A HEALTHCARE PROFESSIONAL'S GUIDE

TO USING LEMTRADA® (ALEMTUZUMAB) IN PATIENTS WITH RELAPSING REMITTING MULTIPLE SCLEROSIS (RRMS)

This HCP Guide is part of the LEMTRADA® (alemtuzumab) risk management strategy and is to be used in conjunction with Lemtrada Prescribing Checklist and Product Information

Important safety information for healthcare professionals prescribing LEMTRADA

LEMTRADA® alemtuzumab 12mg IV

Adverse events should be reported. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

RISK MINIMISATION INFORMATION FOR HEALTHCARE PROFESSIONALS

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OVERVIEW OF LEMTRADA

LEMTRADA is indicated for the treatment of relapsing forms of multiple sclerosis (MS) for patients with active disease defined by clinical or imaging features to slow the accumulation of physical disability and reduce the frequency of clinical relapses.

This guide has been developed as part of the Risk Management Plan (RMP) for prescribers and other healthcare professionals (HCPs) involved in the care of patients treated with LEMTRADA. 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's 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 **LEMTRADA Patient Guide** and **LEMTRADA Patient Alert Card** have been developed and these should be given to patients at the time of LEMTRADA treatment initiation.

- **LEMTRADA Patient Guide:** to be carefully reviewed with your patient at initial prescription, and on a regular basis at follow-up visits. It aims to educate patients regarding the signs and symptoms of potential safety events and to make them aware of the need to be compliant with testing, keep an eye out for symptoms and to seek immediate medical attention should they occur
- **LEMTRADA 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 Sanofi Medical Information on 1800 818 806.

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 Product Information (PI).

SECTION 1: INTRODUCTION TO LEMTRADA

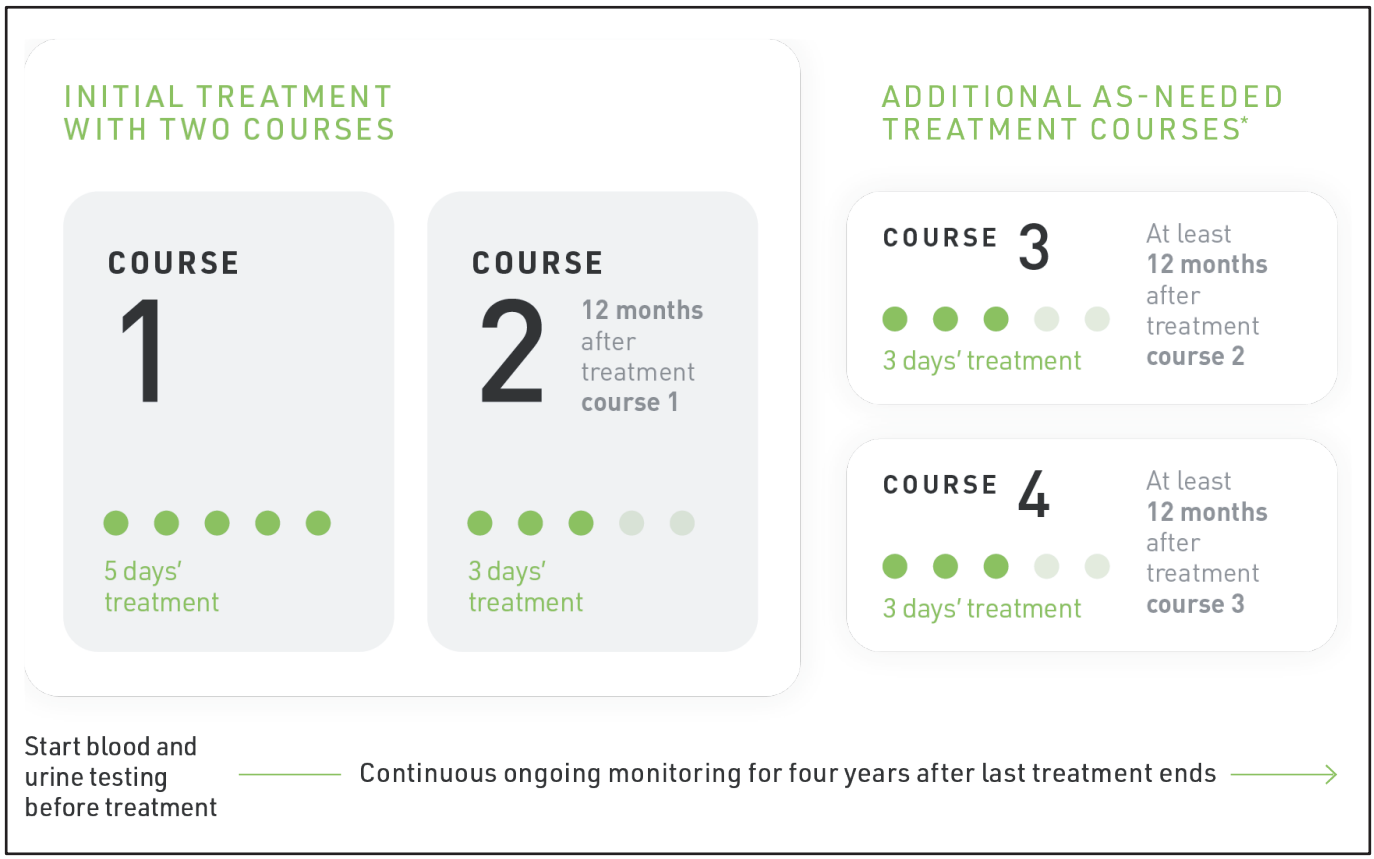
LEMTRADA treatment should only be initiated and supervised by a neurologist. Specialists and equipment required for the timely diagnosis and management of serious adverse reactions, especially autoimmune conditions and infections, should be available. Lemtrada should be administered in a setting in which equipment and personnel are available to appropriately manage anaphylaxis, serious infusion reactions, myocardial ischaemia, myocardial infarction, and cerebrovascular adverse reactions.

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 TREATMENT



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

SECTION 2: WHAT ARE THE MAIN RISKS ASSOCIATED WITH THE USE OF LEMTRADA?

1. Serious infections (affect ≥ 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:

- Consider delaying start of treatment when active infection is present until fully controlled
- 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
- In symptomatic patients, clinical assessment should be performed for CMV infection during and for at least two months following each Lemtrada treatment course.
- 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 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 re-administration of alemtuzumab treatment, 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 (affect < 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 (affects ≥ 1 in 10 patients)
- Immune thrombocytopenic purpura (ITP) (affects < 1 in 10 patients)
- Nephropathies, including anti-Glomerular Basement Membrane (anti-GBM) disease (affects < 1 in 100 patients)
- Autoimmune hepatitis (unknown incidence)
- Haemophagocytic lymphohistiocytosis (HLH) (affects < 1 in 1,000 patients)
- Acquired haemophilia A (affects < 1 in 100 patients)
- Thrombotic thrombocytopenic purpura (TTP) (affects < 1 in 1,000 patients)
- Adult onset Still's disease (AOSD) (unknown incidence)
- Autoimmune encephalitis (AIE) (affects < 1 in 100 patients)

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-month 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 (AFFECT ≥ 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)

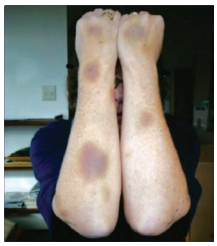
ITP is an autoimmune disorder usually associated with anti-platelet antibodies. Please refer to Figure 2 for examples of ITP. Symptoms of ITP could include (but are not limited to) easy bruising, easy bleeding, and heavier than normal or irregular menstrual bleeding. These clinical signs of ITP may or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

- Full blood counts (FBC) 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

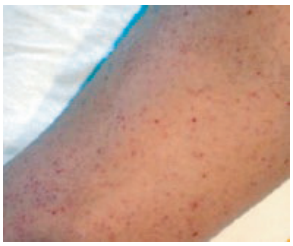
The potential risk associated with retreatment with LEMTRADA following the occurrence of ITP is unknown.

FIGURE 2 – EXAMPLES OF ITP



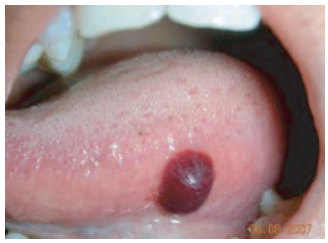
Example of arms with easy or excessive bruising.

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



Example of a leg with petechiae. 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 (AFFECT < 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 urine cell counts 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 characterised by thrombocytopenia, microangiopathic haemolytic anaemia, neurological sequelae, fever and renal impairment. It is associated with high morbidity and mortality rates if not recognised and treated early.

ADULT ONSET STILL'S DISEASE (AOSD) (UNKNOWN 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 aetiology for the signs or symptoms cannot be established.

AUTOIMMUNE ENCEPHALITIS (AIE) (AFFECTS < 1 IN 100 PATIENTS)

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 aetiologies.

SECTION 3: 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 symptoms suggesting development of a serious adverse event	
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 > Full Blood Count (FBC) with differential > Serum creatinine > Urinalysis with cell counts > Serum transaminases	> Full Blood Count (FBC) with differential > Serum creatinine > Urinalysis with cell counts > 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 Consumer Medicine Information (CMI) 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 LEMTRADA Patient Alert Card with them at all times. Patients should show the LEMTRADA 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.

As 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.

SECTION 4: 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 consider delaying the initiation of LEMTRADA administration in patients with severe active infection until fully controlled. 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 PI 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

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:

- Full Blood Count (FCB) with differential
- Serum transaminases
- Serum creatinine
- Urinalysis with cell counts
- 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.

Managing side effects

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

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

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

It is important to monitor patients for myocardial ischaemia and infarction, pulmonary alveolar haemorrhage, haemorrhagic stroke, cervicocephalic arterial dissection and thrombocytopenia. Vital sign monitoring including blood pressure and heart rate is advised at baseline and regularly thereafter. 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, Full Blood Count (FBC) 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 cell counts) 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).

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.

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

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

How should I manage a patient with suspected HLH?

Regular laboratory monitoring should be carried out and if patients develop early manifestations of pathologic immune activation 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?

Full Blood Count (FBC) 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 TTP?

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

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

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 aetiology 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 aetiologies

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?

In male transgenic mice, intravenous administration of alemtuzumab at doses of 3 and up to 10 mg/kg/day for 5 consecutive days (respective plasma AUC exposure 4 and 12 times clinical exposure at the MRHD) had no effect on fertility or reproductive performance. Effects on sperm were observed, with a significant increase in abnormal (detached head/no head) sperm; (respective incidences of 11%, 15%, 17% in control 3 and 10 mg/kg dose groups; a no-effect dose was not determined. The clinical significance of these effects is unknown.

In female transgenic mice treated intravenously with alemtuzumab for 5 consecutive days, the numbers of corpora lutea and implantation sites were significantly reduced at 10 mg/kg/day (plasma AUC 8 times clinical exposure at the MRHD); the no-effect dose was 3 mg/kg/day (3 times clinical exposure). Other mating and fertility parameters were unaffected at these doses.

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.

PBS Information: Authority required. Alemtuzumab (Lemtrada) is listed on the PBS as a section 100 item, for a maximum of two treatment courses per patient (12 months apart).

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