SANOFI GENZYME

HealthCareProfessionalGuide

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

Important Safety Information

TEXT VERSION HCP GUIDE, DATED 27 November 2017

LEMTRADA®
alemtuzumab 12mg IV

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

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 **HCP guide** has been developed as part of the LEMTRADA Educational Program and is intended for HCPs who initiate and supervise LEMTRADA treatment. This guide is intended to improve the management of LEMTRADA by positively influencing appropriate actions. It contains:

1. A description of the immediate and delayed risks associated with the use of LEMTRADA that may occur many years after treatment and may be serious or life-threatening, including:
- Serious infections
- Autoimmune conditions:
    - Thyroid disorders
    - Immune Thrombocytopenic Purpura (ITP)
    - Nephropathies including anti-Glomerular Basement Membrane (anti-GBM) disease
2. Recommendations on how to mitigate these risks through appropriate patient 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 that you should give 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 on symptoms of autoimmune conditions and serious infections and to make patients aware of the need to be compliant with testing and be vigilant for symptoms and to seek immediate medical attention should they occur.
- **Patient Alert Card:** a liaison tool to inform any HCPs who are treating patients receiving LEMTRADA. The patient (or care givers when appropriate) should carry and show this card at all times to any HCP.

These materials are available upon request from Sanofi Malta Ltd on 21493022

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).

SECTION 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.

LEMTRADA should be initiated and supervised by a neurologist experienced in the treatment of multiple sclerosis (MS).

In order to minimise possible risks and side effects of LEMTRADA, prescribers and patients must commit to 48 months (4 years) 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 your patient and -his/her MS healthcare team, along with careful review about how to use the patient education tools, will help your patient to:

- Comply with periodic tests
- Identify and report symptoms timely
- 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 Figure 1 and Table 1.

Figure 1 - Overview of LEMTRADA treatment for autoimmune conditions

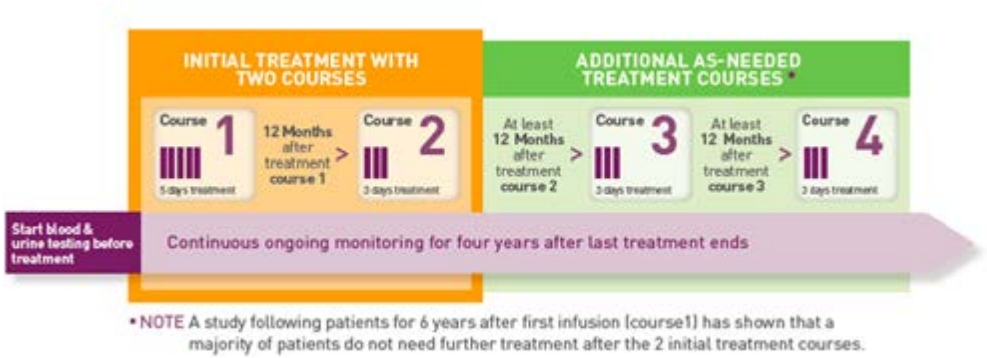


Table 1 - Overview of LEMTRADA Monitoring

Autoimmune Conditions	Laboratory test	Prior to treatment	Every month	Every 3 months	Continue for 48 months
Thyroid disorders	***Thyroid function test, such as thyroid stimulating hormone (TSH) levels***	x	-	x	x
ITP and other cytopenias	***Complete blood count with differential***	x	x	-	x
Nephropathies, including anti-GBM disease	***Serum creatinine***	x	x	-	x
	Urinalysis with microscopy	x	x	-	x

SECTION 2:- What are the risks associated with use of LEMTRADA?

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 SmPC.

Serious infections
LEMTRADA use is associated with risk of serious infections. To minimize the risk, it is important to:

- Delay start of treatment when active infection is present until 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) and repeat screening annually. Consider vaccination prior to treatment
- Complete vaccination program at least 6 weeks prior to start treatment
- Recommend listeriosis-prevention diet two weeks prior to, during and for at least 1 month after infusion
- Anti-herpes prophylaxis should be started on day 1 of treatment and continued for at least 1 month following each course of treatment
- Avoid concomitant therapies with other immunomodulating agents

Autoimmune conditions
LEMTRADA use is associated with risk of autoimmune conditions including, in order of frequency (most to least) :

a. Thyroid disorders
b. ITP
c. Nephropathies, including anti-GBM disease

These events can be serious, leading to morbidity and/or mortality, and may occur until many years after treatment. Event 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.

a. 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 LEMTRADA exposure. Some cases were transient and did not require treatment. The majority of thyroid related events were managed with conventional medical therapy where some patients required surgical intervention.

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

- Thyroid function tests such as TSH levels should be obtained prior to initiation of treatment, and then every 3 months thereafter continuing for 48 months following the last infusion. If TSH is abnormal, free T3 and T4 should be measured.
- 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 TSH 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.

b. ITP
ITP is an autoimmune disorder usually associated with anti-platelet antibodies. It is a clinical syndrome in which a decreased number of circulating platelets (thrombocytopenia) manifests as a bleeding tendency, easy bruising (purpura), or extravasation of blood from capillaries into skin and mucous membranes (petechiae). Please refer to Figure 2 for examples of ITP.

Symptoms of ITP could include (but are not limited to) easy bruising, easy bleeding, heavier than normal or irregular menstrual bleeding. These clinical signs of ITP may or may not be apparent before serious bleeding develops.

ITP can be a serious condition leading to morbidity and mortality, and may occur until 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:

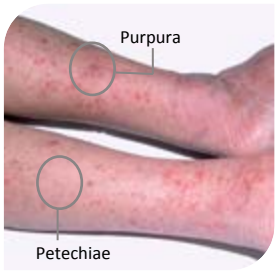
- Complete blood counts with differential should be obtained prior to initiation of treatment and at monthly intervals thereafter until 48 months following the last infusion.
- Check the patient for clinical symptoms of ITP.
- Counsel the patient on the importance of complying with monthly monitoring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

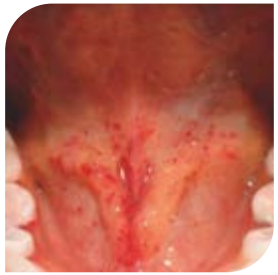
See section on ***'3. Managing Patients treated with LEMTRADA'*** for important information on safe use of the product.

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

Figure 2 - Examples of ITP

Examples of ITP





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.

Example of a leg with easy or excessive bruising.

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

Example of legs 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 and gums).

c. Nephropathies including anti-GBM disease
Nephropathy, including anti-GBM disease, has been rarely reported after treatment with LEMTRADA in MS 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 (Goodpasture Syndrome). Since patients may be asymptomatic, it is important that 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. In menstruating females, consider the timing of urinalysis to avoid false positives.
- 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 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.

SECTION 3: Managing patients treated with LEMTRADA

- It is extremely important that your patient understands the commitment to have periodic testing performed (for 48 months after last LEMTRADA 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 evaluate their test results and remain vigilant for symptoms of adverse events (AEs).
- 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, and to seek medical help if they have any concerns.
- Encourage the patient to carry the Patient Alert Card on 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.
- Specialists and equipment required for the timely diagnosis and management of the most frequent adverse reactions, especially autoimmune conditions and infections, should be available.

SECTION 4: Frequently Asked Questions (FAQs)

Please consider the following before prescribing LEMTRADA:

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 creatinine
- Urinalysis with microscopy
- Thyroid function tests, such as TSH

More information can be found in ***Table 1- Overview of LEMTRADA monitoring***.

Can I prescribe LEMTRADA to patients receiving other MS treatments?

LEMTRADA has not been administered for treatment of MS concomitantly with 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. Sequential use of LEMTRADA after other MS disease modifying therapies should be performed according to the Summary of of Product Characteristics (SmPC) of LEMTRADA and/or the therapy concerned.

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 ***Overview of LEMTRADA Monitoring.***

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 resolution.

HIV infection is a contraindication for the use of LEMTRADA.

Treatment

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

Initial treatment with LEMTRADA is administered by intravenous infusion in two annual courses. The first 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. Upon evidence of MS disease activity by clinical or imaging criteria, additional third and fourth as-needed treatment course(s) can be considered, and consists of a daily infusion over a period of 3 consecutive days administered at least 12 months after the prior treatment course.

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 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 bradycardia and 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 premedicated 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 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 of 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 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 that 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 thereafter until 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 hematologist. 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.

Pregnancy, contraception and breast feeding counseling

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.It needs to be taken into account that full treatment of LEMTRADA consists of two courses with 12 months in between. Women of childbearing potential need to be alerted to this and discouraged to stop contraception in between two treatment courses.

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 IgG is known to cross the placental barrier; alemtuzumab 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?
As women should use effective contraceptive measures for 4 months following each course of LEMTRADA treatment, they should wait at least 4 months before trying to become pregnant. It needs to be taken into account that full treatment of alemtuzumab consists of two courses with 12 months in between. Women of childbearing potential need to be alerted to this and discouraged to stop contraception in between two 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 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 breast feeding 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.

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 before commencing treatment with LEMTRADA. Consider varicella zoster virus (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, Sir Temi Żammit Buildings,Malta Life Sciences Park, San Ġwann SĠN 3000 Malta or sent by email to postlicensing.medicinesauthority@gov.mt

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LEMTRADA®
alemtuzumab 12mg IV

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