HSE Prescribing Protocol

Alemtuzumab (Lemtrada®)

for

the Treatment of Relapsing Remitting Multiple Sclerosis (RRMS)

This document is intended for use by healthcare professionals only.

This guideline should be used in conjunction with the full prescribing and administration details in the Alemtuzumab (Lemtrada®) Summary of Product Characteristics (SmPC) https://www.ema.europa.eu/en/documents/product-information/lemtrada-epar-product-information_en.pdf[1]

INDICATIONS FOR USE[1]:

TREATMENT	INDICATION	ICD10	PROTOCOL CODE
Alemtuzumab (Lemtrada®)	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)	G35	MS100a
	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	MS100b

TREATMENT[1]:

Cycle	TREATMENT	DOSE	ROUTE	FREQUENCY	DURATION OF THERAPY
1	Alemtuzumab (Lemtrada®)	12mg	IV Infusion	Once daily	5 days (60mg total dose over 5 days)
12 months later					
2	Alemtuzumab (Lemtrada®)	12mg	IV Infusion	Once daily	3 days (36mg total dose over 5 days)
Missed doses should not be given on the same day as a scheduled dose					

- **Alemtuzumab 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. See SmPC and guidance issued by the EMA for full information.**
- 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.

- Alemtuzumab therapy is recommended as two 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. See SmPC for further information.

PREMEDICATIONS:

Patients should be pre-treated with corticosteroids immediately prior to 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 alemtuzumab treatment course. Pre-treatment with antihistamines and/or antipyretics prior to alemtuzumab administration may also be considered. See SmPC for further information.

DOSE MODIFICATIONS:

No recommended dose modifications.

Renal and Hepatic impairment:

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

ELIGIBILTY CRITERIA:

- Patient has a confirmed diagnosis of RRMS and is being treated as per the Indications above
- Patients over 18 years
- Patient must attend for medical appointments and investigations as determined by the clinical team.

EXCLUSION CRITERIA:

Patients who do not meet the eligibility criteria above.

CONTRAINDICATIONS:

- Hypersensitivity to alemtuzumab (Lemtrada®) or to any of the excipients listed in SmPC
- 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

PREGNANCY AND BREASTFEEDING:

See SmPC

BASELINE TESTS AND MONITORING

- Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.
- All vaccinations must be completed 6 weeks prior to treatment

Table 1: Recommended baseline tests and schedule of assessments for patients treatment with Alemtuzumab

Assessment	Baseline	Monthly	3 Monthly	At Each Infusion	Annually
MRI	X[1]				X
Full Blood Count (with differential)	X	X[2]			
EDSS Score	X			X	
Urea & electrolytes, Serum Creatinine, Urinalysis and microscopy	X	X[2]			
Liver profile (including AST, GGT and albumin)	X	X[2]			
Thyroid function tests (TFTs)	X		X[2]		
Clotting Screen	X[3]				
Blood Pressure Monitoring	X[3]				
Cardiovascular History	X[3]				
HIV Serology	X				
Cytomegalovirus (CMV) immune serostatus	X				
Hepatitis B and C virus serology	X[4]				
Varicella Zoster Virus (VZV) Serology	X[5]				
Evaluation for active or latent TB as per local guidelines	X				
Annual cervical (HPV) screening for females	X				

[1] Within 3 months prior to treatment, within 3 months of each treatment course to allow for assessment of response and annually

[2] 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.

[3] See alemtuzumab contraindications

[4] 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

[5] VZV vaccination of antibody-negative patients should be considered. VZV vaccination should be administered at least 6 weeks in advance of treatment.

SPECIAL WARNINGS AND PRECAUTION FOR USE

- See SmPC for full information
- Women of childbearing potential should use effective contraceptive measures during treatment and for 4 months following each course of alemtuzumab treatment.

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 as per SmPC.

Listeriosis/*Listeria meningitis* has been reported in patients treated with alemtuzumab, generally within one month of infusion. The risk is estimated to be 0.25% in the first month after each cycle of alemtuzumab treatment without prophylaxis[6].

Prophylaxis Options:

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

   OR

2. Where alemtuzumab treatment can be predicted some months in advance (for instance with cycles 2 and 3), it would be reasonable to offer a second option to patients who will comply rigorously with the Listeria-free diet (avoid ingestion of uncooked or undercooked meats, soft cheeses and unpasteurized dairy products): going on the Listeria-free diet for ninety days before, and for one month after, alemtuzumab.

ADVERSE EFFECTS

See SmPC for full information.

This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

The following infusion instructions are intended to reduce serious reactions temporally associated with 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** table 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, 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.

DRUG INTERACTIONS

No formal drug interaction studies have been conducted with alemtuzumab using the recommended dose in patients with MS. See SmPC for full information.

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.

REFERENCES

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2. Cohen JA et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial Lancet 2012; 380: 1819–28.

3. Coles AJ et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet 2012; 380: 1829–39.

4. European Medicines Agency. ALEMTUZUMAB 12 mg concentrate for solution for infusion. Accessed February 2020. Available at: https://www.ema.europa.eu/en/documents/product-information/lemtrada-epar-product-information_en.pdf

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6. Cauchi M, et al. Pract Neurol 2022;0:1–20. doi:10.1136/practneurol-2022-003370. Multiple sclerosis and the risk of infection: Association of British Neurologists consensus guideline.

7. European Medicines Agency. (2020). Measure to minimise risk of serious effects of multiple sclerosis medicine Lemtrada. Accessed February 2024. Available at: https://www.ema.europa.eu/en/documents/referral/lemtrada-article-20-procedure-measures-minimise-risk-serious-side-effects-multiple-sclerosis-medicine-lemtrada_en.pdf-0

Version	Date	Amendment	Approved By
2	09/07/2019	- Update of protocol to include recommendation into 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 - "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	- 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	
4	May 2024	- Routine two year review - Updated to reflect standard AHDMP Template for Prescribing Protocols - Advice on Listeria prophylaxis updated.	

Comments and feedback welcome at ahdmp@hse.ie.