PROFESSIONAL INFORMATION

Tuberculosis screening for active and inactive ("latent") tuberculosis, and if required, the prescribing of appropriate treatment if the patient has an active tuberculosis infection, or appropriate prophylactic treatment if the patient presents with latent tuberculosis to prevent tuberculosis infection, should be undertaken according to the relevant South African guidelines prior to initiation or re-administration of LEMTRADA treatment.
Health care providers should delay initiation or re-administration of LEMTRADA treatment in patients at risk, with detected active or latent tuberculosis until the infection is fully controlled.
Further, preventative and post-treatment monitoring approaches for active and latent tuberculosis should be tailored to individual patient and treatment risk factors as assessed by the treating health care provider.

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE

LEMTRADA® concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-use vial contains 12 mg/1,2 mL alemtuzumab (10 mg/mL).

Sugar free.

Excipients with known effect

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

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

A clear, colourless to slightly yellow concentrate with pH 7,0 – 7,4, containing no antimicrobial preservatives.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

Posology

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

Initial treatment of 2 courses:

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

Additional as needed treatment courses:

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

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

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

Pre-treatment

Patients should be premedicated with corticosteroids immediately prior to LEMTRADA administration for 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. Pre-treatment 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.

Special populations

Elderly population

Clinical studies of LEMTRADA did not include sufficient numbers of patients aged over 65 years old to determine 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 paediatric MS patients below the age of 18 years have not been established.

Method of administration

Route of administration: intravenous (IV) infusion.

LEMTRADA must be diluted before infusion.

The diluted solution should be administered by IV infusion over a period of approximately 4 hours.

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

Special handling conditions

LEMTRADA vials should be inspected for particulate matter and discolouration prior to administration. Do not use if particulate matter is present or the solution is discoloured. Do not freeze or shake vials prior to use. Protect from light.

4.3 Contraindications

LEMTRADA is contraindicated in:

- Patients with known Type 1 hypersensitivity or anaphylactic reactions to alemtuzumab or any of the ingredients of the formulation (see section 6.1).
- Patients who are infected with human immunodeficiency virus (HIV).
- Patients with severe active infection.
- Patients with uncontrolled hypertension.
- Patients with a history of arterial dissection of the cervicocephalic arteries.
- Patients with a history of stroke.
- Patients with a history of angina pectoris or myocardial infarction.
- Patients with known coagulopathy or on concomitant anti-coagulant therapy.

4.4 Special warnings and precautions for use

Before treatment, patients must receive educational information and be informed about the risks and benefits, and the need to commit to follow up from treatment initiation until 48 months after the last infusion of the second LEMTRADA treatment course. If an additional course is administered,

continue safety follow-up until 48 months after the last infusion. Remind the patient to remain vigilant for symptoms they may experience and to seek immediate medical help if they have any concerns.

Autoimmunity

Treatment with LEMTRADA may result in the formation of autoantibodies and increase the risk of autoimmune-mediated conditions, which may be serious and life-threatening. Reported autoimmune conditions include thyroid disorders, immune thrombocytopenic purpura (ITP), or, rarely, nephropathies (e.g. anti-glomerular basement membrane disease), autoimmune hepatitis (AIH), acquired haemophilia A, thrombotic thrombocytopenic purpura (TTP) and autoimmune encephalitis. In the post-marketing setting, patients developing multiple autoimmune disorders after LEMTRADA treatment have been observed. Patients who develop autoimmunity should be assessed for other autoimmune-mediated conditions. Patients and medical practitioners should be made aware of the potential later onset of autoimmune disorders after the 48 months monitoring period.

Acquired haemophilia A

Cases of acquired haemophilia A (anti-factor VIII antibodies) have been reported in both clinical trial and post-marketing setting. Patients typically present with spontaneous subcutaneous haematomas and extensive bruising although haematuria, epistaxis, gastrointestinal or other types of bleeding may occur. A coagulopathy panel including aPTT must be obtained in all patients who present with such symptoms. Patients should be informed about the signs and symptoms of acquired haemophilia A and advised to seek immediate medical attention if any of these symptoms occur.

Immune thrombocytopenic purpura (ITP)

Serious events of ITP have been observed in 12 (1 %) patients treated with LEMTRADA in controlled clinical trials in MS (corresponding to an annualised rate 0,0047 events/patient/year).

In a controlled clinical trial in patients with MS, 1 patient developed ITP that went unrecognised prior to the implementation of monthly blood monitoring requirements and died from intracerebral haemorrhage.

An additional 12 serious events of ITP have been observed through a median of 6,1 years (maximum 12 years) of follow-up (cumulative annualised rate 0,0028 events/patient/year).

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

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

If ITP onset is confirmed, appropriate medical intervention should be promptly initiated, including immediate referral to a specialist. Data from clinical trials in MS have 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 re-treatment with LEMTRADA following the occurrence of ITP is unknown.

Nephropathies

Nephropathies, including anti-glomerular basement membrane (anti-GBM) disease, have been observed in 6 (0,4 %) patients in clinical trials in MS through a median of 6,1 years (maximum 12 years) of follow-up and generally occurred within 39 months following 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 as a component of anti-GBM disease.

Anti-GBM disease may lead to renal failure requiring dialysis and/or transplantation if not treated rapidly and can be life-threatening if left untreated. The patient should be reminded to remain

vigilant for symptoms they may experience and to seek immediate medical help if they have any concerns.

Serum creatinine levels and urinalysis with cell counts should be obtained prior to initiation of treatment and at monthly intervals thereafter until 48 months after the last infusion. The observation of clinically significant changes from baseline in serum creatinine, unexplained 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.

The potential risk associated with re-treatment with LEMTRADA following the occurrence of nephropathies is unknown.

Thyroid disorders

Thyroid endocrine disorders including autoimmune thyroid disorders have been observed in an estimated 36,8 % of patients treated with LEMTRADA 12 mg in clinical trials in MS with a median of 6,1 years (maximum 12 years) of follow-up from the first LEMTRADA exposure.

Observed autoimmune thyroid disorders included hyperthyroidism or hypothyroidism. Most events were mild to moderate in severity. Serious endocrine events occurred in 4,4 % of patients, with Basedow's disease (also known as Graves' disease), hyperthyroidism, hypothyroidism, autoimmune thyroiditis, and goitre occurring in more than 1 patient.

Most thyroid events were managed with conventional medical therapy, however, some patients required surgical intervention.

In clinical trials, patients who developed thyroid adverse events were permitted to receive re-treatment with LEMTRADA. Approximately 5 % of patients from the total study population developed a thyroid adverse event during the year following the initial treatment course of alemtuzumab and were re-treated. The majority of those patients did not experience a worsening in severity of thyroid disorders.

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

last infusion.

After this period of time, testing should be performed based on clinical findings suggestive of thyroid dysfunction or in case of pregnancy.

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

Cytopenias

Suspected autoimmune cytopenias such as neutropenia, haemolytic anaemia and pancytopenia have been infrequently reported in patients in clinical trials in MS. CBC results should be used to monitor for cytopenias. If a cytopenia is confirmed, appropriate medical intervention should be promptly initiated, including referral to a specialist.

Autoimmune hepatitis (AIH)

Cases of autoimmune hepatitis (including fatal cases and cases requiring liver transplantation) causing clinically significant liver injury, including acute liver failure requiring transplant, have been reported in patients treated with LEMTRADA in the post-marketing setting. If a patient develops clinical signs, including unexplained liver enzyme elevations or symptoms suggestive of hepatic dysfunction (e.g. unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine), promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment with LEMTRADA, as appropriate. Liver function tests should be performed before initial treatment and at monthly intervals until at least 48 months after the last infusion. Patients should be informed about the risk of autoimmune hepatitis, hepatic injury and related symptoms.

Thrombotic thrombocytopenic purpura (TTP)

During post-marketing use, TTP, which can be fatal, has been reported in patients treated with LEMTRADA. TTP is a serious condition that requires urgent evaluation and treatment. TTP may be characterised by thrombocytopenia, microangiopathic haemolytic anaemia, neurological sequelae, fever and renal impairment. It is associated with high morbidity and mortality rates if not recognised

and treated early.

Autoimmune encephalitis

Cases of autoimmune encephalitis during post-marketing use have been reported in patients treated with LEMTRADA. Autoimmune encephalitis is confirmed by the presence of neural autoantibodies as well as a variety of clinical manifestations like subacute onset of memory impairment, altered mental status, psychiatric symptoms, neurological findings and seizures.

Infusion-associated reactions (IARs)

In clinical trials, infusion-associated reactions (IARs) were defined as any adverse event occurring during or within 24 hours of LEMTRADA infusion. Most patients treated with LEMTRADA in controlled clinical trials in MS experienced IARs during and/or up to 24 hours after LEMTRADA 12 mg administration. The incidence of IARs was higher in course 1 than in subsequent courses. Through all available follow-up, including patients who received additional treatment courses, the most common IARs included headache, rash, pyrexia, nausea, urticaria, pruritus, insomnia, chills, flushing, fatigue, dyspnoea, dysgeusia, chest discomfort, generalised rash, tachycardia, bradycardia, dyspepsia, dizziness and pain. Serious reactions occurred in 3 % of patients including cases of headache, pyrexia, urticaria, tachycardia, atrial fibrillation, nausea, chest discomfort and hypotension. In addition, anaphylaxis has been reported.

During post-marketing use, serious, sometimes fatal and unpredictable adverse events from various organ systems have been reported. Cases of pulmonary alveolar haemorrhage, myocardial ischaemia, myocardial infarction, stroke (including ischaemic and haemorrhagic stroke), cervicocephalic (e.g. vertebral, carotid) arterial dissection, and thrombocytopenia have been reported. Reactions may occur following any of the doses during the treatment course. In the majority of cases, time to onset was within 1 – 3 days of LEMTRADA infusion. Patients should be informed about the signs and symptoms and advised to seek immediate medical attention if any of these symptoms occur.

Haemorrhagic stroke

In patients with available documentation, it was noted that there was increased blood pressure from baseline before the haemorrhage. There were no obvious risk factors in the majority of patients.

Myocardial ischaemia and myocardial infarction

It was noted that in some of the patients, blood pressure and/or heart rate was temporarily abnormal during the infusion. There were no obvious risk factors in the majority of patients.

Dissection of the cervicocephalic arteries

Cases of cervicocephalic arterial dissections, including multiple dissections, have been reported both within the first days after the LEMTRADA infusion or later on within the first month after the infusion.

Pulmonary alveolar haemorrhage

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

Thrombocytopenia

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

It is recommended that patients be pre-medicated with corticosteroids immediately prior to the initiation of the LEMTRADA infusion for the first 3 days of any treatment course to ameliorate the effects of infusion reactions. In clinical trials, patients were pre-treated with 1 000 mg methylprednisolone for the first 3 days of each LEMTRADA treatment course. Pre-treatment with antihistamines and/or antipyretics prior to LEMTRADA administration may also be considered.

Most patients in controlled clinical trials received antihistamines and/or antipyretics before at least 1 LEMTRADA infusion. IARs may occur in patients despite pre-treatment. Observation for infusion reactions is recommended during and for at least 2 hours after each LEMTRADA infusion. Medical practitioners should alert patients that an IAR could occur within 48 hours of infusion. Monitor vital signs before the infusion and periodically during the infusion. Extended observation time should be considered, as appropriate. If severe infusion reactions occur, immediate discontinuation of the IV infusion should be considered. Resources for the management of anaphylaxis or serious reactions should be available.

Infusion instructions to reduce serious reactions temporally associated with LEMTRADA infusion

- Pre-infusion evaluations:
    - Obtain a baseline ECG and vital signs, including heart rate and blood pressure measurement.
    - Perform laboratory tests (complete blood count with differential, serum transaminases, serum creatinine, test of thyroid function and 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.
        - In case of a severe adverse event:
            - Interrupt infusion.
            - Medically evaluate the patient guided by the adverse event profile of LEMTRADA prior to considering restarting therapy.
            - Provide appropriate treatment as needed.
        - Consider permanently discontinuing the LEMTRADA infusion if the patient shows clinical symptoms suggesting development of a serious adverse event associated with the infusion (myocardial ischaemia, 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 ischaemia, 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 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.

Haemophagocytic lymphohistiocytosis (HLH)

During post-marketing use, HLH (including fatal cases) has been reported in patients treated with LEMTRADA. HLH is a life-threatening syndrome of pathologic immune activation characterised by clinical signs and symptoms of extreme systemic inflammation. HLH is characterised by fever, hepatomegaly and cytopenias. It is associated with high mortality rates if not recognised and treated early. Symptoms have been reported to occur within a few months to four years following the initiation of treatment. Patients should be informed about symptoms of HLH and time to onset. Patients who develop early manifestations of pathologic immune activation should be evaluated immediately, and a diagnosis of HLH should be considered.

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 aetiology for the signs or symptoms cannot be established.

Infections

Infections occurred in 71 % of patients treated with LEMTRADA 12 mg in controlled clinical trials in MS up to 2 years in duration and were predominantly mild to moderate in severity. Infections 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 in controlled clinical trials in MS. Serious infections in the LEMTRADA group included: appendicitis, gastroenteritis, pneumonia, herpes zoster and tooth infection. Infections were generally of typical duration and resolved following conventional medical treatment.
The cumulative annualised rate of infections was 0,99 through a median of 6,1 years (maximum 12 years) of follow-up from the first LEMTRADA exposure, as compared to 1,27 in controlled clinical trials.

Progressive multifocal leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised and that usually leads to death or severe disability. Typical symptoms associated with PML are diverse, progress over days to weeks and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

No case of PML has been reported in clinical studies of alemtuzumab in patients with multiple sclerosis. PML has been reported in the post-marketing setting in patients with other risk factors, specifically prior treatment with MS medicines associated with PML.

MRI findings may be apparent before clinical signs or symptoms. Cases of PML, diagnosed based on MRI findings and the detection of JCV DNA in the cerebrospinal fluid in the absence of clinical signs or symptoms specific to PML, have been reported in patients treated with other MS

medications associated with PML. Many of these patients subsequently became symptomatic with PML. Therefore, monitoring with MRI, including prior to initiation of LEMTRADA, for signs that may be consistent with PML may be useful, and any suspicious findings should lead to further investigation to allow for an early diagnosis of PML, if present. Following discontinuation of another MS medication associated with PML, lower PML-related mortality and morbidity have been reported in patients who were initially asymptomatic at diagnosis compared to patients who had characteristic clinical signs and symptoms at diagnosis. It is not known whether these differences are due to early detection and discontinuation of MS treatment or due to differences in disease in these patients.

Serious varicella zoster virus infections, including primary varicella and herpes zoster reactivation, occurred in 0,4 % of patients treated with LEMTRADA 12 mg.
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 performed annually for female patients.

Tuberculosis has been reported for patients treated with LEMTRADA 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.

Superficial fungal infections, especially oral and vaginal candidiasis, occurred in 12 % of LEMTRADA-treated patients in controlled clinical trials in MS.

Listeria meningitis has been reported in LEMTRADA-treated patients. The duration of increased risk for listeria meningitis is unclear, although cases of listeria meningitis generally occurred within 1 month of alemtuzumab dosing. Unless treated, listeria infection can lead to significant morbidity or mortality. Patients should avoid or adequately heat foods that are potential sources of *Listeria monocytogenes*.

Medical practitioners should consider delaying initiation of LEMTRADA administration in patients with active infection until the infection is fully controlled.

Prophylaxis with an oral anti-herpes medicine should be initiated starting on the first day of LEMTRADA treatment and continuing for a minimum of 1 month following each course of treatment.

LEMTRADA has not been administered for treatment of MS concomitantly with antineoplastic or immunosuppressive therapies. Concomitant use of LEMTRADA with any of these therapies could increase the risk of immunosuppression.

No data are available on the association of LEMTRADA with hepatitis B virus (HBV) or hepatitis C virus (HCV) reactivation, as patients with evidence of active or chronic infections were excluded from clinical trials. Screening patients at high risk of HBV and/or HCV infection before initiation of LEMTRADA should be considered and caution should be exercised in prescribing LEMTRADA to patients identified as carriers of HBV and/or HCV, as these patients may be at risk of irreversible liver damage relative to a potential virus reactivation as a consequence of their pre-existing status.

Cytomegalovirus infections (CMV) have been reported in LEMTRADA-treated patients with concomitant corticosteroid use. Most cases occurred within 2 months of alemtuzumab dosing. In symptomatic patients, clinical assessment should be performed for CMV infection during and for at least two months following each LEMTRADA treatment course.

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

Pneumonitis has been reported in LEMTRADA-treated patients. Most cases occurred within the

first month after treatment with LEMTRADA. Patients should be advised to report symptoms of pneumonitis, which may include shortness of breath, cough, wheezing, chest pain or tightness and haemoptysis.

Stroke and cervicocephalic arterial dissection

Stroke:

In the post-marketing setting, serious and life-threatening stroke (including ischaemic and haemorrhagic stroke) has been reported with some cases occurring as early as within 3 days of LEMTRADA administration.

Cervicocephalic arterial dissection:

In the post-marketing setting, cases of cervicocephalic (e.g. vertebral, carotid) arterial dissection have been reported within 3 days of LEMTRADA administration.

Educate patients on the symptoms of stroke and cervicocephalic (e.g. carotid, vertebral) arterial dissection. Instruct patients to seek immediate medical attention if symptoms of stroke or cervicocephalic arterial dissection occur.

Acute acalculous cholecystitis

LEMTRADA may increase the risk of acute acalculous cholecystitis. In controlled clinical studies, 0,2 % of LEMTRADA-treated MS patients developed acute acalculous cholecystitis. During post-marketing use, additional cases of acute acalculous cholecystitis have been reported in LEMTRADA-treated patients. Time to onset of symptoms ranged from less than 24 hours to 2 months after LEMTRADA infusion. Most patients were treated conservatively with antibiotics and recovered without surgical intervention, whereas others underwent cholecystectomy.

Symptoms of acute acalculous cholecystitis include abdominal pain, abdominal tenderness, fever, nausea and vomiting. Acute acalculous cholecystitis is a condition that may be associated with high morbidity and mortality rates if not diagnosed early and treated. If acute acalculous

cholecystitis is suspected, evaluate and treat promptly.

Contraception

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

Vaccines

It is recommended that patients have completed local 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

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.

Laboratory tests for monitoring patients

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

- CBC with differential cell count, serum transaminases and serum creatinine levels (prior to treatment initiation and at monthly intervals thereafter).

- Urinalysis with urine cell counts (prior to treatment initiation and at monthly intervals thereafter).
- A test of thyroid function, such as TSH level (prior to treatment initiation and every 3 months thereafter).

4.5 Interaction with other medicines and other forms of interaction

No formal 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

Safety in pregnancy and lactation has not been established.

Pregnancy

There are no adequate and well-controlled studies of LEMTRADA in pregnant women.

LEMTRADA should not be administered during pregnancy.

Human IgG is known to cross the placental barrier; alemtuzumab may cross the placental barrier as well and thus potentially pose a risk to the fetus. It is not known whether alemtuzumab can cause fetal harm when administered to pregnant women or whether it can affect reproductive capacity.

Women of childbearing potential should use effective contraceptive measures when receiving a course of treatment with LEMTRADA and for 4 months following that course of treatment.

Thyroid disease (see section 4.4) poses special risks in women who are pregnant. Without treatment of hypothyroidism during pregnancy, there is an increased risk for miscarriage and fetal effects such as mental retardation and dwarfism. In mothers with Graves' disease, maternal thyroid stimulating hormone receptor antibodies can be transferred to a developing fetus and can cause transient neonatal Graves' disease.

Breastfeeding

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

Breastfeeding should be discontinued during each course of treatment with LEMTRADA and for 4 months following the last infusion of each treatment course.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

A total of 1 486 patients treated with LEMTRADA (12 mg or 24 mg) constituted the safety population in a pooled analysis of MS clinical studies with a median follow-up of 6,1 years (maximum 12 years), resulting in 8 635 patient-years of safety follow-up. Study 1 and Study 2 were 2-year active-controlled trials in RRMS patients treated with LEMTRADA 12 mg/day on 5 consecutive days at study entry and on 3 consecutive days at Study Month 12, or subcutaneous (SC) IFNB-1a 44 µg 3 times per week. Study 3 (CAMMS223) evaluated the safety and efficacy of LEMTRADA in patients with RRMS over the course of 3 years. Study 4 (CAMMS03409) was an uncontrolled extension study to evaluate the long-term safety and efficacy (4 additional years) of LEMTRADA in patients from Studies 1, 2 or 3. As the number of courses increases, data from fewer patients and shorter-term follow-up are available.

Table 1 lists adverse reactions occurring in ≥ 5 % of LEMTRADA-treated patients (12 mg/day) through complete follow-up by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT).

Table 1: Side effects in Study 1, 2, 3 and 4 observed in ≥ 5 % of LEMTRADA 12 mg treated patients

System organ class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**
Infections and infestations	Nasopharyngitis, urinary tract infection, upper respiratory tract infection, sinusitis	Oral herpes, influenza, bronchitis, herpes zoster
Blood and lymphatic system disorders	Lymphopenia, leukopenia	Thrombocytopenia
Endocrine disorders	Hyperthyroidism	Hypothyroidism, autoimmune thyroiditis
Psychiatric disorders		Insomnia, depression, anxiety
Nervous system disorders	Headache, MS relapse, paraesthesia	Dysgeusia, hypaesthesia, dizziness
Cardiac disorders	Tachycardia	
Vascular disorders	Flushing	
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	Cough, dyspnoea
Gastrointestinal disorders	Nausea	Dyspepsia, abdominal pain, diarrhoea, vomiting
Skin and subcutaneous tissue disorders	Rash, urticaria, pruritus, generalised rash	Erythema
Musculoskeletal and connective tissue disorders	Back pain, pain in extremity, arthralgia	Muscular weakness, myalgia, muscle spasms
Renal and urinary disorders		Proteinuria, haematuria
General disorders and	Pyrexia, fatigue, chills	Chest discomfort, pain, influenza-

administration site conditions		like illness, peripheral oedema
Investigations		CD4 lymphocytes decreased, CD8 lymphocytes decreased
Injury, poisoning and procedural complications	Contusion	

The type of adverse events including seriousness and severity observed in LEMTRADA treatment groups through all available follow-up, including patients who received additional treatment courses were similar to those in the active-controlled studies.

In patients continuing from controlled clinical studies and who did not receive any additional LEMTRADA after the initial 2 treatment courses, the rate (events per person-year) of most adverse reactions was comparable to or reduced in years 3 – 6 as compared to years 1 and 2. The rate of thyroid adverse reactions was highest in year three and declined thereafter.

Immunogenicity

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. Through 2 treatment courses, there was no apparent association of the presence of anti-alemtuzumab or inhibitory anti-alemtuzumab antibodies with a reduction in efficacy, change in pharmacodynamics,

or the occurrence of adverse reactions, including infusion-associated reactions. High titre anti-alemtuzumab antibodies observed in some patients were associated with incomplete lymphocyte depletion following a third or fourth treatment course but there was no clear impact of anti-alemtuzumab antibodies on the clinical efficacy or safety profile of LEMTRADA.
The incidence of antibodies is highly dependent on the sensitivity and specificity of the assay.

Post-marketing experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to alemtuzumab exposure.

The following adverse reactions were identified during post-approval use of LEMTRADA for the treatment of relapsing forms of multiple sclerosis (MS):

- Nervous system disorders: Stroke, including haemorrhagic and ischaemic stroke, cervicocephalic arterial dissection and autoimmune encephalitis, see section 4.4.
- Gastrointestinal system disorders: Cases of cholecystitis including acalculous cholecystitis and acute acalculous cholecystitis have been reported with LEMTRADA, see section 4.4.
- Infections and infestations: Cytomegalovirus infections have been reported in LEMTRADA-treated patients with concomitant corticosteroid use, Epstein-Barr virus (EBV) infection, see section 4.4.
- Respiratory, thoracic and mediastinal disorders: Pulmonary alveolar haemorrhage, see section 4.4.
- Blood and lymphatic system disorders: Cases of severe (including fatal) neutropenia, acquired haemophilia A, thrombotic thrombocytopenic purpura (TTP), see section 4.4.
- Cardiac disorders: Myocardial ischaemia and myocardial infarction, see section 4.4.
- Hepatobiliary disorders: Autoimmune hepatitis, hepatitis (associated with EBV infection), see section 4.4.
- Immune system disorders: Haemophagocytic lymphohistiocytosis, see section 4.4, sarcoidosis.

- Musculoskeletal and connective tissue disorders: Adult-onset Still's disease (AOSD), see section 4.4.
- Skin disorders: Vitiligo.

The following adverse reactions were identified during post-approval 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 (> 12 mg/day). Because these reactions are reported voluntarily from a population of uncertain size, it is not 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, dysrhythmias, acute cardiac insufficiency and cardiac arrest have been observed in non-MS patients treated with alemtuzumab. 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 LEMTRADA at higher and more frequent doses than used in MS. Progressive multifocal leukoencephalopathy (PML) has been reported with B-CLL with or without treatment with alemtuzumab. The frequency of PML in B-CLL patients treated with alemtuzumab is no greater than the background frequency.

Blood and lymphatic system disorders

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

Cardiac disorders

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

Epstein-Barr virus-associated lymphoproliferative disorders

Epstein-Barr virus-associated lymphoproliferative disorders have been observed in post-marketing experience.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of LEMTRADA is important. It allows continued monitoring of the benefit/risk balance of LEMTRADA. Health care providers are asked to report any suspected adverse reactions to:

- The Pharmacovigilance Unit at Sanofi: za.drugsafety@sanofi.com (email) or 011 256 3700 (tel), or
- SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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 overdosage. Treatment consists of discontinuation of LEMTRADA and supportive therapy.

5. PHARMACOLOGICAL PROPERTIES

Category and class: A 30.1 Antibodies

Pharmacotherapeutic group: Immunosuppressants, Selective immunosuppressants, ATC code: L04AA34

5.1 Pharmacodynamic properties

Alemtuzumab binds to CD52, a cell surface antigen, present at high levels on T and B lymphocytes, and at lower levels on natural killer cells, monocytes and macrophages.

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

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

Alemtuzumab depletes circulating T and B lymphocytes after each treatment course with the lowest observed values occurring 1 month after a course of treatment.

Lymphocytes repopulate over time with B-cell recovery usually completed within 6 months. T lymphocyte counts rise more slowly towards normal, but generally do not return to baseline by 12 months post-treatment. Approximately 40 % of patients had total lymphocyte counts reaching

the lower limit of normal (LLN) by 6 months after each treatment course, and approximately 80 % of patients had total lymphocyte counts reaching the LLN by 12 months after each course. Neutrophils, monocytes, eosinophils, basophils and natural killer cells are only transiently affected by alemtuzumab.

Fertility in males

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

5.2 Pharmacokinetic properties

The pharmacokinetics of alemtuzumab were evaluated in a total of 216 patients with relapsing remitting multiple sclerosis (RRMS) who received IV 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 3 014 ng/mL on Day 5 of the initial treatment course and 2 276 ng/mL on Day 3 of the second treatment course. The alpha half-life approximated 2 days and was comparable between courses leading to low or undetectable serum concentrations within approximately 30 days following each treatment course.

The population pharmacokinetics of alemtuzumab was best described by a linear, 2-compartment model. Systemic clearance decreased with lymphocyte count due to loss of CD52 antigen in the periphery; however, the decrease from Course 1 to Course 2 was less than 20 %. The central volume of distribution was proportional to body mass, and approximated extracellular fluid volume (14,1 L), suggesting that alemtuzumab is largely confined to the blood and interstitial space. No effect of age, race or gender on the pharmacokinetics of alemtuzumab was observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate dihydrate

Polysorbate 80

Potassium chloride

Potassium dihydrogen phosphate

Sodium chloride

Sodium phosphate dibasic

Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, LEMTRADA should not be mixed with other medicines. Do not add or simultaneously infuse other medicines through the same intravenous line.
LEMTRADA should not be diluted with solvents other than those mentioned in section 6.6, Special precautions for disposal and other handling.

There are no known incompatibilities between alemtuzumab and polyvinyl chloride (PVC) infusion bags, PVC or polyethylene-lined PVC administration sets or low protein binding filters.

6.3 Shelf life

48 months

Vials

Store refrigerated at 2 °C to 8 °C.

Infusion solution

LEMTRADA diluted product may be stored at room temperature (15 °C to 25 °C) or refrigerated (2 °C to 8 °C) for up to 8 hours.

6.4 Special precautions for storage

Vials

Protect from light.

Do not freeze or shake.

Keep the vial in the outer carton until required for use.

For storage conditions of the vial, see section 6.3.

Infusion solution

Protect from light.

Partially used, unused, or damaged medicine vials should be discarded appropriately.

For the reconstituted product, from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user and would normally be 2 – 8 °C, unless reconstitution/dilution has taken place in controlled and validated conditions.

For storage conditions after dilution, see section 6.3.

6.5 Nature and contents of container

LEMTRADA is supplied in a clear, 2 mL Type 1 glass vial, with a grey butyl rubber stopper and aluminium seal with a green plastic flip-off cap.

Pack size: carton with 1 vial.

6.6 Special precautions for disposal and other handling

For IV administration, withdraw 1,2 mL of LEMTRADA from the vial and inject into 100 mL sterile 0,9 % sodium chloride or 5 % dextrose/glucose in water. Gently invert the bag to mix the solution. LEMTRADA contains no antimicrobial preservatives and therefore care should be taken to ensure the sterility of the prepared solution. Each vial is intended for single use only.

7. HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

Hertford Office Park, Building I, 5th Floor

90 Bekker Road, Vorna Valley

Midrand 2196

South Africa

8. REGISTRATION NUMBER

48/30.1/0263

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 February 2020

10. DATE OF REVISION OF THE TEXT

20 November 2023