

## MEDICAL POLICY – 8.01.36

# Extracorporeal Photopheresis

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Effective Date: Jan. 1, 2025

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Replaces: 8.01.501

RELATED MEDICAL POLICIES:

5.01.532 Cutaneous T-Cell Lymphomas (CTCL): Systemic Therapies

Select a hyperlink below to be directed to that section.

[POLICY CRITERIA](#) | [DOCUMENTATION REQUIREMENTS](#) | [CODING](#)  
[RELATED INFORMATION](#) | [EVIDENCE REVIEW](#) | [REFERENCES](#) | [HISTORY](#)

 Clicking this icon returns you to the hyperlinks menu above.

## Introduction

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 Blood is withdrawn and a specialized machine separates the whole blood into its different components — red blood cells, white blood, cells, platelets, and plasma.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 individual. 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 individual. 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

Indication	Medical Necessity
<p><b>Organ rejection after solid organ transplant; example:</b></p> <ul style="list-style-type: none"> <li>• Heart</li> <li>• Lung</li> <li>• Liver</li> <li>• Kidney</li> </ul>	<p><b>Extracorporeal photopheresis may be considered medically necessary to treat cardiac allograft rejection when ONE of the following criteria is met:</b></p> <ul style="list-style-type: none"> <li>• There is acute* rejection that is <u>refractory</u> to standard immunosuppressive drug treatment (see <a href="#">Related Information</a>);</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>• There is <u>recurrent</u> graft rejection (see <a href="#">Related Information</a>)</li> </ul> <p><b>Extracorporeal photopheresis is considered investigational for the prophylactic prevention of rejection after cardiac transplantation</b></p> <p><b>Extracorporeal photopheresis is considered investigational in all other situations related to treatment or prevention of rejection in solid organ transplantation (e.g., lung**, liver, kidney).</b></p> <p><b>Note:</b> *Rejection is considered acute when occurring within the first 100 days after transplantation</p> <p><b>Note:</b> **This includes development of bronchiolitis obliterans syndrome</p>
<p><b>Graft-versus-host disease</b></p>	<p><b>Extracorporeal photopheresis may be considered medically necessary as a technique to treat:</b></p> <ul style="list-style-type: none"> <li>• Acute graft-versus-host disease (GVHD) that is refractory to medical therapy</li> <li>• Chronic GVHD that is refractory to medical therapy</li> </ul> <p><b>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.</b></p>
<p><b>Cutaneous T-cell lymphoma</b></p>	<p><b>Extracorporeal photopheresis may be considered medically necessary as a technique to treat:</b></p> <ul style="list-style-type: none"> <li>• Late stage (III/IV) cutaneous T-cell lymphoma</li> </ul>



Indication	Medical Necessity
	<ul style="list-style-type: none"> <li>• Early stage (I/II) cutaneous T-cell lymphoma that is progressive and refractory to established nonsystemic therapies</li> </ul> <p><b>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.</b></p>

Indication	Investigational
<b>Autoimmune diseases</b>	<p><b>Extracorporeal photopheresis is considered investigational as a technique to treat either the cutaneous or visceral manifestations of autoimmune diseases, including but not limited to:</b></p> <ul style="list-style-type: none"> <li>• Autoimmune bullous disorders</li> <li>• Crohn’s disease</li> <li>• Diabetes</li> <li>• Multiple sclerosis</li> <li>• Pemphigus</li> <li>• Psoriasis</li> <li>• Rheumatoid arthritis</li> <li>• Scleroderma</li> <li>• Severe atopic dermatitis</li> <li>• Systemic lupus erythematosus</li> </ul>
<b>Other</b>	<p><b>Extracorporeal photopheresis is considered investigational for all other indications.</b></p>

Documentation Requirements
<p><b>The individual’s medical records submitted for review should document that medical necessity criteria are met. The record should include clinical documentation of:</b></p> <ul style="list-style-type: none"> <li>• Diagnosis/condition</li> <li>• History and physical examination documenting the severity of the condition</li> <li>• The medical therapy that has been attempted</li> </ul>

## Coding



Code	Description
<b>Reviewed for Medical Necessity</b>	
<b>CPT</b>	
36522	Photopheresis, extracorporeal

**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 respond adequately to a standard regimen of immunosuppressive therapy.

**Recurrent** allograft rejection is defined as having at least two 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 two and three, then monthly on two consecutive days in months four through six.

### 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 one cycle (i.e., ECP on two consecutive



days) weekly for acute GVHD and every two 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**

Stage	Tumor T, N, and M Categories
IA	T1N0M0
IB	T2N0M0
IIA	T1-2N1M1
IIB	T3N0-1M0
III	T4N0-1M0
IVA	T1-4N2-3M0
IVB	T1-4N0-3M1

## 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 ECP and chronic GVHD.

## Evidence Review

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### Description

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

- The individual's 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/cm<sup>2</sup>.
- The light-sensitized lymphocytes are reinfused into the individual.

The use of ECP has been investigated for individuals 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 individuals 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 infections 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), ECP has more recently been used as a supplement to conventional therapies in the area of solid organ transplantation.<sup>1</sup> Reports of the successful use of ECP in human cardiac transplant recipients were published in 1992<sup>2,3</sup> and use in other transplant individuals followed. Although the specific mechanism of action of ECP is unknown, the reinfusion of treated leukocytes seems specifically to suppress the individual's immune response to the donor organ, although maintaining the body's ability to respond to other antigens.<sup>4</sup> 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.<sup>5</sup>

## Graft-Versus-Host Disease

Given that 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 neoplasia 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, which should be 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 to 10 years) as waxing and waning cutaneous eruptions. The prognosis of individuals 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 individuals with stage IA disease exceeds 20 years, with most deaths in this group typically unrelated to mycosis fungoides. In contrast, median survival in individuals with stage III or IV disease is less than 5 years; more than 50% of these individuals die of their disease.





Appropriate therapy of CTCL depends on a variety of factors, including stage, the individual'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 individuals require lifelong treatment and monitoring.

## Summary of Evidence

### Graft 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. The 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 individuals and longer follow-up are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. (See [clinical input](#) below)

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. The 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 individuals with graft rejection refractory to standard therapy. The evidence is sufficient to determine that the technology results in an 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 and a prospective pilot study. The 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. The pilot study was non-comparative and evaluated outcomes in high-risk cardiac transplant patients. Studies with more individuals and longer follow-up are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.



## **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. The 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 individuals with acute graft rejection. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are lung transplant recipients with bronchiolitis obliterans syndrome (BOS) refractory to corticosteroids who receive ECP, the evidence includes a prospective study and numerous retrospective analyses. The 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 that the technology results in an improvement in the net health outcome.

## **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. The 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 that the technology results in an improvement in the net health outcome.

## **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. The 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. There is a need for RCTs comparing immunosuppressive therapy with and without the use of ECP and examining histologic confirmation of treatment response. The



evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

## **Graft-Versus-Host Disease**

For individuals who have acute or chronic GVHD refractory to medical treatment who receive ECP, the evidence includes systematic reviews, a randomized study, retrospective studies, and case series. The 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 individuals; adverse events related to ECP are minimal; and, if there is a response to ECP, individuals 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 an improvement in the net health outcome.

## **Other Indications, Not Related to Solid Organ Transplant**

### **Autoimmune Disease**

For individuals who have autoimmune diseases (e.g., 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's disease) who receive ECP, the evidence includes isolated RCTs, small prospective and retrospective studies, and case reports. The 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 that the technology results in an improvement in the net health outcome.

### **Cutaneous 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. The 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 individuals. The evidence is sufficient to determine that the technology results in an 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. The relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Given the unfavorable prognosis for individuals 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 an improvement in the net health outcome.

## Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in [Table 2](#).

**Table 2. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<b>Ongoing</b>			
<b>Solid organ transplants</b>			
<a href="#">NCT02181257</a>	Extracorporeal Photopheresis for the Management of Progressive Bronchiolitis Obliterans Syndrome in Medicare-Eligible Recipients of Lung Allografts	280	Dec 2028 (ongoing)
<b>Graft-versus-host disease</b>			
<a href="#">NCT00637689</a>	Improving Outcomes Assessment in Chronic GVHD	601	Feb 2026 (ongoing)
<a href="#">NCT01460914</a>	Outcomes of Cutaneous T-Cell Lymphoma and Chronic Graft-Versus-Host Disease in Patients Treated with Extracorporeal Photopheresis	100	Oct 2050 (ongoing)
<b>Cutaneous T-cell lymphoma</b>			
<a href="#">NCT01460914</a>	Outcomes of Cutaneous T-Cell Lymphoma and Chronic Graft-Versus-Host Disease in Patients Treated with Extracorporeal Photopheresis	100	Oct 2050 (ongoing)



NCT No.	Trial Name	Planned Enrollment	Completion Date
<a href="#">NCT05680558</a>	THERAKOS CELLEX Photopheresis System as an Interventional Therapy for the Treatment of Early Stage CTCL (Mycosis Fungoides), an Open-label, Single-arm, Multi-center, Phase II Study	74	Jul 2026 (recruiting)
<a href="#">NCT05157581</a>	Open Label, Single-cohort, and Single-center Phase II Study Evaluating Tumor-specific Immunity After Extracorporeal Photopheresis in Patients With Sézary Syndrome at Single-cell Resolution	15	Dec 2026 (recruiting)
<b>Diabetes</b>			
<a href="#">NCT05413005</a>	Efficacy of Extracorporeal Photopheresis (ECP) in the Treatment of Type 1 Diabetes Mellitus (OPERA)	10	Jun 2025 (ongoing)
<b>Multiple Sclerosis</b>			
<a href="#">NCT05168384</a>	Safety and Efficacy of Extracorporeal Photopheresis (ECP) in the Treatment of Multiple Sclerosis (PHOMS)	45	Jun 2025 (ongoing)
<b>Systemic Sclerosis</b>			
<a href="#">NCT04986605</a>	The Effectiveness of ECP in Diffuse Cutaneous Systemic Sclerosis	15	June 2027 (ongoing)
<b>Unpublished</b>			
<b>Solid organ transplants</b>			
<a href="#">NCT05721079</a>	Prophylactic Use of Extracorporeal Photopheresis (ECP) After Lung Transplantation	62	Dec 2022
<b>Graft-versus-host disease</b>			
<a href="#">NCT03204721</a>	Prevention of Graft-versus-host Disease in Patients Treated With Allogeneic Stem Cell Transplantation: Possible Role of Extracorporeal Photopheresis	158	Apr 2021

CTCL: cutaneous T-cell lymphoma; GVHD: graft-versus-host disease; NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

## Clinical Input from Physician Specialty Societies and Academic Medical Centers

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the policy conclusions.



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.

## 2014 Input

In response to requests, input was received through two academic medical centers and five Blue Distinction Centers for Transplant when this policy was under review in 2014. Respondents agreed unanimously that ECP should not be medically necessary for previously untreated acute GVHD but should be medically necessary for acute GVHD that is refractory to medical therapy.

## Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

## Transplant

### Lung Transplant

#### ***International Society for Heart and Lung Transplantation***

A 2019 document from the International Society for Heart and Lung Transplantation addressed the use of ECP in patients with chronic lung allograft dysfunction/bronchiolitis obliterans syndrome.<sup>88</sup> The guideline listed ECP as a therapeutic option and stated that ECP may be most beneficial in patients with a slow decline in forced expiratory volume in 1 second (FEV1) and increased neutrophilia on bronchoalveolar lavage. Patients with rapidly declining FEV1, lack of significant neutrophilia, or restrictive allograft syndrome.



## Graft Versus Host Disease

### Acute Graft-Versus-Host Disease

#### ***American Society of Blood and Marrow Transplantation***

In 2012, evidence-based recommendations from the American Society of Blood and Marrow Transplantation advised that ECP cannot be considered superior to horse antithymocyte globulin for treatment of acute GVHD.<sup>89</sup> This conclusion was based on older studies.<sup>53,90</sup>

### Acute and Chronic Graft-Versus-Host Disease

#### ***European Society for Blood and Marrow Transplantation***

In 2024, the European Society for Blood and Marrow Transplantation published updated prophylaxis and management guidelines for acute and chronic GVHD.<sup>91</sup> The guidelines state that while there is no standard second-line treatment for both acute and chronic GVHD, ECP is listed as therapy for use for second-line treatment. The guideline does comment that not enough data exists to compare the efficacy of different second-line treatments.

## Cutaneous T-Cell Lymphoma

### National Comprehensive Cancer Network

National Comprehensive Cancer Network guidelines on primary cutaneous lymphomas (v.3.2024) list the use of ECP as a category 2A treatment alone or in combination with other agents as first-line systemic therapy for advanced (stages III-IV) disease, as well as for individuals with earlier stage mycosis fungoides with Sézary syndrome involvement. The guidelines add that ECP may be more appropriate as systemic therapy in individuals with or at risk of blood involvement (B1 or B2).<sup>92</sup>

### National Cancer Institute

The National Cancer Institute lists ECP (alone or in combination with total-skin electron-beam radiation) as a phototherapeutic option for patients with stage III or IV Sézary syndrome or erythrodermic mycosis fungoides.<sup>85</sup>



## 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”.<sup>93</sup>

Effective 2012, CMS also provided coverage for ECP for the treatment of “BOS following lung allograft transplantation only when extracorporeal photopheresis is provided under a clinical research study” that meets certain conditions.<sup>93</sup>

### Graft-Versus-Host Disease

Effective 2006, CMS provided coverage of ECP for individuals with chronic GVHD “whose disease is refractory to standard immunosuppressive drug treatment.”<sup>93</sup>

### Autoimmune Disorders

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

### Cutaneous 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.”<sup>93</sup>

## Regulatory Status

Two photopheresis systems (Therakos; now Mallinckrodt) were approved by the US 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; Therakos; now Mallinckrodt) 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.

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## History

Date	Comments
11/16/00	Add to Therapy Section - New Policy.
01/08/02	Replace Policy - Revised; added information on photopheresis for graft vs. host disease; considered medically necessary for chronic disease.
05/11/04	Replace Policy - Policy reviewed; literature updated; no change in policy statement.
06/14/05	Replace Policy - Policy reviewed with literature search; no change in policy statement.
06/16/06	Replace Policy - Policy updated with literature search; policy statement unchanged. Scope and Disclaimer updated.
01/08/08	Replace Policy - Policy updated with literature search; no change in policy statement. "Extracorporeal" added to the title. References and code added.
12/16/08	Minor Updates - Spelling Corrected.
06/09/09	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.
02/09/10	Replace Policy - Policy updated with literature search. Policy statement minor update "chronic" added to medically necessary statement, no other changes. References added.
06/10/10	Delete Policy - Policy deleted from active status.
11/09/10	Reinstate Policy - Policy reinstated. Requests are being received.
03/08/11	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.
05/12/11	Reviewed by OAP - No changes recommend to the policy.
04/10/12	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 and coding updated.
09/10/12	Update Coding Section – ICD-10 codes are now effective 10/01/2014.



Date	Comments
09/21/12	Update Related Policy, add 5.01.532.
02/12/13	Update Related Policies, change title on Policy 8.02.02.
04/08/13	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".
03/11/14	Coding Update. Code 99.88 was removed per ICD-10 mapping project; this code is not utilized for adjudication of policy.
07/14/14	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.
06/17/15	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.
12/01/16	Annual Review, approved November 8, 2016. Policy updated with literature review. Added reference 38. No changes to policy statements.
01/01/18	Annual Review, approved December 6, 2017. Policy updated with literature review through August 2017; no references added. Policy statement unchanged.
11/01/18	Minor update, removed 8.02.02 from related policies as it was archived.
01/01/19	Annual Review, approved December 19, 2018. Policy updated with literature review through August 2018; no references added. Policy statement unchanged.
04/01/19	Minor update, added Documentation Requirements section.
01/01/20	Annual Review, approved December 10, 2019. Policy updated with literature review through August 2019; no references added. Policy statements unchanged.
04/01/20	Delete policy, approved March 10, 2020. This policy will be deleted effective July 2, 2020, and replaced with InterQual criteria for dates of service on or after July 2, 2020.
06/12/20	Correction: This policy is reinstated immediately and will no longer be deleted or replaced with InterQual criteria on July 2, 2020, as this policy was deleted in error.
01/01/21	Annual Review, approved December 1, 2020. Policy updated with literature review through September 23, 2020; reference added. Policy statements unchanged.
04/01/21	Interim Review, approved March 23, 2021. Organ rejection after solid organ transplant policy statements edited for greater clarity; policy intent unchanged.
01/01/22	Annual Review, approved December 2, 2021. Policy updated with literature review through August 31, 2021; references added. Policy statements unchanged.





Date	Comments
01/01/23	Annual Review, approved December 12, 2022. Policy updated with literature review through August 27, 2022; references added. Policy statements unchanged. Changed the wording from "patient" to "individual" throughout the policy for standardization.
01/01/24	Annual Review, approved December 11, 2023. Policy updated with literature review through September 1, 2023; references added. Policy statements unchanged.
01/01/25	Annual Review, approved December 9, 2024. Policy updated with literature review through August 27, 2024; references added. Policy statements unchanged.

**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). ©2025 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

