LEMTRADA®
alemtuzumab 12mg IV

A healthcare professional's guide to using LEMTRADA® (alemtuzumab) in **adult** patients with **highly active** relapsing remitting multiple sclerosis (RRMS)

Important safety and risk minimisation information for healthcare professionals prescribing LEMTRADA®

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare Professionals (HCPs) are advised to report any suspected adverse reactions.

For full prescribing information refer to the professional information approved by the medicines regulatory authority.

To report an adverse event:

- Use the Med Safety App [accessible from the Apple store (for iOS devices) and Google Play (for android devices)] via https://medsafety.sahpra.org.za/ **alternatively,**
- Complete the ADR reporting form accessible via the SAHPRA website at www.sahpra.org.za and email it to adr@sahpra.org.za **and**
- Adverse events should also be reported to the Pharmacovigilance Department of Sanofi by emailing za.drugsafety@sanofi.com or calling 011 256 3700

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Section 1. Executive summary

Using LEMTRADA® (alemtuzumab) in **adult** patients with **highly active** relapsing remitting multiple sclerosis (RRMS) – a guide for healthcare professionals.

This section is an abbreviated guide – refer to the full guide which follows (sections 2-7) for more information.

Please be aware that this guide does not cover all the identified safety events associated with the use of LEMTRADA® and does not take the place of the Professional Information (PI) as approved by the medicines regulatory authority.

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LEMTRADA® is indicated as a single disease modifying therapy for special populations of adults with highly active relapsing remitting multiple sclerosis (RRMS).

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.*

This guide has been developed as part of the LEMTRADA® Educational Programme to support you in initiating and supervising LEMTRADA® treatment, to provide further information about the potential serious risks associated with its use, and to improve the monitoring and management of patients who are being treated.

In order to minimise potential risks and side effects of LEMTRADA®, prescribers and patients must commit to at least 48 months of follow-up after the last infusion. It is important that patients understand that they should continue with the monitoring, even if they are feeling well and their multiple sclerosis (MS) is well controlled.

Patients should be informed about the signs of side effects and advised to seek urgent medical attention should any occur.

Serious side effects temporally associated with LEMTRADA® infusion*

Side effect	Monitoring procedures	Management
Myocardial ischaemia and/or infarction	• **Pre-infusion:** Baseline ECG and vital signs, including heart rate and BP • **During infusion:** Regular monitoring of vital signs and overall clinical status at least once every hour • **Post-infusion:** Observation for at least 2 hours post-infusion. Patients should be informed about the symptoms associated with serious reactions so they can self-monitor post-infusion	• Patients who develop abnormal vital signs or report sudden onset of symptoms should be evaluated immediately • Immediate discontinuation of treatment if reaction occurs during infusion • Patients with clinical symptoms should be closely monitored until complete resolution of symptoms
Pulmonary alveolar haemorrhage		
Haemorrhagic stroke		
Cervicocephalic arterial dissection		
Thrombocytopenia	• **Pre-infusion:** Baseline platelet count • **Post-infusion:** Platelet count immediately after infusion on Day 3 and Day 5 of first course, and on Day 3 of any subsequent course. Observation for at least 2 hours after infusion. Patients should be informed about the symptoms associated with thrombocytopenia so they can self-monitor post-infusion	• Clinically significant thrombocytopenia should be followed until resolved • Consider referral to a haematologist

BP=blood pressure; ECG=electrocardiogram

* Alert patients that Infusion-Associated Reactions (IARs) could occur within 1-3 days of a LEMTRADA® infusion. Educate patients to report symptoms and to seek appropriate medical care.

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Delayed autoimmune side effects*

Side effect	Monitoring procedures	Management
Thyroid disorders	• Thyroid function tests pre- and post-infusion. Patients should be informed about the symptoms associated with thyroid disorders so they can self-monitor post-infusion	• Consider referral to an endocrinologist
Immune thrombocytopenic purpura (ITP)	• Complete blood count with differential pre- and post-infusion. Patients should be informed about the symptoms associated with ITP so they can self-monitor post-infusion	• Appropriate medical intervention should be initiated promptly, including immediate referral to a haematologist
Nephropathies, including anti-Glomerular Basement Membrane (anti-GBM) disease	• Serum creatinine levels and urinalysis with microscopy pre- and post-infusion. Patients should be informed about the symptoms associated with nephropathies so they can self-monitor post-infusion	• Consider referral to a nephrologist for diagnosis and treatment
Autoimmune hepatitis	• Liver function tests pre- and post-infusion. Patients should be informed about the symptoms associated with autoimmune hepatitis so they can self-monitor post-infusion	• Consider referral to a specialist for diagnosis and treatment
Haemophagocytic lymphohistiocytosis (HLH)	• Patients should be informed about the symptoms associated with HLH so they can self-monitor post-infusion	• Consider referral to a specialist for diagnosis and treatment
Acquired haemophilia A	• Patients should be informed about the symptoms associated with acquired haemophilia A so they can self-monitor post-infusion	• Consider referral to a haematologist for diagnosis and treatment
Thrombotic thrombocytopenic purpura (TTP)	• Complete blood count with differential pre- and post-infusion. Patients should be informed about symptoms associated with TTP so they can self-monitor post-infusion	• Appropriate medical intervention should be initiated promptly, including immediate referral to a haematologist

* To facilitate surveillance for and management of delayed autoimmune side effects it is important that prescribers and patients commit to at least 48 months of monitoring after the last infusion (see section 5, page 34, Table 3 for recommended monitoring)

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Serious infections

Side effect	Monitoring procedures	Management
Serious infections	• **Post-infusion:** Patients should be informed about the symptoms associated with serious infections so they can self-monitor post-infusion	• Various risk minimisation procedures.
	• **Tuberculosis:** - Screen patients for active and inactive ("latent") tuberculosis according to the relevant South African guidelines before, during and after treatment with LEMTRADA® - 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 healthcare provider. - Patients should be informed about the symptoms of tuberculosis so that they can self-monitor.	• For tuberculosis: 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. Healthcare 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.
Progressive Multifocal Leukoencephalopathy (PML)	• **Prior to initiation and readministration of treatment:** MRI scan should be done and evaluated for signs that are consistent with PML • **Post-infusion:** Patients should be informed about the symptoms associated with PML and should inform their relatives or caregivers about their treatment	• Further evaluation, including cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments should be performed as appropriate

Exposure to LEMTRADA® in case of pregnancy and lactation

Women of childbearing potential should use effective contraception when receiving a course of treatment with LEMTRADA® and for 4 months after each course of LEMTRADA® treatment.

There are no adequate and well-controlled studies of LEMTRADA® in pregnant women. LEMTRADA® should not be administered during pregnancy.

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

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Section 2.
Overview of LEMTRADA®

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- 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 RRMS 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

This guide has been developed as part of the LEMTRADA® Educational Programme to support you in initiating and supervising LEMTRADA® treatment. It provides further information about the serious risks associated with LEMTRADA® use, helping to improve the management of patients who are receiving treatment by providing a summary of its usage and monitoring. Take a look at the overview that follows for more on what you can expect from this guide:

1. A description of the most important safety events associated with the use of LEMTRADA® that may occur in proximity of the infusion or delayed after the lymphocyte repopulation.

Serious infections

Progressive Multifocal Leukoencephalopathy (PML) - 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.

Tuberculosis - Active and latent tuberculosis have been reported in 0,3% of the patients treated with LEMTRADA®, most often in endemic regions.

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.

Healthcare 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 healthcare provider.

Infusion-Associated Reactions (IARs)

The most frequent side effects are infusion reactions which can happen at the time of the infusion or within 24 hours after the infusion. In most cases these are mild, but some serious reactions are possible. Occasionally allergic reactions could occur.

Temporally associated side effects occurring during or shortly after infusion

Myocardial ischaemia and infarction, pulmonary alveolar haemorrhage, stroke (including ischaemic and haemorrhagic), cervicocephalic arterial dissection and thrombocytopenia.

Delayed autoimmune conditions (in order of frequency, most to least events)

- Thyroid disorders
- Immune Thrombocytopenic Purpura (ITP)
- Nephropathies, including anti-Glomerular Basement Membrane (anti-GBM) disease
- Autoimmune hepatitis
- Haemophagocytic lymphohistiocytosis (HLH)
- Acquired haemophilia A
- Cytopenias
- Thrombotic thrombocytopenic purpura (TTP)

2. Recommendations on how to mitigate these potential safety events through appropriate patient selection, counselling, monitoring and management.

3. A frequently asked questions (FAQs) section.

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A Prescriber Checklist is also to be used at initial LEMTRADA® prescription and patient follow-up visits.

In addition, a **Patient Guide** and **Patient Alert Card** have been developed and these must be given to patients prior to LEMTRADA® treatment initiation.

Patient Guide

To be carefully reviewed with your patient at initial prescription, and on a regular basis at follow-up visits. It aims to educate patients regarding the signs and symptoms of potential safety events and to make them aware of the need to be compliant with testing, keep an eye out for symptoms and to seek immediate medical attention should they occur.

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These materials are available and must be distributed to all patients considered for LEMTRADA® treatment. Please request patient risk mitigation education materials from the Sanofi Medical Affairs Department or the Patient Program Service Provider.

Please be aware that this guide does not cover all the identified safety events associated with the use of LEMTRADA® and does not take the place of the Professional Information.

Patient Alert Card

To be used as a tool to inform any HCPs treating patients receiving LEMTRADA®. Patients (or care givers, when appropriate) should carry this card at all times and show this to any HCPs treating them.

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Section 3. Introduction to LEMTRADA®

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LEMTRADA® treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital setting with ready access to intensive care.

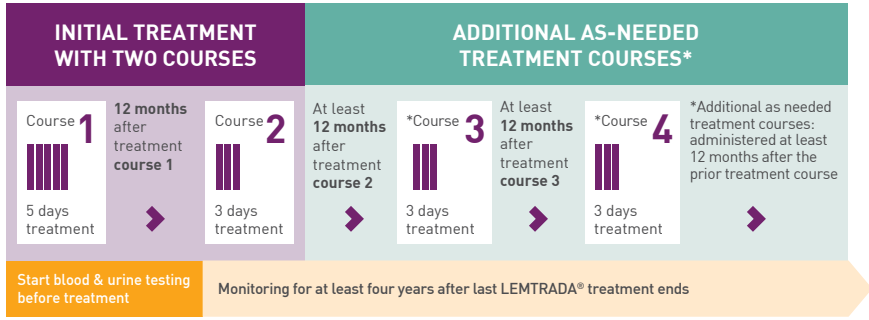
Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction, pulmonary alveolar haemorrhage, cervicocephalic arterial dissection, haemorrhagic stroke, autoimmune conditions and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.

In order to minimise possible risks and side effects of LEMTRADA®, prescribers and patients must commit to the monitoring program during treatment courses, in between treatment courses and for at least 48 months after the last infusion of LEMTRADA®. It is important that patients understand that they should continue with the monitoring, even if they are feeling well and their MS disease is well controlled.

Creating a partnership between you, your patient and their MS care team, along with careful review on how to use the patient education tools, will help your patient to comply with periodic tests, identify and report symptoms in a timely manner and receive prompt and appropriate treatment if needed. **Detailed monitoring requirements are described in Section 5.**

To enhance your understanding of the treatment and the length of required follow-up, please refer to Figure 1.

Figure 1 – Overview of LEMTRADA® posology



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Section 4. What are the main risks associated with the use of LEMTRADA®?

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Important safety events associated with the use of LEMTRADA® that may occur in proximity of the infusion or delayed after lymphocyte repopulation

Serious infections

LEMTRADA® use is associated with a risk of serious infections which may occur in the weeks following treatment, but can also arise years later.

To minimise the risk of serious infection, it is important to:

- Delay start of treatment when active infection is present until completely resolved
- Screen for HIV, hepatitis B virus (HBV) and hepatitis C virus (HCV)
- Screen for and monitor for both active and inactive ("latent") tuberculosis risk according to the relevant South African guidelines
- Screen for human papillomavirus (HPV) in female patients and repeat screening annually. Consider vaccination prior to treatment
- Consider completing local immunisation requirements at least 6 weeks prior to starting treatment. The ability to generate an immune response to any vaccine following LEMTRADA® treatment has not been studied
- Before initiation of therapy, evaluation of cytomegalovirus (CMV) immune serostatus could be considered according to local guidelines
- Recommend listeriosis-prevention diet two weeks prior to, during and for at least 1 month after infusion. To reduce the risk of infection, patients receiving LEMTRADA® should 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 infusion. Discuss with patients appropriate steps to avoid food that has potentially been contaminated with listeria
- Start anti-herpes prophylaxis on Day 1 of treatment and continue for at least 1 month following each course of treatment
- 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®.
- Avoid concomitant therapy with antineoplastics or immunosuppressive agents

Progressive Multifocal Leukoencephalopathy (PML)

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

Prior to initiation and re-administration of LEMTRADA® treatment, an MRI scan should be done and evaluated for signs that are consistent with PML. Further evaluation, including cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments should be performed as appropriate. The healthcare practitioner should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive, neurological or psychiatric symptoms).

Tuberculosis

South Africa has a high incidence of Mycobacterium Tuberculosis infection.

Initiation of treatment with LEMTRADA® should be delayed in patients with any severe active infection until resolution. Active and latent tuberculosis cases have been reported in 0,3% of patients treated with LEMTRADA®, most often in endemic regions.

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.

Healthcare 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 healthcare provider.

Infusion-Associated Reactions (IARs)

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.

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Serious side effects temporally associated with LEMTRADA® infusion

During post-marketing use, serious and sometimes fatal temporally associated adverse events have been reported. In the majority of cases, time to onset was within 1-3 days of the LEMTRADA® infusion. Reactions have occurred following any of the doses and after subsequent courses. These safety events included:

- Myocardial ischaemia and/or myocardial infarction (unknown incidence)
- Pulmonary alveolar haemorrhage (unknown incidence)
- Haemorrhagic stroke (unknown incidence)
- Cervicocephalic arterial dissection (unknown incidence)
- Thrombocytopenia (affects ≥ 1/100 to < 1/10 patients)

Patients who develop abnormal vital signs, including heart rate and blood pressure, or report sudden onset of symptoms characteristic of the above, should be advised to seek immediate medical attention. See 'Section 5: Summary of recommended patient monitoring', for important information on infusion instructions.

Delayed autoimmune side effects

LEMTRADA® use is associated with risk of autoimmune conditions that may occur with a delay of months to years following infusion, including:

- Thyroid disorders
- Immune thrombocytopenic purpura (ITP)
- Nephropathies, including anti-Glomerular Basement Membrane (anti-GBM) disease
- Autoimmune hepatitis
- Haemophagocytic lymphohistiocytosis (HLH)
- Acquired haemophilia A
- Cytopenias
- Thrombotic thrombocytopenic purpura (TTP)

These events can be serious, leading to morbidity and/or mortality with peak incidence at 14-36 months post-treatment and in some cases, can occur after the 48-months monitoring period. Monitoring and early detection can improve the outcomes of patients experiencing these events.

It is important to carefully monitor laboratory results and be vigilant for signs and symptoms. Please review the following sections carefully to gain a better understanding of these risks. See Section 5: Summary of recommended patient monitoring, for important information about reducing the risk of LEMTRADA® use.

Thyroid disorders

During clinical trials, autoimmune thyroid disorders including hyperthyroidism and hypothyroidism were reported. Thyroid disorders were very common in clinical trials and most were mild to moderate in severity. Some cases were transient and did not require treatment. The majority of thyroid-related events were managed with medical therapy, however some patients required surgical intervention.

It is important to let your patient know that depending on the type of thyroid condition, they may require lifelong treatment.

- Thyroid function tests such as thyroid-stimulating hormone (TSH) levels should be obtained prior to initiation of treatment, and then every 3 months thereafter continuing for at least 48 months following the last infusion.
- Additionally, watch out for signs and symptoms of thyroid disorders.
- Thyroid disease poses special risks in women who are pregnant. Untreated thyroid disease can cause harm to the unborn and newborn baby. Untreated hypothyroidism during pregnancy increases risk of miscarriage and fetal effects such as mental retardation and dwarfism. Special caution should be taken for pregnant women with Basedow's disease (also known as Graves' disease), as maternal TSH receptor antibodies can be transferred to a developing fetus and can cause transient neonatal Basedow's disease.

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Immune thrombocytopenic purpura (ITP)

ITP is an autoimmune disorder usually associated with anti-platelet antibodies. Please refer to Figure 2 for examples of ITP. Symptoms of ITP could include (but are not limited to) petechiae, purpura, easy bruising, easy bleeding, and heavier than normal or irregular menstrual bleeding.

These clinical signs of ITP may or may not be apparent before serious bleeding develops. It is also not uncommon to observe the signs and symptoms of ITP soon after a normal thrombocyte count.

ITP can be a serious condition leading to morbidity and mortality, and can occur several years after dosing. In clinical trials, patients with ITP were diagnosed and managed in a timely manner with most cases responding to first-line medical therapy. It is important to monitor all patients for ITP as follows:

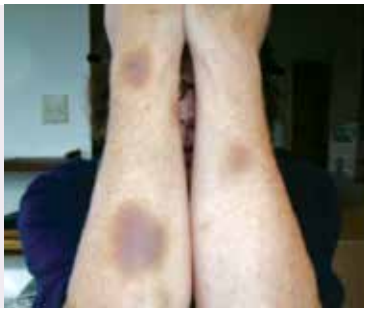
- Complete blood counts with differential should be obtained prior to initiation of treatment and at monthly intervals thereafter until at least 48 months following the last infusion
- Check the patient for clinical signs of ITP
- Counsel the patient on the importance of complying with monthly monitoring of their blood and the need to continue for at least 48 months after their last infusion
- Educate the patient on how to recognise ITP-related signs and symptoms, and emphasise the need to remain vigilant
- If ITP is suspected, appropriate medical intervention should be promptly initiated including immediate referral to a haematologist. Severe or widespread bleeding is life-threatening and demands immediate care

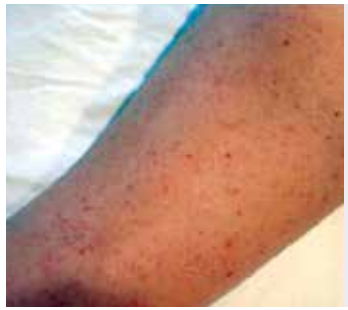
The potential risk associated with retreatment with LEMTRADA® following the occurrence of ITP is unknown.

Figure 2 - Examples of ITP

Example of arms with easy or excessive bruising.

Location: This could occur anywhere on the patient's body, not just the arms.





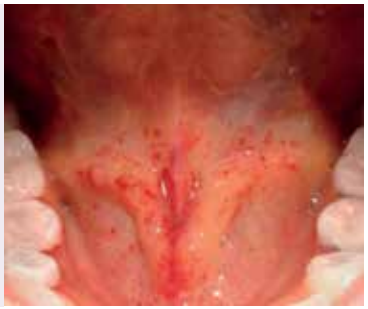
Example of a leg with petechiae and purpura.

Petechiae are small, scattered, "pin prick" spots under the skin that are red, pink or purple.

Location: This could occur anywhere on the patient's body.

Example of purpura under the tongue.

Location: Petechiae and purpura could also occur on any mucous membrane, including anywhere in the mouth (under the tongue, roof of the mouth, inner cheeks, tongue, gums).



Note: These pictures are only a guide in order to show examples of bruises or petechiae. The patient may have a less severe type of bruise or petechiae than these pictures and still have ITP.

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Nephropathies, including anti-GBM disease

Nephropathies, including anti-GBM disease, have rarely been reported after treatment with LEMTRADA® in MS patients in clinical trials, but generally occurred within 39 months following the last administration.

Clinical manifestation of nephropathies may include elevation in serum creatinine, haematuria and/or proteinuria. While not observed in clinical trials, alveolar haemorrhage which manifests as haemoptysis, may occur with anti-GBM disease (Goodpasture Syndrome).

Since patients may be asymptomatic, it is important that periodic laboratory tests are conducted until at least 48 months after the last infusion of LEMTRADA®:

- Serum creatinine levels should be obtained prior to initiation of treatment and at monthly intervals thereafter
- Urinalysis with microscopy should be obtained prior to initiation of treatment and at monthly intervals thereafter. In menstruating females, consider the timing of urinalysis to avoid false positives. After the 48 month period, testing should be performed based on clinical findings suggestive of nephropathies
- The observation of clinically significant changes from baseline in serum creatinine, unexplained haematuria, and/or proteinuria should prompt immediate further evaluation for nephropathies, including immediate referral to a nephrologist. Early detection and treatment of nephropathies may decrease the risk of poor outcomes

Anti-GBM disease is life-threatening if not treated and therefore demands immediate care. Without prompt treatment, patients can rapidly develop renal failure requiring dialysis and/or transplantation, and may lead to death.

Autoimmune hepatitis

Autoimmune hepatitis causing clinically significant liver injury, including fatal cases, has been reported in patients treated with LEMTRADA® in the post-marketing setting.

Patients should be informed about the related symptoms of hepatic injury. If a patient develops clinical signs or symptoms suggestive of hepatic dysfunction (e.g. enlarged liver, spider angiomas, ascites, unexplained nausea, vomiting, abdominal pain and/or swelling, aching joints, fatigue, anorexia, or jaundice and/or dark urine), autoimmune hepatitis should be considered as a differential diagnosis. It is important that liver function tests are performed before initial treatment and at monthly intervals until at least 48 months after the last infusion. Patients should be informed about the risk of autoimmune hepatitis, hepatic injury and related symptoms.

Haemophagocytic lymphohistiocytosis (HLH)

This severe systemic inflammatory syndrome has been reported in patients treated with LEMTRADA® in the post-marketing setting and is associated with high mortality rates if not recognised and treated early.

Signs and symptoms characteristic of HLH include a high and unremitting fever, rash, hepatosplenomegaly, pancytopenias and lymphadenopathy. Patients should be informed about these potential symptoms of HLH. Consider referring your patients to a specialist for evaluation if you suspect they have developed HLH.

Acquired haemophilia A

Cases of acquired haemophilia A have been reported in both clinical trials and the post-marketing setting.

Patients should seek immediate medical attention in case of signs or symptoms of unexplained and excessive bleeding from cuts or injuries, or after surgery or dental work, many large or deep bruises, unusual bleeding after vaccinations, pain or swelling in the joints, haematuria or bloody stool.

Cytopenias

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

Complete blood count 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.

Thrombotic Thrombocytopenic Purpura

During postmarketing 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. TTP is associated with high morbidity and mortality rates if not recognised and treated early.

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Section 5. Summary of recommended patient monitoring

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Table 1 – Overview of pre-treatment recommendations to reduce the risk of side effects

	Pre-infusion
Pre-treatment	• Corticosteroids must be administered immediately prior to LEMTRADA® administration on each of the first 3 days of any treatment course (1000 mg methylprednisolone or equivalent) • Consider pre-treatment with antihistamines and/or antipyretics • 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 after treatment with LEMTRADA®

Table 2 – Overview of peri-infusion risk mitigation and monitoring recommendations

	Pre-infusion	Peri-infusion	Post-infusion
ECG, vital signs including heart rate and BP	• Obtain baseline vital signs, including heart rate and BP • Baseline ECG	• Perform frequent monitoring of heart rate, BP and overall clinical status at least once every hour • Discontinue infusion if patient shows clinical signs and/or symptoms suggesting development of a serious adverse event	
Platelet Counts	• Baseline platelet count		• Obtain platelet count immediately after infusion on Day 3 and Day 5 of the first course, and on Day 3 of any subsequent courses
Observation			• Observation for at least 2 hours – patients displaying clinical symptoms of a serious AE should be closely monitored until complete resolution of symptoms

AE=adverse event; BP=blood pressure; ECG=electrocardiogram

Patients should be educated on the potential for delayed onset of IARs and instructed to report symptoms and seek appropriate medical care.

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Table 3 – Overview of risk minimisation of delayed autoimmune side effects

	Pre-infusion	Post-infusion (Monthly) For at least 48 months*	Post-infusion (Quarterly) For at least 48 months*
Monitoring	• Thyroid function tests, including TSH levels • Complete blood count with differential • Serum creatinine • Urinalysis with microscopy • Serum transaminases	• Complete blood count with differential • Serum creatinine • Urinalysis with microscopy • Serum transaminases	• Thyroid function tests, including TSH levels

TSH = Thyroid Stimulating Hormone

***The treating HCP must ensure that patients commit to monitoring in between treatment courses and for at least 48 months after the last infusion.**

Together with your patient, it is important to plan and manage their periodic monitoring - evaluate their test results and remain vigilant for symptoms of adverse events (AEs).

It is extremely important that you ensure your patient understands the commitment to have periodic testing for at least 48 months following their last LEMTRADA® infusion, even if they are asymptomatic and their MS disease is well controlled.

- Review the LEMTRADA® Patient Guide and Package Leaflet with your patient at initial prescription and on a regular basis at follow-up visits. Before treatment, patients must be informed about the risks and benefits of the treatment. Remind the patient to remain vigilant for symptoms related to autoimmune conditions even after the 48-month monitoring period, and to seek medical help if they have any concerns.
- Encourage the patient to carry the Patient Alert Card with them at all times. Patients should show the Patient Alert Card to any HCP who is treating them for any reason, and especially in case of a medical emergency.

Exposure to LEMTRADA® during Pregnancy and Lactation

Safety in pregnancy and lactation has not been established. There are no adequate and well-controlled studies of LEMTRADA® in pregnant women. There is potential for LEMTRADA® to cross the placental barrier and pose a risk to the fetus. LEMTRADA® should not be administered during pregnancy.

Women of childbearing potential should use effective contraceptive measures during treatment and for 4 months following that course of LEMTRADA® treatment.

It needs to be taken into account that the initial full treatment of LEMTRADA® consists of 2 courses, 12 months apart. Discuss effective contraceptive measures with the patient. See also FAQs, page 48.

It is possible for LEMTRADA® to be transferred through breast milk. Breastfeeding should be discontinued during each course of treatment with LEMTRADA® and for 4 months following the last infusion of each treatment course.

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Section 6. Managing patients treated with LEMTRADA®

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Tools to aid patient compliance

There are tools available to patients receiving LEMTRADA® that can help to support them and ensure they are compliant with laboratory testing.

- **Phone call reminders:**
  Patients registered with the Patient Support Program (MS One-to-One) will receive telephone calls from a MS One-to-One Nurse aimed to educate the patient, co-ordinate infusion days and importantly to remind patients to go for monthly blood and urine monitoring.
- **Calendar:**
  Patients will be given the option of ordering calendars to ensure the relevant date is marked for the monthly laboratory tests. They will have printed instructions to refer to within the calendar.

These services will be offered through a third party, who will collect and process patients' personal data in accordance with appropriate data protection legislation. Patients' personal data will be stored securely and will not be shared with others, **as per the consent form signed when registering with the patient program.**

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Section 7. Frequently Asked Questions (FAQs)

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Patients treated with LEMTRADA® are at risk of experiencing the safety events addressed in this guide. Please consider the steps required to minimise the risks associated with these side effects before prescribing LEMTRADA®.

Contraindications

What if my patient has an infection when I want to begin a course of treatment with LEMTRADA®?

You should delay the initiation of LEMTRADA® administration in patients with active infection until complete resolution. Human Immunodeficiency Virus (HIV) infection is a contraindication for the use of LEMTRADA®.

What are the contraindications of LEMTRADA® treatment?

Do not use LEMTRADA® if a patient:

- Is allergic to alemtuzumab or any of the other excipients listed in the Professional Information (PI)
- Has Human Immunodeficiency Virus (HIV) infection
- Has severe active infection
- Has uncontrolled hypertension
- Has a history of arterial dissection of the cervicocephalic arteries
- Has a history of stroke
- Has a history of angina pectoris or myocardial infarction
- Has known coagulopathy or on concomitant anti-coagulant therapy

Treatment

How is LEMTRADA® administered and how long does the infusion take?

Initial treatment with LEMTRADA® is administered by intravenous infusion over two courses. The first course of treatment consists of a daily infusion for 5 consecutive days (12 mg/day for 5 days, therefore 60 mg total dose). The second course of treatment is administered 12 months later and consists of a daily infusion for 3 consecutive days (12 mg/day for 3 days, therefore 36 mg total dose). Upon evidence of MS disease activity by clinical and/or imaging criteria, additional as-needed treatment course(s) can be considered, which consist of a daily infusion for 3 consecutive days (12 mg/day for 3 days, therefore 36 mg total dose) administered at least 12 months after the prior treatment course.

LEMTRADA® must be diluted before each infusion. The diluted solution should be administered by IV infusion over a period of approximately 4 hours. Refer to the full Professional Information for dosage and dilution instructions before administration.

If a side effect temporally associated with infusion occurs, provide the appropriate symptomatic treatment, as needed. If the infusion is not well tolerated, the infusion duration may be extended. If severe reactions occur, treatment should be discontinued immediately.

Medically evaluate the patient guided by the adverse event profile of LEMTRADA® prior to restarting therapy. Consider permanently discontinuing the LEMTRADA® infusion if the patient is deemed to be at a future risk of a serious clinical outcome (please refer to Section 4 for more details).

Reactions attributed to anaphylaxis have been reported rarely in contrast to infusion-associated reactions. Resources for the management of anaphylaxis or serious reactions should be available.

You should be aware of patient's potential cardiovascular and cerebrovascular risk factors, lung disease, and concomitant medications for timely mitigation of infusion-associated reactions.

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Are there any prophylactic treatments that should be taken?

Patients should be premedicated with corticosteroids (1000 mg methylprednisolone or equivalent) immediately prior to LEMTRADA® administration for the first 3 days of any treatment course. Additionally, 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.

Monitoring side effects

Before starting LEMTRADA® treatment, what laboratory tests need to be performed?

The tests that need to be performed are:

- Complete blood count with differential
- Serum transaminases
- Serum creatinine
- Urinalysis with microscopy
- Thyroid function tests, such as thyroid-stimulating hormone (TSH)

Do I continue the laboratory tests during and after the patient has received treatment with LEMTRADA®? For how long?

Yes. Testing starts before treatment (baseline tests) and should be continued for at least 48 months after receiving the last infusion. Details on which tests to conduct, when and for how long can be found in Section 5: Summary of recommended patient monitoring.

How long should patients be observed for after receiving a LEMTRADA® infusion?

Patients should be observed for at least 2 hours after infusion. Those displaying clinical symptoms of a serious adverse event should be closely monitored until complete resolution of symptoms and hospitalisation extended as appropriate.

When should platelet counts be taken?

A baseline platelet count should be obtained prior to infusion. Platelet counts should also be taken immediately after infusion on Day 3 and Day 5 of the first course and on Day 3 of any subsequent courses.

Managing side effects

What are the signs and symptoms of serious side effects temporally associated with infusion?

Patients who develop abnormal vital signs including blood pressure or report sudden onset of chest pain, neck pain, facial drooping, difficulty breathing, severe dyspnoea, severe headache, weakness on one side, difficulty with speech, coughing up blood or bruising should be evaluated immediately. Patients should be advised to seek immediate medical attention if any of the symptoms occur.

How should I manage a patient with suspected serious side effects temporally associated with their LEMTRADA® infusion?

It is important to monitor patients for myocardial ischaemia and infarction, pulmonary alveolar haemorrhage, haemorrhagic stroke, cervicocephalic arterial dissection and thrombocytopenia. Vital sign monitoring including blood pressure, heart rate and ECG is advised at baseline and regularly thereafter. It is recommended that a platelet count is taken at baseline, on Day 3 and Day 5 of the first treatment course and on Day 3 of any subsequent course. See more details in Section 5: Summary of recommended patient monitoring.

What are the signs and symptoms of immune thrombocytopenic purpura (ITP)?

Symptoms of ITP could include (but are not limited to) easy bruising, petechiae, spontaneous mucocutaneous bleeding (e.g. epistaxis, haemoptysis), heavy or irregular menstrual bleeding. These clinical signs of ITP may be apparent before severe bleeding develops. Low platelet counts, or clinically significant changes from baseline, may also be a sign of ITP. See more details in Figure 2, page 27 (Section 4: What are the main risks associated with the use of LEMTRADA®?)

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How should I manage a patient with suspected ITP?

It is important to monitor all patients for ITP so patients are diagnosed and managed in a timely manner. Therefore, complete blood counts should be obtained prior to initiation of treatment and at monthly intervals for at least 48 months following the last infusion.

If ITP is suspected, a platelet count should be obtained immediately. If onset is confirmed, appropriate medical intervention should be promptly initiated, including immediate referral to a haematologist. Severe or widespread bleeding is life-threatening and demands immediate care.

Which symptoms could be associated with nephropathy, such as anti-Glomerular Basement Membrane (anti-GBM) disease?

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. Since patients may be asymptomatic, it is important that the monthly laboratory tests (serum creatinine and urinalysis with microscopy) are conducted between courses and for at least 48 months after the last infusion of LEMTRADA®.

How should I manage a patient with suspected nephropathy?

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.

What are the signs and symptoms of autoimmune hepatitis?

Symptoms of autoimmune hepatitis could include enzyme elevations and symptoms suggestive of hepatic dysfunction (e.g. unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine).

How should I manage a patient with suspected autoimmune hepatitis?

Serum transaminases should be determined at baseline and monitored monthly for at least 48 months following the last infusion. If hepatic injury is confirmed, appropriate medical intervention should be promptly initiated, including immediate referral to a specialist. Early detection and treatment of hepatic injury, including autoimmune hepatitis, may decrease the risk of poor outcomes.

What are the signs and symptoms of haemophagocytic lymphohistiocytosis (HLH)?

Among the signs and symptoms characteristic of HLH are high and unremitting fever, rash, hepatosplenomegaly, pancytopenias and lymphadenopathy.

How should I manage a patient with suspected HLH?

Regular laboratory monitoring should be carried out and if patients develop early manifestations of pathologic immune activation they should be evaluated immediately, referred to a specialist upon suspicion and a diagnosis of HLH should be considered.

What are the signs and symptoms of acquired haemophilia A?

Patients should be informed to seek immediate medical attention in case of signs or symptoms of unexplained and excessive bleeding from cuts or injuries, or after surgery or dental work, many large or deep bruises, unusual bleeding after vaccinations, pain or swelling in the joints, haematuria or bloody stool.

How should I manage a patient with suspected acquired haemophilia A?

Complete blood count should be monitored on a regular basis and a coagulopathy panel including an activated partial thromboplastin time (aPTT) must be obtained in all patients that present with such symptoms of acquired haemophilia A. In case of a prolonged aPTT, the patient should be referred to an appropriate specialist.

How should I manage a patient with suspected TTP?

It is important to monitor all patients for TTP so that all patients are diagnosed and managed in a timely manner. Therefore, complete blood counts should be obtained prior to initiation of treatment and at monthly intervals for at least 48 months following the last infusion. If TTP is suspected, a platelet count should be obtained immediately. If onset is confirmed, appropriate medical intervention should be promptly initiated, including immediate referral to a haematologist. TTP is life-threatening and demands immediate care.

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Pregnancy, contraception and breastfeeding counselling

Should female patients use contraception?

The alpha half-life of alemtuzumab approximated 2 days and was comparable between courses, leading to low or undetectable serum concentrations within approximately 30 days following each treatment course. 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 LEMTRADA® treatment.

Is it possible to administer LEMTRADA® during 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 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 (also known as Basedow's disease), maternal TSH receptor antibodies can be transferred to a developing fetus and can cause transient neonatal Graves' disease.

If women want to become pregnant, how long should they wait after a LEMTRADA® treatment course?

Women should use effective contraceptive measures and wait at least 4 months following each course of LEMTRADA® treatment before trying to become pregnant. It needs to be taken into account that the initial full treatment of LEMTRADA® consists of 2 courses, 12 months apart. Women of childbearing potential need to be alerted to this and discouraged to stop contraception between these treatment courses.

Will LEMTRADA® affect future female or male fertility?

There are no adequate clinical safety data on the effect of LEMTRADA® on fertility. Data in a small number (N = 13) of male patients in two clinical trials suggest that LEMTRADA® treatment does not have an adverse impact on sperm quality, quantity, or motility.

Should a patient who is breastfeeding receive a course of treatment with LEMTRADA®?

It is possible for LEMTRADA® to be transferred through breast milk. As risk to the breastfed child cannot be excluded, breastfeeding should be discontinued during each course of treatment and for 4 months following the last infusion of each treatment course.

Vaccinations

What considerations should be given to vaccinations when considering LEMTRADA® treatment?

Since the safety of immunisation with live vaccines following LEMTRADA® therapy has not been studied, live vaccines should not be administered to patients who have recently been treated with LEMTRADA®.

It is recommended that patients are up to date with their vaccinations (according to national guidelines) at least 6 weeks prior to commencing treatment with LEMTRADA®. Consider varicella zoster virus (VZV) vaccination of antibody negative patients, prior to treatment with LEMTRADA®.

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For full prescribing information refer to the professional information approved by the medicines regulatory authority.

S4 **LEMTRADA®** (Concentrate for solution for infusion) **COMPOSITION:** Each vial contains 12 mg/1,2 mL alemtuzumab (10 mg/mL). **REGISTRATION NUMBER:** 48/30.1/0263. **NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:** sanofi-aventis south africa (pty) ltd., Reg. no.: 1996/010381/07, Floor 5, Building I, Hertford Office Park, 90 Bekker Road, Midrand, 2196. Tel: (011) 256 3700.

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- Use the Med Safety App [accessible from the Apple store (for iOS devices) and Google Play (for android devices)] via https://medsafety.sahpra.org.za/ **alternatively,**
- Complete the ADR reporting form accessible via the SAHPRA website at www.sahpra.org.za and email it to adr@sahpra.org.za **and**
- Adverse events should also be reported to the Pharmacovigilance Department of Sanofi by emailing za.drugsafety@sanofi.com or calling 011 256 3700

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