Alemtuzumab (Lemtrada)
National Drug Monograph
August 2015
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action	Alemtuzumab is a CD52-directed cytolytic monoclonal antibody, it likely exerts its action via antibody-dependent cellular cytolysis and complementmediated lysis of T and B lymphocytes, leading to immunomodulatory effects as a result of depletion and repopulation of lymphocytes
Indication(s) Under Review in this document (may include off label)	Alemtuzumab is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS). Because of its safety profile, the use of alemtuzumab should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS
Dosage Form(s) Under Review	Injection: 12 mg/1.2 mL (10 mg/mL) in a single-use vial
REMS	☒ REMS ☐ No REMS ☐ Postmarketing Requirements *See Other Considerations for additional REMS information*
Pregnancy Rating	Category C

Executive Summary

Efficacy	• Relapse rate and 6-month sustained disability progression were the co-primary endpoints for the CARE-MS I study. In CARE-MS I, there was a 54.9% relative reduction (p<0.001) in the relapse rate in the alemtuzumab arm (0.18) compared with the interferon beta 1a arm (0.39). Thirty-nine percent of the patients receiving alemtuzumab had freedom from clinical and radiographic disease activity, while only 27% of patients in the interferon beta 1a arm did. Eleven percent of patients on interferon beta-1a had sustained disability progression, while only 8% of patients on alemtuzumab had sustained progression; however, this difference was not statistically significant • Relapse rate and 6-month sustained disability progression were coprimary endpoints for the CARE-MS II study. Relapses were defined as above and were confirmed by a blinded relapse adjudication committee. In CARE-MS II, there was a 49.4% relative reduction in the relapse rate in the alemtuzumab arm (annual rate of 0.26 vs 0.52, p<0.0001) compared with the interferon beta 1a arm. The alemtuzumab group had a 42% reduction (p=0.0084) in sustained disability progression compared with the interferon beta 1a group. The alemtuzumab group had fewer patients with new or enhancing lesions on MRI; this effect was greater in the second year of the study • The studies with alemtuzumab demonstrate superiority over subcutaneous interferon beta 1a, which may suggest superiority over other interferon beta formulations, although these studies have not been performed. Other head-to-head studies comparing alemtuzumab with other MS DMTs also have not been performed, so a data-driven comparison regarding the comparative efficacy of alemtuzumab and other MS DMTs is not possible.
Safety	• Alemtuzumab has a black boxed warning regarding serious, sometimes fatal,

	autoimmune conditions, serious and life-threatening infusion reactions and an increased risk of malignancies. It is available in conjunction with a REMS program mandated by the FDA. • Important adverse events were infusion associated reactions (IARs), serious infections and autoimmune adverse events (thyroid disorders (including thyroid cancers), immune thrombocytopenia (ITP), nephropathies and cytopenias) • The most common autoimmunity after alemtuzumab was thyroid autoimmunity, which occurred in about a third of patients receiving the drug in the clinical trial program. This included Graves' disease and autoimmune hypo-/hyperthyroidism and was most common 3 to 4 years after initiating the drug. Almost 2% of patients who received alemtuzumab in the clinical trials developed an autoimmune platelet disorder (immune thrombocytopenic purpura) that causes easy bruising, spontaneous bleeding, and very low platelet counts (cells involved with clotting). Three tenths of a percent (0.3%) of the patients receiving alemtuzumab for MS developed a serious autoimmune kidney disease that can lead to kidney failure and dialysis if not detected and treated rapidly. Much of the autoimmunity with alemtuzumab occurs years after starting the drug. • The Phase II trials reported three cases of thyroid cancer, four cases of melanoma, and several cases of lymphoma developed in alemtuzumab treated patients. It is possible that alemtuzumab may increase the long term risk of malignancy
Potential Impact	• Alemtuzumab offers a dosing protocol that requires treatment for 5 days given in year 1 and three days given in year 2. The risk benefit ratio must be assessed for each patient. While the efficacy shown in Phase III trials demonstrated statistically significant relapse rates and disability accumulation in the alemtuzumab versus interferon beta 1a groups, an increased risk of autoimmunity, malignancy and infection were associated with alemtuzumab in these trials.

Background

Purpose for review

Issues to be determined:
✔ Is there a need for therapeutic alternatives to be used as therapy in patients with Relapsing, Remitting Multiple Sclerosis (RRMS)?
✔ Does alemtuzumab offer advantages to currently available therapies?
✔ Does alemtuzumab offer advantages over current VANF agents?
✔ What safety issues need to be considered?
✔ Does alemtuzumab have specific characteristics best managed by the non-formulary process, prior authorization, criteria for use?

Other therapeutic options

Formulary Alternatives	Other Considerations
Dimethyl fumarate (Tecfidera)	Oral agent, decreased lymphocyte count which needs to be monitored for, significant GI effects in some patients with impact tolerance and ability to stay on medication
Glatiramer (Copaxone)	Available in two dose regimens, QD or TIW
Interferon beta 1a (Avonex)	Once weekly IM injection, injection site reactions, flu like syndrome
Interferon beta 1a (Rebif)	Development of neutralizing antibodies, flu like syndrome with injections, injection site reactions
Interferon beta 1b (Betaseron, Extavia)	Development of neutralizing antibodies, flu like syndrome with injections, injection site reactions
Natalizumab (Tysabri)	Monthly infusion, development of PML

Non-formulary Alternative (if applicable)	Other Considerations
Fingolimod (Gilyena)	Oral agent, significant cardiac concerns, first dose monitoring is detailed and difficult for some facilities
Pegylated interferon beta 1a (Plegridy)	Twice monthly injection
Teriflunomide (Aubagio)	Oral agent, potential side effect profile similar to leflunomide, extremely long half life that requires accelerated elimination procedure if serious adverse events develop

Efficacy (FDA Approved Indications)

Literature Search Summary
MEDLINE and EMBASE were systematically searched using search terms alemtuzumab, Lemtrada, Multiple Sclerosis disease modifying therapy for randomized controlled trials published from 1980 through February 1, 2015. Additionally, articles relating to pharmacology, pharmacokinetics, tolerability and interactions were examined for inclusion. Published abstracts and websites of the Food and Drug Administration and European Medication Agency were reviewed for additional relevant information. The search was limited to studies performed in humans, in adults and published in the English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy [1-13]
Currently available evidence (Please refer the reader to Appendix A for interpretation) is rated at a moderate level.

The efficacy of alemtuzumab in patients with active RRMS has been investigated in two randomized, blinded, active comparator-controlled, multinational, phase III trials (CARE-MS I and CARE-MS II), and one randomized, rater-blinded, active comparator-controlled, multinational, phase II trial (CAMMS223). Long-term data are available from the CAMMS223 trial (5 years' follow-up) and the CARE-MS I and II studies (3 years' follow-up).

The Phase II trial, CAMMS223, enrolled a total of 334 patients with treatment naïve RRMS and symptom onset no more than 36 months prior to screening were randomized to treatment with an intravenous infusion of alemtuzumab 12 (n = 113) or 24 (n = 110) mg/day on 5 consecutive days, followed by a second treatment course at the same dosage on 3 consecutive days at months 12 and 24, or subcutaneous interferon beta-1a 44 ug three times weekly. During the study, alemtuzumab treatment was suspended as a result of three cases of immune thrombocytopenic purpura, including one death. At that time, 1 % of alemtuzumab recipients had not received the second course of treatment and 75 % had not received the third course. The dosing suspension was lifted after 2.5 years. In patients with treatment-naïve RRMS, alemtuzumab 12 mg/day was significantly (p<0.001) more effective than interferon beta-1a with regard to the co-primary endpoints of relapse rate (total number of events 34 vs. 89; patients with any event 21.4 vs. 40.5 %; hazard ratio [HR] 0.31 [95 % CI 0.18–0.52]) and rate of sustained disability accumulation for 6 months (26.2 vs. 8.5 % of patients; HR 0.25 [95 % CI 0.11–0.57])

 The Phase III trials compared alemtuzumab with an active comparator; subcutaneous interferon beta-1a (Rebif) 44 mcg three times weekly (TIW). One of these was done in a treatment-naïve MS population (CARE-MS I)[4], and the other (CARE-MS II)[5] was in MS patients who had breakthrough disease on another disease-modifying therapy (DMT) for MS.

The CARE-MS I trial was a 2-year randomized, rater-blinded trial comparing alemtuzumab 12 mg with subcutaneous interferon beta-1a in 581 treatment-naïve MS patients. Patients were 18 to 50 years old, with an Expanded Disability Status Scale (EDSS) of 3.0 or less, who had at least two relapses within the past 2 years, at least one relapse within the past year, and an abnormal brain MRI consistent with MS. Given the very different side-effect profiles and route/frequency of administration of the two drugs, only the neurologic rater was blinded to the treatment assignment.

The CARE-MS II trial was a 2-year randomized, rater-blinded trial that compared alemtuzumab 12 mg with subcutaneous interferon beta-1a in 667 MS patients who experienced breakthrough disease after 6 months of being on another DMT (primarily interferon-beta or glatiramer acetate). Patients were between 18 and 55 years of age with an EDSS of 5.0 or lower who had at least two relapses within the past 2 years, at least one relapse within the past year, and an abnormal brain MRI consistent with MS. As above, only the neurologic rater was blinded to treatment assignment

Please see Table 1 for the results of the Phase III studies.

The effect of treatment on MS disease activity persists long-term: preliminary data suggest that over 80% of subjects who remained in the CARE-MS I and CARE-MS II extension study did not require further doses of alemtuzumab at 3 years. Preliminary data also suggest that the risk of autoimmune side effects from treatment with alemtuzumab appears to be highest between 3 and 4 years after treatment

	CARE MS I		CARE MS II	
	Treatment Naïve		Previous DMT	
	A (N=376)	IFN (N=187)	A (N=426)	IFN (N=187)
ARR	0.18	0.39	0.26	0.52
New/Enlarging T2 lesions	2.29	3.15	3.59	8.44
New/Enlarging Gd lesions	0.16	0.33	0.32	1.11
Patients with disability progression over 6 months	8%	11%	13%	21%
EDSS change from baseline	-0.14*	-0.14	-0.17	0.24

All results were statistically significant except those marked with * ARR annualized relapse rate

Potential Off-Label Use

- Use in secondary progressive Multiple Sclerosis

Safety [14-24]
(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	**Autoimmune effects:** Alemtuzumab causes serious, sometimes fatal, autoimmune conditions, such as immune thrombocytopenia and antiglomerular basement membrane disease. Monitor complete blood counts with differential, serum creatinine levels, and urinalysis with urine cell counts at periodic intervals (see page 7) for 48 months after the last dose of alemtuzumab. **Infusion reactions:** Alemtuzumab causes serious and life threatening infusion reactions. Alemtuzumab must be administered in a setting with appropriate equipment and personnel to manage anaphylaxis or serious infusion reactions. Monitor patients for 2 hours after each infusion. Make patients aware that serious infusion reactions can also occur after the 2-hour monitoring period. **Malignancy:** Alemtuzumab may cause an increased risk of malignancies, including thyroid cancer, melanoma, and lymphoproliferative disorders. Perform baseline and yearly skin exams. **REMS program:** Because of the risk of autoimmunity, infusion reactions, and malignancies, alemtuzumab is available only through restricted distribution under a Risk Evaluation Mitigation Strategy (REMS) program.
Contraindications	Infection with human immunodeficiency virus (HIV)
Warnings/Precautions	Thyroid Disorders: Obtain thyroid function tests prior to initiation of

treatment and every 3 months until 48 months after the last infusion.
- Other Autoimmune Cytopenias: Monitor complete blood counts monthly until 48 months after the last infusion.
- Consider delaying initiation of alemtuzumab in patients with active infections until the infection is fully controlled.
- Do not administer live viral vaccines following a course of alemtuzumab

Adverse Reactions

Common adverse reactions	alemtuzumab (in at least 10% 358 of patients and more frequently than in interferon beta-1a) were rash, headache, pyrexia, nasopharyngitis, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract infection, herpes viral infection, urticaria, pruritus, thyroid gland disorders, fungal infection, arthralgia, pain in extremity, back pain, diarrhea, sinusitis, oropharyngeal pain, paresthesia, dizziness, abdominal pain, flushing, and vomiting
Death/Serious adverse reactions	In CAMMS22 one patient died from ITP and 1 from MI (N=334) In CARE MS I one patient died from car accident (N= 563) In CARE MS II 1 patient died from aspiration pneumonia and 1 from car accident (N= 798)
Discontinuations due to adverse reactions	In CAMSS22 5 yr extension, 4.6% of alemtuzumab patients discontinued therapy compared with 12.1% of interferon beta 1a treated patients

Because alemtuzumab causes long-lasting immune suppression, a potentially increased risk of infection exists long after the drug is infused. A subset of lymphocytes called T cells takes years to recover after a patient receives alemtuzumab, while B lymphocytes recover more quickly. This perturbation of the immune system can also lead to eventual autoimmune disease and malignancy.

The most common autoimmunity after alemtuzumab was thyroid autoimmunity, which occurred in about a third of patients receiving the drug in the clinical trial program. This included Graves' disease and autoimmune hypo-/hyperthyroidism and was most common 3 to 4 years after initiating the drug. About 2% of patients who received alemtuzumab in the clinical trials developed an autoimmune platelet disorder (immune thrombocytopenic purpura) that causes easy bruising, spontaneous bleeding, and very low platelet counts (cells involved with clotting). Three tenths of a percent (0.3%) of the patients receiving alemtuzumab for MS developed a serious autoimmune kidney disease that can lead to kidney failure and dialysis if not detected and treated rapidly. Much of the autoimmunity with alemtuzumab occurs years after starting the drug. A recent review (Tuohy OJ et al 2014) of long-term safety in patients treated with alemtuzumab at Cambridge, England, reported secondary autoimmunity in 41/86 subjects (47%) and included some individuals treated with three or more cycles.

Several cases of cancer were identified in patients who received alemtuzumab, including three cases of thyroid cancer, four cases of melanoma, and several cases of lymphoma. Although these numbers are low, it is felt that alemtuzumab may increase the long term risk of malignancy.

Pneumonitis occurred in 6 of 1217 (0.5%) alemtuzumab-treated subjects, including hypersensitivity pneumonitis and pneumonitis with fibrosis.

HPV (human papillomavirus) screening is recommended annually.

Complete blood counts with differential, serum creatinine levels, and urinalysis with urine cell counts should be obtained prior to initiation of treatment and at monthly intervals until 48 months after the last infusion.

If an individual has not been immunized for varicella zoster virus, antibody testing should be performed (and vaccination performed if appropriate) at least 6 weeks prior to initiating therapy.

Thyroid function tests should be obtained prior to the initiation of treatment and every 3 months until 48 months after the last infusion. Monitoring may need to continue past 48 months based on clinical findings of autoimmune conditions in post marketing studies.

Skin examination for melanoma should be performed prior to treatment and yearly thereafter.

Drug Interactions

There are no known drug interactions based on metabolism or transport systems (P glycoprotein).

Risk Evaluation

As of February 15, 2015

	Comments
Sentinel event advisories	• None • Sources: ISMP, FDA, TJC

Dosing and Administration

Administer alemtuzumab by intravenous infusion over 4 hours for 2 treatment courses:
- First course: 12 mg/day on 5 consecutive days.
- Second course: 12 mg/day on 3 consecutive days 12 months after first treatment course.

Patients require premedication with the following:

Corticosteroids
Premedicate patients with high dose corticosteroids (1,000 mg methylprednisolone or quivalent) immediately prior to alemtuzumab infusion and for the first 3 days of each treatment course

Herpes Prophylaxis
Administer anti-viral prophylaxis for herpetic viral infections starting on the first day of each treatment course and continue for a minimum of two months following treatment with alemtuzumab or until the CD4+ lymphocyte count is > 200 cells per microliter, whichever occurs later

Special Populations (Adults)
Dose adjustment is not required with body weight, gender, and age.

	Comments
Elderly	• Clinical studies of alemtuzumab did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients.
Pregnancy	• To avoid in utero exposure to alemtuzumab, women of child bearing potential should use effective contraceptive measures when receiving a course of treatment with alemtuzumab and for 4 months following that course of treatment
Lactation	• Alemtuzumab was detected in the milk of lactating mice administered 10 mg/kg on Days 8 through 12 postpartum. Serum levels of alemtuzumab similar in lactating mice and offspring on Day 13 postpartum, and were associated with evidence of pharmacological activity (decrease in lymphocyte counts) in the offspring. • It is not known whether alemtuzumab is excreted in human milk
Renal Impairment	• There are no dosage adjustments provided in the manufacturer's labeling (has not been studied)
Hepatic Impairment	• There are no dosage adjustments provided in the manufacturer's labeling (has not been studied)

Projected Place in Therapy
- The VHA MS Center of Excellence Data Repository has a confirmed cohort of 26,238 Veterans with MS from 1999 - present. In 2013, there were 15,484 Veterans with a confirmed diagnosis of MS who made 132,903 unique outpatient visits. Since 2001, there has been a 73% increase in Veterans using VA specialty care and a 99% increase in specialty care visits. The numbers of Veterans with MS who are using VA services has increased steadily since the inception of the MSCoE. In FY2013 there were 8,200 patients receiving DMT agents to treat Multiple Sclerosis
- The studies with alemtuzumab demonstrate superiority over subcutaneous interferon beta 1a, which may suggest superiority over other interferon beta formulations, although these studies have not been performed. The results of these trials demonstrate a significant effect of alemtuzumab on relapse rates and accumulation of disability. Other head-to-head studies comparing alemtuzumab with other MS DMTs have not been performed, so a data-driven comparison regarding the comparative effect of alemtuzumab and other MS DMTs is not possible. Alemtuzumab may be most appropriate for patients with active inflammatory disease.
- Over 90% of patients receiving alemtuzumab in the clinical trials experienced infusion reactions. Other severe adverse events include; thyroid autoimmunity, immune thrombocytopenic purpura and an autoimmune kidney disease that can lead to kidney failure and dialysis if not detected and treated rapidly. Several cases of cancer were identified in patients who received alemtuzumab, including three cases of thyroid cancer, four cases of melanoma, and several cases of lymphoma.
- The FDA has mandated a REMS program to mitigate the risks of autoimmune conditions, infusion reactions, and malignancies associated with alemtuzumab as part of the approval to help ensure informed decisions about

safe use of alemtuzumab. Part of this program mandates monthly laboratory monitoring which must be done for 48 months after the last dose of alemtuzumab.

- The decision to begin therapy with alemtuzumab must consider the risk-benefit profile of therapy; including potential development of autoimmunity or malignancy as well as the need for long term monitoring. The patient and provider need to engage in these discussions and make an informed choice to begin alemtuzumab therapy.

References

1. Genzyme: Lemtrada 2015. Available at http://products.sanofi.us/Lemtrada/Lemtrada.pdf Accessed May 3, 2015.
2. Dossier for Lemtrada. Provided by Genzyme. 2015.
3. FDA Hearing Transcripts available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM374188.pdf
4. Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP, Havrdova E, Selmaj KW, Weiner HL, Fisher E, Brinar VV, Giovannoni G, Stojanovic M, Ertik BI, Lake SL, Margolin DH, Panzara MA, Compston DA; CARE-MS I investigators.Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet. 2012 Nov 24;380(9856):1819-28.
5. Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ, Hartung HP, Havrdova E, Selmaj KW, Weiner HL, Miller T, Fisher E, Sandbrink R, Lake SL, Margolin DH, Oyuela P, Panzara MA, Compston DA; CARE-MS II investigators. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet. 2012 Nov 24;380(9856):1829-39.
6. Fox EJ, Sullivan HC, Gazda SK, Mayer L, O'Donnell L, Melia K, Lake SL. A single-arm, open-label study of alemtuzumab in treatment-refractory patients with multiple sclerosis. Eur J Neurol. 2012 Feb;19(2):307-11.
7. Coles AJ, Fox E, Vladic A, Gazda SK, Brinar V, Selmaj KW, Bass AD, Wynn DR, Margolin DH, Lake SL, Moran S, Palmer J, Smith MS, Compston DA. Alemtuzumab versus interferon β-1a in early relapsing-remitting multiple sclerosis: post-hoc and subset analyses of clinical efficacy outcomes. Lancet Neurol. 2011 Apr;10(4):338-48
8. Jones DE, Goldman MD. Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis: a review of its clinical pharmacology, efficacy and safety.Expert Rev Clin Immunol. 2014 Oct;10(10):1281-91
9. Montalban X, Inshasi JS, Coles AJ, Hartung HP, Havrdova E, Selmaj KW, Margolin DH, Palmer J, Oyuela P. Efficacy and safety of Alemtuzumab in treatment-naïve patients with relapsing-remitting multiple sclerosis: Four-year follow-up of the Care-MS I study. Mult Scler Relat Disord. 2014 Nov;3(6):761-2.
10. Kieseier BC, Sahraian MA, Coles AJ, Hartung HP, Havrdova E, Selmaj KW, Margolin DH, Palmer J, Oyuela P. Efficacy and safety of alemtuzumab in patients with relapsing-remitting multiple sclerosis who relapsed on prior therapy: Four-year follow-up of the Care-MS II study. Mult Scler Relat Disord. 2014 Nov;3(6):756.
11. Le Page E, Deburghgraeve V, Lester MA, Cardiet I, Leray E, Edan G. Alemtuzumab as rescue therapy in a cohort of 16 aggressive multiple sclerosis patients previously treated by Mitoxantrone: an observational study. J Neurol. 2015 Feb
12. Deisenhammer F, Hegen H. Alemtuzumab more effective than interferon β-1a at 5-year follow-up of CAMMS223 clinical trial. Neurology. 2012 Sep 4;79(10):1071-2.
13. Coles AJ, Fox E, Vladic A, Gazda SK, Brinar V, Selmaj KW, Skoromets A, Stolyarov I, Bass A, Sullivan H, Margolin DH, Lake SL, Moran S, Palmer J, Smith MS, Compston DA. Alemtuzumab more effective than interferon β-1a at 5-year follow-up of CAMMS223 clinical trial. Neurology. 2012 Apr 3;78(14):1069-78.
14. Meyer D, Coles A, Oyuela P, Purvis A, Margolin DH. Case report of anti-glomerular basement membrane disease following alemtuzumab treatment of relapsing-remitting multiple sclerosis. Mult Scler Relat Disord. 2013 Jan;2(1):60-3
15. Tsourdi E, Gruber M, Rauner M, Blankenburg J, Ziemssen T, Hofbauer LC. Graves' disease after treatment with lemtuzumab for multiple sclerosis. Hormones (Athens). 2015 Jan;14(1):148-53.
16. Willis M, Robertson NP. Drug safety evaluation of alemtuzumab for multiple sclerosis. Expert Opin Drug Saf. 2014 Aug;13(8):1115-24
17. Menge T, Stüve O, Kieseier BC, Hartung HP. Alemtuzumab: the advantages and challenges of a novel therapy in MS. Neurology. 2014 Jul 1;83(1):87-97.
18. Tuohy O, Costelloe L, Hill-Cawthorne G, Bjornson I, Harding K, Robertson N, May K, Button T, Azzopardi L, Kousin-Ezewu O, Fahey MT, Jones J, Compston DA, Coles A. Alemtuzumab treatment of multiple sclerosis: long-term safety and efficacy. J Neurol Neurosurg Psychiatry. 2015 Feb;86(2):208-15..
19. Robertson NP, Scolding NJ. Immune reconstitution and treatment response in multiple sclerosis following alemtuzumab. Neurology. 2014 Jun 17;82(24):2150-1.
20. Mullard A. FDA's rejection of alemtuzumab divides neurologists. Lancet. 2014 Mar 8;383(9920):859. Erratum in: Lancet. 2014 Mar 22;383(9922):1040.
21. Daniels GH, Vladic A, Brinar V, Zavalishin I, Valente W, Oyuela P, Palmer J, Margolin DH, Hollenstein J. Alemtuzumab-related thyroid dysfunction in a phase 2 trial of patients with relapsing-remitting multiple sclerosis. J Clin Endocrinol Metab. 2014 Jan;99(1):80-9.

22. Aranha AA, Amer S, Reda ES, Broadley SA, Davoren PM. Autoimmune thyroid disease in the use of alemtuzumab for multiple sclerosis: a review. Endocr Pract. 2013 Sep-Oct;19(5):821-8.
23. Sprenger T, Kappos L. Alemtuzumab for multiple sclerosis: who and when to treat? Lancet. 2012 Nov 24;380(9856):1795-7.
24. Costelloe L, Jones J, Coles A. Secondary autoimmune diseases following alemtuzumab therapy for multiple sclerosis. Expert Rev Neurother. 2012 Mar;12(3):335-41.

Prepared June 2015 Contact Person: Kathryn Tortorice Pharm D, BCPS

Appendix A: GRADEing the Evidence
Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.