IE

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 alemtuzumab.**

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via contacting HPRA Pharmacovigilance website: www.hpra.ie. Side effects should also be reported to Sanofi: Tel: 01 403 5600 e-mail: IEPharmacovigilance@sanofi.com

SANOFI GENZYME

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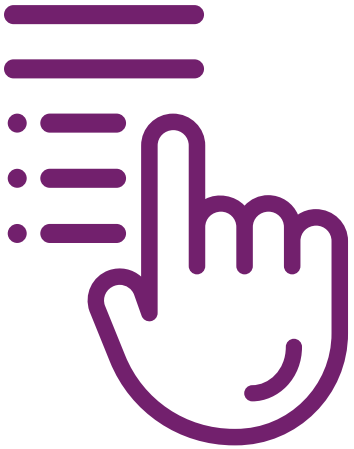
# Contents





# Executive summary

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

This is an abbreviated guide.

**Please be aware that this guide does not cover all the identified safety events associated with the use of alemtuzumab and does not take the place of the Summary of Product Characteristics (SmPC).**

If you have any enquiries or wish to request extra hard copies of any of these materials please contact Sanofi Medical Information:
Telephone: 01 403 5600;
Email: IEmedinfo@sanofi.com

Additionally, electronic versions of these materials are available to download on the following website: https://www.hpra.ie/homepage/medicines/safety-information/educational-material

Alemtuzumab 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 alemtuzumab Educational Programme to support you in initiating and supervising alemtuzumab 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 alemtuzumab, prescribers and patients must commit to at least 48 months of follow-up after the last infusion. It is important that patients understand that they should continue with the monitoring, even if they are feeling well and their multiple sclerosis (MS) is well controlled.

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

## Serious side effects temporally associated with alemtuzumab infusion

| Side effect | Monitoring procedures | Management |
|---|---|---|
| Myocardial ischaemia and/or infarction | • **Pre-infusion:** Baseline ECG and vital signs, including heart rate and BP<br>• **During infusion:** Regular monitoring of vital signs and overall clinical status at least once every hour<br>• **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<br>• Immediate discontinuation of treatment if reaction occurs during infusion<br>• Patients with clinical symptoms should be closely monitored until complete resolution of symptoms |
| Pulmonary alveolar haemorrhage | | |
| Haemorrhagic stroke | | |
| Cervicocephalic arterial dissection | | |
| Thrombocytopenia | • **Pre-infusion:** Baseline platelet count<br>• **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<br>• Consider referral to a haematologist |

BP=blood pressure; ECG=electrocardiogram

## Delayed autoimmune side effects

| Side effect | Monitoring procedures | Management |
|---|---|---|
| Thyroid disorders | • Thyroid function tests are required pre-infusion and every 3 months thereafter, until at least 48 months following the last treatment course. 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) | • Full blood count with differential required pre-infusion and at monthly intervals thereafter, until at least 48 months following the last treatment course. Patients should be informed about the symptoms associated with ITP so they can self-monitor post-infusion | • Appropriate medical intervention should be initiated promptly, including immediate referral to a haematologist |
| Nephropathies, including anti-Glomerular Basement Membrane (anti-GBM) disease | • Serum creatinine levels and urinalysis with microscopy required pre-infusion and at monthly intervals thereafter, until at least 48 months following the last treatment course. 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 are required pre-infusion and at monthly intervals thereafter, until at least 48 months following the last treatment course. 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) | • Full blood counts should be obtained prior to initiation of treatment and at monthly intervals for at least 48 months following the last 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's 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 |



## 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<br>• **Post-infusion:** Patients should be informed about the symptoms associated with PML and should inform their relatives or caregivers about their treatment | • Further evaluation, including cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments should be performed as appropriate |

## Exposure to alemtuzumab in case of Pregnancy

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

Alemtuzumab 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 or in 4 months following a treatment course even if it is unknown whether alemtuzumab is excreted in human milk. However, the benefits of conferred immunity through breast milk may outweigh the risks of potential exposure to alemtuzumab for the suckling newborn.

# Overview of LEMTRADA

Alemtuzumab 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 alemtuzumab Educational Programme to support you in initiating and supervising alemtuzumab treatment. It provides further information about the serious risks associated with alemtuzumab 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 alemtuzumab 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

- Thyroid disorders
- Immune Thrombocytopenic Purpura (ITP)
- Nephropathies, including anti-Glomerular Basement Membrane (anti-GBM) disease
- Autoimmune hepatitis
- Haemophagocytic 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 alemtuzumab 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 alemtuzumab treatment initiation.


### Patient Guide

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

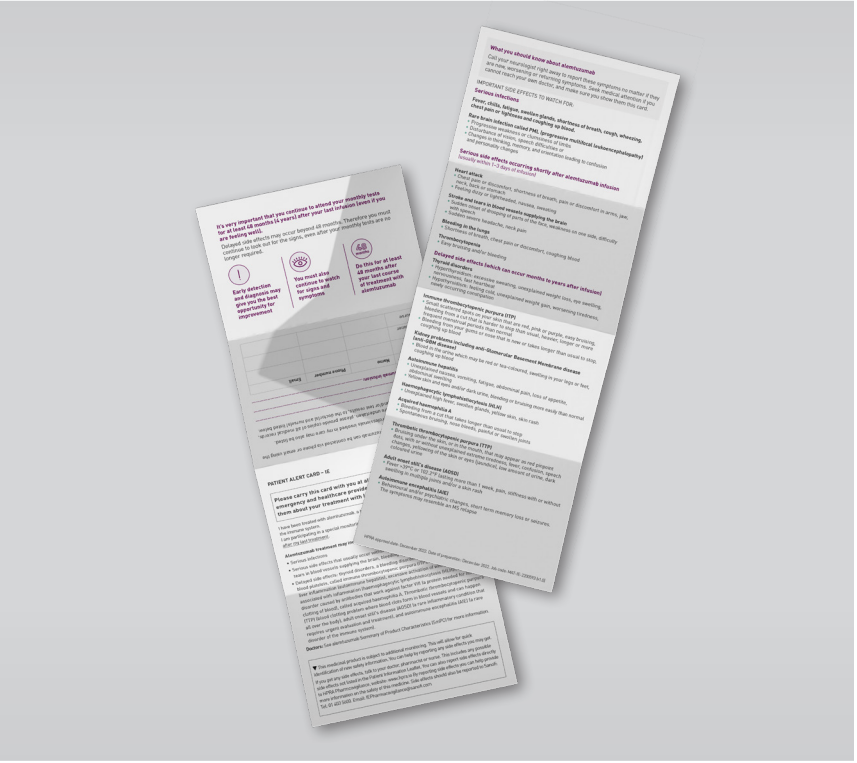
These materials are available upon request from the Sanofi Genzyme Medical Affairs Department. Medical information details: Telephone: 01 403 5600; Email: IEmedinfo@sanofi.com

Additionally, electronic versions of these materials are available to download on the following website: https://www.hpra.ie/homepage/medicines/safety-information/educational-material

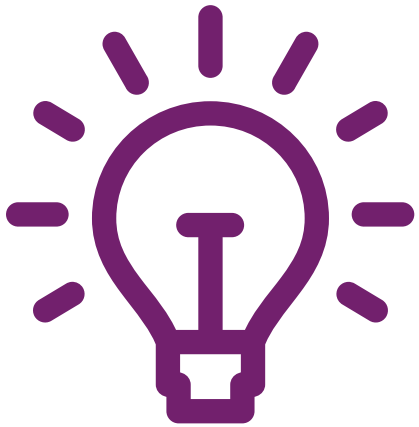
**Please be aware that this guide does not cover all the identified safety events associated with the use of alemtuzumab and does not take the place of the SmPC.**

### Patient Alert Card

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



# Introduction to LEMTRADA



Alemtuzumab 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.

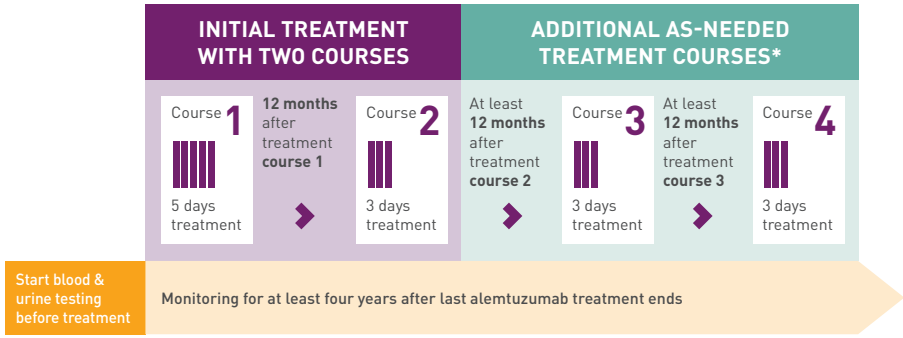
In order to minimise possible risks and side effects of alemtuzumab, prescribers and patients must commit to at least 48 months of follow-up after the last infusion of alemtuzumab. It is important that patients understand that they should continue with the monitoring, even if they are feeling well and 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 "Summary of recommended patient monitoring".**

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

## Figure 1 – Overview of alemtuzumab 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.

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

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

Alemtuzumab 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 alemtuzumab 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 alemtuzumab 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. Information about dietary recommendations can be found at: https://www.nhs.uk/conditions/listeriosis/
- 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.

Advise the patient to seek immediate medical attention in case of sudden onset of progressive weakness or clumsiness of limbs, disturbance of vision, speech difficulties or changes in thinking, memory, and orientation leading to confusion and personality changes. 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 alemtuzumab 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 alemtuzumab infusion. Reactions have occurred following any of the doses and after the second course. These safety events included:

- Myocardial ischaemia and/or myocardial infarction (not known incidence)
- Pulmonary alveolar haemorrhage (not known incidence)
- Haemorrhagic stroke (not known incidence)
- Cervicocephalic arterial dissection (not known 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 'Summary of recommended patient monitoring', for important information on infusion instructions.

## 4. Delayed autoimmune side effects

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

- Thyroid disorders (affect ⩾ 1 in 10 patients)
- Immune thrombocytopenic purpura (ITP) (affects < 1 in 10 patients)
- Nephropathies, including anti-Glomerular Basement Membrane (anti-GBM) disease (affect < 1 in 100 patients)
- Autoimmune hepatitis (not known 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) (not known 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-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 'Summary of recommended patient monitoring', for important information about reducing the risk of alemtuzumab 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. After this period of time testing should be performed based on clinical findings suggestive of thyroid dysfunction or in case of pregnancy
- 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 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

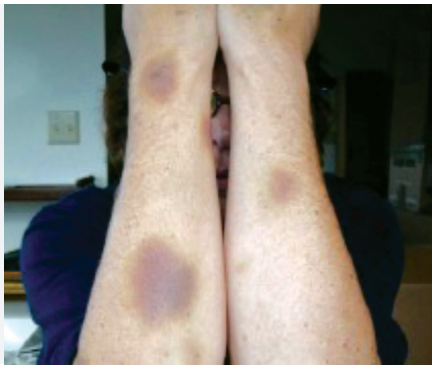
The potential risk associated with retreatment with alemtuzumab following the occurrence of ITP is unknown.

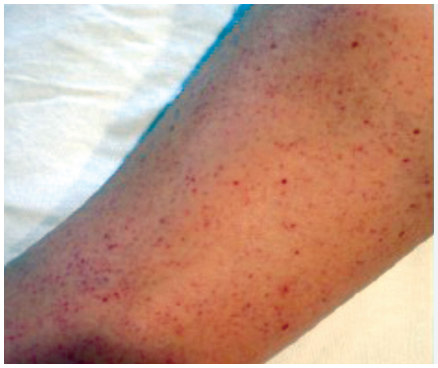


## Figure 2 – Examples of ITP

Example of arms with easy or excessive bruising.

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





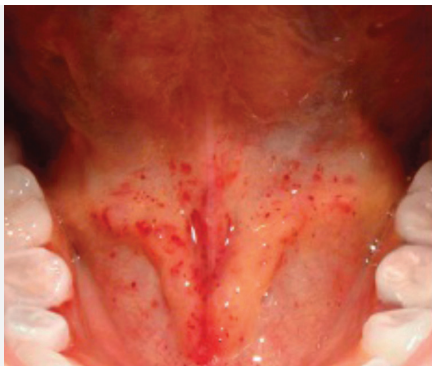
Example of a leg with petechia and purpura.

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 uncommonly been reported after treatment with alemtuzumab 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 alemtuzumab:

- 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
(not known incidence)

Autoimmune hepatitis causing clinically significant liver injury, including fatal cases, has been rarely reported in patients treated with alemtuzumab 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 alemtuzumab 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. Coagulopathy panel including aPTT must be obtained in all patients that present with such symptoms. In case of a prolonged aPTT patient should be referred to a haematologist.

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

During postmarketing use, TTP, which can be fatal, has been reported in patients treated with alemtuzumab. TTP is a serious condition that requires urgent evaluation and treatment. TTP may be characterised by thrombocytopenia, microangiopathic haemolytic anaemia, confusion, altered mental status, vision or speech changes, seizures, fever and renal impairment. It is associated with high morbidity and mortality rates if not recognised and treated early. Patients should be informed of the potential symptoms of TTP.

In case of suspected TTP, patient should be referred to a haematologist.



## Adult Onset Still's disease (AOSD)
(not known incidence)

During postmarketing use, AOSD has been reported in patients treated with alemtuzumab. 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 alemtuzumab if an alternate etiology 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 alemtuzumab.

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)<br>• Consider pre-treatment with antihistamines and/or antipyretics<br>• 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 alemtuzumab (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<br>• Baseline ECG | • Perform frequent monitoring of heart rate, BP and overall clinical status at least once every hour<br>• 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)<br>**For at least 48 months** | Post-infusion (Quarterly)<br>**For at least 48 months** |
|---|---|---|---|
| Monitoring | • Thyroid function tests, including TSH levels<br>• Full blood count with differential<br>• Serum creatinine<br>• Urinalysis with microscopy<br>• Serum transaminases | • Full blood count with differential<br>• Serum creatinine<br>• Urinalysis with microscopy<br>• 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 alemtuzumab infusion, even if they are asymptomatic and their MS disease is well controlled.

- Review the alemtuzumab 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.
- Remind patient of the importance of reporting adverse events.

## Exposure to alemtuzumab in case of Pregnancy

Although there are limited available data evaluating the use of alemtuzumab in pregnant women, there is the potential for alemtuzumab to cross the placental barrier and pose a risk to the foetus. Therefore, alemtuzumab 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 alemtuzumab treatment.

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

# Frequently Asked Questions (FAQs)

Patients treated with alemtuzumab 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 alemtuzumab.

## Contraindications

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

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

### What are the contraindications of alemtuzumab treatment?

Do not use alemtuzumab if a patient:

- Hypersensitivity to alemtuzumab or any of the other excipients listed in SmPC 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 cervicocephalic 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 alemtuzumab administered and how long does the infusion take?

Initial treatment with alemtuzumab 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 (see Figure 1, page 19). 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 alemtuzumab prior to restarting therapy. Consider permanently discontinuing the alemtuzumab infusion if the patient is deemed to be at a future risk of a serious clinical outcome (please refer to "Summary of recommended patient monitoring" 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 alemtuzumab administration for the first 3 days of any treatment course. Additionally, pre-treatment with antihistamines and/or antipyretics prior to alemtuzumab 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 alemtuzumab treatment, what laboratory tests need to be performed?

The tests that need to be performed are:

- Full 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 alemtuzumab? 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 'Summary of recommended patient monitoring'.

### How long should patients be observed for after receiving an alemtuzumab 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 should be 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 monitor a patient for serious side effects temporally associated with their alemtuzumab 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. 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 '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 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, loss of appetite, yellow skin or eyes, 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 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 HLH?

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

Full 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 prolonged aPTT the patient should be referred to a haematologist.

## What are the signs and symptoms of Thrombotic Thrombocytopenic Purpura?

TTP is a serious condition that requires urgent evaluation and treatment. TTP may be characterised by thrombocytopenia, microangiopathic haemolytic anaemia, confusion, altered mental status, vision or speech changes, seizures, fever and renal impairment.

### 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.

### What are the signs and symptoms of Adult Onset Still's Disease (ASOD)?

Symptoms of AOSD may include fever >39°C or 102.2°F lasting more than 1 week, pain, stiffness with or without swelling in multiple joints and/or a skin rash.

### 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 alemtuzumab if an alternate etiology for the signs or symptoms of AOSD cannot be established.

### What are the signs and symptoms of Autoimmune Encephalitis (AIE)?

Symptoms of Autoimmune encephalitis (an immune mediated brain disorder), may include symptoms such as behavioural and/or psychiatric changes, short term memory loss or seizures. The symptoms may resemble an MS relapse.

### 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 alemtuzumab treatment.

### Is it possible to administer alemtuzumab during pregnancy?

Alemtuzumab 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; alemtuzumab may cross the placental barrier as well and thus potentially pose a risk to the foetus. It is not known whether alemtuzumab 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 alemtuzumab treatment course?

Women should use effective contraceptive measures and wait at least 4 months following each course of alemtuzumab treatment before trying to become pregnant. It needs to be taken into account that full treatment of alemtuzumab 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 alemtuzumab affect future female or male fertility?

There are no adequate clinical safety data on the effect of alemtuzumab 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 (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 alemtuzumab?

It is unknown whether alemtuzumab 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 alemtuzumab for the baby.

## Vaccinations

### What considerations should be given to vaccinations when considering alemtuzumab treatment?

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

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 alemtuzumab. Consider varicella zoster virus (VZV) vaccination of antibody negative patients, prior to treatment with alemtuzumab.

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