Clinical Policy Title: Alemtuzumab induction therapy in lung transplantation

Clinical Policy Number: 07.02.09

Effective Date: March 1, 2017
Initial Review Date: February 15, 2017
Most Recent Review Date: February 6, 2018
Next Review Date: February 2019

Related policies:

CP# 07.02.07 Lung transplants

ABOUT THIS POLICY: Select Health of South Carolina has developed clinical policies to assist with making coverage determinations. Select Health of South Carolina’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Select Health of South Carolina when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements shall control. Select Health of South Carolina’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Select Health of South Carolina’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Select Health of South Carolina will update its clinical policies as necessary. Select Health of South Carolina’s clinical policies are not guarantees of payment.

Coverage policy

Select Health of South Carolina considers the use of alemtuzumab as induction therapy in lung transplantation to be investigational and, therefore, not medically necessary (Saldanha, 2015; Penninga, 2013).

Limitations:

This policy does not address alemtuzumab as treatment for B-cell chronic lymphocytic leukemia, multiple sclerosis, or other solid organ transplantation.

Effective September 4, 2012, alemtuzumab, marketed as Campath® (Genzyme Corporation, Cambridge, Massachusetts), is no longer available commercially and therefore is not eligible for reimbursement. It may be provided through the Campath Distribution Program free of charge. Please contact the manufacturer.

Alternative covered services:

Conventional maintenance immunosuppression comprising anti-proliferative agents, calcineurin inhibitors, and corticosteroids.
Background

Lung transplantation is a treatment of last resort for end-stage lung disease. The most common indications for lung transplantation are advanced chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), cystic fibrosis (CF), emphysema due to alpha-1 antitrypsin deficiency, and pulmonary arterial hypertension (PAH) (Yusen, 2015).

In the United States, 2,327 lung transplantations were performed in 2016 (Organ Procurement and Transplant [OPTN], 2017). Among those age 12 and older, 57.1 percent of transplants were performed for a diagnosis of a restrictive lung disease, 26.1 percent were performed on those with an obstructive lung disease, 12.0 percent were performed on those with cystic fibrosis, and 4.0 percent were performed for pulmonary vascular disease (Valipour, 2018). For persons with cystic fibrosis, contemporary registry analyses have confirmed a survival disadvantage among children compared to adults after lung transplantation (Hayes, 2016; Moreno, 2016). While the proportion of lung transplantations performed for cystic fibrosis has decreased significantly over time, especially in pediatric patients, proportions are increasing in patients who are older and more clinically ill (Kinmura, 2016; Moreno, 2016).

Acute and chronic allograft rejection limit long-term graft and patient survival, with a median survival of approximately six years after lung transplantation (Yusen, 2015). Immunosuppressive regimens, consisting of maintenance and induction therapies, are used to reduce graft failure. Conventional maintenance immunosuppression is lifelong therapy comprising anti-proliferative agents, calcineurin inhibitors, and corticosteroids. These drugs primarily target T-cell activation and proliferation involved in cell-mediated rejection, but they are associated with serious adverse effects, including drug-specific toxicities, opportunistic infections, and malignancy (Scheffert, 2014; Yusen, 2015).

Approximately 50 percent of lung transplant centers use induction therapy (Scheffert, 2014). Induction therapy is intensive immunosuppressant therapy given peri-operatively to cause significant T-cell depletion immediately after transplantation. The aim of induction therapy is to reduce the risk of acute rejection and delay initiation of maintenance therapy following transplantation, particularly the nephrotoxic calcineurin inhibitors. Induction therapy is usually administered for a short period of time to avoid risks of severe infection and sepsis. Drugs used in induction immunosuppression after lung transplantation include polyclonal antibody preparations (anti-thymocyte globulin), interleukin 2 receptor antagonists (daclizumab or basiliximab), or alemtuzumab (Scheffert, 2014).

Alemtuzumab:

Alemtuzumab is a recombinant humanized monoclonal antibody that binds to the CD52 glycoprotein located on the cell surface of mature T-lymphocytes and B-lymphocytes. The mechanism of action is believed to recruit antibodies that target and destroy the CD52-bearing lymphocytes treated with alemtuzumab, thereby depleting circulating T- and B-cells and improving graft survival. Originally, the U.S. Food and Drug Administration (FDA) approved alemtuzumab as Campath in 2001 for treatment of B-cell
chronic lymphocytic leukemia (FDA, 2016). Campath was discontinued commercially in 2012, but remains available through the Campath Distribution Program free of charge (Campath, 2016).

In 2014, the FDA approved alemtuzumab as Lemtrada™ (Genzyme Corporation, Cambridge, Massachusetts) for treatment of individuals with relapsing forms of multiple sclerosis who have had an inadequate response to two or more drugs indicated for the treatment of multiple sclerosis (FDA, 2016). Its mechanism of action may have value as an immunosuppressive agent in solid organ transplantation. Alemtuzumab as induction therapy in lung transplant recipients is an off-label use.

**Searches**

Select Health of South Carolina searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on December 28, 2017. Search terms were: "Lung Transplantation" (MeSH), "alemtuzumab" (Supplementary Concept), and free text terms "alemtuzumab induction" and "lung transplant."

We included:
- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

We found two Cochrane reviews for this policy (Saldanha, 2015; Penninga, 2013). Neither review identified any randomized controlled trials (RCTs) of alemtuzumab as induction therapy in lung transplantation recipients. Results from individual retrospective cohort studies and registry analyses provide conflicting evidence of the relative safety and efficacy of alemtuzumab induction therapy in this population (Kirby, 2015; Whited, 2015; Hayes, 2014; Jaksch, 2014; Wehman, 2013; Shyu, 2011).

Several risk factors are significantly associated with mortality during the first post-transplant year. These risk factors include recipient age; severity of illness and cytomegalovirus status of the recipient; indication for transplant; era in which the transplant was performed; and type of transplant (Yusen, 2015).
Retrospective analyses failed to account for these factors in their analyses, which may contribute to the variability in outcomes. Therefore, there is insufficient evidence to determine the safety or efficacy of alemtuzumab as induction therapy in lung transplantation recipients. Robust RCTs are needed to assess the role of alemtuzumab compared to no induction therapy or to other induction therapy agents.

In the February 2018 update, one website was added to the professional guidelines/other section. Two publications were added to the peer-reviewed reference list, one of which was added to the Summary of Clinical evidence.

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tbody>
<tr>
<td><strong>Benden (2017)</strong></td>
<td><strong>Key points:</strong></td>
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</tbody>
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| Therapy options for chronic lung allograft dysfunction–bronchiolitis obliterans syndrome following first-line immunosuppressive strategies | - This systematic review examined the context of immunosuppressive treatment, which included extracorporeal photopheresis, aerosolized cyclosporine, total lymphoid irradiation, alemtuzumab, and montelukast for the treatment of chronic lung allograft dysfunction-bronchiolitis obliterans syndrome.  
  - There were a total of 40 studies, which generated 47 publications.  
  - Most of the included study designs had features that did not prevent bias; i.e., they were uncontrolled and retrospective.  
  - Compared with standard therapy alone, improved lung function and survival was reported for extracorporeal photopheresis in two studies that weren’t randomized. The authors found lower-quality evidence for improved lung function for total lymphoid irradiation, montelukast, and aerosolized cyclosporine. |
| **Saldanha (2015)**       | **Key points:**                                                                                    |
| Cochrane review           | - Systematic review found no RCTs or quasi-randomized studies that met inclusion criteria.          |
| Immunosuppressive drug therapy for preventing rejection following lung transplantation in CF | - Insufficient evidence to compare efficacy and safety of the various immunosuppressive drugs among people with CF after lung transplantation. |
| **Penninga (2013)**       | **Key points:**                                                                                    |
| Cochrane review           | - Systematic review and meta-analysis of six RCTs (278 total adult lung transplantation recipients) that assessed T-cell antibody induction.  
  - Overall quality: low with high risk of bias and limited numbers of subjects.  
  - No evidence for alemtuzumab from RCTs found.  
  - For other induction therapies, there was no significant difference in mortality, acute rejection, adverse effects, infection, pneumonia, cytomegalovirus infection, bronchiolitis obliterans syndrome, post-transplantation lymphoproliferative disease, or cancer.  
  - Robust assessments from RCTs are needed. |

**References**

**Professional society guidelines/other:**

Drugs@FDA: FDA Approved Drug Products searched using term Alemtuzumab. FDA website. 


Peer-reviewed references:


**CMS National Coverage Determinations (NCDs):**

No NCDs were identified as of the writing of this policy. Several policy articles were found.


Local Coverage Determinations (LCDs):

A55310 Billing and Coding Instructions for Lemtrada® (ALEMTUZUMAB) When Used in the Treatment of Relapsing Multiple Sclerosis. [https://www.cms.gov/medicare-coverage-database/details/article-details.aspx?articleId=55310&ver=4&CoverageSelection=Local&ArticleType=All&PolicyType=Final&s=All&KeyWord=alemtuzumab&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAAACAAAAA&](https://www.cms.gov/medicare-coverage-database/details/article-details.aspx?articleId=55310&ver=4&CoverageSelection=Local&ArticleType=All&PolicyType=Final&s=All&KeyWord=alemtuzumab&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAAACAAAAA&). Accessed December 28, 2017.

Commonly submitted codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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