Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

Alemtuzumab Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Protocol Code
*Treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features	G35	MS100

*NOTE: on 12 April 2019 the EMA issued the following temporary restrictions on the prescription of alemtuzumab pending the conclusion of a safety review by the Pharmacovigilance Risk Assessment Committee (PRAC):

- New treatment should only be initiated in adults with relapsing-remitting multiple sclerosis that is highly active despite a full and adequate course of treatment with at least two other disease-modifying therapies, or in adults with highly active relapsing-remitting multiple sclerosis where all other disease-modifying therapies are contraindicated or otherwise unsuitable.
- Patients already being treated with alemtuzumab who are benefitting from it may continue treatment in consultation with their doctor.

***Further information about the EMA temporary restriction can be found at:**
https://www.ema.europa.eu/en/documents/referral/alemtuzumab-article-20-referral-use-multiple-sclerosis-medicine-alemtuzumab-restricted-while-ema-review_en.pdf

ELIGIBILTY:

- 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 a course of alemtuzumab treatment

EXCLUSIONS:

- Hypersensitivity to alemtuzumab or to any of the excipients
- Human Immunodeficiency Virus [HIV] infection
- Patients with severe active infection until resolution

USE WITH CAUTION:

- In patients with previous autoimmune conditions e.g. ITP, thyroid disorders, nephropathies
- In pregnancy and lactation

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TESTS:

Baseline Measures:
MRI 3 months prior to treatment

Baseline tests:

- FBC, U&E, LFTs and TFT
- Urinalysis and microscopy
- HIV test
- Varicella Zoster Virus (VZV) Serology - VZV vaccination of antibody-negative patients should be considered at least 6 weeks in advance of treatment
- Evaluation of CMV immune sero-status could be considered according to local guidelines.
- All vaccinations must be completed 6 weeks prior to treatment
- Evaluation for active or 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, LFTs, serum creatinine levels, urinalysis with microscopy at monthly intervals.
- Thyroid Function Tests every 3 months.

These laboratory tests should be conducted for 48 months following the last treatment course of alemtuzumab 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:

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.

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.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1-5	Alemtuzumab	12mg	IV infusion	100ml 0.9% Sodium Chloride or 5% Glucose over 4 hours	1
12 months later					
1-3	Alemtuzumab	12mg	IV infusion	100ml 0.9% Sodium Chloride or 5% Glucose over 4 hours	2
Missed doses should not be given on the same day as a scheduled dose.					

- Resources for the management of anaphylaxis or serious reactions should be available.
- Vital signs should be monitored before and during the intravenous infusion. If clinically significant changes are observed, discontinuation of infusion and additional monitoring, including ECG, 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:

PREMEDICATIONS:
Patients should be pre-treated with corticosteroids (such as 1g methylprednisolone) immediately prior to alemtuzumab administration on each of the first 3 days of any treatment course. Additionally, pre-treatment with antihistamines and/or antipyretics prior to alemtuzumab administration may also be considered.

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:

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.

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

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 during and for 2 hours after alemtuzumab infusion. If an IAR occurs, provide the appropriate symptomatic treatment, as needed. If the infusion is not well tolerated, the infusion duration may be extended. If severe infusion reactions occur, immediate discontinuation of the intravenous infusion should be considered.

Physicians should be aware of the patient's cardiac history as infusion-associated reactions can include cardiac symptoms such as tachycardia.

Autoimmunity: Treatment may result in the formation of autoantibodies and increase the risk of autoimmune mediated conditions including immune thrombocytopenic purpura (ITP), thyroid disorders, and nephropathies (e.g. anti-glomerular basement membrane disease with possible pulmonary haemorrhage).

Suspected autoimmune cytopenias such as neutropenia, haemolytic anaemia and pancytopenia have been infrequently reported in clinical trials in MS. Complete blood count 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.

Caution should be exercised in patients with previous autoimmune conditions other than MS, although available data suggests there is no worsening of pre-existing autoimmune conditions after alemtuzumab treatment.

Patients who develop signs of pathological immune activation should be evaluated immediately, and a diagnosis of haemophagocytic lymphohistiocytosis considered. Symptoms of immune activation may occur up to 4 years after the start of treatment.

Liver function tests should be carried out before and during treatment to monitor for autoimmune hepatitis. If patients develop signs of liver damage, unexplained liver enzyme elevations or symptoms suggestive of hepatic dysfunction (e.g. unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, jaundice or dark urine). Alemtuzumab should only be re-administered following careful consideration.

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.

Cardiovascular complications: There have been reports of serious cardiovascular adverse events occurring within 1–3 days of receiving alemtuzumab, including pulmonary haemorrhage, myocardial infarction, stroke, and cervicocephalic arterial dissection.

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 alemtuzumab. For more detail please refer to the SmPC (https://www.ema.europa.eu/en/documents/product-information/alemtuzumab-epar-product-information_en.pdf).

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.

SUPPORT RESOURCES:

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

ALEMTUZUMAB: Health Professional Guide. Available at http://www.hpra.ie/img/uploaded/swedocuments/edumat_auto_472ee9c2-89ef-4282-a92b-6e290a88a976.pdf

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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5. European Medicines Agency. Use of multiple sclerosis medicine Alemtuzumab restricted while EMA review is ongoing. Accessed April 2019. Available at: https://www.ema.europa.eu/en/documents/referral/alemtuzumab-article-20-referral-use-multiple-sclerosis-medicine-alemtuzumab-restricted-while-ema-review_en.pdf

6. Association of British Neurologists. Guidance on the prevention of Listeria infection after alemtuzumab treatment of multiple sclerosis. May 2017. Accessed June 2019. Available at: https://www.theabn.org/media/Guidance%20on%20the%20prevention%20of%20Listeria%20infection%20after%20alemtuzumab%20treatment%20of%20multiple%20sclerosis.pdf

Version	Date	Amendment	Approved By
2	09/07/2019	- 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 - "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	

Comments and feedback welcome at ndmp@hse.ie.