



Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

ALEMTUZUMAB PROTOCOL FOR THE TREATMENT OF RELAPSING REMITTING MULTIPLE SCLEROSIS (RRMS)

Multiple Sclerosis Alemtuzumab Treatment Protocol

Alemtuzumab (Lemtrada®) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Protocol Code
<p>*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:</p> <ul style="list-style-type: none"> Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT) <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI. 	G35	MS100

*NOTE: alemtuzumab (Lemtrada®) is associated with the risk of serious, sometimes fatal adverse reactions. The European Medicines Agency (EMA) introduced restrictions on its use as well as measures to identify and manage potential serious adverse reactions.

- Alemtuzumab should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care, since serious reactions such as myocardial ischemia or myocardial infarction, cerebral haemorrhage or pulmonary haemorrhage can occur during or shortly after the infusion.
- Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available.
- Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.
- Patients treated with alemtuzumab must be given the Patient Alert Card and Patient Guide and be informed about the risks (see also package leaflet). Patients must be informed about the risks and benefits and the need to commit to follow-up from treatment initiation until at least 48 months after the last administered infusion.

Full prescribing information is available in the Summary of Product Characteristics for Lemtrada® which can be found at: <https://www.medicines.ie/medicines/lemtrada-12-mg-concentrate-for-solution-for-infusion-32670/smpc>

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ELIGIBILITY:

- Indications as above
- Patients aged 18-55 (use with caution outside of this age range)
- Women of childbearing potential should use effective contraceptive measures during treatment and for 4 months following each course of Lemtrada® (alemtuzumab) treatment

EXCLUSIONS/CONTRAINDICATIONS:

- Hypersensitivity to Lemtrada® (alemtuzumab) or to any of the excipients
- Human Immunodeficiency Virus [HIV] infection
- Severe active infection until complete resolution
- Uncontrolled hypertension
- History of angina pectoris or myocardial infarction
- History of stroke
- History of arterial dissection of the cervicocephalic arteries
- Coagulopathy
- Patients on antiplatelet or anticoagulant therapy
- Concomitant autoimmune diseases other than multiple sclerosis

USE WITH CAUTION:

- In pregnancy and lactation (full information available in the Summary of Product Characteristics for Lemtrada® which can be found at: <https://www.medicines.ie/medicines/lemtrada-12-mg-concentrate-for-solution-for-infusion-32670/smpc>)

TESTS:

Baseline Measures:

MRI 3 months prior to treatment

Baseline tests:

- Full blood count (FBC) with differential, urea and electrolytes (U&E), serum creatinine, urinalysis and microscopy, liver function tests (LFTs) and thyroid function tests (TFTs)
- Clotting Screen (alemtuzumab contraindicated if coagulopathy)
- Establish if patient is on antiplatelet or anticoagulant therapy (alemtuzumab contraindicated with antiplatelets or anticoagulants)
- Blood pressure monitoring (alemtuzumab contraindicated if uncontrolled hypertension)
- Confirm if history of angina pectoris, myocardial infarction, stroke, or dissection of the cervicocephalic arteries (contraindications)
- HIV test (contraindication if HIV positive)
- Varicella Zoster Virus (VZV) Serology - VZV vaccination of antibody-negative patients should be considered at least 6 weeks in advance of treatment

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- Evaluation of cytomegalovirus (CMV) immune serostatus should be considered according to local guidelines.
- All vaccinations must be completed 6 weeks prior to treatment
- Evaluation for active or inactive ("latent") TB as per local guidelines
- Screening patients at high risk of HBV and/or HCV infection before initiation of alemtuzumab should be considered. Caution should be exercised in prescribing alemtuzumab to patients identified as carriers of HBV and/or HCV as these patients may be at risk of irreversible liver damage relative to a potential virus reactivation as a consequence of their pre-existing status.
- Annual cervical (HPV) screening for female patients

Regular tests:

- FBC with differential, LFTs, serum creatinine levels, urinalysis with microscopy at monthly intervals.
- Thyroid Function Tests every 3 months.

These laboratory tests should be conducted **for at least 48 months** following the last treatment course of alemtuzumab (Lemtrada®) in order to monitor for early signs of autoimmune disease.

An MRI scan should be performed within 3 months of each course of treatment to allow for assessment of disease response.

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant. An annual MRI scan for disease activity should be carried out. An EDSS score should be included prior to each treatment or change to treatment.

TREATMENT:

PREMEDICATIONS:

Patients should be pre-treated with corticosteroids immediately prior to Lemtrada® (alemtuzumab) administration on each of the first 3 days of any treatment course. In clinical trials, patients were pre-treated with 1,000 mg methylprednisolone for the first 3 days of each Lemtrada® (alemtuzumab) treatment course. Pre-treatment with antihistamines and/or antipyretics prior to Lemtrada® (alemtuzumab) administration may also be considered.

Lemtrada® (alemtuzumab) therapy is recommended as 2 treatment courses, (Day 1-5 on Year 1 and Day 1-3 on Year 2) with safety follow-up of patients from initiation of treatment and until 48 months after the last infusion.

Additional treatment courses:

- Up to two additional treatment courses, as needed, may be considered. A third or fourth course of 12 mg/day on 3 consecutive days should be administered at least 12 months after the prior treatment course.

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- In the extension phases of the phase 3 clinical trials a 3rd cycle was given in patients if there was a single clinical relapse or two new MRI lesions. A third dose should not be used where the clinician considers the patient not to have fully responded to the 2nd treatment course i.e. in cases where there is breakthrough clinical or MRI activity at least 12 months since the last course.
- If an additional third or fourth course is administered, continue safety follow-up for at least 48 months after the last infusion.

Cycle Number	Day	Drug	Dose	Route	Diluent & Rate
CYCLE ONE	1-5	Alemtuzumab (Lemtrada®)	12mg	IV infusion	100ml 0.9% Sodium Chloride or 5% Glucose over 4 hours
12 MONTHS LATER					
CYCLE TWO	1-3	Alemtuzumab (Lemtrada®)	12mg	IV infusion	100ml 0.9% Sodium Chloride or 5% Glucose over 4 hours
Missed doses should not be given on the same day as a scheduled dose.					

The following infusion instructions are intended to reduce serious reactions temporally associated with Lemtrada® (alemtuzumab) infusion:

- Pre-infusion evaluation:
 - Obtain a baseline ECG and vital signs, including heart rate and blood pressure measurement.
 - Perform laboratory tests as recommended in **Baseline Tests** section above.
- During infusion:
 - Perform continuous/frequent (at least every hour) monitoring of heart rate, blood pressure, and overall clinical status of the patient.
 - Discontinue the infusion if:
 - The patient develops a severe adverse event
 - If the patient shows clinical symptoms suggesting development of a serious adverse event associated with the infusion (e.g. myocardial ischaemia,

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haemorrhagic stroke, cervicocephalic arterial dissection or pulmonary alveolar haemorrhage)

- Post-infusion:
 - Observation for infusion reactions is recommended for a minimum of 2 hours after the infusion. Patients with clinical symptoms suggesting development of a serious adverse event temporally associated with the infusion (e.g. myocardial ischaemia, haemorrhagic stroke, cervicocephalic arterial dissection or pulmonary alveolar haemorrhage) should be closely monitored until complete resolution of the symptoms. Observation time should be extended (hospitalisation) as appropriate. Patients should be educated on the potential for delayed onset of infusion-associated reactions and instructed to report symptoms and seek appropriate medical care.
 - Platelet count should be obtained immediately after infusion on Days 3 and 5 of the first infusion course, as well as immediately after infusion on Day 3 of any subsequent course. Clinically significant thrombocytopenia needs to be followed until resolution. Referral to a haematologist for management should be considered.

DOSE MODIFICATIONS:

No recommended dose modifications.

Renal and Hepatic impairment:

Alemtuzumab has not been studied in patients with renal or hepatic impairment

SUPPORTIVE CARE:

TAKE HOME MEDICATIONS:

Oral prophylaxis for herpes infection (such as acyclovir 200mg twice a day or equivalent) should be administered to all patients starting on the first day of each treatment course and continuing for a minimum of 1 month following treatment with alemtuzumab.

Listeriosis/*Listeria meningitis* has been reported in patients treated with alemtuzumab, generally within one month of infusion. The first version of this guideline recommended a Listeria-free diet (avoid ingestion of uncooked or undercooked meats, soft cheeses and unpasteurized dairy products) as the sole means of prophylaxis. The Association of British Neurologists (ABN) subsequently issued new recommendations for Listeria prophylaxis post-alemtuzumab. The ABN states that in order for a Listeria-free diet to be effective it would ideally need to be initiated ninety days in advance of treatment to ensure decolonisation of Listeria. This is considered too prolonged for most patients especially if there is an immediate clinical need for initiation of alemtuzumab therapy. While a Listeria-free diet remains an option antibiotic prophylaxis is now recommended preferentially.

The ABN recommends one of three options for Listeria prophylaxis after each course of alemtuzumab:

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1. Co-trimoxazole 960mg three times a week starting Day 1 of alemtuzumab and continuing for 4weeks

OR

2. If the patient will comply rigorously with the Listeria-free diet: either a) amoxicillin 1g three times a day or b) co-trimoxazole 960mg twice a day for one week to eliminate Listeria from the bowel (for instance for 8 days starting the Friday before treatment on the Monday). The 7 day course of antibiotics must be followed by a Listeria-free diet for 4weeks post-alemtuzumab.

OR

3. Finally, where alemtuzumab treatment can be predicted some months in advance (for instance with cycles 2 and 3), it would be reasonable to offer a third option to patients who will comply rigorously with the Listeria-free diet: going on the Listeria-free diet for ninety days before, and for one month after, alemtuzumab.

Women of childbearing potential should use effective contraceptive measures during treatment and for 4 months following a course of alemtuzumab treatment.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details, available at: <https://www.medicines.ie/medicines/lemtrada-12-mg-concentrate-for-solution-for-infusion-32670/smpc>

This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions. Patients treated with alemtuzumab (Lemtrada®) must be given a Patient Alert Card and Patient Guide and be informed about risks of alemtuzumab (Lemtrada®).

Infusion-Associated Reactions (IARs): It is recommended that patients be pre-medicated to ameliorate the effects of infusion reactions as detailed above. IARs may occur in patients despite pre-treatment. Observation for infusion reactions is recommended; if an IAR occurs provide the appropriate symptomatic treatment, as needed. See **TREATMENT** section above for further information. Please refer to the relevant Summary of Product Characteristics for full details, available at: <https://www.medicines.ie/medicines/lemtrada-12-mg-concentrate-for-solution-for-infusion-32670/smpc>

Serious reactions temporally associated with infusion:

The EMA has concluded that myocardial ischaemia, myocardial infarction, cerebral haemorrhage, dissection of the cervicocephalic arteries, pulmonary alveolar haemorrhage, and thrombocytopenia may infrequently occur in close temporal association with Lemtrada® (alemtuzumab) infusion.

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Reactions may occur following any of the doses during the treatment course; in the majority of cases time to onset was within 1-3 days of infusion. Patients should be informed about the signs and symptoms, and advised to seek immediate medical attention if any of these symptoms occur. Vital signs, including blood pressure measures, should be monitored before and periodically during Lemtrada® (alemtuzumab) infusion. If clinically significant changes in vital functions are observed, discontinuation of infusion and additional monitoring, including ECG, should be considered.

Autoimmunity: Treatment with Lemtrada® (alemtuzumab) may result in the formation of autoantibodies and increase the risk of autoimmune mediated conditions which may be serious and life threatening. Autoimmune disorders may occur within 48 months or longer after the last dose of Lemtrada® (alemtuzumab). Clinical examination and laboratory tests should be conducted periodically until at least 48 months after the last infusion to monitor for early signs of autoimmune conditions. Patients who develop autoimmunity should be evaluated for other autoimmune mediated conditions as patients developing multiple autoimmune disorders have been observed in the post-marketing setting. Patients should be advised that these disorders may also occur later than 48 months after the last infusion.

Reported autoimmune conditions include thyroid disorders, immune thrombocytopenic purpura (ITP), nephropathies (e.g. anti-glomerular basement membrane disease), autoimmune hepatitis and acquired haemophilia A. Haemophagocytic lymphohistiocytosis, a syndrome of immune activation characterised by fever, hepatomegaly and cytopenia, has also been reported.

Serious events of ITP have been observed in clinical studies and post-marketing reports; the majority of cases occurred within 4 years after first exposure however, in some cases ITP developed years later. Symptoms of ITP could include (but are not limited to) easy bruising, petechiae, spontaneous mucocutaneous bleeding (e.g. epistaxis, haemoptysis), heavier than normal or irregular menstrual bleeding. Haemoptysis may also be indicative of anti-glomerular basement membrane disease, and an appropriate differential diagnosis has to be undertaken. Remind the patient to remain vigilant for symptoms they may experience and to seek immediate medical help if they have any concerns. Full blood counts with differential should be obtained prior to initiation of treatment and at monthly intervals thereafter until at least 48 months after the last infusion. After this period of time, testing should be performed based on clinical findings suggestive of ITP. If ITP is suspected a full blood count should be obtained immediately. If ITP onset is confirmed, appropriate medical intervention should be promptly initiated, including immediate referral to a specialist. Data from clinical trials in MS has shown that adherence to the blood monitoring requirements and education relative to signs and symptoms of ITP has led to early detection and treatment of ITP with most cases responding to first-line medical therapy.

Other autoimmune cytopenias such as neutropenia, haemolytic anaemia and pancytopenia have been infrequently reported in clinical trials in MS. Full blood count should be performed as recommended in **Baseline tests** and **Regular tests** sections above, continuing for at least 48 months after the last infusion, and results should be used to monitor for cytopenias. If a cytopenia is confirmed, appropriate medical intervention should be promptly initiated, including referral to a specialist.

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Cases of acquired haemophilia A (anti-factor VIII antibodies) have been reported in both clinical trial and post-marketing setting. Patients typically present with spontaneous subcutaneous haematomas and extensive bruising although haematuria, epistaxis, gastrointestinal or other types of bleeding may occur. A coagulopathy panel including aPTT must be obtained in all patients that present with such symptoms. Educate patients on the signs and symptoms of acquired haemophilia A and to seek immediate medical attention, if any of these symptoms are observed.

Nephropathies, including anti-glomerular basement membrane (anti-GBM) disease, have been observed in clinical trials of Lemtrada® (alemtuzumab) in MS. Clinical manifestations may include elevation in serum creatinine, haematuria, and/or proteinuria. Alveolar haemorrhage, manifested as haemoptysis, may occur with anti-GBM disease. Haemoptysis may also be indicative of ITP or acquired haemophilia A and appropriate differential diagnosis must be undertaken. The patient should be reminded to remain vigilant for symptoms they may experience and to seek immediate medical help if they have any concerns. Anti-GBM disease may lead to renal failure requiring dialysis and/or renal transplantation if not treated rapidly and can be life-threatening if left untreated. Monitoring of serum creatinine and urinalysis with microscopy should be performed as recommended in **Baseline tests** and **Regular tests** sections above, continuing for at least 48 months after the last infusion. 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. After this period of time, testing should be performed based on clinical findings suggestive of nephropathies.

Thyroid endocrine disorders, including both hypothyroidism and hyperthyroidism, have been reported in MS patients treated with Lemtrada® (alemtuzumab). The incidence was higher in patients with a medical history of thyroid disorders. Thyroid functions tests should be performed as recommended in **Baseline tests** and **Regular tests** sections above, continuing for at least 48 months after 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. Thyroid disease poses special risks in women who are pregnant. Without treatment of hypothyroidism during pregnancy there is a risk for miscarriage and foetal effects such as mental retardation and dwarfism. In mothers with Graves' disease, maternal thyroid stimulating hormone receptor antibodies can be transferred to a developing foetus and cause transient neonatal Graves' disease.

Haemophagocytic lymphohistiocytosis (HLH), including fatal cases, has been reported in MS patients treated with Lemtrada® (alemtuzumab). HLH is a life-threatening syndrome of pathological immune activation characterised by clinical signs and symptoms of extreme systemic inflammation (including but not limited to: fever, hepatomegaly, and cytopenias). It is associated with high mortality rates if not recognised early and treated. Symptoms have been reported to occur within a few months to 4 years after the start of treatment. Patients should be informed about the symptoms of HLH including the time to onset. Patients who develop signs of pathological immune activation should be evaluated immediately, and a diagnosis of HLH considered.

Autoimmune hepatitis (AIH), including fatal cases and cases requiring liver transplantation, and hepatic injury related to infections have been reported in MS patients treated with Lemtrada®

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(alemtuzumab). Liver function tests should be performed as recommended in **Baseline tests** and **Regular tests** sections above, continuing for at least 48 months after the last infusion. Patients should be informed about the risk of AIH, hepatic injury and related symptoms (including but not limited to: unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, jaundice or dark urine).

Patients should be informed of the risk of transfusion-associated graft versus host disease and that they should receive irradiated blood products to eliminate this risk. Cases of alopecia and Type 1 Diabetes Mellitus have also been reported post-alemtuzumab.

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

Infections: Infections may occur at a higher rate in patients treated with Lemtrada® (alemtuzumab). Serious infection as well as reactivation of Epstein-Barr virus (EBV), including cases of severe EBV hepatitis, has been reported. Patients should be instructed to report any symptoms of infections to their physician. For more detail please refer to the Summary of Product Characteristics: <https://www.medicines.ie/medicines/lemtrada-12-mg-concentrate-for-solution-for-infusion-32670/smpc>.

Malignancy As with other immunomodulatory therapies, caution should be exercised in initiating alemtuzumab therapy in patients with pre-existing and/or an on-going malignancy. It is not currently known if alemtuzumab confers a higher risk for developing thyroid malignancies, since thyroid autoimmunity may itself be a risk factor for thyroid malignancies.

Vaccinations: It is recommended that patients have completed local immunisation requirements at least 6 weeks prior to treatment with alemtuzumab. The ability to generate an immune response to any vaccine following treatment has not been studied.

The safety of immunisation with live viral vaccines following a course of alemtuzumab treatment has not been formally studied in controlled clinical trials in MS and should not be administered to patients who have recently received a course of alemtuzumab.

As for any immune modulating medicinal product, before initiating a course of alemtuzumab treatment, patients without a history of chickenpox or without vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV. VZV vaccination of antibody-negative patients should be considered prior to treatment initiation. To allow for the full effect of the VZV vaccination to occur, treatment with alemtuzumab should be postponed for 6 weeks following vaccination.

DRUG INTERACTIONS:

No formal drug interaction studies have been conducted with alemtuzumab using the recommended dose in patients with MS.

Current drug interaction databases should be consulted for more information.

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SUPPORT RESOURCES:

Please note that this is for information only and does not constitute endorsement by the NDMP

ALEMTUZUMAB: Health Professional Guide. Available at <https://www.lemtradahcp.com/>.

ATC CODE:

Alemtuzumab L04AA34

REIMBURSEMENT CATEGORY:

National Drugs Management Scheme (NDMS)

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Neurologist experienced in the treatment of MS.

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Version	Date	Amendment	Approved By
2	09/07/2019	<ul style="list-style-type: none"> - Update of protocol to include recommendation in to the April 2019 EMA PRAC safety update. - “Severe active infection until resolution” added to exclusions. - Recommendation to consider Varicella Zoster vaccination in antibody negative patients added 	

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Multiple Sclerosis Alemtuzumab Treatment Protocol

		<ul style="list-style-type: none"> - "Evaluation of CMV immune sero-status could be considered according to local guidelines" added to baseline monitoring - LFTs added to regular tests - "Vital signs should be monitored before and during the intravenous infusion" add to treatment section - Listeria prophylaxis updated to reflect recommendations of the Association of British Neurologists - Recommendation added to use irradiated blood products to reduce risk of transfusion-associated graft versus host disease - Recommendations on vaccinations updated - Alopecia and Type 1 Diabetes Mellitus added to adverse effects 	
3	June 2020	<ul style="list-style-type: none"> - The final recommendations from the EMA PRAC safety review were incorporated into the protocol - The new contraindications, restrictions on prescribing, and monitoring requirements were incorporated 	

Comments and feedback welcome at ahdmp@hse.ie.

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