection, herpes virus infection	Herpes zoster infections, 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-Barr virus (EBV) infection (including reactivation)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)[1]		Skin papilloma			
Blood and lymphatic system disorders[1]	Lymphopenia, leukopenia, including neutropenia	Lymphadenopathy, immune thrombocytopenic purpura, thrombocytopenia, anaemia haematocrit decreased, leukocytosis	Pancytopenia, haemolytic anaemia, acquired haemophilia A	Haemophagocytic lymphohistiocytosis (HLH)	
Immune system disorders[1]		Cytokine release syndrome*, hypersensitivity including anaphylaxis*	Sarcoidosis		
Endocrine disorders[1]	Basedow's disease, hyperthyroidism, hypothyroidism	Autoimmune thyroiditis including thyroiditis subacute, goitre, anti-thyroid antibody positive			

System Organ Class	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)	Not known (cannot be estimated from the available data)
Metabolism and nutrition disorders[1]			Decreased appetite		
Psychiatric disorders[1]		Insomnia*, anxiety, depression			
Nervous system disorders[1]	Headache*	MS relapse, dizziness*, hypoaesthesia, paraesthesia, tremor, dysgeusia*, migraine*	Sensory disturbance, hyperaesthesia, tension headache, autoimmune encephalitis		Haemorrhagic stroke**, cervicocephalic arterial dissection**
Eye disorders[1]		Conjunctivitis, endocrine ophthalmopathy, vision blurred	Diplopia		
Ear and labyrinth disorders[1]		Vertigo	Ear pain		
Cardiac disorders[1]	Tachycardia*	Bradycardia*, palpitations	Atrial fibrillation		Myocardial ischaemia**, myocardial infarction**
Vascular disorders[1]	Flushing*	Hypotension*, hypertension*			

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System Organ Class	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)	Not known (cannot be estimated from the available data)
Respiratory, thoracic and mediastinal disorders[1]		Dyspnoea*, cough, epistaxis, hiccups, oropharyngeal pain, asthma	Throat tightness, throat irritation, pneumonitis		Pulmonary alveolar haemorrhage
Gastrointestinal disorders[1]	Nausea*	Abdominal pain, vomiting, diarrhoea, dyspepsia*, stomatitis	Constipation, gastro-oesophageal reflux disease, gingival bleeding, dry mouth, dysphagia, gastrointestinal disorder, haematochezia		
Hepatobiliary disorders[1]		Aspartate aminotransferase increased, alanine aminotransferase increased	Cholecystitis including acalculous cholecystitis and acute acalculous cholecystitis		Autoimmune hepatitis (associated with EBV infection)
Skin and subcutaneous tissue disorders[1]	Urticaria*, rash, pruritus*, generalised rash*	Erythema*, ecchymosis, alopecia, hyperhidrosis, acne, skin lesion, dermatitis	Blister, night sweats, swelling face, eczema, vitiligo		
Musculoskeletal and connective tissue disorders[1]		Myalgia, muscle weakness, arthralgia, back pain, pain in extremity, muscle spasms, neck pain, musculoskeletal pain	Musculoskeletal stiffness, limb discomfort		Adult Onset Still's Disease (AOSD)
Renal and urinary disorder[1]		Proteinuria, haematuria	Nephrolithiasis, ketonuria, nephropathies including anti-GBM disease		

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System Organ Class	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)	Not known (cannot be estimated from the available data)
Reproductive system and breast disorders[1]		Menorrhagia, menstruation irregular	Cervical dysplasia, amenorrhoea		
General disorders and administration site conditions[1]	Pyrexia*, fatigue*, chills*	Chest discomfort*, pain*, oedema peripheral, asthenia, influenza-like illness, malaise, infusion site pain			
Investigations[1]		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[1]		Contusion, infusion related reaction			

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How does LEMTRADA work?

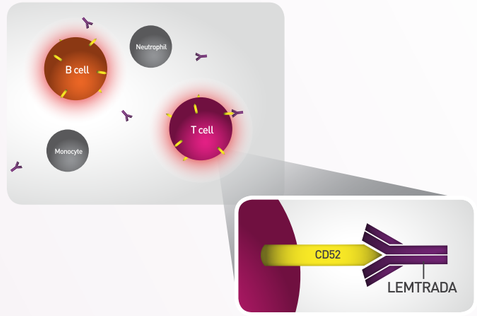
LEMTRADA is a humanised monoclonal antibody directed against the 21–28 kD cell surface glycoprotein CD52, a cell surface antigen present on T and B lymphocytes and at lower levels on natural killer (NK) cells, monocytes and macrophages.[1] There is little or no CD52 detected on neutrophils, plasma cells or bone marrow stem cells.[1] The mechanism of action by which LEMTRADA exerts its therapeutic effects in MS is not fully elucidated.[1]

Research suggests an immunomodulatory effect through the depletion and repopulation of lymphocytes, including:[1]

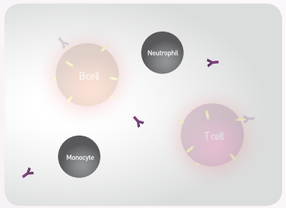
- Alterations in the number, proportions and properties of some lymphocyte subsets post-treatment
- Increased representation of regulatory T cell subsets
- Increased representation of memory T- and B-lymphocytes
- Transient effects on components of innate immunity (i.e., neutrophils, macrophages, NK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

THE REDUCTION IN THE NUMBER OF CIRCULATING T AND B CELLS BY LEMTRADA, AND SUBSEQUENT REPOPULATION, MAY REDUCE THE POTENTIAL FOR RELAPSE, WHICH ULTIMATELY DELAYS DISEASE PROGRESSION.[1]

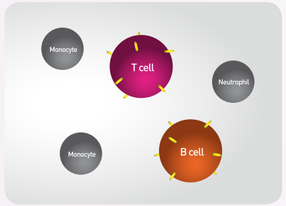
1. SELECTION
CD52 is selectively targeted



2. DEPLETION
Circulating T and B cells are depleted



3. REPOPULATION
B and T cells emerge in circulation



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Dosage and administration

What hospital setting criteria is required in order to administer LEMTRADA?

Treatment with LEMTRADA should only be initiated and supervised by a neurologist who is experienced in the treatment of patients with MS in a hospital with ready access to intensive care.[1]

Specialists and equipment required for the timely diagnosis and management of adverse reactions should be available. Especially:[1]

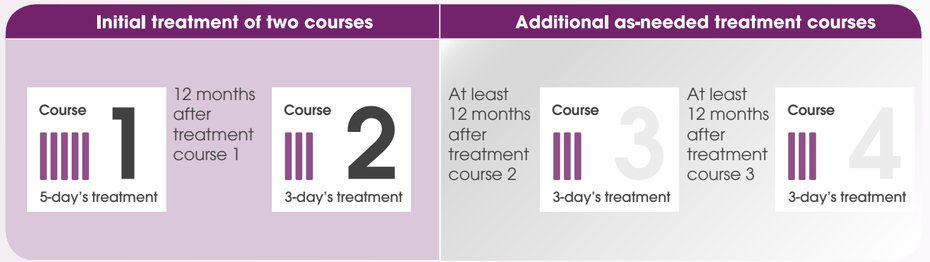
- Myocardial ischaemia
- Myocardial infarction
- Cerebrovascular adverse reactions
- Autoimmune conditions
- Infections

Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.[1]

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).

How is LEMTRADA administered?

The recommended dose of LEMTRADA is 12 mg/day administered by IV infusion for 2 initial treatment courses, with up to 2 additional treatment courses if needed.[1]



Missed doses should not be given on the same day as a scheduled dose.[1]

What follow-up is required?

Safety follow-up from initiation of the first treatment course and for **at least 48 months** after the last infusion of the second treatment course is required.[1] If an additional third or fourth course is administered, continue safety follow-up for at least 48 months after the last infusion.[1]

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How should LEMTRADA be stored?

Concentrate

- Store in a refrigerator (2°C – 8°C)[1]
- Do not freeze[1]
- Keep the vial in the outer carton in order to protect from light[1]

Diluted solution

- 8 hours of stability at 2°C – 8°C[1]
- Recommend product is used immediately[1]
- If not used immediately, store for no longer than 8 hours at 2°C – 8°C, under protection from light[1]

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Contraindications[1]

Patients with:

- Hypersensitivity to the active substance, or to any of the excipients
- Human immunodeficiency virus (HIV) infection
- Severe active infection until complete resolution
- Uncontrolled hypertension
- History of arterial dissection of the cervicocephalic arteries
- History of stroke
- History of angina pectoris or myocardial infarction
- Known coagulopathy, on anti-platelet or anti-coagulant therapy
- Other concomitant autoimmune diseases (besides MS)

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Special warnings and precautions for use

Autoimmunity

Treatment with LEMTRADA may result in the formation of autoantibodies and increase the risk of autoimmune mediated conditions which may be serious and life threatening.[1]

Patients and physicians should be made aware of the potential later onset of autoimmune disorders after the 48 months monitoring period.[1]

	Notes
Acquired haemophilia A[1]	
ITP[1]	
Nephropathies[1]	Includes anti-glomerular basement membrane (anti-GBM) disease
Thyroid disorders[1]	Includes Basedow's disease (Graves' disease), hyperthyroidism, hypothyroidism, autoimmune thyroiditis and goitre
Cytopenias[1]	For example, neutropenia, haemolytic anaemia and pancytopenia
Autoimmune hepatitis and hepatic injury[1]	

Please refer to the full SmPC for all details.

HLH

HLH (including fatal cases) has been reported in patients treated with LEMTRADA in post-marketing studies.[1]

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IARs

Most patients treated with LEMTRADA in controlled clinical trials experienced mild to moderate IARs during and/or up to 24 hours after LEMTRADA 12 mg administration.[1] The most common IARs included:[1]

- Headache
- Rash
- Pyrexia
- Nausea
- Urticaria
- Pruritus
- Insomnia
- Chills
- Flushing
- Fatigue
- Dyspnoea
- Dysgeusia
- Chest discomfort
- Generalised rash
- Tachycardia
- Bradycardia
- Dyspepsia
- Dizziness
- Pain

Serious reactions occurred in 3% of patients and included cases of headache, pyrexia, urticaria, tachycardia, atrial fibrillation, nausea, chest discomfort, and hypotension.[1]

It is recommended that patients be pre-medicated to ameliorate the effects of infusion reactions.[1] IARs may occur in patients despite pre-treatment.[1] Observation for infusion reactions is recommended during and for **at least 2 hours after LEMTRADA infusion**.[1] Extended observation time (hospitalisation) should be considered, as appropriate.[1] If severe infusion reactions occur, infusion should be discontinued immediately.[1]

Other serious reactions temporally associated with LEMTRADA infusion

Rare, serious, sometimes fatal and unpredictable adverse events from various organ systems have been reported during post-marketing use.[1] This includes:[1]

- Haemorrhagic stroke
- Myocardial ischaemia and myocardial infarction
- Dissection of the cervicocephalic arteries
- Pulmonary alveolar haemorrhage
- Thrombocytopenia
- Pericarditis
- Pneumonitis

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What additional caution should be exercised?

	Notes
Infections[1]	Including nasopharyngitis, urinary tract infection, upper respiratory tract infection, sinusitis, oral herpes, influenza, and bronchitis. Potentially serious infections include appendicitis, gastroenteritis, pneumonia, herpes zoster, tooth infection, serious varicella zoster, CMV, tuberculosis, listeriosis, cervical human papilloma virus and superficial fungal infections
EBV infection[1]	Including infection, reactivation and severe and sometimes fatal EBV hepatitis
Acute acalculous cholecystitis[1]	
Malignancy[1]	Caution should be exercised in initiating LEMTRADA therapy in patients with pre-existing and/or an on-going malignancy
Contraception[1]	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

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Infusion pre-treatment and screening

Pre-treatment

	Notes
To reduce the incidence and severity of IARs[1]	Pre-treatment with corticosteroids immediately prior to LEMTRADA administration and on each of the 3 days of any treatment course. Pre-treatment with antihistamines/ and or antipyretics prior to LEMTRADA administration
To reduce the risk of herpes infection[1]	Oral prophylaxis starting on the first day of each treatment course and continuing for a minimum of 1 month following treatment with LEMTRADA
To reduce the risk of listeriosis[1]	Avoid ingestion of uncooked or undercooked meats, soft cheeses and unpasteurised dairy products two weeks prior to, during, and for at least one month after LEMTRADA infusion

Screening

The following screening is recommended for potential LEMTRADA patients:[1]

- Human papilloma virus (HPV) – female patients should be screened annually
- Tuberculosis – screen before treatment
- Patients at high risk of Hepatitis B virus (HBV) and/or Hepatitis C virus (HCV) – screen before treatment

Recommended vaccinations

It is recommended that patients have completed local immunisation requirements **at least 6 weeks** prior to treatment with LEMTRADA.[1]

Patients without a history of chickenpox or without vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV and vaccination of antibody-negative patients should be considered prior to treatment initiation with LEMTRADA.[1] To allow for the full effect of the VZV vaccination to occur, treatment with LEMTRADA should be **postponed for 6 weeks following vaccination.**[1]

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Monitoring

Pre-infusion

Clinical tests
Recommended test
Baseline electrocardiograph (ECG)[1]
Vital signs, including heart rate and blood pressure[1]
Laboratory tests
Recommended test
Serum transaminases[1]
Serum creatinine levels[1]
Full blood count (FBC) with differential[1]
Urinalysis with microscopy[1]
Test of thyroid function[1]

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).

During infusion

Perform continuous/frequent (at least every hour) monitoring of heart rate, blood pressure and overall clinical status of the patients.[1]

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Post-infusion

Observation for infusion reactions (e.g. myocardial ischaemia, haemorrhagic stroke, cervicocephalic arterial dissection or pulmonary alveolar haemorrhage) is recommended during and for a minimum of 2 hours after LEMTRADA infusion.[1]

Patients with clinical symptoms suggesting development of a serious adverse event should be closely monitored until complete resolution of the symptoms.[1]

The observation time should be extended (hospitalisation) as appropriate.[1]

Patients should be educated on the potential for delayed onset of infusion-associated reactions and instructed to report symptoms and seek appropriate medical care.[1]

Platelet counts 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.[1]

Clinically significant thrombocytopenia needs to be followed until resolution. Consider referral to a haematologist for management.[1]

Serum transaminases, serum creatinine levels, full blood count with differential and urinalysis with microscopy should be obtained at monthly intervals for at least until 48 months after the last infusion course.[1]

A test of thyroid function should be obtained every 3 months at least until 48 months after the last infusion course.[1]

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Family planning

What is the recommendation for pregnant patients or patients planning for a family?

LEMTRADA should only be administered during pregnancy if the **potential benefit justifies the potential risk to the foetus.**[1] Women of childbearing potential have to use effective contraception when receiving treatment with LEMTRADA and **up to 4 months** after each course of treatment.[1]

What evidence is there of LEMTRADA use during pregnancy?

There is a **limited amount of data** from the use of alemtuzumab in pregnant women.[1] Human IgG is known to cross the placental barrier; alemtuzumab may cross the placental barrier and thus potentially pose a risk to the foetus.[1] Animal studies have shown reproductive toxicity.[1] It is not known whether alemtuzumab can cause foetal harm when administered to pregnant women or whether it can affect reproductive capacity.[1]

Thyroid disease in pregnancy

Thyroid disease poses special risks in women who are pregnant.[1] Without treatment of hypothyroidism during pregnancy, there is an increased risk for miscarriage and foetal effects such as mental retardation and dwarfism.[1] 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.[1]

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Family planning

Is it possible to breastfeed whilst on LEMTRADA?

Alemtuzumab was detected in the milk and offspring of lactating female mice.[1] It is unknown whether alemtuzumab is excreted in human milk.[1] A risk to the suckling newborn/infant cannot be excluded.[1] 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.[1] However, benefits of conferred immunity through breast-milk may outweigh the risks of potential exposure to alemtuzumab for the suckling newborn/infant.[1]

Is there any known impact on fertility?

There are **no adequate clinical safety data** on the effect of LEMTRADA on fertility.[1] In a sub-study in 13 male LEMTRADA-treated patients, there was no evidence of aspermia, azoospermia, consistently depressed sperm count, motility disorders or an increase in sperm morphological abnormalities.[1]

CD52 is known to be present in human and rodent reproductive tissues.[1] Animal data have shown effects on fertility in humanised mice, however a potential impact on human fertility during the period of exposure is unknown based on the available data.[1]

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Summary

- Consider LEMTRADA for appropriate RRMS, RES or second line highly-active patients[1]
- LEMTRADA has demonstrated up to 9 years of efficacy in the highly-active patient cohort of the CARE-MS II population[2,3,5,6]
- The most important adverse reactions with LEMTRADA are IARs, infections and autoimmunity (ITP, thyroid disorders, nephropathies, cytopenias)[1]
- The LEMTRADA Risk Management Program has been designed to help manage patient safety

LEMTRADA OFFERS YOUR PATIENTS THE CHANCE OF PROVEN EFFICACY SUPPORTED BY A FINITE DOSING SCHEDULE AND COMPREHENSIVE MONITORING PROGRAMME[1–3]

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PRACTICAL INFORMATION GUIDE

LEMTRADA® alemtuzumab 12mg IV

PRESCRIBING INFORMATION – GB LEMTRADA▼ (alemtuzumab) 12mg concentrate for solution for infusion.
Please refer to the Summary of Product Characteristics (SmPC) before prescribing.
Presentation: Each vial contains 12 mg alemtuzumab in 1.2 ml solution (10 mg/ml).
Indication: 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.
Dosage and Administration: LEMTRADA treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with 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. The recommended dose of LEMTRADA is 12 mg/day administered by intravenous (IV) infusion for 2 initial, treatment courses, with up to 2 additional treatment courses if needed. Missed doses should not be given on the same day as a scheduled dose. The diluted LEMTRADA solution should be administered by IV infusion over a period of approximately 4 hours. 1st *treatment course:* 12 mg/day on 5 consecutive days (60 mg total dose). *2nd treatment course:* 12 mg/day on 3 consecutive days (36 mg total dose) administered 12 months after the 1st treatment course. *Additional as-needed treatment course(s) 3rd/4th:* 12 mg/day on 3 consecutive days (36 mg total dose) administered at least 12 months after the prior treatment course. *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. 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. *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. **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:* No data available. *Paediatric (0-18 years):* No data available.
Contraindications: Patients with: Hypersensitivity to the active substance, or to any of the excipients. HIV infection. Severe active infection until complete resolution. Uncontrolled hypertension. A history of arterial dissection of the cervicocephalic arteries. A history of stroke. A history of angina pectoris or myocardial infarction. Known coagulopathy, on anti-platelet or anti-coagulant therapy. Other concomitant autoimmune diseases (besides MS).
Precautions and warnings: 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, benefits, and the need to commit to follow up from treatment initiation for at least 48 months after the last infusion of LEMTRADA. Patients and physicians should be made aware of the potential later onset of adverse events after the 48 months monitoring period. Educate patients on the signs and symptoms of all conditions, and to seek immediate medical attention if any of these symptoms are observed. If confirmed, seek specialist advice. *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 including anti-glomerular basement membrane (anti-GBM) disease, autoimmune hepatitis (AIH), acquired haemophilia A, thrombotic thrombocytopenic purpura (TTP), sarcoidosis, and autoimmune encephalitis. Patients who develop autoimmunity should be assessed for other autoimmune mediated conditions. *Acquired haemophilia A:* 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. *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 characterised 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 characterised 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 aetiologies. *ITP:* Symptoms 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, and an appropriate differential diagnosis has to be undertaken. 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 which, 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 is confirmed, appropriate medical intervention should be promptly initiated, including immediate referral to a specialist. *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. *Nephropathies including anti-GBM disease:* 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 and an appropriate differential diagnosis has to be undertaken. 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 and urinalysis with microscopy should be obtained prior to initiation of treatment and at monthly intervals thereafter until at least 48 months after the last infusion. *Thyroid disorders:* Observed autoimmune thyroid disorders included hyperthyroidism or hypothyroidism. Most events were mild to moderate in severity. Regardless of pretreatment anti-TPO antibody status patients may develop a thyroid adverse reaction and must have all tests periodically performed as described above. Thyroid function tests 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. In the post-marketing setting several patients who developed biopsy proven auto-immune hepatitis had previously developed autoimmune thyroid disorders. *Cytopenia:* Use of LEMTRADA has been associated with suspected autoimmune cytopenias such as neutropenia, haemolytic anaemia and pancytopenia. FBC results should be used to monitor for cytopenias, including neutropenia. *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. Liver function tests should be performed before initial treatment and at monthly intervals until at least 48 months after the last infusion. *Haemophagocytic lymphohistiocytosis (HLH):* HLH (including fatal cases) have 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, such as 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 who develop early manifestations of pathologic immune activation should be evaluated immediately. *Infusion-Associated Reactions (IARs):* Most patients treated with LEMTRADA experienced mild to moderate IARs during and/or up to 24 hours after. Observe patients for IARs 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 should be available. *Adult Onset Still's Disease (AOSD):* During post-marketing use, AOSD has been reported in patients treated with LEMTRADA. AOSD is a rare inflammatory condition that requires urgent evaluation and treatment. Patients with AOSD may have a combination of the following signs and symptoms: fever, arthritis, rash and leukocytosis in the absence of infections, malignancies, and other rheumatic conditions. Consider interruption or discontinuation of treatment with LEMTRADA if an alternate etiology for the signs or symptoms cannot be established. *Other serious reactions temporally associated with LEMTRADA infusion:* During post-marketing use, rare, serious, sometimes fatal and unpredictable adverse events from various organ systems (such as, haemorrhagic stroke; myocardial ischaemia and myocardial infarction; dissection of the cervico-cephalic arteries; pulmonary alveolar haemorrhage; thrombocytopenia; pericarditis; pneumonitis) have been reported. Reactions have occurred following any of the doses and

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also after course number 2. *Infusion instructions to reduce serious reactions temporally associated with LEMTRADA infusion: Pre-infusion:* 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. *Serious infections included:* Appendicitis, gastroenteritis, herpes zoster, and tooth infection were seen during clinical trials. 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, Cervical human papilloma virus (HPV) infection, including cervical dysplasia and anogenital warts have been reported. It is recommended that HPV screening be completed annually for female patients. Cytomegalovirus infections (CMV) including cases of CMV reactivation have been reported. 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. Active and latent tuberculosis (TB), including a few cases of disseminated tuberculosis, have been reported. 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, was reported. Pneumonitis has been reported in patients who received LEMTRADA infusions. Most cases occurred within the first month after treatment with LEMTRADA. *Immunomodulation:* As with other immunomodulating therapies, potential combined effects on the patient's immune system should be taken into account when considering administration of LEMTRADA, due to the potential increase risk of immunosuppression. 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. *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 (e.g. cognitive, neurological or psychiatric symptoms). If a diagnosis of PML has been made, treatment with alemtuzumab should not be started or restarted. *Acute acalculous cholecystitis (AAC):* LEMTRADA may increase the risk of AAC. Cases of AAC have been reported in LEMTRADA- treated patients during post marketing. Time to onset of symptoms ranged from <24 hours-2 months after infusion. Symptoms include abdominal pain, abdominal tenderness, fever, nausea, and vomiting. AAC may be associated with high morbidity and mortality rates if not diagnosed early and treated. If suspected, evaluate and treat promptly. *Malignancy:* As with other immunomodulatory therapies, caution advised when initiating treatment in patients with pre-existing and/or on-going malignancy. *Vaccination:* It is recommended that patients have completed local immunisation requirements ≥6 weeks prior to treatment with LEMTRADA. Live viral vaccines should not be administered following a course of LEMTRADA. Varicella zoster virus vaccination of antibody-negative patients should be considered ≥6 weeks prior to treatment initiation. *Fertility, pregnancy and lactation:* Women of childbearing potential have to use effective contraception during and for 4 months following a course of LEMTRADA. There is a limited data from the use in pregnant women. LEMTRADA should be administered during pregnancy only if the potential benefit justifies the potential risk to the foetus. Animal studies have shown reproductive toxicity. Special risks are associated with thyroid disorders in pregnant women. Untreated hypothyroidism in pregnant women increases miscarriage risk and foetal effects (e.g. mental retardation, dwarfism). Pregnant women with Graves' disease may transfer thyroid stimulating hormone receptor antibodies to foetus so may cause transient neonatal Graves' disease. Discontinue breastfeeding during LEMTRADA treatment and for 4 months following that course. Benefits of breastfeeding may outweigh potential risks of LEMTRADA exposure. Animal data have shown effects on fertility in humanised mice however a potential impact on human fertility during the period of exposure is unknown based on the available data. **Interactions:** In a controlled clinical trial, MS patients recently treated with beta interferon and glatiramer acetate, were required to discontinue treatment 28 days before initiating treatment with LEMTRADA.

Adverse reactions: *Very common (≥1/10):* Upper respiratory tract infection, urinary tract infection, Herpes virus infection, lymphopenia, leukopenia, (including neutropenia), Basedow's disease, hyperthyroidism, hypothyroidism, headache, tachycardia, flushing, nausea, urticaria, rash, pruritus, generalised rash, pyrexia, fatigue, chills. *Common (≥1/100<1/10):* Herpes Zoster infection, lower respiratory tract infections, gastroenteritis, oral candidiasis, vulvovaginal candidiasis, influenza, ear infection, pneumonia, vaginal infection, tooth infection, skin papilloma, lymphadenopathy, immune thrombocytopenic purpura, thrombocytopenia, anaemia, haematocrit decreased, leukocytosis, cytokine release syndrome, hypersensitivity including anaphylaxis, autoimmune thyroiditis, goitre, anti-thyroid antibody positive, insomnia, anxiety, depression, MS relapse, dizziness, hypoaesthesia, paraesthesia, tremor, dysgeusia, migraine, conjunctivitis, endocrine ophthalmopathy, vision blurred, vertigo, bradycardia, palpitations, hypotension, hypertension, dyspnoea, cough, epistaxis, hiccups, oropharyngeal pain, asthma, abdominal pain, vomiting, diarrhoea dyspepsia, stomatitis, aspartate aminotransferase increased, alanine aminotransferase increase, erythema, ecchymosis, alopecia, hyperhidrosis, acne, skin lesion, dermatitis, myalgia, muscle weakness, arthralgia, back pain, pain in extremity, muscle spasms, neck pain, musculoskeletal pain, proteinuria, haematuria, menorrhagia, menstruation irregular, chest discomfort, pain, oedema peripheral, asthenia, influenza-like illness, malaise, infusion site pain, blood creatinine increased, contusion and infusion related reaction. *Uncommon (≥1/1,000<1/100):* Onychomycosis, gingivitis, fungal skin infection, tonsillitis, acute sinusitis, cellulitis, tuberculosis, cytomegalovirus infection, pancytopenia, haemolytic anaemia, acquired haemophilia A, sarcoidosis, decreased appetite, sensory disturbance, hyperaesthesia, tension headache, autoimmune encephalitis, diplopia, ear pain, atrial fibrillation, throat tightness, throat irritation, pneumonitis, constipation, gastro-oesophageal reflux disease, gingival bleeding, dry mouth, dysphagia, gastrointestinal disorder, haematochezia, cholecystitis including acalculous cholecystitis and AAC. Blister, night sweats, swelling face, eczema, vitiligo, alopecia areata, musculoskeletal stiffness, limb discomfort, nephrolithiasis, ketonuria, nephropathies including anti-GBM disease, cervical dysplasia, amenorrhoea, weight decreased, weight increased, red blood cell count decreased, bacterial test positive, blood glucose increased and mean cell volume increase. *Rare (≥1/10,000<1/1,000):* Haemophagocytic lymphohistiocytosis and thrombotic thrombocytopenic purpura. *Unknown:* Listeriosis/listeria meningitis, EBV infection (including reactivation), Haemorrhagic stroke, cervicocephalic arterial dissection, myocardial ischaemia, myocardial infarction, Pulmonary alveolar haemorrhage, autoimmune hepatitis and hepatitis (associated with EBV infection), Adult Onset Still's Disease. **Please refer to the SmPC for full details on adverse reactions. List Price:** £7,045 per 12mg vial. **Legal category:** POM. **Marketing Authorisation Number:** PLGB 04425/0787. **Marketing Authorisation Holder:** Aventis Pharma Ltd, 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT, UK. **Further information is available from:** Sanofi, 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT, UK or contact uk-medicalinformation@sanofi.com
SmPC Date: 11/08/2023
Date of preparation: August 2023

Adverse events should be reported. Reporting forms and information can be found at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Adverse events should also be reported to the Sanofi Drug Safety department on Tel: 0800 0902314. Alternatively, send via email to UK-drugsafety@sanofi.com

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PRACTICAL INFORMATION GUIDE

LEMTRADA® alemtuzumab 12mg IV

PRESCRIBING INFORMATION – IE & NI LEMTRADA▼(alemtuzumab) 12mg concentrate for solution for infusion
Please refer to the Summary of Product Characteristics (SmPC) before prescribing.
Presentation: Each vial contains 12 mg alemtuzumab in 1.2 ml solution (10 mg/ml).
Indication: 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.
Dosage and Administration: LEMTRADA treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with 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. The recommended dose of LEMTRADA is 12 mg/day administered by intravenous (IV) infusion for 2 initial, treatment courses, with up to 2 additional treatment courses if needed. Missed doses should not be given on the same day as a scheduled dose. The diluted LEMTRADA solution should be administered by IV infusion over a period of approximately 4 hours. 1st *treatment course:* 12 mg/day on 5 consecutive days (60 mg total dose). *2nd treatment course:* 12 mg/day on 3 consecutive days (36 mg total dose) administered 12 months after the 1st treatment course. *Additional as-needed treatment course(s) 3rd/4th:* 12 mg/day on 3 consecutive days (36 mg total dose) administered at least 12 months after the prior treatment course. *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. 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. *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. **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:* No data available. *Paediatric (0-18 years):* No data available.
Contraindications: Patients with: Hypersensitivity to the active substance, or to any of the excipients. HIV infection. Severe active infection until complete resolution. Uncontrolled hypertension. A history of arterial dissection of the cervicocephalic arteries. A history of stroke. A history of angina pectoris or myocardial infarction. Known coagulopathy, on anti-platelet or anti-coagulant therapy. Other concomitant autoimmune diseases (besides MS).
Precautions and warnings: 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, benefits, and the need to commit to follow up from treatment initiation for at least 48 months after the last infusion of LEMTRADA. Patients and physicians should be made aware of the potential later onset of adverse events after the 48 months monitoring period. Educate patients on the signs and symptoms of all conditions, and to seek immediate medical attention if any of these symptoms are observed. If confirmed, seek specialist advice. *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 including anti-Glomerular Basement Membrane (anti-GBM) disease, autoimmune hepatitis (AIH), acquired haemophilia A, thrombotic thrombocytopenic purpura (TTP), sarcoidosis, and autoimmune encephalitis (AIE). Patients who develop autoimmunity should be assessed for other autoimmune mediated conditions. *Acquired haemophilia A:* 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. *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. *AIE:* Cases of AIE have been reported in patients treated with LEMTRADA. AIE is characterised 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 AIE should have neuroimaging (MRI), EEG, lumbar puncture and serologic testing for appropriate biomarkers (e.g. neural autoantibodies) to confirm diagnosis and exclude alternative etiologies. *ITP:* Symptoms 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, and an appropriate differential diagnosis has to be undertaken. 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 which, 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 is confirmed, appropriate medical intervention should be promptly initiated, including immediate referral to a specialist. *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. *Nephropathies including anti-GBM disease:* 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 and an appropriate differential diagnosis has to be undertaken. 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 and urinalysis with microscopy should be obtained prior to initiation of treatment and at monthly intervals thereafter until at least 48 months after the last infusion. *Thyroid disorders:* Observed autoimmune thyroid disorders included hyperthyroidism or hypothyroidism. Most events were mild to moderate in severity. Regardless of pretreatment anti-TPO antibody status patients may develop a thyroid adverse reaction and must have all tests periodically performed as described above. Thyroid function tests 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. In the post-marketing setting several patients who developed biopsy proven auto-immune hepatitis had previously developed autoimmune thyroid disorders. *Cytopenia:* Use of LEMTRADA has been associated with suspected autoimmune cytopenias such as neutropenia, haemolytic anaemia and pancytopenia. FBC results should be used to monitor for cytopenias, including neutropenia. *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. Liver function tests should be performed before initial treatment and at monthly intervals until at least 48 months after the last infusion. *Haemophagocytic lymphohistiocytosis (HLH):* HLH (including fatal cases) have 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, such as 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 who develop early manifestations of pathologic immune activation should be evaluated immediately. *Infusion-Associated Reactions (IARs):* Most patients treated with LEMTRADA experienced mild to moderate IARs during and/or up to 24 hours after. Observe patients for IARs 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. 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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 (such as, haemorrhagic stroke; myocardial ischaemia and myocardial infarction; dissection of the cervicocephalic arteries; pulmonary alveolar haemorrhage; thrombocytopenia; Pericarditis) have been reported. Reactions have occurred following any of the doses and also after course number 2. Pneumonitis has been reported in patients who received

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LEMTRADA infusions. Most cases occurred within the first month after treatment with LEMTRADA. *Infusion instructions to reduce serious reactions temporally associated with LEMTRADA infusion: Pre-infusion:* 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, cervicocephalic 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, cervicocephalic 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. 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Varicella zoster virus vaccination of antibody- negative patients should be considered ≥6 weeks prior to treatment initiation. *Fertility, pregnancy and lactation:* Women of childbearing potential have to use effective contraception during and for 4 months following a course of LEMTRADA. There is a limited data from the use in pregnant women. LEMTRADA should be administered during pregnancy only if the potential benefit justifies the potential risk to the foetus. Animal studies have shown reproductive toxicity. Special risks are associated with thyroid disorders in pregnant women. Untreated hypothyroidism in pregnant women increases miscarriage risk and foetal effects (e.g. mental retardation, dwarfism). Pregnant women with Graves' disease may transfer thyroid stimulating hormone receptor antibodies to foetus so may cause transient neonatal Graves' disease. Discontinue breastfeeding during LEMTRADA treatment and for 4 months following that course. Benefits of breastfeeding may outweigh potential risks of LEMTRADA exposure. Animal data have shown effects on fertility in humanised mice however a potential impact on human fertility during the period of exposure is unknown based on the available data. **Interactions:** In a controlled clinical trial, MS patients recently treated with beta interferon and glatiramer acetate, were required to discontinue treatment 28 days before initiating treatment with LEMTRADA.

Adverse reactions: *Very common (≥1/10):* Upper respiratory tract infection, urinary tract infection, Herpes virus infection, lymphopenia, leukopenia, (including neutropenia), Basedow's disease, hyperthyroidism, hypothyroidism, headache, tachycardia, flushing, nausea, urticaria, rash, pruritus, generalised rash, pyrexia, fatigue, chills. *Common (≥1/100<1/10):* Herpes Zoster infection, lower respiratory tract infections, gastroenteritis, oral candidiasis, vulvovaginal candidiasis, influenza, ear infection, pneumonia, vaginal infection, tooth infection, skin papilloma, lymphadenopathy, immune thrombocytopenic purpura, thrombocytopenia, anaemia, haematocrit decreased, leukocytosis, cytokine release syndrome, hypersensitivity including anaphylaxis, autoimmune thyroiditis, goitre, anti-thyroid antibody positive, insomnia, anxiety, depression, MS relapse, dizziness, hypoaesthesia, paraesthesia, tremor, dysgeusia, migraine, conjunctivitis, endocrine ophthalmopathy, vision blurred, vertigo, bradycardia, palpitations, hypotension, hypertension, dyspnoea, cough, epistaxis, hiccups, oropharyngeal pain, asthma, abdominal pain, vomiting, diarrhoea dyspepsia, stomatitis, aspartate aminotransferase increased, alanine aminotransferase increase, erythema, ecchymosis, alopecia, hyperhidrosis, acne, skin lesion, dermatitis, myalgia, muscle weakness, arthralgia, back pain, pain in extremity, muscle spasms, neck pain, musculoskeletal pain, proteinuria, haematuria, menorrhagia, menstruation irregular, chest discomfort, pain, oedema peripheral, asthenia, influenza-like illness, malaise, infusion site pain, blood creatinine increased, contusion and infusion related reaction. *Uncommon (≥1/1,000<1/100):* Onychomycosis, gingivitis, fungal skin infection, tonsillitis, acute sinusitis, cellulitis, pneumonitis, tuberculosis, cytomegalovirus infection, pancytopenia, haemolytic anaemia, acquired haemophilia A, sarcoidosis, decreased appetite, sensory disturbance, hyperaesthesia, tension headache, autoimmune encephalitis, diplopia, ear pain, atrial fibrillation, throat tightness, throat irritation, constipation, gastro-oesophageal reflux disease, gingival bleeding, dry mouth, dysphagia, gastrointestinal disorder, haematochezia, cholecystitis including acalculous cholecystitis and AAC. Blister, night sweats, swelling face, eczema, vitiligo, alopecia areata, musculoskeletal stiffness, limb discomfort, nephrolithiasis, ketonuria, nephropathies including anti-GBM disease, cervical dysplasia, amenorrhoea, weight decreased, weight increased, red blood cell count decreased, bacterial test positive, blood glucose increased and mean cell volume increase. *Rare (≥1/10,000<1/1,000):* Haemophagocytic lymphohistiocytosis, thrombotic thrombocytopenic purpura. *Unknown:* Listeriosis/listeria meningitis, EBV infection (including reactivation), Haemorrhagic stroke, cervicocephalic arterial dissection, myocardial ischaemia, myocardial infarction, Pulmonary alveolar haemorrhage, autoimmune hepatitis, hepatitis (associated with EBV infection) and Adult Onset Still's Disease. **Please refer to the SmPC for full details on adverse reactions.**

List Price: UK: £7,045 per 12mg vial. **IE:** Price on Application. **Legal classification:** POM. **Marketing Authorisation Holder:** Sanofi Belgium, Leonardo Da Vincilaan 19, B-1831 Diegem, Belgium. **MA number:** EU/1/13/869/001. **For more information please contact:** ***UK:*** Sanofi, 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT, UK or contact ukmedicalinformation@sanofi.com ***IE:*** Sanofi, 18 Riverwalk, Citywest Business Campus, Dublin 24 or contact IEmedinfo@sanofi.com.

SmPC Date: 7 July 2023

Date of preparation: July 2023.

Adverse events should be reported.
Reporting forms and information can be found at:

In the UK: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store Adverse events should also be reported to the Sanofi Drug Safety department on Tel: 0800 0902314. Alternatively, send via email to UK-drugsafety@sanofi.com.

In Ireland: www.hpra.ie; email: medsafety@hpra.ie. Adverse events should also be reported to Sanofi Ireland Ltd. Tel: 01 403 5600. Alternatively, send via email to IEPharmacovigilance@sanofi.com

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Footnotes

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

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