Health Care Professional Guide

Using LEMTRADA® (alemtuzumab) in Patients with Relapsing-Remitting Multiple Sclerosis (RRMS)

LEMTRADA®
alemtuzumab 12mg IV

Table of Contents

Overview of Lemtrada

LEMTRADA® (alemtuzumab) is indicated for adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features.

This Guide has been developed as part of a Risk Management Plan (RMP) for prescribers and health care professionals (HCPs) involved in the care of patients treated with LEMTRADA, to provide further information about the potential serious risks associated with the use of LEMTRADA.

On the following pages there is a description of the risks associated with LEMTRADA use including:

Autoimmune conditions, including:

- Immune Thrombocytopenic Purpura (ITP),
- Nephropathies including anti-Glomerular Basement Membrane (anti-GBM) disease,
- Thyroid disorders

This Guide also provides important recommendations on how to mitigate these risks through appropriate patient counseling, monitoring and management.

Please be aware that this Guide does not cover all the risks associated with the use of LEMTRADA and does not take the place of the Summary of Product Characteristics (SmPC).

1> Introduction to LEMTRADA

LEMTRADA® (alemtuzumab) is indicated for adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features.

LEMTRADA is a monoclonal antibody administered intravenously. It binds to CD52, an antigen present at high levels on the surface of T and B lymphocytes, and at lower levels on natural killer cells, monocytes, and macrophages.

The mechanism by which LEMTRADA exerts its therapeutic effects in MS is not fully elucidated. However, research suggests immunomodulatory effects through the depletion and repopulation of lymphocytes, including:

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

The reduction in the level of circulating B and T cells by LEMTRADA and subsequent repopulation may account for the therapeutic effect.

The use of alemtuzumab has been associated with risk of serious infection and autoimmune conditions. Autoimmune events may occur many years after treatment and may be serious or life-threatening.

Lemtrada should be initiated and supervised by a neurologist experienced in the treatment of MS.

In order to minimise possible risks and side effects of LEMTRADA, prescribers and patients must commit to 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.

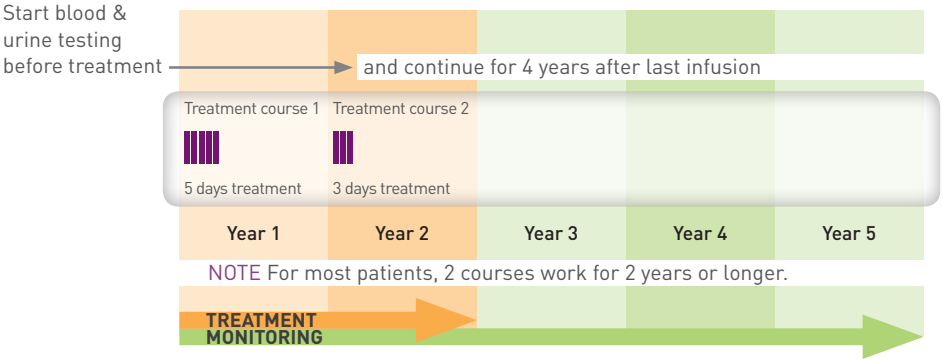
Creating a partnership between you, your patient and your healthcare team, along with careful review about how to use the patient education tools, will help patients to:

- Comply with periodic tests.
- Identify and report symptoms early.
- Receive prompt and appropriate treatment if needed.

For more details, refer to the section in this guide called Managing Patients treated with LEMTRADA. ▸

To enhance your understanding of the duration of the effects of treatment and the length of required follow-up, please refer to the diagrams below titled Overview of LEMTRADA Treatment and Overview of LEMTRADA Monitoring. ▸

Overview of LEMTRADA Treatment



Overview of LEMTRADA Monitoring

Condition	Activity	Timing	
Immune Thrombocy-topenic Purpura (ITP)	Complete blood count with differential	Prior to initiating LEMTRADA treatment	Monthly until 48 months after last infusion
Nephropathies, including anti-GBM disease	Serum creatinine	Prior to initiating LEMTRADA treatment	Monthly until 48 months after last infusion
Nephropathies, including anti-GBM disease	Urinalysis with microscopy	Prior to initiating LEMTRADA treatment	Monthly until 48 months after last infusion
Thyroid Disorders	Thyroid function tests (such as TSH)	Prior to initiating LEMTRADA treatment	Every 3 months until 48 months after last infusion

2> What are the delayed risks associated with use of LEMTRADA?

Autoimmune Conditions

Alemtuzumab use is associated with risk of autoimmune conditions including:

- Immune Thrombocytopenic Purpura (ITP)
- Thyroid disorders
- Nephropathies including anti-GBM disease

These events can be serious, leading to morbidity and/or mortality, and may occur many years after treatment. Early detection can improve the outcomes of patients experiencing these events.

It is important to **carefully monitor lab values** and **be vigilant for signs and symptoms**. Please review the following sections carefully to gain a better understanding of these risks.

Immune Thrombocytopenic Purpura (ITP)

Immune thrombocytopenic purpura is an autoimmune disorder usually associated with anti-platelet antibodies. Platelet depletion reduces the ability of the blood to clot. Symptoms of ITP could include (but are not limited to) easy bruising, petechiae, spontaneous mucocutaneous bleeding (e.g. epistaxis, haemoptysis), heavier than normal or irregular menstrual bleeding. These clinical signs of ITP may be apparent before serious bleeding develops.

The goal of the risk minimisation measures described in this document is to detect and treat potential cases of ITP as early as possible.

ITP can be a serious condition leading to morbidity and mortality, and may occur several years after dosing. In clinical trials patients were regularly monitored and were educated on the signs and symptoms of ITP for early detection of ITP. Following these provisions, 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 48 months following the last infusion.
- Check the patient for clinical symptoms of ITP. ▸

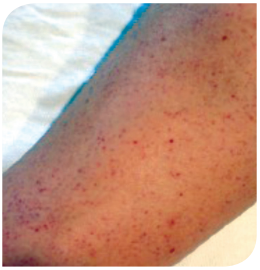
- Counsel the patient on the importance of complying with monthly monitoring of their blood and the need to continue for 48 months after their last infusion.
- Educate the patient on how to recognise ITP related symptoms, and emphasise the need to remain vigilant for them.
- If ITP is suspected, appropriate medical intervention should be promptly initiated, including immediate referral to a specialist. Severe or widespread bleeding is life-threatening and demands immediate care.

See section on Managing Patients treated with LEMTRADA for important information on safe use of the product.

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

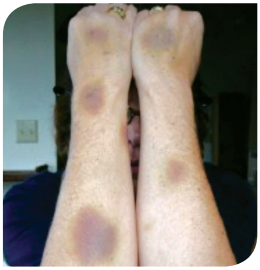
In order to support patient compliance, patient education tools have been developed. Please see the section on Managing Patients treated with LEMTRADA for a further description of these tools.

Examples of ITP



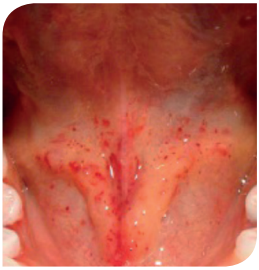
This is an example of a leg with petechiae.

Petechiae are small, scattered, "pin prick" spots under the skin that are red, pink or purple. Petechiae can occur anywhere on the patient's body, not just the legs.



This is an example of easy or excessive bruising.

This could occur anywhere on the patient's body.



This is an example of purpura under the tongue.

Purpura could 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

Nephropathy, including anti-GBM disease, has been rarely reported after treatment with LEMTRADA in multiple sclerosis patients in clinical trials, and generally occurred within 39 months following the last administration of LEMTRADA.

Clinical manifestations of nephropathy may include elevation in serum creatinine, haematuria and/or proteinuria. While not observed in clinical trials, alveolar haemorrhage manifested as haemoptysis may occur with anti-GBM disease. Since patients may be asymptomatic, it is important that the periodic lab tests are conducted.

- Serum creatinine levels should be obtained prior to initiation of treatment and at monthly intervals thereafter until 48 months after the last infusion.
- Urinalysis with microscopy should be obtained prior to initiation of treatment and at monthly intervals thereafter until 48 months after the last infusion. After this 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 further evaluation for nephropathies, including referral to a specialist.
- Early detection and treatment of nephropathies may decrease the risk of poor outcomes.
- In menstruating females, consider the timing of quarterly urinalysis to avoid false positives.
- Immediate referral to a specialist for further assessment for patients with suspected nephropathy, is strongly recommended.

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.

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 and occurred through 48 months following first LEMTRADA exposure. Most thyroid disorders were managed with conventional medical therapy; some patients required surgical intervention.

It is important to let the patient know that depending on the thyroid condition, they may require lifelong treatment (e.g. as with hypothyroidism). ▸

- 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 48 months following the last infusion. After this period, testing should be performed based on clinical findings suggestive of thyroid dysfunction.
- 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. Special caution should be taken for pregnant women with Basedow's disease (also known as Graves' disease), as maternal thyroid stimulating hormone receptor antibodies can be transferred to a developing foetus and can cause transient neonatal Basedow's disease. The HCP responsible for managing the patient's pregnancy must be made aware of the increased risk of thyroid disorders due to the patient's Lemtrada treatment, and the need for these to be appropriately treated.

3> Summary of recommended patient monitoring

For a summary table of recommended monitoring milestones, please refer to the table below. You will also find a packet of pre-printed checklists to use for each of your patients for whom you prescribe LEMTRADA. Be sure to check the Contraindications Section of the attached SmPC prior to beginning LEMTRADA treatment.

Condition	Activity	Timing	
Immune Thrombocy-topenic Purpura (ITP)	Complete blood count with differential	Prior to initiating LEMTRADA treatment	Monthly until 48 months after last infusion
Nephropathies, including anti-GBM disease	Serum creatinine	Prior to initiating LEMTRADA treatment	Monthly until 48 months after last infusion
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4> Managing patients treated with LEMTRADA

- It is extremely important that your patient understands the commitment to having periodic testing performed (for 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.

<<Note: Delete as appropriate according to national approvals>>

Web-based reminder: Patients log-in to provide their email address or telephone number to generate automatic reminders by email or SMS relating to monthly lab tests. A web address will be provided in the patient guide.

Paper-based reminder: Patients provide their mailing address (via a freepost card) so that they can be sent a reminder by postal mail.

Calendar: Patients will be given the option of ordering calendars with customized reminder stickers to ensure the relevant date is marked for the periodic lab 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 applicable data protection legislation. Patients' personal data will be stored securely and will not be disseminated to others, including the manufacturer of LEMTRADA.

Log on to www.msonetoone.xx to find additional resources help your patient manage their testing.

5> Other Information

Vaccines

- It is recommended that patients are up to date with their vaccinations (according to national guidelines) at least 6 weeks before commencing treatment with LEMTRADA.
- 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 received a course of LEMTRADA.
- Consider VZV vaccination of antibody negative patients prior to treatment with LEMTRADA.

Fertility, Contraception, Pregnancy and Breast-Feeding

- Women of childbearing potential should use effective contraceptive measures during treatment with LEMTRADA and for 4 months following LEMTRADA treatment.
- There are no adequate and well-controlled studies of LEMTRADA in pregnant women. LEMTRADA should be administered during pregnancy only if the potential benefit justifies the potential risk to the foetus.

- Thyroid disease poses special risks in women who are pregnant (see Section 2, Thyroid Disorders). In mothers with Basedow's disease (also called Graves' disease), maternal thyroid stimulating hormone receptor antibodies can be transferred to a developing foetus and can cause transient neonatal Basedow's disease.
- It is unknown whether alemtuzumab is excreted in human milk. A risk to the breastfed child cannot be excluded. Therefore, breast feeding should be discontinued during each course of treatment with LEMTRADA and for 4 months following the last infusion of each treatment course. However, benefits of conferred immunity through breast-milk may outweigh the risks of potential exposure to LEMTRADA for the baby.
- 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 SmPC), however a potential impact on human fertility during the period of exposure is unknown based on the available data.

6> Frequently Asked Questions (FAQ)

Please consider the following before prescribing LEMTRADA:

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

The tests that need to be done are:

- Complete blood count with differential
- Serum creatinine
- Thyroid function tests, such as TSH
- Urinalysis with microscopy

More information can be found in Section 3, Summary of Recommended Patient Monitoring.

Can I prescribe LEMTRADA to patients receiving other MS treatments?

LEMTRADA has not been administered for treatment of MS concomitantly with or following antineoplastic or immunosuppressive therapies. As with other immunomodulating therapies, potential combined effects on the patient's immune system should be taken into account when considering administration of LEMTRADA. Concomitant use of LEMTRADA with any of these therapies could increase the risk of immunosuppression.

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 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.

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

You should consider to delay the initiation of LEMTRADA administration in patients with active infection until the infection is fully controlled. ▸

Treatment

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

LEMTRADA is administered by intravenous infusion in two annual courses. The initial course of treatment consists of a daily infusion over a period of 5 consecutive days. The second course of treatment is administered 12 months later and consists of a daily infusion over a period of 3 consecutive days.

If an infusion-associated reaction occurs, provide the appropriate symptomatic treatment, as needed. If the infusion is not well tolerated, the infusion duration may be extended. If severe infusion reactions occur, immediate discontinuation of the intravenous infusion should be considered. Within the clinical trials, anaphylaxis or serious reactions that necessitated treatment discontinuation were very rare. Resources for the management of anaphylaxis or serious reactions should be available. Physicians should be aware of the patient's cardiac history as infusion-associated reactions can include cardiac symptoms such as tachycardia. Resources for the management of anaphylaxis or serious reactions should be available.

Are there any prophylactic treatments that should be taken?

Patients should be pre-medicated with corticosteroids (1,000 mg methylprednisolone or equivalent) immediately prior to LEMTRADA administration for the first 3 days of any treatment course. Additionally, pretreatment with anti-histamines and/or anti-pyretics prior to LEMTRADA administration may also be considered.

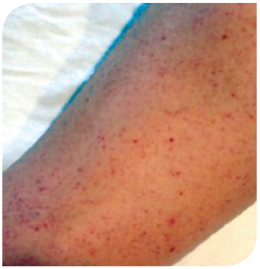
Oral prophylaxis for herpes infection should be administered to all patients during and for a minimum of 1 month following treatment. In clinical trials, patients were administered 200 mg aciclovir [or equivalent] twice a day.

Monitoring Side Effects

What are the signs and symptoms of 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 serious bleeding develops. Low platelet counts, or clinically significant changes from baseline, as determined by complete blood count with differential, is also a sign of ITP.

Examples of ITP



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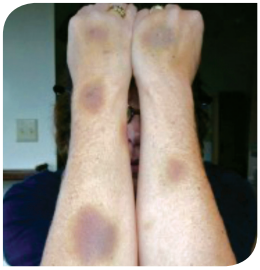

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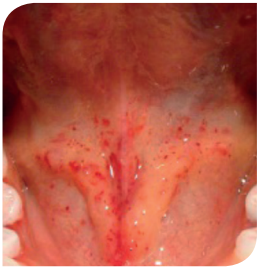

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Purpura could occur on any mucous membrane, including anywhere in the mouth (under the tongue, roof of the mouth, inner cheeks, tongue, gums).

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How should I manage a patient with suspected ITP?

It is important to monitor all patients for ITP so that patients are diagnosed and managed in a timely manner. Therefore complete blood counts with differential should be obtained prior to initiation of treatment and at monthly intervals thereafter until 48 months following the last infusion. If ITP is suspected a complete blood count should be obtained immediately and if onset is confirmed, appropriate medical intervention should be promptly initiated, including immediate referral to a specialist. Severe or widespread bleeding is life-threatening and demands immediate care.

Which symptoms could be associated with nephropathy, such as anti-GBM?

Manifestations of nephropathy may include elevation in serum creatinine, haematuria and/or proteinuria. While not observed in clinical trials, alveolar hemorrhage ▸

manifested as hemoptysis may occur with anti-GBM disease. Since patients may be asymptomatic, it is important that the periodic lab 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.

Are there any special considerations in treating patients who have developed an infection?

There are no special considerations. Treat infections with standard therapies.

Pregnancy and Contraception Counseling

Should female patients use contraception? If they want to become pregnant, how long should they wait after a LEMTRADA treatment course?

The alpha half-life 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.

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 SmPC), 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 alemtuzumab is excreted in human milk. A risk to the breastfed child cannot be excluded. Therefore, breast feeding should be discontinued during each course of treatment with LEMTRADA and for 4 months following the last infusion of each treatment course. However, benefits of conferred immunity through breast-milk may outweigh the risks of potential exposure to LEMTRADA for the baby.

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 before commencing treatment with LEMTRADA.

Consider VZV vaccination of antibody negative patients, prior to treatment with LEMTRADA.

Call for reporting:
Healthcare professionals should report any adverse events suspected to be associated with the use of Lemtrada to Sanofi Malta Ltd., 3rd Floor, Avantech Building, St. Julian's Road, San Gwann SGN 2805. Tel: 21493022, fax 21493024

Alternatively any suspected ADRs and medication errors can be reported to the Medicines Authority. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Medicines Authority Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt

Notes

Notes

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LEMTRADA®
alemtuzumab 12mg IV