LEMTRADA®
alemtuzumab 12mg IV

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

Important safety and risk minimisation information for healthcare professionals prescribing LEMTRADA

Adverse events should be reported. Healthcare proffesionals can report any suspected adverse reactions to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/
Additionally adverse reactions can be reported to Sanofi by calling 09-8633081

sanofi

Contents

Executive summary

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

This is an abbreviated guide – refer to the full guide 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 Physician Prescribing Information (referred hereafter as SPC)[1].

[1]Reference: Lemtrada Product information as updated in accordance with the instructions of the Ministry of Health, July 2022.

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

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.

Exposure to LEMTRADA in case of Pregnancy

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

LEMTRADA should only be administered during pregnancy if you consider the potential patient benefit to justify the potential risk to the foetus. Breastfeeding is not recommended during and for at least 4 months following a treatment course even if it is unknown whether LEMTRADA is excreted in human milk. However, the benefits of conferred immunity through breast milk may outweigh the risks of potential exposure to LEMTRADA for the suckling newborn.

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.
Progressive Multifocal Leukoencephalopathy (PML)	• **Prior to initiation and readministration of treatment:** MRI scan should be made 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

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 haemorhage		
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

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 creatine levels test 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 the symptoms associated with TTP so they can self-monitor post-infusion	• Appropriate medical intervention should be initiated promptly, including immediate referral to a haematologist
Adult onset still disease (AOSD)	• Patients should be informed about the symptoms associated with AOSD so they can self-monitor post-infusion	• Consider referral to a specialist for diagnosis and treatment
Autoimmune encephalitis (AIE)	• Patients with suspected autoimmune encephalitis should have appropriate complementary exams to confirm diagnosis and exclude alternative etiologies. Patients should be informed about the symptoms associated with AIE so they can self-monitor post-infusion	• Consider referral to a specialist for diagnosis and treatment

Overview of LEMTRADA

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 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 below 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)

Temporally associated side effects occurring during or shortly after infusion

- Myocardial ischaemia and infarction, pulmonary alveolar haemorrhage, haemorrhagic stroke, 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
- Hemophagocytic lymphohistiocytosis (HLH)
- Acquired haemophilia A
- Thrombotic thrombocytopenic purpura (TTP)
- Adult Onset Still Disease (AOSD)
- Autoimmune encephalitis (AIE)

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

3. A frequently asked questions (FAQ) section

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 should be given to patients at the time of 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.

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.

These materials are available upon request from the Sanofi Medical Affairs Department by calling 09-8633081.

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 SPC.

Introduction to LEMTRADA

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.

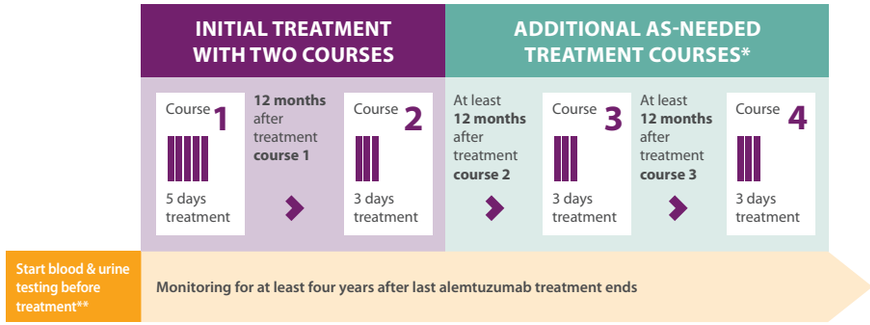
Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction, cervicocephalic arterial dissection, haemorrhagic stroke, autoimmune conditions and infections, should be available. Resources for the management 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 at least 48 months of follow-up 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 3.**

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



* **Note:** A study following patients for 6 years after the first infusion (course 1) has shown that a majority of patients do not need further treatment after the 2 initial treatment courses.

** Please see additional tests and recommendations prior to Lemtrada treatment listed below

What are the main risks associated with the use of LEMTRADA?

1. Serious infections
(affects ≥ 1 in 10 patients)

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, evaluate both active or inactive ("latent") tuberculosis risk according to local guidelines, screen for hepatitis B virus (HBV) and hepatitis C virus (HCV)
- 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 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
- Start anti-herpes prophylaxis on Day 1 of treatment and continue for at least 1 month following each course of treatment
- Avoid concomitant therapy with other immunomodulating agents

2. Progressive Multifocal Leukoencephalopathy

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

Prior to initiation and readministration of alemtuzumab treatment, an MRI scan should be made 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 physician should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive, neurological or psychiatric symptoms).

3. Serious side effects temporally associated with LEMTRADA infusion

During post-marketing use, rare, 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 the second course. 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 in 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 3: Summary of recommended patient monitoring', for important information on infusion instructions.

4. 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
  (very common ADR: (≥ 1/10))
- Immune thrombocytopenic purpura (ITP)
  (common ADR: (≥ 1/100 to < 1/10))
- Nephropathies, including anti-Glomerular Basement Membrane (anti-GBM) disease
  (uncommon ADR: (≥ 1/1,000 to < 1/100))
- Autoimmune hepatitis
  (unknown incidence)
- Haemophagocytic lymphohistiocytosis (HLH)
  (rare ADR: (≥ 1/10,000 to < 1/1,000))
- Acquired haemophilia A
  (uncommon ADR: (≥ 1/1,000 to < 1/100))
- Thrombotic thrombocytopenic purpura (TTP)
  (rare ADR: (≥ 1/10,000 to < 1/1,000))
- Adult Onset Still Disease (AOSD) (Not known incidence)
- Autoimmune encephalitis (AIE) (uncommon incidence)

These events can be serious, leading to morbidity and/or mortality with peak incidence at 18–36 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 values and be vigilant for signs and symptoms. Please review the following sections carefully to gain a better understanding of these risks. See Section 3: Summary of recommended patient monitoring, for important information about reducing the risk of LEMTRADA use.

Thyroid disorders (affects ≥ 1 in 10 patients)

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 become pregnant. Untreated thyroid disease can cause harm to the unborn and newborn baby. Untreated hypothyroidism during pregnancy increases risk of miscarriage and damage to the foetus, 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 foetus and can cause transient neonatal Basedow's disease

Immune thrombocytopenic purpura (ITP)
(affects < 1 in 10 patients)

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) 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:

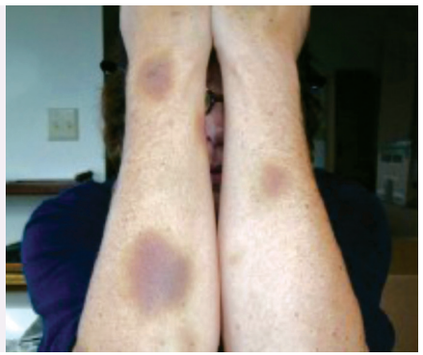
- Complete blood counts with differential should be obtained prior to initiation of treatment and at monthly intervals thereafter until at least 48 months following the last infusion
- Check the patient for clinical symptoms of ITP
- Counsel the patient on the importance of complying with monthly monitoring 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 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

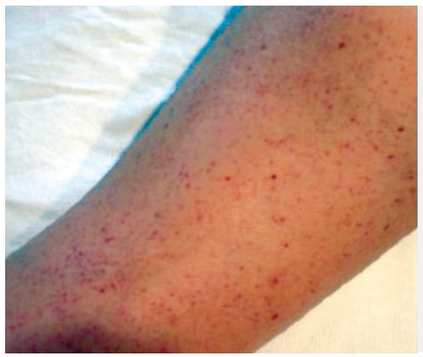
The potential risk associated with retreatment with LEMTRADA following the occurrence of ITP is unknown.

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.





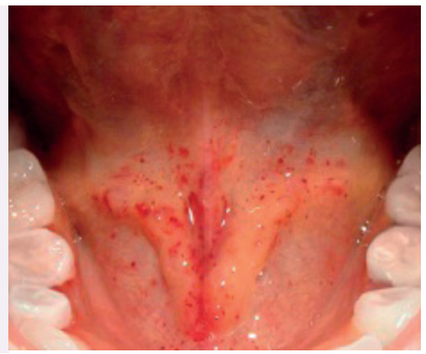
Example of a leg with petechia and purpura.

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.

Nephropathies, including anti-GBM disease
(affects < 1 in 100 patients)

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 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 (unknown incidence)

Autoimmune hepatitis causing clinically significant liver injury, including fatal cases, has been rarely 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.

Haemophagocytic lymphohistiocytosis (HLH) (affects < 1 in 1,000 patients)

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

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 (affects < 1 in 100 patients)

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.

Thrombotic Trombocytopenic Purpura (TTP) (affects < 1 in 1,000 patients)

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 characterized by thrombocytopenia, microangiopathic hemolytic anemia, neurological sequelae, fever and renal impairment. It is associated with high morbidity and mortality rates if not recognized and treated early.

Adult Onset Still's disease (AOSD) (Not known incidence)

During postmarketing use, AOSD has been reported in patients treated with LEMTRADA. AOSD is a rare inflammatory condition that requires urgent evaluation and treatment.

Patients with AOSD may have a combination of the following signs and symptoms: fever, arthritis, rash and leukocytosis in the absence of infections, malignancies, and other rheumatic conditions. Consider interruption or discontinuation of treatment with LEMTRADA if an alternate etiology for the signs or symptoms cannot be established.

Autoimmune Encephalitis (AIE) (uncommon incidence)

Cases of autoimmune encephalitis have been reported in patients treated with LEMTRADA.

Autoimmune encephalitis is characterized by subacute onset (with rapid progression over months) of memory impairment, altered mental status or psychiatric symptoms, generally in combination with new onset focal neurological findings and seizures. Patients with suspected autoimmune encephalitis should have neuroimaging (MRI), EEG, lumbar puncture and serologic testing for appropriate biomarkers (e.g. neural autoantibodies) to confirm diagnosis and exclude alternative etiologies.

Summary of recommended patient monitoring

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 treatment on each of the first 3 days of any treatment course (1,000 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 (200 mg aciclovir twice a day or equivalent)

Table 2 – Overview of peri-infusion prevention and monitoring recommendations

	Pre-infusion	During 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

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 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

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 in case of Pregnancy

Although there are limited available data evaluating the use of LEMTRADA in pregnant women, there is the potential for LEMTRADA to cross the placental barrier and pose a risk to the foetus. Therefore, LEMTRADA should only be administered during pregnancy if you consider the potential benefit to justify the potential risk to the foetus.

Women of childbearing potential should use effective contraception when receiving and up to 4 months after each course of LEMTRADA treatment.

It is also possible for LEMTRADA to be transferred through breast milk, therefore breastfeeding is not recommended during or for at least 4 months following a treatment course. However, the benefits of conferred immunity through breast milk may outweigh the risks of potential exposure to LEMTRADA for the suckling newborn.

Managing patients treated with LEMTRADA

- It is extremely important that your patient understands the commitment to having periodic testing performed (for at least 48 months after last infusion) even if they are asymptomatic and their MS disease is well controlled.
- Together with your patient you need to plan and manage their periodic monitoring.
- If non-compliant, patients may need further counseling to highlight the risks of missing scheduled monitoring tests.
- You should monitor their test results and remain vigilant for symptoms of adverse events.
- Review the LEMTRADA Patient Guide and Package Leaflet with your patient. Before treatment, patients must be informed about the risks and benefits. Remind the patient to remain vigilant for symptoms related to autoimmune conditions, and to seek medical help if they have any concerns.
- Encourage the patient to carry the Patient Alert Card on them at all times. They should show the Patient Alert Card to any HCP who is treating them for any reason, or in case of a medical emergency.
- Specialists and equipment required for the timely diagnosis and management of the most frequent adverse reactions, especially autoimmune conditions and infections, should be available.

Tools to aid patient compliance

According to the patients' preferences, patients prescribed LEMTRADA will have the opportunity to use optional tools to aid their compliance with laboratory testing. The tools provide different ways for patients to be reminded about periodic testing.

Frequently Asked Questions (FAQs)

Patients treated with LEMTRADA are at a higher risk of experiencing the safety events addressed in this guide than the general population. 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 severe 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 SPC section 6.1.
- Has Human Immunodeficiency Virus (HIV) infection
- Has severe active infections until complete resolution
- Has uncontrolled hypertension
- Has a history of arterial dissection of the cervico-cephalic arteries
- Has a history of stroke
- Has a history of angina pectoris or myocardial infarction
- Has a known coagulopathy, and is on anti-platelet or anti-coagulant therapy
- Has other concomitant autoimmune diseases (besides MS)

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 over 5 consecutive days. The second course of treatment is administered 12 months later and consists of a daily infusion over 3 consecutive days. Upon evidence of MS disease activity by clinical and/or imaging criteria, additional third and fourth as-needed treatment course(s) can be considered, which consist of a daily infusion over 3 consecutive days administered at least 12 months after the prior treatment course.

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 3 for more details).

Reactions attributed to anaphylaxis have been reported rarely in contrast to infusion-associated reactions. However, 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.

Are there any prophylactic treatments that should be taken?

Patients should be premedicated with corticosteroids (1,000 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 during and for a minimum of 1 month following treatment. In clinical trials, patients were administered 200 mg aciclovir (or equivalent) twice a day.

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 receiving 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 3 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 treatment. Those displaying clinical symptoms of a serious adverse event should be closely monitored until complete resolution of symptoms and hospitalisation is 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 thrompocytopenia. Vital sign monitoring including blood pressure and heart rate is advised at baseline and regularly thereafter. It is recommended that a platelet count is taken on Day 3 and Day 5 of the first treatment course and on Day 3 of any subsequent course. See more details in Section 3: 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.

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 periodic laboratory tests (serum creatinine and urinalysis with microscopy) are conducted.

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).

What are the signs and symptoms of haemophagocytic lymphohitiocytosis (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 autoimmune hepatitis?

Serum transaminases should be monitored on a regular basis. 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.

How should I manage a patient with suspected HLH?

Regular laboratory monitoring should be carried out and if patients develop early manifestations of pathogic immune activation they should be evaluated immediately, and a diagnosis of HLH should be considered.

What are the signs and symptoms of acquired haemophilia A?

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.

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 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 a haematologist.

How should I manage a patient with suspected Thrombotic Thrombocytopenic Purpura (TTP)?

It is important to monitor all patients for TTP so patients are diagnosed and managed in a timely manner. Therefore, complete blood counts should be obtained prior to initiation of treatment, immediately after infusion on Days 3 and 5 of the first infusion course, as well as immediately after infusion on Day 3 of any subsequent course and at monthly intervals for at least 48 months following the last infusion. Clinically significant thrombocytopenia needs to be followed until resolution.

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.

How should I manage a patient with suspected AOSD?

AOSD is a rare inflammatory condition that requires urgent evaluation and treatment. Consider interruption or discontinuation of treatment with LEMTRADA if an alternate etiology for the signs or symptoms of AOSD cannot be established.

How should I manage a patient with suspected AIE?

Patients with suspected autoimmune encephalitis should have neuroimaging (MRI), EEG, lumbar puncture and serologic testing for appropriate biomarkers (e.g. neural autoantibodies) to confirm diagnosis and exclude alternative etiologies.

Pregnancy, contraception and breastfeeding counselling

Should female patients use contraception?

The alpha half-life of alemtuzumab approximated 4–5 days and was comparable between courses, leading to low or undetectable serum concentrations within approximately 30 days following each treatment course. Therefore, women of childbearing potential should use effective contraceptive measures during treatment and for 4 months following each course of LEMTRADA treatment.

Is it possible to administer LEMTRADA during pregnancy?

LEMTRADA should be administered during pregnancy only if the potential benefit justifies the potential risk to the foetus. Human immunoglobulin G (IgG) is known to cross the placental barrier; LEMTRADA may cross the placental barrier as well and thus potentially pose a risk to the foetus. It is not known whether LEMTRADA can cause foetal harm when administered to pregnant women or whether it can affect reproductive capacity.

Thyroid disease poses special risks in women who are pregnant. Without treatment of hypothyroidism during pregnancy, there is an increased risk for miscarriage and foetal effects such as mental retardation and dwarfism. In mothers with Graves' disease (also known as Basedow's disease), maternal TSH receptor antibodies can be transferred to a developing foetus 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 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 treatment courses.

Will LEMTRADA affect future female or male fertility?

There are no adequate clinical safety data on the effect of LEMTRADA on fertility. In a sub-study in 13 male alemtuzumab-treated patients (treated with either 12 mg or 24 mg), there was no evidence of aspermia, azoospermia, consistently depressed sperm count, motility disorders or an increase in sperm morphological abnormalities. CD52 is known to be present in human and rodent reproductive tissues. Animal data have shown effects on fertility in humanised mice (see section 5.3 of the Summary of Product Characteristics (SPC)), however a potential impact on human fertility during the period of exposure is unknown based on the available data.

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

It is unknown whether LEMTRADA is excreted in human 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 course. However, benefits of conferred immunity through breast milk may outweigh the risks of potential exposure to LEMTRADA for the baby.

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.

Notes

LEMTRADA®
alemtuzumab 12mg IV

The format and the content of this HCP guide was checked and approved by the Ministry of Health on December 2022

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