Prescribing Information: 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 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

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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