Extracorporeal Photopheresis

Extracorporeal photopheresis is a treatment of white blood cells. Blood is withdrawn and a specialized machine separates the whole blood into its different components — red blood cells, white blood cells, platelets, and plasma. White blood cells are kept back and the rest of the blood is returned to the patient. The white blood cells are mixed with medication that makes them sensitive to ultraviolet light. After being exposed to ultraviolet light, the white blood cells are returned to the patient. White blood cells are part of the immune system, and treating them in this way stimulates the immune system. High quality medical studies have shown this technique is successful in treating a number of conditions. These include organ rejection after a heart transplant, graft-versus-host disease, and cutaneous T-cell lymphoma in certain situations. It has also been proposed to treat a number of autoimmune conditions, like Crohn disease or multiple sclerosis. Because more medical studies are needed to show if it works for other conditions, using this technique for autoimmune conditions is investigational (unproven).

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
## Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Indication</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organ rejection after solid organ transplant</strong></td>
<td>Extracorporeal photopheresis may be considered medically necessary to treat cardiac allograft rejection, including acute rejection, that is either recurrent or that is refractory to standard immunosuppressive drug treatment. Extracorporeal photopheresis is considered investigational in all other situations related to treatment or prevention of rejection in solid organ transplantation.</td>
</tr>
</tbody>
</table>
| **Graft-versus-host disease** | Extracorporeal photopheresis may be considered medically necessary as a technique to treat:  
- Acute graft-versus-host disease (GVHD) that is refractory to medical therapy  
- Chronic GVHD that is refractory to medical therapy  
Extracorporeal photopheresis is considered investigational as a technique to treat acute GVHD or chronic GVHD that is either previously untreated or is responding to established therapies. |
| **Cutaneous T-cell lymphoma** | Extracorporeal photopheresis may be considered medically necessary as a technique to treat:  
- Late stage (III/IV) cutaneous T-cell lymphoma  
- Early stage (I/II) cutaneous T-cell lymphoma that is progressive and refractory to established nonsystemic therapies  
Extracorporeal photopheresis is considered investigational as a technique to treat early stage (I/II) cutaneous T-cell lymphoma that is either previously untreated or responsive to established nonsystemic therapies. |
<p>| <strong>Autoimmune diseases</strong> | Extracorporeal photopheresis is considered investigational as a technique to treat either the cutaneous or visceral manifestations of autoimmune diseases, including but not limited to: |</p>
<table>
<thead>
<tr>
<th>Indication</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Autoimmune bullous disorders</td>
</tr>
<tr>
<td></td>
<td>• Crohn disease</td>
</tr>
<tr>
<td></td>
<td>• Diabetes</td>
</tr>
<tr>
<td></td>
<td>• Multiple sclerosis</td>
</tr>
<tr>
<td></td>
<td>• Pemphigus</td>
</tr>
<tr>
<td></td>
<td>• Psoriasis</td>
</tr>
<tr>
<td></td>
<td>• Rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td>• Scleroderma</td>
</tr>
<tr>
<td></td>
<td>• Severe atopic dermatitis</td>
</tr>
<tr>
<td></td>
<td>• Systemic lupus erythematosus</td>
</tr>
</tbody>
</table>

**Other**

Extracorporeal photopheresis is considered investigational for all other indications.

**Documentation Requirements**

The patient’s medical records submitted for review should document that medical necessity criteria are met. The record should include clinical documentation of:

- Diagnosis/condition
- History and physical examination documenting the severity of the condition
- The medical therapy that has been attempted

**Coding**

<table>
<thead>
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<th>Code</th>
<th>Description</th>
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<td>CPT</td>
<td></td>
</tr>
<tr>
<td>36522</td>
<td>Photopheresis, extracorporeal</td>
</tr>
</tbody>
</table>

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

**Related Information**
Organ Rejection after Solid Organ Transplant

A regimen of immunosuppressive therapy is standard of care for the treatment of solid organ rejection. Therefore, refractory rejection is defined as rejection that fails to adequately respond to a standard regimen of immunosuppressive therapy.

Recurrent allograft rejection is defined as having at least 2 rejection episodes after standard immunosuppressive therapy.

There is no standard schedule for extracorporeal photopheresis (ECP) and reported schedules vary by the organ type. However, most reported cardiac and lung schedules initiate therapy with two consecutive days of ECP in month 1, followed by biweekly therapy on two consecutive days in months 2 and 3, then monthly on two consecutive days in months 4 through 6.

Graft-Versus-Host Disease

Methylprednisolone is considered first-line treatment of acute graft-versus-host disease (GVHD). For chronic GVHD, an alternating regimen of cyclosporine and prednisone is commonly used; other therapies include antithymocyte globulin, corticosteroid monotherapy, and cytotoxic immunosuppressive drugs such as procarbazine, cyclophosphamide, or azathioprine. Therefore, refractory disease is defined as GVHD that fails to respond adequately to a trial of any of these therapies.

Treatment schedule and duration of ECP for GVHD have not been optimally defined. Guidelines and consensus statements have generally recommended 1 cycle (ie, ECP on two consecutive days) weekly for acute GVHD and every 2 weeks for chronic GVHD. Treatment duration is based on clinical response (see Practice Guidelines and Position Statements section); discontinuation is generally recommended for no or minimal response.

Cutaneous T-Cell Lymphoma Staging

Cutaneous T-cell lymphoma staging is based on the tumor, node, metastases (TNM) classification system (see Table 1).
Table 1. Cutaneous T-cell Lymphoma Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor T, N, and M Categories</th>
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</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1N0M0</td>
</tr>
<tr>
<td>IB</td>
<td>T2N0M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T1-2N1M1</td>
</tr>
<tr>
<td>IIB</td>
<td>T3N0-1M0</td>
</tr>
<tr>
<td>III</td>
<td>T4N0-1M0</td>
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<tr>
<td>IVA</td>
<td>T1-4N2-3M0</td>
</tr>
<tr>
<td>IVB</td>
<td>T1-4N0-3M1</td>
</tr>
</tbody>
</table>

**Sézary Syndrome**

According to the World Health Organization–European Organization for Research and Treatment of Cancer, Sézary syndrome is defined by the triad of erythroderma, generalized lymphadenopathy, and the presence of neoplastic T cells (Sézary cells) in the skin, lymph nodes, and peripheral blood. The International Society of Cutaneous Lymphomas recommends an absolute Sézary cell count of at least 1000 cells per cubic millimeter, in the presence of immunophenotypical abnormalities (CD4/CD8 ratio >10; loss of any or all of the T-cell antigens CD2, CD3, CD4, and CD5; or both), or the demonstration of a T-cell clone in the peripheral blood by molecular or cytogenetic methods.

**Benefit Application**

Refer to contract or benefit language for specific language regarding extracorporeal photopheresis and chronic graft versus host disease.

**Evidence Review**
Description

Extracorporeal photopheresis (ECP) is a leukapheresis-based immunomodulatory procedure that involves the following three steps:

- Patient blood is collected into a centrifuge system that separates the leukocyte-rich portion (buffy coat) from the rest of the blood.
- The photosensitizer agent 8-methoxypsoralen is added to the lymphocyte fraction, which is then exposed to ultraviolet A (320-400 nm wavelength) light at a dose of 1-2 J/cm².
- The light-sensitized lymphocytes are reinfused into the patient.

The use of ECP has been investigated for patients needing treatment for organ rejection after solid organ transplant, graft-versus-host disease (GVHD), autoimmune diseases, and T-cell lymphoma.

Background

Organ Rejection Treatment after Solid Organ Transplant

The standard treatment for organ transplant rejection is immunosuppression, with the particular regimen dictated by the organ being transplanted. As organ transplantation success rates have improved, more patients are facing the morbidity and mortality associated with immunosuppressive therapies developed to prevent rejection of the transplanted organ. Immunosuppressive therapies are used to lower the responsiveness of the recipient’s immune system, decreasing the chance of rejection. Unfortunately, portions of the immune system responsible for the prevention of viral, fungal, and bacterial infection also are affected. This can, in turn, lead to serious infections, including opportunistic infections.

Although first approved for the treatment of cutaneous T-cell lymphoma (CTCL), extracorporeal photopheresis (ECP) has more recently been used as a supplement to conventional therapies in the area of solid organ transplantation. Reports of the successful use of ECP in human cardiac transplant recipients were published in 1992 and use in other transplant patients followed. Although the specific mechanism of action of ECP is unknown, the reinfusion of treated leukocytes seems specifically to suppress the patient’s immune response to the donor organ, although maintaining the body's ability to respond to other antigens. The specificity of ECP to target the immune response to the transplanted organ allows ECP to decrease organ rejection without the increased risk of infection, common with immunosuppressive drugs.
**Graft-Versus-Host Disease**

Given that graft-versus-host disease (GVHD) is an immune mediated disease, ECP can be used to treat GVHD after a prior allogeneic cell transplant. In fact, GVHD can be categorized in two ways: (1) as an acute disease, occurring within the first 100 days after infusion of allogeneic cells; or (2) as a chronic disease, which develops sometime after 100 days. Acute GVHD is commonly graded from I to IV, ranging from mild disease, which is characterized by a skin rash without involvement of the liver or gut, to grades III and IV, which are characterized by generalized erythroderma, elevated bilirubin levels, or diarrhea. Grade III acute GVHD is considered severe, and grade IV is considered life-threatening. Chronic GVHD typically presents with more diverse symptomatology resembling autoimmune diseases such as progressive systemic sclerosis, systemic lupus erythematosus, or rheumatoid arthritis. Chronic GVHD may affect the mouth, eyes, respiratory tract, musculoskeletal system, and peripheral nerves, as well as the skin, liver, or gut — the usual sites of acute GVHD.

**Autoimmune Disease**

The use of ECP as a treatment of autoimmune disease is based on the premise that pathogenic lymphocytes form an expanded clone of cells, which are damaged when exposed to ultraviolet light in the presence of agent 8-methoxypsoralen. It is hypothesized that the resulting damage induces a population of circulating suppressor T-cells targeted against the light-damaged cells. It is further hypothesized that these suppressor T-cells are targeted at a component of the cell that is common to the entire clone of abnormal cells (i.e., not just the light-sensitized cells), thus inducing a systemic effect. However, although scleroderma and other autoimmune diseases are associated with the presence of circulating autoantibodies, it is unknown how these antibodies are related to the pathogenesis of the disease. As discussed in this policy, photopheresis is not associated with consistent changes in autoantibody levels.

**T-Cell Lymphoma**

**Cutaneous T-Cell Lymphoma**

According to the National Cancer Institute, CTCL is a neoplasm of malignant T lymphocytes that initially presents as skin involvement. CTCL is extremely rare, with an estimated incidence of approximately 0.4 per 100,000 annually, but because most are low-grade malignancies with long
survival, overall prevalence is much higher. Two CTCL variants, mycosis fungoides and the Sézary syndrome, account for approximately 60% and 5% of new cases of CTCL, respectively.

CTCL is included in the Revised European-American Lymphoma classification as a group of low-grade T-cell lymphomas. They are distinguished from other T-cell lymphomas that involve the skin such as anaplastic large cell lymphoma, peripheral T-cell lymphoma, adult T-cell leukemia/lymphoma (usually with systemic involvement), and subcutaneous panniculitis T-cell lymphoma. In addition, a number of benign or very indolent conditions can be confused with mycosis fungoides, further complicating diagnosis.

Mycosis fungoides typically progresses from an eczematous patch/plaque stage, covering less than 10% of the body surface (T1), to a plaque stage, covering 10% or more of the body surface (T2), and finally to tumors (T3) that frequently undergo necrotic ulceration. Sézary syndrome is an advanced form of mycosis fungoides with generalized erythroderma (T4) and peripheral blood involvement (B1) at presentation. The cytologic transformation from a low-grade lymphoma to a high-grade lymphoma sometimes occurs during the course of these diseases and is associated with poor prognosis. A common cause of death during the tumor phase is sepsis from Pseudomonas aeruginosa or Staphylococcus aureus caused by chronic skin infection with staphylococcus species and subsequent systemic infections.

The natural history of mycosis fungoides is typically indolent. Symptoms may present for long periods (mean, 2-10 years) as waxing and waning cutaneous eruptions. The prognosis of patients with mycosis fungoides or Sézary syndrome is based on the extent of disease at presentation and its stage. Lymphadenopathy and involvement of peripheral blood and viscera increase in likelihood with worsening cutaneous involvement and define poor prognostic groups. Median survival after diagnosis varies according by stage. Median survival in patients with stage IA disease exceeds 20 years, with most deaths in this group typically unrelated to mycosis fungoides. In contrast, median survival in patients with stage III or IV disease is less than 5 years; more than 50% of these patients die of their disease.

Appropriate therapy of CTCL depends on a variety of factors, including stage, the patient’s overall health, and the presence of symptoms. In general, therapies can be categorized into topical and systemic treatments that include ECP. In contrast to more conventional lymphomas, CTCL is usually not curable (unless caught in its earliest stages). Thus, systemic cytotoxic chemotherapy is avoided except for advanced stage cases. Partial or complete remission is achievable, although most patients require lifelong treatment and monitoring.
Summary of Evidence

Organ Rejection after Solid Organ Transplant

Heart Transplant

For individuals who are heart transplant recipients who experience acute graft rejection refractory to immunosuppression who receive ECP, the evidence includes a small RCT. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. The small RCT, while suggesting similar outcomes for ECP and corticosteroids, is insufficient to permit conclusions on the utility of ECP. Studies with more patients and longer follow-up are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are heart transplant recipients who experience recurrent and/or refractory graft rejection who receive ECP, the evidence includes a comparative study and small case series. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Current evidence is consistent on the beneficial effect of ECP for cardiac transplant patients with graft rejection refractory to standard therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are heart transplant recipients who require prophylaxis to prevent graft rejection who receive ECP, the evidence includes a small RCT. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. The small randomized trial is insufficient to permit conclusions on the utility of ECP. Studies with more patients and longer follow-up are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Lung Transplant

For individuals who are lung transplant recipients who experience acute graft rejection who receive ECP, the evidence includes a small retrospective study and small case series. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Current evidence is very limited and any conclusions drawn lack certainty. A prospective, randomized trial is needed specifically evaluating the treatment of patients with acute graft rejection. The evidence is insufficient to determine the effects of the technology on health outcomes.
For individuals who are lung transplant recipients with BOS refractory to corticosteroids who receive ECP, the evidence includes a prospective study and numerous retrospective analyses. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Studies have shown inconsistent results across BOS grades. Prospective, RCTs are necessary with analyses stratified by syndrome grade. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Liver Transplant**

For individuals who are liver transplant recipients who experience graft rejection and receive ECP, the evidence includes a small nonrandomized study, a retrospective study, and a case series. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Current evidence does not permit conclusions on the utility of ECP in this population. There is a need for RCTs comparing immunosuppressive therapy alone with immunosuppressive therapy with ECP. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Kidney Transplant**

For individuals who are kidney transplant recipients who experience recurrent graft rejection who receive ECP, the evidence includes a small prospective study and numerous case reports. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Current evidence does not permit conclusions on the effect of ECP on net health outcome. RCTs, comparing immunosuppressive therapy with immunosuppressive therapy using ECP and examining histologic confirmation of treatment response, are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Graft-Versus-Host Disease**

For individuals who have acute or GVHD refractory to medical treatment who receive ECP, the evidence includes systematic reviews, retrospective studies, and case series. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Current evidence has consistently shown that ECP reduces the incidence of GVHD that is unresponsive to standard therapy. Additionally, there is a lack of other treatment options for these patients; adverse events related to ECP are minimal; and, if there is a response to ECP,
patients may be able to reduce or discontinue treatment with corticosteroids and other immunosuppressive agents. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Clinical input obtained in 2014 supported the use of ECP in patients with refractory acute GVHD.

**Autoimmune Disease**

For individuals who have autoimmune diseases (eg, cutaneous or visceral manifestations of autoimmune diseases including but not limited to scleroderma, systemic lupus erythematosus, rheumatoid arthritis, pemphigus, psoriasis, multiple sclerosis, diabetes, autoimmune bullous disorders, severe atopic dermatitis, and Crohn disease) who receive ECP, the evidence includes isolated RCTs, small prospective and retrospective studies, and case reports. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. The current literature assessing the various autoimmune diseases is not sufficiently robust to support conclusions. The evidence is insufficient to determine the effects of the technology on health outcomes.

**T-Cell Lymphoma**

For individuals who have advanced-stage (stage III or IV) CTCL who receive ECP, the evidence includes a systematic review and numerous small case series. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Evidence from these small case series has shown a favorable response to ECP treatment and an increase in survival in a proportion of these patients. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have refractory or progressive early-stage (stage I or II) CTCL who receive ECP, the evidence includes a systematic review. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Given the unfavorable prognosis for patients with early-stage CTCL that progresses on nonsystemic therapies, the relative lack of adverse events with ECP compared with other systemic treatments, and the good response rates often observed with ECP, this therapy is an option for those with refractory or progressive early-stage CTCL. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.
Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this policy are listed in **Table 2**.

### Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Graft-versus-host disease</strong></td>
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<tr>
<td>NCT00637689</td>
<td>Improving Outcomes Assessment in Chronic GVHD</td>
<td>601</td>
<td>Feb 2020</td>
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<tr>
<td>NCT01460914</td>
<td>Outcomes of Cutaneous T-Cell Lymphoma and Chronic Graft-Versus-Host Disease in Patients Treated with Extracorporeal Photopheresis</td>
<td>100</td>
<td>Oct 2050</td>
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<td><strong>Autoimmune disorders</strong></td>
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<tr>
<td>NCT02296346a</td>
<td>Open-Label Study to Evaluate the Efficacy of ECP in Secondary Progressive Multiple Sclerosis</td>
<td>66</td>
<td>Oct 2017 (suspended)</td>
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<td><strong>T-cell lymphoma</strong></td>
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<tr>
<td>NCT01460914</td>
<td>Outcomes of Cutaneous T-Cell Lymphoma and Chronic Graft-Versus-Host Disease in Patients Treated with Extracorporeal Photopheresis</td>
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<tr>
<td><strong>Unpublished</strong></td>
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<td></td>
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<tr>
<td><strong>Solid organ transplants</strong></td>
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<tr>
<td>NCT01824368</td>
<td>Extracorporeal Photopheresis in Liver Transplantation. Phase 2 Clinical Trial in Safety and Efficacy in Patients With Gradual Decrease of Immunosuppression (FEC-TH)</td>
<td>10</td>
<td>Apr 2016 (completed)</td>
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<td><strong>Graft-versus-host disease</strong></td>
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<tr>
<td>NCT01380535a</td>
<td>A Randomized Controlled Study of Extracorporeal Photopheresis (ECP) Therapy With UVADEX for the Treatment of Patients With Moderate to Severe Chronic Graft-versus-Host Disease (cGvHD)</td>
<td>60</td>
<td>Mar 2017 (completed)</td>
</tr>
<tr>
<td>NCT00609609</td>
<td>A Randomized Phase 2 Study for the Evaluation of Extracorporeal Photopheresis (ECP) in Combination With Corticosteroids for the Initial Treatment of Acute Graft-Versus-Host Disease (GVHD)</td>
<td>81</td>
<td>Jan 2016 (completed)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.
Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received through two academic medical centers and 5 Blue Distinction Centers for Transplant when this policy was under review in 2014. Respondents agreed unanimously that extracorporeal photopheresis should not be medically necessary for previously untreated acute graft-versus-host disease but should be medically necessary for acute graft-versus-host disease that is refractory to medical therapy.

Practice Guidelines and Position Statements

**Graft Versus Host Disease**

**Acute GVHD**

**UK Photopheresis Society**

An evidence-based consensus statement from the UK Photopheresis Society (2014) recommended ECP as second-line therapy in combination with other agents for patients with steroid-refractory, steroid-dependent, or steroid-intolerant grade II, III, or IV acute graft-versus-host disease (GVHD).\(^75\)

**American Society of Blood and Marrow Transplantation**

Evidence-based recommendations from the American Society of Blood and Marrow Transplantation (2012) advised that ECP cannot be considered superior to horse antithymocyte globulin for treatment of acute GVHD.\(^76\) This conclusion was based on older studies.\(^43,77\)
Acute GVHD and Chronic GVHD

British Committee for Standards in Haematology et al

Evidence-based guidelines from the British Committee for Standards in Haematology and the British Society for Bone Marrow Transplantation (2012) recommend ECP in acute GVHD as a second-line treatment for steroid-refractory disease\(^7\)\(^8\) and in chronic GVHD as a second-line treatment for skin, oral, or liver involvement.\(^7\)\(^9\)

Italian Society of Hemapheresis and Cell Manipulation et al

A nine-member panel representing the Italian Society of Hemapheresis and Cell Manipulation and the Italian Group for Bone Marrow Transplantation (2013) published consensus recommendations for ECP in adults and children with acute GVHD or chronic GVHD.\(^8\)\(^1\) The panel recommended ECP for treatment of acute GVHD in adults and children who are nonresponsive to steroids or calcineurin inhibitors or have contraindications to immunosuppressive therapy because of viral reactivation or other infectious complication (“better results are expected in patients with isolated skin involvement”) and for treatment of chronic GVHD in adults and children who are steroid-resistant or steroid-dependent.

National Cancer Institute

In its guideline on childhood hematopoietic cell transplantation, the National Cancer Institute listed ECP as a second-line treatment for patients with acute GVHD resistant to first-line methylprednisolone.\(^8\)\(^2\) For chronic GVHD therapy, the guidelines recommended that steroids are first-line therapy, but steroid-sparing approaches, including ECP, are being developed. In this setting, ECP has shown “some efficacy in a percentage of patients.”

Cancer Care Ontario

Cancer Care Ontario (2014) published evidence-based consensus guidelines on ECP for GVHD.\(^8\)\(^3\) ECP was recommended as “an acceptable therapy for the treatment of steroid-dependent or refractory acute GVHD in adult and pediatric patients” and for “steroid-dependent or refractory chronic GVHD in adult and pediatric patients.” The strength of the recommendations was not graded.
**T-Cell Lymphoma**

**National Comprehensive Cancer Network**

National Comprehensive Cancer Network guidelines on T-cell lymphomas (v.5.2018) lists the use of ECP as a category A treatment alone or in combination with other agents as first-line systemic therapy for advanced (stages III-IV) disease, as well as for patients with either earlier stage mycosis fungoides with Sézary syndrome involvement.84

**Medicare National Coverage**

**Solid-Organ Transplants**

Effective 2006, the Centers for Medicare and Medicaid Services (CMS) concluded that ECP is reasonable and necessary for persons with “acute cardiac allograft rejection whose disease is refractory to standard immunosuppressive drug treatment”.85

Effective 2012, CMS also provided coverage for ECP for the treatment of “bronchiolitis obliterans syndrome (BOS) following lung allograft transplantation only when extracorporeal photopheresis is provided under a clinical research study” that meets certain conditions.85

**Graft Versus Host Disease**

Effective 2006, CMS provided coverage of ECP for patients with chronic GVHD “whose disease is refractory to standard immunosuppressive drug treatment.”85

**Autoimmune Disorders**

There are no national coverage decisions on the use of ECP for the treatment of autoimmune disease.

**T-Cell Lymphoma**

Effective 1988, CMS provided coverage for ECP as “palliative treatment of skin manifestations of cutaneous T-cell lymphoma that has not responded to other therapy.”85
Regulatory Status

Two photopheresis systems (Therakos; now Mallinckrodt) were approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process. Both systems are approved for use in ultraviolet-A irradiation treatment, in the presence of the photoactive drug 8-methoxypsoralen, of extracorporeally circulating leukocyte-enriched blood, in the palliative treatment of skin manifestations of CTCL, in persons who have not been responsive to other forms of treatment. The two systems are:

- **UVAR® XTS Photopheresis System** (FDA-approved in 1987)
- **CELLEX®** (FDA approved in 2009)

Photoactive 8-methoxypsoralen (UVADEX®) is FDA-approved for extracorporeal administration with the UVAR® XTS or CELLEX® Photopheresis System in the palliative treatment of the skin manifestations of CTCL unresponsive to other forms of treatment.

The use of either Therakos photopheresis system or UVADEX® for other conditions is off-label.

FDA product code: LNR.

References


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/16/00</td>
<td>Add to Therapy Section - New Policy.</td>
</tr>
<tr>
<td>01/08/02</td>
<td>Replace Policy - Revised; added information on photopheresis for graft vs. host disease; considered medically necessary for chronic disease.</td>
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<tr>
<td>05/11/04</td>
<td>Replace Policy - Policy reviewed; literature updated; no change in policy statement.</td>
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<td>06/14/05</td>
<td>Replace Policy - Policy reviewed with literature search; no change in policy statement.</td>
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<tr>
<td>06/16/06</td>
<td>Replace Policy - Policy updated with literature search; policy statement unchanged. Scope and Disclaimer updated.</td>
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<td>01/08/08</td>
<td>Replace Policy - Policy updated with literature search; no change in policy statement. &quot;Extracorporeal&quot; added to the title. References and code added.</td>
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<td>Minor Updates - Spelling Corrected.</td>
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<td>06/09/09</td>
<td>Replace Policy - Policy updated with literature search. Three new policy statements for CTCL added (two medically necessary statements). Title changed to reflect cutaneous T-cell lymphoma (CTCL) indication. References added. Policy reviewed and recommended by Oncology Advisory Panel on May 21, 2009. OAP recommended removing chronic from first policy statement.</td>
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<td>02/09/10</td>
<td>Replace Policy - Policy updated with literature search. Policy statement minor update &quot;chronic&quot; added to medically necessary statement, no other changes. References added.</td>
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<td>06/10/10</td>
<td>Delete Policy - Policy deleted from active status.</td>
</tr>
<tr>
<td>11/09/10</td>
<td>Reinstate Policy - Policy reinstated. Requests are being received.</td>
</tr>
<tr>
<td>03/08/11</td>
<td>Replace Policy - Policy updated with literature search; reference numbers 8, 9 and 17 added; autoimmune bullous disorders added as investigational. No other changes to policy statements.</td>
</tr>
<tr>
<td>05/12/11</td>
<td>Reviewed by OAP - No changes recommend to the policy.</td>
</tr>
<tr>
<td>04/10/12</td>
<td>Replace policy. Policy updated with literature search; reference numbers 8, 9, 17 and 28 added; autoimmune bullous disorders added as investigational; no other changes to policy statements. Policy 8.01.51 (Extracorporeal Photopheresis as Treatment for and Prevention of Organ Rejection after Solid-Organ Transplant) combined with this policy; 8.01.51 deleted as a separate policy. Title changed to reflect combined policies</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
<td>-------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>09/10/12</td>
<td>and coding updated.</td>
</tr>
<tr>
<td>09/21/12</td>
<td>Update Coding Section – ICD-10 codes are now effective 10/01/2014.</td>
</tr>
<tr>
<td>02/12/13</td>
<td>Update Related Policies, change title on Policy 8.02.02.</td>
</tr>
<tr>
<td>04/08/13</td>
<td>Replace policy. Policy updated with literature search; policy statement added that ECP is investigational for any other indications; references 6, 15, 60, 61, 62 added. Title changed to “Extracorporeal Photopheresis”.</td>
</tr>
<tr>
<td>03/11/14</td>
<td>Coding Update. Code 99.88 was removed per ICD-10 mapping project; this code is not utilized for adjudication of policy.</td>
</tr>
<tr>
<td>07/14/14</td>
<td>Annual Review. Policy updated with literature review through April 16, 2014; references 15, 35-36, 39, 43-45, 51-56, 65-68, 70, and 84 added; references 6, 29, 37, and 78 updated. Clinical input reviewed. New policy statement added that ECP is medically necessary in refractory acute graft-versus-host disease. For autoimmune diseases, Investigational policy statement updated to include severe atopic dermatitis and Crohn disease; no other changes to policy statements.</td>
</tr>
<tr>
<td>06/17/15</td>
<td>Annual Review. Policy updated with literature review through March 2, 2015; references 11, 39-40, 43, 49, 54, and 63 added. Policy statements unchanged. Benefit Application clarified. ICD-9 and ICD-10 diagnosis and procedure codes removed; these do not facilitate adjudication.</td>
</tr>
<tr>
<td>01/01/18</td>
<td>Annual Review, approved December 6, 2017. Policy updated with literature review through August 2017; no references added. Policy statement unchanged.</td>
</tr>
<tr>
<td>11/01/18</td>
<td>Minor update, removed 8.02.02 from related policies as it was archived.</td>
</tr>
<tr>
<td>01/01/19</td>
<td>Annual Review, approved December 19, 2018. Policy updated with literature review through August 2018; no references added. Policy statement unchanged.</td>
</tr>
<tr>
<td>04/01/19</td>
<td>Minor update, added Documentation Requirements section.</td>
</tr>
</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2019 Premera All Rights Reserved.

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PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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