CAMPATH® (alemtuzumab)

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INSTRUCTIONS FOR USE

This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee’s document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD)) may differ greatly. In the event of a conflict, the enrollee’s specific benefit document supersedes this Drug Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Drug Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

COVERAGE RATIONALE

This drug policy will ONLY be updated for non-oncology indications. Please refer to the Oncology Medication Clinical Coverage Policy for updated information based on the National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium for oncology indications.

Alemutuzumab is proven for the treatment of:

1) ** Patients undergoing peripheral blood stem cell (PBSC) and/or bone marrow transplantation

2) ** Patients undergoing solid organ transplantation

3) Relapsing-remitting multiple sclerosis (RRMS)

Additional information to support medical necessity review where applicable:

Alemutuzumab is medically necessary for treatment of relapsing-remitting multiple sclerosis when all of the following criteria are met:

A. Diagnosis of relapsing-remitting multiple sclerosis (RRMS)
B. **One** of the following:

1. **Treatment-naive to alemtuzumab:**
   a. Patient has history of failure following a trial for at least 4 weeks or history of intolerance or contraindication to two of the following:
      (1) interferon β-1a (Avonex®)
      (2) interferon β-1b (Betaseron® or Extavia®)
      (3) glatiramer acetate (Copaxone®)
      (4) dimethyl fumarate (Tecfidera®)
      (5) teriflunomide (Aubagio®)
      (6) fingolimod (Gilenya®)

   AND

   b. Patient has not been previously treated with alemtuzumab

   AND

   c. Patient is not receiving alemtuzumab in combination with another disease modifying agent (e.g., interferon beta preparations, glatiramer acetate, natalizumab, fingolimod, or teriflunomide)

   AND

   d. Initial dosing is administered: 12 mg intravenously daily for 5 consecutive days

   AND

   e. Regimen is administered only once within 12 months

   **OR**

2. **Treatment-experienced with alemtuzumab:**
   a. Patient has previously received treatment with alemtuzumab

   AND

   b. Patient is not receiving alemtuzumab in combination with another disease modifying agent (e.g., interferon beta preparations, glatiramer acetate, natalizumab, fingolimod, or teriflunomide)

   AND

   c. Retreatment dosing is administered: 12 mg intravenously daily for 3 consecutive days

   AND

   d. Regimen is administered only once within 12 months

** Effective September 4th, 2012, Campath will no longer be available commercially, but will be provided through the Campath Distribution Program free of charge. Additional details about this program may be found at www.campath.com.

Alemtuzumab is **unproven** for the treatment of:
1) Rheumatoid arthritis
2) Autoimmune neutropenia
3) Autoimmune hemolytic anemia
4) Pure red cell aplasia
5) Immune thrombocytopenic purpura
6) Evans syndrome
7) Autoimmune pancytopenia

**Centers for Medicare and Medicaid Services (CMS):**
Medicare does not have a National Coverage Determination (NCD) for alemtuzumab (Campath®). In general, Medicare covers outpatient (Part B) drugs that are furnished “incident to” a physician’s service provided that the drugs are not usually self-administered by the patients who take them. See the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals at http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf.

Local Coverage Determinations (LCDs) do exist. Refer to the LCDs for Alemtuzumab (Campath®).
BENEFIT CONSIDERATIONS

Some Certificates of Coverage allow coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The enrollee-specific benefit document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy.

Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.

CLINICAL EVIDENCE

Proven Uses:
Peripheral Blood Stem Cell or Bone Marrow Transplantation:
In a retrospective evaluation of 2 prospective studies, the efficacy of alemtuzumab (Grp A) to prevent graft-vs-host disease (GVHD) was compared to methotrexate (Grp B) in 129 patients receiving a nonmyeloablative peripheral blood stem cell transplant for chronic lymphoproliferative disorders. Both studies included patients with a high risk of transplant related mortality due to advanced age or other medical conditions. Patient demographics were similar in the 2 studies except that patients in Grp A (n = 78) had more sex-mismatched transplants (56% vs. 35%, p=0.031) and had more cases where both the donor and recipients were cytomegalovirus (CMV) negative (37% vs. 9%, p=0.009) than in Grp B (n = 51). Both studies used similar mobilization and conditioning regimens. Acute and chronic GVHD were evaluated using the same established criteria. Both studies used cyclosporine A (CSA) as part of the GVHD prophylactic regimen and maintained levels in the therapeutic range of 150 to 300 ng/mL until tapering. Patients in Grp A received 20 mg/day alemtuzumab on days 4 to 8 prior to transplant and patients in Grp B received 10 mg/day of methotrexate on days 1, 3 and 6 post transplant. Patients in Grp B also received folinic acid rescue after each dose of methotrexate. Patients with relapse or progression of disease after transplant and who did not achieve 100% donor chimerism after immunosuppression were eligible for donor lymphocyte infusions (DLI) in both studies. Patients in Grp A had significantly shorter recovery time to granulocyte counts of 500/mm$^3$ (12.8 vs. 14.7 days, p<0.001) and 1000/mm$^3$ (13.7 vs. 17.6, p<0.001). In contrast, patients Grp B had significantly shorter recovery times for platelet counts of 20 x 10$^9$/L (11.2 vs. 14.4 days, p = 0.009) and 50 x 10$^9$/L (14.1 vs. 21.7, p = 0.001). Acute GVHD occurred in significantly fewer patients in Grp A than Grp B (20.5% vs. 45.1%, p = 0.001). Chronic GVHD occurred in 2 patients in Grp A and in 22 of 33 patients at risk of chronic GVHD in Grp B (p<0.001). More patients in Grp A had CMV reactivation (47% vs. 22.7%, p=0.018) than patients in Grp B. Disease status 3 months after transplant found significantly more patients in CR/PR in Grp B than Grp A (67.5% vs. 21.1%, p<0.001). Eighteen patients in Grp A vs. 4 patients in Grp B received DLI for relapse/persistent disease. At last follow-up, disease status was not significantly different between the 2 groups. Overall and event-free survival rates were similar between the 2 groups.

In another study, in vitro T-cell depletion using alemtuzumab was assessed in 24 patients receiving peripheral blood stem cell (PBSC) grafts vs. a 23 patient retrospective cohort without T-cell depletion. All 47 patients received their transplant from the same institution between June 1996 and September 2001. All patients transplanted after July 1998 received T-cell depleted PBSC grafts (TCD) and all receiving their transplant prior to July 1998 received unmanipulated PBSC grafts (UM). For the TCD group the target CD34$^+$ cell dose was 5 x 10$^5$/kg of body weight. Any excess cells were stored for use as DLI. After the cells were collected and pooled, alemtuzumab 20 mg (n=14) or 10 mg (n=10) was added to the bag and agitated for 30 minutes immediately prior to infusion in the recipient. GVHD prophylaxis consisted of CSA maintained at...
plasma levels between 150 and 250 ng/mL for all patients and methotrexate was given to all
patients who received UM. Platelet engraftment occurred significantly quicker in the TCD group
vs. the UM group (11 vs. 14 days, p=0.0004). Acute GVHD occurred in significantly fewer
patients in the TCD group vs. the UM group (8.7% vs. 47.7%, p=0.003). Chronic GVHD occurred
in 10 of 18 UM patients who could be evaluated vs. 1 of 23 TCD patients (56.3% vs. 4.2%,
p=0.0005). Nine of 24 patients in the TCD group relapsed including 5 of 6 with chronic myeloid
leukemia (CML) vs. 3 of 23 in the UM group and 0 of 6 with CML. Four of the relapsed CML
patients had either a molecular or cytogenetic relapse and the fifth had a hematologic relapse. All
four of the CML patients with either molecular or cytogenetic relapse received DLI and were in
remission at the last follow-up. Overall survival at 2 years was similar between the 2 groups,
63.4% for the UM and 73.1% for the TCD group. However, 3 year survival was significantly better
in the TCD group (73.1% vs. 19%, p=0.05) due to 5 deaths from severe chronic GVHD and its
treatment in the UM group in the third year post transplant.

Other open-label studies using alemtuzumab as either a conditioning regimen for graft
recipients or used in vitro to deplete the graft of T-cell found similar results to those found in
the previous 2 studies.

Renal and Solid Organ Transplantation:
Zhang et al. conducted a meta-analysis comparing the safety and efficacy of alemtuzumab with
traditional induction therapies including basiliximab, daclizumab and rabbit antithymocyte globulin
(ATG) in renal transplantation. Utilizing MEDLINE, EMBASE and the Cochrane Library,
researchers conducted a literature search for all randomized controlled trials comparing
alemtuzumab with traditional antibodies for post renal transplant induction therapy. Quality
assessment was performed in each trial and meta-analyses were then performed to demonstrate
the pooled effects of relative risk (RR) with 95% confidence intervals (CI). A total of 808
participants from six randomized controlled trials (RCTs) were included in the analysis. Treatment
with alemtuzumab was associated with lower incidence of biopsy-proven acute rejection (BPAR)
over traditional antibodies (RR 0.63, CI 0.45-0.87, p=0.005). Researchers noted that this
difference remained when only studies comparing alemtuzumab with ATG were included (RR
0.32, CI 0.11-0.91, p=0.03), but lost significance when only patients at high-risk were included
(RR 0.86, CI 0.48-1.55, p=0.62). No significant differences were found between alemtuzumab
and traditional antibodies in terms of delayed graft function, patient death, graft loss, and safety
profile. Authors concluded that alemtuzumab induction is superior to traditional antibodies in
preventing acute rejection of renal transplantation, however, this benefit may not extend to
transplant recipients at high immunologic risk. These lower rejection rates do not translate into a
uniform increase in graft or patient survival. Additional meta-analysis have shown alemtuzumab
and daclizumab to be as effective as ATG for induction therapy in kidney transplantation based
on 24-month follow-up data. At 36 months, alemtuzumab showed lower rates of infection at 36
months compared to ATG.

In a prospective, open-label, randomized, multicenter, controlled trial, patients were randomly
assigned to receive alemtuzumab or conventional induction therapy (basiliximab or rabbit
antithymocyte globulin). Eligible patients (18 years or older and receipt of a live-donor or
deceased-donor kidney) were stratified according to acute rejection risk, with a high risk defined
by a repeat transplant, a peak or current value of panel-reactive antibodies of 20% or more, or
black race. The 139 high-risk patients received alemtuzumab (one dose of 30 mg, in 70 patients)
or rabbit antithymocyte globulin (a total of 6 mg/kg given over 4 days, in 68 patients). The 335
low-risk patients received alemtuzumab (one dose of 30 mg, in 164 patients) or basiliximab (a
total of 40 mg over 4 days, in 171 patients). All patients received tacrolimus and mycophenolate
mofetil and underwent a 5-day glucocorticoid taper in a regimen of early steroid withdrawal.
Primary outcomes included biopsy-confirmed acute rejection at 6 months and 12 months.
Secondary outcomes included measures of rejection, efficacy, patient and graft survival, graft
function, infection, cancer, and metabolic measures. All outcomes were monitored at 6, 12, 24,
and 36 months. Biopsy-confirmed acute rejection rate was significantly lower in the alemtuzumab
group than in the conventional-therapy group at both 6 months (3% vs. 15%, p<0.001) and 12
months (5% vs. 17%, p<0.001). At 3 years, the rate of biopsy-confirmed acute rejection in low-risk patients was lower with alemtuzumab than with basiliximab (10% vs. 22%, p=0.003), but no significant difference was seen between alemtuzumab and rabbit antithymocyte globulin in the high-risk group (18% vs. 15%, p=0.63). Rate of adverse-events at 3 years was similar among treatment groups. Researchers concluded that based on this study, alemtuzumab is more effective in preventing biopsy-confirmed acute rejection than conventional induction therapy and is as effective as rabbit antithymocyte globulin in high-risk transplant recipients.

In another prospective, randomized, single-center trial, researchers assessed the safety and efficacy of alemtuzumab compared to rabbit antithymocyte globulin (rATG) induction in 222 adult kidney and pancreas transplant patients treated with similar maintenance immunosuppression (mycophenolate mofetil and either tacrolimus or cyclosporine A). Patients were randomized to receive either alemtuzumab (n=113) or rATG (n=109) induction; 180 (81%) underwent kidney alone, 38 (17%) simultaneous pancreas-kidney, and 4 (2%) pancreas after kidney transplants. Primary outcomes included patient death and graft loss. Additional outcomes measured were biopsy-proven acute rejection (BPAR) and infection. Both induction groups have similar characteristics in regards to retransplantation, human leukocyte antigen match, antibody titer, expanded criteria donors, race, cytomegalovirus status, delayed graft function, and immunologic risks. Using a median follow-up of 2 years (minimum 1 year), the calculated overall patient, kidney, and pancreas graft survival rates (both treatment groups combined) were 96%, 89%, and 90%, respectively (p=not significant). Similar outcomes in regards to survival, initial length of stay, and maintenance immunosuppression (including early steroid elimination) were reported in both groups. BPAR episodes occurred in 16 (14%) alemtuzumab patients compared with 28 (26%) rATG patients (p=0.02). Late BPAR (> 12 months after transplant) was reported in 1 (8%) alemtuzumab patient and 3 (11%) rATG patients (p=NS). Infections and malignancy were similar between the two induction arms. Midterm results suggested that alemtuzumab is safe and effective in a dual maintenance drug regimen that eliminates steroids in low immunologic risk patients or in a triple maintenance protocol that minimizes steroids in higher immunologic risk patients.

Efficacy and safety of alemtuzumab induction with tacrolimus monotherapy as compared to a tacrolimus, mycophenolate mofetil and steroid triple-drug regimen in deceased donor kidney transplant recipients was assessed in a prospective randomized, controlled, multicenter trial. Out of the 131 eligible patients, 65 patients in the study group received induction with alemtuzumab followed by delayed tacrolimus monotherapy, while the 66 patients in the control group were started on tacrolimus in combination with mycophenolate mofetil and steroids. Tacrolimus levels of 8-12 ng/mL for the first 6 months and 5-8 ng/mL thereafter were aimed for in both groups. The primary outcome measurement was the proportion of patients with a first biopsy-proven acute rejection within 6 months of transplantation. Secondary outcomes included biopsy-proven acute rejection episodes for 12 months after transplantation, time to first biopsy-proven rejection, patient and graft survival, incidence of corticosteroid-resistant rejection, serum creatinine as well as clearance at 1 year and adverse events. Researchers reported that the frequency of biopsy-proven rejection at 6 months was 15% (n=10) in the study group and 29% (n=19) in the control group (p=0.05) and at 12 months, the biopsy-proven rejection rate was 20% (n=13) in the study group and 32% (n=21) in the control group (p=0.09). Calculated graft survival at year 1 was 96% in the study group and 90% in the control group (HR=0.33; 95% CI 0.07–1.66). Graft function and adverse events were similar in both groups, however, more CMV infections were reported in the study group (RR=2.28, 95% CI 1.07–4.88). At year one, 82% of the patients in the study group were steroid-free and 71% continued on tacrolimus monotherapy. Authors concluded antibody pre-conditioning with alemtuzumab together with tacrolimus monotherapy is at least as efficient as a tacrolimus based triple-drug regimen with a similar safety profile except for more CMV infections.

To assess long-term safety and efficacy of alemtuzumab induction therapy in combination with low-dose maintenance cyclosporine, 33 cadaveric renal transplant recipients received 20 mg
alemtuzumab on day 0 and 1, followed by half-dose cyclosporine monotherapy (trough concentration 75-125 ng/mL) from day 3 and were then followed-up at 5 years.\textsuperscript{23} They were compared in a retrospective contemporaneous-controlled manner with 66 kidney transplant recipients transplanted in the same period and center who received conventional immunosuppression including cyclosporine, azathioprine and prednisolone (control group). Deaths were reported in 12% of recipients in the compared to 17% in the control group (p=0.48). Reported incidence of graft loss was similar for both groups (21% vs. 26%, respectively, p=0.58) and incidence of acute rejection was also comparable at 5 years (31.5% vs. 33.6). There was no significant difference between groups in terms of infection or serious adverse events. Authors concluded that results suggest that alemtuzumab induction allows for satisfactory long-term patient and graft survival equivalent to that seen with standard triple immunosuppression, while avoiding steroid therapy.

In another open label trial, the safety and efficacy of alemtuzumab induction therapy was assessed in 3 groups of patients receiving intestinal or multiviseral grafts.\textsuperscript{6} The same induction and maintenance regimen was used in all 3 groups, consisting of alemtuzumab 0.3 mg/kg given pretransplant, immediately postoperatively and 3 and 7 days postoperatively. Low dose tacrolimus monotherapy was begun with a goal of 10 to 15 ng/mL for intestinal transplants and 5 to 10 ng/mL for liver transplants. The first group consisted of 21 adult patients who received 14 isolated intestinal grafts, 1 combined liver-intestinal graft and 9 multiviseral grafts. Seven patients died, 2 from severe rejection. Sixteen patients have been followed for a minimum of 2 months (2.4 to 16 months) and in this group there have been 7 mild, 3 mild to moderate and 2 severe rejection episodes. Three were treated with OKT3 and the rest with steroids. Four patients did not experience a rejection episode. At the end of the follow-up period, all sixteen patients are receiving low-dose tacrolimus and 4 are also receiving low dose steroids. The second group consisted of 11 high-risk pediatric patients who received 2 intestinal grafts, 9 multiviseral grafts and 1 liver-intestinal graft. Four patients died, one of a suspected rejection episode. Seven patients have been followed for 1 month or more (1 to 8.5 months) and 4 have not experienced a rejection episode. Two had mild rejection episodes treated with steroids and 2 patients had moderate rejection episodes treated with OKT3 in one case and OKT3 and steroids in the other. The last group consisted of 5 liver transplant recipients and these were compared to a control group of 5 liver transplant recipients who received standard dose tacrolimus and low dose corticosteroids without alemtuzumab. In the group receiving alemtuzumab there were no episodes of rejection compared to 3 episodes (1 mild, 2 moderate) in the 5 control patients after 2 to 6.2 months of follow-up.

**Multiple Sclerosis:**

Efficacy and safety of alemtuzumab as first-line treatment was compared with interferon β-1a (IFNβ-1a) in a randomized, controlled phase 3 trial over 2 years in patients with early, active relapsing-remitting multiple sclerosis (RRMS) (CARE-MS I).\textsuperscript{19} Inclusion criteria are as follows: aged 18-50 years with previously untreated RRMS, a disease duration up to 5 years, at least two relapses in the previous 2 years and at least one in the previous year, expanded disability status scale (EDSS) scores of 3.0 or lower, and cranial abnormalities on MRI attributable to multiple sclerosis. Patients were randomly allocated in a 2:1 ratio to receive alemtuzumab (12 mg daily for 5 days at baseline and for 3 days at 12 months) or IFNβ-1a (44 mcg subcutaneously three-times per week after dose titration). Primary endpoints measured were relapse rate and time to 6 month sustained accumulation of disability in patients that received at least one dose of study drug. Primary analyses were based on 187 (96%) of 195 patients randomly allocated IFNβ-1a and 376 (97%) of 386 patients allocated alemtuzumab. Researchers reported that 40% of IFNβ-1a treated patients relapsed (122 events) compared with 22% of patients in the alemtuzumab group (119 events; rate ratio 0.45 [95% CI 0.32-0.63]; p<0.0001), which correlates to a 54.9% risk reduction in the alemtuzumab group. Based on Kaplan-Meier estimates, 58.7% of patients in the interferon beta 1a group were relapse-free at 2 years compared with 77.6% of patients in the alemtuzumab group (p<0.001). Sustained accumulation of disability was documented in 11% of patients in the IFNβ-1a group compared to 8% of patients in the alemtuzumab group (HR 0.70 [95% CI 0.40-1.23]; p=0.22). Infusion-associated reactions were reported in 90% of patients in
the alemtuzumab group (3% of those reactions were regarded as serious). Mild to moderate infections occurred in 67% of patients in the alemtuzumab group compared to 45% of patients treated with IFNβ-1a. Additionally, 16% of patients treated with alemtuzumab had herpes infections compared with 2% of patients treated with IFNβ-1a. By 24 months, thyroid-associated adverse events were reported in 18% of patients in the alemtuzumab group compared with 6% in the IFNβ-1a group, and three patients had immune thrombocytopenia compared with none in the IFNβ-1a group. Two patients in the alemtuzumab treatment cohort developed thyroid papillary carcinoma. Researchers concluded that this phase 3 study supports and extends previous findings (CAMMS223) that alemtuzumab is more effective than high-dose IFNβ-1a for reduction of rates of relapse in previously untreated patients with early, active relapsing-remitting multiple sclerosis. However, benefit in regards to rate of sustained accumulation of disability noted in previous trials was not observed during this study.

Efficacy and safety of alemtuzumab compared with interferon β-1a (IFNβ-1a) in relapsing-remitting multiple sclerosis (RRMS) patients who have relapsed while taking a standard disease-modifying therapy was assessed in a randomized controlled phase 3 trial (CARE-MS II).18 RRMS patients aged 18-55 years with at least one relapse while on interferon beta or glatiramer were randomly allocated in a 1:2:2 ratio to receive subcutaneous IFNβ-1a 44 mcg, intravenous alemtuzumab 12 mg per day, or intravenous alemtuzumab 24 mg per day. IFNβ-1a was given three-times per week and alemtuzumab was given once per day for 5 days at baseline and for 3 days at 12 months. The 24 mg per day group was utilized to aid recruitment to the two other study groups, but data are included for safety assessments. Primary endpoints included both relapse rate (defined as a change of one point on two functional system scales or two points on one functional system scale or increase in EDSS score) and time to 6 month sustained accumulation of disability (defined as an increase from baseline of at least one EDSS point [or ≥1.5 points if the baseline EDSS score was 0] confirmed over 6 months), comparing alemtuzumab 12 mg and IFNβ-1a in all patients who received at least one dose of study drug. Analyses were based on 202 (87%) of 231 patients randomly allocated IFNβ-1a and 426 (98%) of 436 patients allocated alemtuzumab 12 mg, or intravenous alemtuzumab 24 mg per day. IFNβ-1a was given three-times per week and alemtuzumab was given once per day for 5 days at baseline and for 3 days at 12 months. The 24 mg per day group was utilized to aid recruitment to the two other study groups, but data are included for safety assessments. Primary endpoints included both relapse rate (defined as a change of one point on two functional system scales or two points on one functional system scale or increase in EDSS score) and time to 6 month sustained accumulation of disability (defined as an increase from baseline of at least one EDSS point [or ≥1.5 points if the baseline EDSS score was 0] confirmed over 6 months), comparing alemtuzumab 12 mg and IFNβ-1a in all patients who received at least one dose of study drug. Analyses were based on 202 (87%) of 231 patients randomly allocated IFNβ-1a and 426 (98%) of 436 patients allocated alemtuzumab 12 mg. Researchers reported 51% of patients (n=104) in the IFNβ-1a group had 201 relapse events compared with 35% of patients (n=147) in the alemtuzumab group (236 events; rate ratio 0.51 [95% CI 0.39-0.65]; p<0.0001) which corresponds to a 49.4% improvement with alemtuzumab. Patients were relapse-free at 2 years in 47% of the IFNβ-1a group compared to 65% of patients in the alemtuzumab group (p<0.0001). Sustained accumulation of disability was reported in 20% of patients in the IFNβ-1a compared with 13% of patients in the alemtuzumab group (hazard ratio 0.58 [95% CI 0.38-0.87]; p=0.008) which corresponds to a 42% improvement in the alemtuzumab group. Adverse events reported are as follows: 90% of patients in the alemtuzumab had infusion-associated reactions; 77% of alemtuzumab patients had infections compared with 66% of patients in the IFNβ-1a group that were predominately mild to moderate severity with none fatal; the alemtuzumab treated group reported 16% thyroid disorders (compared to 5% in the IFNβ-1a group) and 1% (n=3) had immune thrombocytopenia (none reported in the IFNβ-1a group). Authors concluded, with appropriate monitoring to reduce the risk of potentially serious but treatable adverse events, alemtuzumab may be used as effective immunotherapy in patients with RRMS whose disease has advanced despite use of a standard disease-modifying treatment.

Long-term safety and efficacy results of the CAMMS223 trial comparing alemtuzumab with interferon β-1a (IFNβ-1a) in active relapsing-remitting multiple sclerosis (RRMS) was analyzed through an extended follow-up phase (up to 60 months from baseline).17 Of the 334 patients originally randomized, 198 participated in the extension phase (151 [68%] alemtuzumab and 47 [42%] IFNβ-1a). Disability, relapses, and safety were assessed utilizing the same measuring parameters as defined within the original CAMMS223 trial. Efficacy outcomes were analyzed from baseline of the original trial period to 60 month and safety data extended beyond 60 months. Five year post hoc analyses found that alemtuzumab lowered the risk of sustained accumulation of disability by 72% and the rate of relapse by 69% compared with IFNβ-1a (p<0.0001). Researchers reported that annualized relapse rate from baseline to month 60 was 0.11 for alemtuzumab and 0.35 for IFNβ-1a. Serious infections were documented in 7% of alemtuzumab
patients vs 3% of IFNβ-1a patients, and thyroid disorders were reported in 30% of alemtuzumab patients vs 4% of IFNβ-1a patients. Immune thrombocytopenia occurred in 3% of alemtuzumab patients and 0.9% of IFNβ-1a patients during the initial study period, however, no additional events were reported during the extension phase. Researchers concluded that the outcomes of this extension trial provides Class III evidence that alemtuzumab is more effective than interferon β-1a in reducing relapses and disability in patients with RRMS in a long-term follow-up of a rater-blinded, randomized clinical trial with 59.5% of patients participating in the extended follow-up period, and that the safety profile is consistent with previous reports.

Post-hoc and subset analyses of the patients free from clinically-active disease (CDA; defined as no relapses and no sustained accumulation of disability) were performed using data obtained from patients participating in CAMMS223. Researchers further analyzed the CAMMS223 data with the aim of determining whether demographic and baseline disease-related characteristics (age, sex, geographic region, MRI-T1 brain volume, MRI-T2 lesion volume, disease duration, number of previous relapses within 2 years, and EDSS) affect the beneficial effects of alemtuzumab. Additionally, efficacy was evaluated using occurrence of sustained reduction in disability (SRD; a ≥1 point decrease on the EDSS sustained for 6 consecutive months for patients with a baseline EDSS ≥2). 322 patients that received treatment were included in the analysis. Of the 215 patients treated with alemtuzumab, 161 were free of CDA at 36 months (Kaplan-Meier estimate 71.8%, 95% CI 61.1 - 78.8%) compared with 52 of 107 patients treated with interferon beta-1a (42.6%, 32.4 - 52.4%; hazard ratio [HR]=0.31, 0.20 - 0.46; p<0.0001). For the 199 patients with a baseline EDSS score greater than or equal to 2, SRD was more likely (HR=2.61, 1.54 - 4.43; p=0.0004) among patients treated with alemtuzumab (66 of 133 patients, Kaplan-Meier estimate 51.6%, 95% CI 43.2 - 60.7%) than patients treated with interferon beta-1a (15 of 66 patients, 27.2%, 17.2 - 41.4%). Disability and relapse outcomes showed evidence of beneficial effects of alemtuzumab compared with interferon beta-1a across all analyzed patient subsets, and no subgroup of patients consistently responded better than others to alemtuzumab amongst all measurements. Authors concluded that alemtuzumab reduced disease activity compared with interferon beta-1a in most of the analyzed subgroups, and a significantly greater numbers of patients experienced sustained improvement in disability after treatment with alemtuzumab than interferon beta-1a.

The efficacy and safety of alemtuzumab in multiple sclerosis was assessed in a randomized, single-blinded trial involving 334 treatment-naïve, early relapsing-remitting multiple sclerosis patients with EDSS scores ≤ 3.0 and disease duration of ≤ 3 years (CAMMS223). Patients were randomly assigned to receive either annual intravenous cycles of alemtuzumab (12 mg or 24 mg per day) or subcutaneous interferon beta-1a (44 mcg) three times per week for 36 months. Primary endpoints included both the time to sustained accumulation of disability (defined as an increase of at least 1.5 points for patients with an EDSS baselines score of 0 and of least 1.0 for patients with baseline score of 1.0) and the rate of relapse (defined as a new or worsening symptom with an objective change in neurologic examination attributable to multiple sclerosis that lasted for at least 48 hours, that were present at normal body temperature, and that were preceded by at least 30 days of clinical stability). Secondary outcomes were the proportion of patients who did not have a relapse, changes in lesion burden, and changes in brain volume. Alemtuzumab reduced the rate of sustained accumulation of disability, as compared with interferon beta-1a (9.0% vs. 26.2%; hazard ratio, 0.29; 95% confidence interval [CI], 0.16 to 0.54; p<0.001) and the annualized rate of relapse (0.10 vs. 0.36; hazard ratio, 0.26; 95% CI, 0.16 to 0.41; p<0.001). The mean disability score on a 10-point scale improved by 0.39 point in the alemtuzumab group and worsened by 0.38 point in the interferon beta-1a group (p<0.001). In the alemtuzumab group, the lesion burden (as seen on T(2)-weighted magnetic resonance imaging) was reduced, as compared with that in the interferon beta-1a group (p=0.005). From month 12 to month 36, brain volume (as seen on T(1)-weighted magnetic resonance imaging) increased in the alemtuzumab group but decreased in the interferon beta-1a group (p=0.02). Adverse events in the alemtuzumab group, as compared with the interferon beta-1a group, included autoimmunity (thyroid disorders [23% vs. 3%] and immune thrombocytopenic purpura [2.8% vs. 0.9%]) and infections (66% vs. 47%). Immune thrombocytopenic purpura caused the death of one patient,
and after the report of two further cases, the data and safety monitoring board suspended the administration of alemtuzumab between September 2005 and May 2007. The suspension was lifted in April 2008 with implementation of a program to ensure prompt identification and management of immune thrombocytopenia.5

Efficacy of alemtuzumab in 45 relapsing-remitting multiple sclerosis (RRMS) patients who had failed prior interferon-beta therapy was evaluated in a single-arm, open-label trial over 2 years. Interferon-beta therapy failure was defined as ≥ 2 confirmed relapses during at least a 6 month course of treatment within the 2 years prior to initiation of study.8 Patients were administered 24 mg IV alemtuzumab/day for 5 consecutive days at baseline and 3 consecutive days 12 months later. All patients received premedication with 1 g IV methylprednisolone on days 1–3 at both times. Efficacy measures included analysis of relapses (annualized relapse rate, time to first relapse and proportion of patients relapse free), time to SAD [sustained accumulation of disability] and changes from baseline in EDSS and Multiple Sclerosis Functional Composite (MSFC) scores. After 2-year follow-up, the annualized relapse rate was reduced by 94% compared to pre-treatment levels, from 1.6 (2 years prior to treatment) to 0.17 for the 2 years following (p<0.0001). Additionally, 42 of 43 (97.7%) patients with EDSS data at month 24 had no sustained increase in disability during this study (95% CI = 93.2%, 100%). Mean changes from baseline in MSFC composite and subscale scores at year 2 were not statistically significant. However, examination of individual patient data revealed that 70% of the patients had stable or improved MSFC composite scores at year 2. Serious adverse events observed in single patients were transient neutropenia and pneumonia, pulmonary emboli and deep vein thrombosis. Five patients developed clinical thyroid disorders but no opportunist infections or cases of immune thrombocytopenic purpura were observed. Researchers concluded that alemtuzumab effectively reduced relapse rates and improved clinical scores in patients with active RRMS not controlled by interferon therapy.

Unproven Uses:
Miscellaneous:
Alemtuzumab has been used in the treatment of other conditions including rheumatoid arthritis,10,11 autoimmune neutropenia,12 autoimmune hemolytic anemia,12,13,15 pure red cell aplasia,12,14 immune thrombocytopenic purpura12,13 Evans syndrome,12 and autoimmune pancytopenia.12 While a beneficial effect of alemtuzumab has been reported in some of these conditions, none of them have been studied in large, controlled clinical trials or studies were discontinued before completion due to alemtuzumab associated toxicity.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Campath is a CD52-directed cytolytic antibody indicated as a single agent for the treatment of B-cell chronic lymphocytic leukemia.16

The statement above is for information only. Oncology indications for alemtuzumab are listed in the NCCN Drugs & Biologics Compendium.

APPLICABLE CODES

The [Current Procedural Terminology (CPT), HCPCS and/or ICD-9] codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the benefit document

<table>
<thead>
<tr>
<th>HCPCS Code</th>
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<table>
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<tr>
<th>ICD-9 Code For Non Oncology Diagnoses</th>
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<td>340</td>
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<td>Other specified organ or tissue replaced by transplant; Peripheral Stem Cells</td>
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<td>V42.83</td>
<td>Other specified organ or tissue replaced by transplant; Pancreas</td>
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<td>Other specified organ or tissue replaced by transplant; Intestines</td>
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This list is not all-inclusive. The codes above are used post-transplant in the absence of complications.

**ICD-10 Codes (Preview Draft)**

In preparation for the transition from ICD-9 to ICD-10 medical coding on **October 1, 2014***, a sample listing of the ICD-10 CM and/or ICD-10 PCS codes associated with this policy has been provided below for your reference. This list of codes may not be all inclusive and will be updated to reflect any applicable revisions to the ICD-10 code set and/or clinical guidelines outlined in this policy. *The effective date for ICD-10 code set implementation is subject to change.*

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<td>Z94.3</td>
<td>Heart and lungs transplant status</td>
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<td>Lung transplant status</td>
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<td>Liver transplant status</td>
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<td>Bone marrow transplant status</td>
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<td>Stem cells transplant status</td>
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**REFERENCES**


**POLICY HISTORY/REVISION INFORMATION**

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<td>Policy updated per annual review. Approved by the National Pharmacy &amp; Therapeutics Committee 11/12/2013. Policy 2013D0023H archived.</td>
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<tr>
<td>4/1/2013</td>
<td>Policy updated per annual review. Added medical necessity language to multiple sclerosis in Coverage Rationale. Added Campath Distribution Program information. Updated clinical evidence for renal/solid organ transplantation and multiple sclerosis. Removed V42.2, V42.3, V42.4, V42.5, V42.89 and V42.9. Approved by the National Pharmacy &amp; Therapeutics Committee 2/19/2013. Policy 2012D0023G archived.</td>
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