



# Cigna Medical Coverage Policy

**Subject Photopheresis (Extracorporeal Photochemotherapy)**

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## Table of Contents

Coverage Policy .....	1
General Background .....	2
Coding/Billing Information .....	7
References .....	8

## Hyperlink to Related Coverage Policies

- [Breath Test for Detection of Heart Transplantation Rejection](#)
- [Genetic Expression Profiles for Detection of Heart Transplantation Rejection \(e.g., AlloMap®\)](#)
- [Heart, Lung and Heart-Lung Transplantation Photodynamic Therapy for Dermatologic and Ocular Conditions](#)
- [Phototherapy, Photochemotherapy, and Excimer Laser Therapy for Dermatological Conditions](#)

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## Coverage Policy

**Cigna covers extracorporeal photopheresis as medically necessary for ANY of the following indications:**

- advanced or refractory cutaneous T-cell lymphoma (CTCL) (e.g., mycosis fungoides and Sézary syndrome)
- refractory systemic graft-versus-host disease (GVHD)
- recurrent heart or heart/lung transplant rejection
- lung transplant rejection when conventional therapies do not produce an adequate response

**Cigna does not cover extracorporeal photopheresis for ANY other indication, including ANY of the following, because it is considered experimental, investigational or unproven (this list may not be all-inclusive):**

- solid organ graft rejection, not listed above as covered
- autoimmune diseases (e.g., multiple sclerosis, scleroderma, diabetes mellitus [DM] type 1, rheumatoid arthritis, systemic lupus erythematosus [SLE], psoriasis, and pemphigus)
- atopic dermatitis
- Crohn's disease
- chronic B cell leukemia

- chronic obstructive bronchitis
  - eosinophilic fasciitis
  - hepatitis C
  - human immunodeficiency virus (HIV)
  - myasthenia gravis
  - nephrogenic fibrosing sclerosis/dermopathy
  - nephrogenic peritonitis
  - prevention of re-stenosis after percutaneous transluminal coronary angioplasty (PTCA)
  - composite tissue allotransplantation
- 

## General Background

Extracorporeal photopheresis, also referred to as extracorporeal photochemotherapy, or ECP, involves the use of a centrifugal apheresis machine to separate white blood cells (WBCs) from whole blood. The separated WBCs are treated with a photoactive compound (e.g., 8-methoxypsoralen) then exposed to ultraviolet A light within a photoactivation chamber, such as the UVAR<sup>®</sup> Photopheresis System (Therakos, Inc., Raritan, NJ). The red blood cells, plasma and treated WBCs are re-infused into the patient during the same procedure.

The exact mechanism of action for ECP is not known (Geskin, 2007). The WBCs that are treated and reinfused are thought to cause lymphocyte death and transformation of monocytes into dendritic cells, which induce a host-immune response to the cells causing the disease or reaction. Adverse effects are mild, including transient hypotension during the blood collection and low-grade fever for two to twelve hours after reinfusion (Wilson, 2005).

The use of ECP, either alone or in combination with other modalities has been proposed for the treatment of a number of disorders including cutaneous T-cell lymphoma (CTCL), primarily mycosis fungoides and Sézary syndrome when the condition is advanced or patients are refractory to medical management, graft-versus-host disease, solid organ graft rejection, and several autoimmune disorders and dermatologic conditions.

**Cutaneous T-Cell Lymphoma (CTCL):** According to the National Cancer Institute ([NCI], 2014), CTCLs are any of a group of relatively uncommon T-cell non-Hodgkin lymphomas. The World Health Organization (WHO)-European Organization for Research and Treatment of Cancer (EORTC) classification includes several CTCLs of indolent clinical behavior (e.g., mycosis fungoides, pagetoid reticulosis, granulomatous slack skin) as well as those of aggressive clinical behavior (e.g., Sézary syndrome, primary cutaneous CD8<sup>+</sup> aggressive lymphoma) (Habermann, 2008). Mycosis fungoides and Sézary syndrome are the most common types of CTCL; Sézary syndrome is an advanced form of mycosis fungoides. The prognosis of individuals with mycosis fungoides/Sézary syndrome is based on the stage of the disease, type and extent of skin lesions, and on the presence of extracutaneous disease (Willemze, 2005). Individuals with stage III–IV disease have a median survival of < five years, with more than half of the deaths caused by mycosis fungoides.

ECP is frequently used as monotherapy for advanced or refractory CTCL, most commonly mycosis fungoides and Sézary syndrome. Its combination with other therapies is currently under study. Clinical response varies from control of itching to clearing of skin lesions (Schwartz, 2013). Individuals undergoing treatment may begin to show sustained clinical improvement as early as the second month of therapy; however, some patients do not clear or achieve their maximal response until 12 months after starting therapy (Foss, 2008).

While the use of ECP for this indication has not been proven in controlled clinical trials, improved disease-free and overall survival rates, as well as reduction in skin scores and Sézary cell count have been noted in several cohort studies (Querfeld, 2005, Evans, 2001). Girardi et al. (2003) and Miller et al. (2007) also performed reviews of the scientific literature, noting response rates for the use of ECP as monotherapy of 33%–88%; ECP plus adjuvant therapy yielded response rates of 50%–60%. Complete response was reported in 25% of patients.

Weberschock et al. (2012) reported on a systematic review of interventions for mycosis fungoides, including extracorporeal photochemotherapy (ECP). Primary endpoint for the systematic review was the side effects of treatment; secondary endpoint was clearance (i.e., defined as clearance of at least 90% of all lesion surfaces, lesions, or tumor size). Of 14 included studies one randomized controlled trial (RCT) compared the effect of

ECP to psoralen plus long-wave ultraviolet radiation (PUVA) in a crossover design. Overall curative intentions for mycosis fungoides were not identified by this review. The authors note that the studies suggest more aggressive approaches result in a higher percentage of clearance but also lead to substantially more adverse effects. In the comparison between ECP and PUVA, side effects of mild nausea and hypotension were noted; however, incidence and timepoints were not included. There were no significant differences between ECP and PUVA for clearance (RR 0.14, 95% CI 0.01 to 2.39,  $p < 0.23$ ). Differences were seen in improvement (i.e., at least 50% of all lesion surfaces, lesions, or tumor size) between ECP and PUVA (RR 0.07,  $p < 0.002$ ). Because of limited randomized controlled trial (RCT) results data, a small patient population, and potential bias, this systematic review did not demonstrate improved effectiveness of ECP for the treatment of mycosis fungoides. The authors encourage continued enrollment in multicenter RCTs.

In 2006, the Ontario Health Technology Advisory Committee (OHTAC) performed a systematic review and analysis regarding the use of extracorporeal photochemotherapy (ECP) in the treatment of refractory erythrodermic cutaneous T-cell lymphoma (CTCL). The OHTAC notes ECP is a potential treatment option for selected patients with refractory erythrodermic cutaneous T-cell lymphoma (CTCL) and refractory chronic graft versus host disease (GVHD).

Despite the lack of robust evidence, ECP is an accepted therapy for the treatment of advanced or refractory CTCL, such as mycosis fungoides and Sézary syndrome.

**Graft-Versus-Host Disease:** Graft-versus-host disease (GVHD) is a common complication of allogeneic hematopoietic stem-cell transplantation (HSCT); it may also be seen after solid organ transplantation. In GVHD, activated T-cells attack transplanted hematopoietic stem cells or solid organs. The disease may be acute or chronic and may present with minimal to severe, life-threatening symptoms.

Currently no single therapy is effective in the treatment of refractory, systemic acute and chronic graft-versus-host disease (GVHD). Treatment options depend on the stage of the disease. ECP has been proposed as salvage therapy for refractory systemic disease (Bhushan, 2003; Vogelsang, 2001).

ECP is theorized to induce a tolerance to alloantigens (Gorgun, 2002; Alcindor, 2001). A number of retrospective and prospective cohort studies using ECP for GVHD have been reported. Overall response rates for acute GVHD vary from 52%–100%, depending on site of involvement. Response rates range from 40%–83%, 63%–100%, and 27%–71% for skin, gastrointestinal system, and liver involvement, respectively, for steroid-refractory acute GVHD (Schwartz, 2013). For chronic GVHD response rates of skin, oral and ocular manifestations respond in 30–100% of cases while liver, joint, and GI complications improve in 30–80%, 50% and 0–50%, respectively (Schwartz, 2013).

Weitz et al. (2014) found no studies meeting the criteria for inclusion in a systematic review to evaluate the effectiveness and safety of ECP for the management of acute GVHD in children and adolescents after hematopoietic stem-cell transplantation (HSCT). The study authors reported “The efficacy of ECP in the treatment of acute GVHD in pediatric patients after HSCT is unknown and its use should be restricted within the context of randomized controlled trials. Such studies should address a comparison of ECP alone or in combination with standard treatment versus standard treatment alone.”

An RCT comparing standard therapy alone and ECP combined with standard therapy in corticosteroid-refractory patients with chronic GVHD did not demonstrate significant improvement in total skin scores (TSS) when blinded ( $p = 0.48$ ); however, patients who had at least a 50% reduction in steroid dose and at least a 25% decrease from baseline in TSS were improved in the ECP arm ( $p = 0.04$ ). Non-blinded investigator assessment revealed a significant improvement with the use of ECP ( $p < 0.001$ ). Statistically significant improvement was also noted in extracutaneous organ systems such as eye ( $p = 0.04$ ) and oral involvement ( $p = 0.06$ ) for patients who received ECP compared with the control arm (Flowers, 2008).

Favorable outcomes have been reported for the use of ECP for chronic GVHD refractory to conventional immunosuppression. Response rates range from 0%–100%, depending on stage of disease. Improved survival rates of 38%–73% were noted for individuals receiving ECP (Perfetti, 2008; Kanold, 2007; Massimo, 2007; Couriel, 2006; Foss, 2005; Seaton, 2003). There was an absence of long-term side effects with the use of ECP compared with the long-term side effects associated with steroid treatment such as bone necrosis, growth retardation, cataracts (Massimo, 2007).

In a systematic review the OHTAC (2006) noted there was low quality evidence that ECP improves response rate and survival in patients with chronic GVHD who are unresponsive to other forms of therapy. Limitations in the published medical literature included heterogeneity in treatment regimens and diagnostic criteria, small sample sizes and most studies were uncontrolled, retrospective case series. Additionally, response criteria were not clearly defined or inconsistent. Based on this assessment, the Committee recommended that a two-year field evaluation be undertaken.

There are limited data from controlled studies regarding the effectiveness of extracorporeal photochemotherapy (ECP) for the treatment of refractory systemic graft-versus-host disease (GVHD); however, ECP is considered an accepted therapy for this indication.

### **Solid Organ Graft Rejection**

In solid organ rejection, the immune system of the organ recipient recognizes proteins on the surface of the cells of the transplanted organ (i.e., major histocompatibility antigens) as foreign and responds by attacking the donor organ. The immune response can be limited by the use of donor organs with similar major histocompatibility antigens, and by the use of immunosuppressive drugs that reduce the immune response to the transplanted organ. The standard of care for solid organ rejection is immunosuppression; however, complications and risks from immunosuppressive therapies remain a significant problem. ECP has been proposed for the treatment of solid organ graft rejection, including recurrent rejection of the heart, heart/lung, and lung.

**Heart and Heart/Lung Transplantation Rejection:** Although the mechanism of ECP remains unknown, it is thought that it stimulates the immune system to destroy clone-specific T cells causing allograft rejection and induces immunotolerance via expansion of regulatory T cells (Schwartz, 2013). Data are not robust for this indication. Results from a case series study by Kirklin (2006), demonstrated a decreased rejection rate with the use of ECP in patients with refractory acute cardiac allograft rejection who have failed multiple attempts with several immunosuppressive regimens. An early randomized controlled trial (RCT) by Costanzo-Nordin et al. (1992) comparing patients randomized to receive either corticosteroids or ECP for the treatment of cardiac graft rejection did not show significantly different outcomes between the groups. Another RCT demonstrated no statistically significant differences between overall survival between patients receiving standard immunosuppressive therapy compared with ECP plus standard therapy for cardiac graft rejection; however, rejection rates were lower in the group receiving ECP ( $p=0.02$ ) (Barr, 1998). Potentially confounding factors include small populations, the differing lengths of time between diagnosis of disease and entry into the protocols, and the heterogeneity of previous treatments that the subjects had received. There was no increase in infection rates or other adverse effects identified while using this therapy.

**Lung Transplantation Rejection:** Despite a shift towards more potent immunosuppressive regimens, the development of chronic allograft rejection continues to negatively impact the long-term survival of lung transplant recipients. It is estimated that acute rejection of the transplanted lung occurs in 50%–75% of recipients; chronic rejection is the most common cause of death in lung transplant recipients after the first year of transplant. Bronchiolitis obliterans syndrome represents chronic allograft rejection and occurs in approximately 60%–80% of lung transplant survivors five to ten years after the transplant. ECP has been utilized to stabilize lung function for persistent lung transplant rejection and early bronchiolitis obliterans when conventional therapies do not produce an adequate response (Schwartz, 2013; Bhorade, 2009).

Although the specific mechanism of action is not known, the reinfusion of the treated leukocytes mediates suppression of rejection responses, prolonging the survival of transplanted tissues and organs. Importantly, ECP is not associated with an increased risk of infection, common with immunosuppressant drugs (Szczepiorkoski, 2007). In several case series reports, lung transplant recipients who were unresponsive to standard immunosuppressive therapy and had deterioration of graft function due to refractory bronchiolitis obliterans syndrome or persistent acute rejection received ECP. Patients experienced stabilization of lung function and/or symptoms (Benden, 2008; Meloni, 2007; O'Hagan, 1999; Slovis, 1995).

Promising results have been obtained in treating individuals with life-threatening recurrent heart, heart/lung, and lung graft rejection. Despite a lack of robust evidence, ECP is an accepted therapy for the treatment of these conditions.

**Other Solid Organ Transplantation Rejection:** ECP has been proposed for the treatment of rejection of other solid organs. There are insufficient data to support the use of ECP for graft rejection in other solid organs, including, but not limited to, the liver and kidney. Additional studies are needed to determine if ECP will improve survival in these subsets of patients. The role of extracorporeal photochemotherapy (ECP) in treating solid organ graft rejection, other than for heart, heart/lung, and lung allografts, has not yet been established.

### **Autoimmune Diseases**

Autoimmune disease is a broad term used to describe any of a number of abnormal conditions caused when the body produces antibodies to its own substances. While the pathogenesis is not completely clear, it appears that T-cells play a role in the development of autoimmune disease. Autoimmune diseases include, but are not limited to, multiple sclerosis (MS), scleroderma (systemic sclerosis, [SS]), and type I diabetes mellitus (DM). Standard treatment options for autoimmune diseases include the use of immunosuppressive medications and/or supportive care directed at the particular symptoms of the disease. ECP has been investigated as a therapy for a variety of autoimmune diseases; most commonly ECP is proposed as a treatment for MS, SS, and DM.

**Multiple Sclerosis (MS):** A small cohort of patients with refractory relapsing-remitting MS participated in a pilot study that was conducted by Cavaletti et al. (2006) to assess the safety, tolerability and effectiveness of ECP treatments within this patient population. Adverse events included mild anticoagulant related distal and/or perioral paraesthesias. During the first year of ECP treatments, response rates were initially decreased; however, response rates ultimately increased to those of pre-treatment levels in several of the patients. Larger studies of ECP treatment are needed to determine the most effective treatment protocol and potential tapering that may be needed to obtain improved and prolonged patient outcomes.

A randomized controlled trial (RCT) investigating a regimen of monthly extracorporeal photochemotherapy (ECP) for the treatment of clinically definite multiple sclerosis (MS) with progressive deterioration in neurologic status in the 12 months prior to enrollment was performed by Rostami et al. (1999). Patients were clinically evaluated by the Expanded Disability Status Scale, Ambulation Index, and Scripp's Quantitative Neurologic Assessment. There were no differences in disability measures between the two groups after treatment, and no significant differences in lymphocyte populations at baseline or at 12 months after therapy in either group. Additionally, ECP did not significantly alter the course of chronic progressive MS.

**Scleroderma (SS):** Several RCTs have investigated ECP compared with other therapies for this indication. Knobler et al. (2006) compared ECP and sham pheresis treatment. Comparison of skin scores between the two study arms did not achieve statistical significance because of small sample size. This study lacked sufficient statistical power to determine any effect when ECP was compared with sham treatment. Rook (1992), reported on patients with SS who were randomized to receive treatment with ECP or D-penicillamine. The study demonstrated improved skin symptoms in patients who received ECP; however, the study was of short duration, and an excessive number of patients were lost to follow-up. Additional studies include small feasibility trials that demonstrate some improvement in patient status during the course of therapy; however, long-term effectiveness of this treatment has not been shown (Seibold, 2005; Besnier, 2002; French, 2001).

**Type I Diabetes Mellitus (DM):** Gandhi et al. (2008) performed a systematic review and meta-analysis to determine the effectiveness of non-antigen based immunotherapies, including ECP, for the treatment of patients with type I DM. Meta-analysis found a small-to-moderate improvement in beta-cell function with immunotherapy versus placebo. The authors noted that further high-quality research is needed and that patients must participate in, and await the conduct of rigorous trials reporting on diabetes resolution, adverse events and other patient-important outcomes.

Ernerudh et al. (2004) performed a RCT to assess the effect of photopheresis related to changes in the balance of lymphocyte populations in children with newly diagnosed (i.e. first insulin injection) DM. Children received photopheresis or sham pheresis (placebo group). The number of lymphocytes decreased significantly during treatment in the active treatment group ( $p < 0.02$ ), resulting in decreased numbers of both B and T cells; however, the distribution of the cells did not change. No relation between lymphocyte subsets and clinical outcome was found one year after the treatment with photopheresis. No major effect of photopheresis on lymphocyte populations in a group of children with newly diagnosed type 1 DM was noted.

At this time there is insufficient evidence supporting the effectiveness of ECP for autoimmune diseases, including, but not limited to, MS, SS, and type I DM, in the published, peer-reviewed scientific literature. The role of this therapy for the treatment of autoimmune diseases has not yet been established.

### **Other Proposed Indications for ECP**

There is insufficient evidence in the peer-reviewed scientific literature to evaluate the effectiveness of extracorporeal photochemotherapy (ECP) for the treatment of the following proposed indications: atopic dermatitis, Crohn's disease, chronic B cell leukemia, chronic obstructive bronchitis, eosinophilic fasciitis, hepatitis C, human immunodeficiency virus (HIV), myasthenia gravis, nephrogenic fibrosing sclerosis/dermopathy, nephrogenic peritonitis, pemphigus (e.g., bullous pemphigoid [BP], pemphigus vulgaris), prevention of re-stenosis after percutaneous transluminal coronary angioplasty (PTCA), psoriasis, rheumatic arthritis, systemic lupus erythematosus (SLE), and composite tissue allotransplantation. Small patient populations and uncontrolled study design limit the ability to determine whether there are improved health outcomes compared with standard treatment options. Length of therapy, concomitant use of other treatments, including immunosuppressive therapy, and patient selection criteria vary between studies, and long-term outcomes are unknown. Randomized, placebo-controlled trials of ECP should be performed to more specifically assess improved outcomes. At this time the role of ECP for these indications has not been established.

### **U.S. Food and Drug Administration (FDA)**

In 1987, the FDA approved the use of the UVAR<sup>®</sup> Photopheresis System (Therakos, Inc., Raritan, NJ) to provide extracorporeal photochemotherapy (ECP) for the treatment of cutaneous T-cell lymphoma. The device is indicated for use in ultraviolet-A (UVA) irradiation, in the presence of the photoactive drug methoxsalen (8-methoxypsoralen or 8-MOP) of extracorporeally circulating leukocyte-enriched blood, and in the palliative treatment of the skin manifestations of cutaneous T-cell lymphoma in persons who have not been responsive to other therapy.

### **Professional Societies/Organizations**

**American Society for Apheresis ([ASA], 2010):** On behalf of the Apheresis Applications Committee, Schwartz et al. (2013) published Guidelines on the Use of Therapeutic Apheresis in Clinical Practice-Evidence-Based Approach. The Guidelines suggest that extracorporeal photopheresis (ECP) may be appropriate in selected individuals for the treatment of cutaneous T-cell lymphoma (CTCL), erythrodermic mycosis fungoides and Sézary syndrome, steroid-refractory acute and steroid-dependent chronic graft-versus-host disease (GVHD), and for lung transplant rejection in individuals with persistent acute rejection and early bronchiolitis obliterans syndrome, and for prophylaxis and treatment of cardiac allograft rejection.

The Guidelines note that the role for using ECP in the treatment of pemphigus vulgaris, and scleroderma has not been established. The recommendation is weak, with moderate, low or very low quality evidence.

**National Cancer Institute ([NCI], 2014):** The NCI lists extracorporeal photochemotherapy as a standard treatment option for stage III mycosis fungoides/ Sézary syndrome. ECP alone or in combination with total-skin electron-beam radiation is listed as a standard treatment option for the treatment of stage IV mycosis fungoides/ Sézary syndrome. The NCI also notes that this therapy has produced tumor regression in patients resistant to other therapies for recurrent mycosis fungoides/ Sézary syndrome.

**National Comprehensive Cancer Network Guidelines<sup>™</sup> ([NCCN Guidelines<sup>™</sup>], 2014):** The Guidelines note that extracorporeal photopheresis (ECP) is a systemic therapy that is preferred over traditional chemotherapy for patients with mycosis fungoides who do not respond to initial skin-directed therapies. It is particularly indicated in patients with or at risk of blood involvement (erythrodermic stage III disease or IVA with Sézary syndrome).

### **Use Outside of the US**

**British Photodermatology Group and the U.K. Skin Lymphoma Group (2006):** On behalf of these professional societies, McKenna et al. published a systematic review of the literature and "An Evidence-Based Practice of Photopheresis 1987–2001", with recommendations for photopheresis. The authors noted that there was:

- fair evidence to support the use of ECP for erythrodermic mycosis fungoides (MF)/ Sézary syndrome
- good evidence to support the rejection of ECP for the treatment of nonerythrodermic mycosis fungoides

- fair evidence to support the use of ECP for chronic graft-versus-host disease with cutaneous or mucosal involvement, but the evidence in hepatic disease is poor
- fair evidence to support rejection of the use of ECP for gastrointestinal or pulmonary chronic graft-versus-host disease
- poor evidence to support the use of ECP for cutaneous or hepatic acute graft-versus-host disease
- good evidence to support the use of ECP for the treatment of acute rejection, recurrent acute rejection, prophylaxis of rejection and chronic cardiac rejection
- poor evidence to support the use of ECP for the management of renal allograft rejection
- fair evidence to support the rejection of the use of extracorporeal photochemotherapy (ECP) for the treatment of multiple sclerosis
- the effect of ECP on the disease process at the onset of type I diabetes mellitus is weak and further studies are required before it can be considered a routine treatment modality
- randomized, controlled trials are needed to define and clarify the use of ECP in rheumatoid arthritis, Crohn's disease, and other T-cell mediated disorders

**National Institute for Health and Care Excellence ([NICE], 2009):** Regarding Crohn's disease NICE notes "Current evidence on extracorporeal photopheresis (ECP) for Crohn's disease is based on reports that include a very small number of patients. These reports describe no major safety issues but they provide little evidence of efficacy. Therefore, this procedure should not be used outside the context of research."

**United Kingdom (U.K.) Photopheresis Expert Group (2008):** Scarisbrick et al., published a consensus statement on the use of ECP for the treatment of cutaneous T-cell lymphoma and chronic graft-versus-host disease. The Statement notes ECP should be considered for the treatment of patients with cutaneous T-cell lymphoma who have erythroderma and stage III cutaneous T-cell lymphoma and have one of the following: circulating clonal disease by polymerase chain reaction or southern blot analysis or evidence of circulating Sézary cells or CD4/CD8 ration >0. In regards to the use of ECP for chronic graft-versus-host disease, the Statement notes ECP should be considered for patients who require second-line/third-line salvage therapy because of either steroid-refractory or steroid-dependent disease. Alternately, patients must be unable to tolerate standard first-line corticosteroid therapy. Patients must have chronic graft-versus-host disease primarily affecting at least one of the following organs: skin; mucosal membranes; liver.

**Summary**

Although data are not robust, the published, peer-reviewed scientific literature supports the safety and effectiveness of photopheresis (i.e., extracorporeal photochemotherapy [ECP]) for the treatment of selected individuals with advanced or refractory cutaneous T-cell lymphoma, refractory systemic graft-versus-host disease, and recurrent heart, heart/lung and lung allograft rejection when conventional therapies do not produce an adequate response. Further, there is consensus support in the form of published clinical guidelines supporting ECP as a standard care option for these indications.

There is insufficient evidence in the published, peer-reviewed scientific literature to support the safety or effectiveness of ECP for the treatment of allograft rejection in solid organs other than the heart, heart/lung, and lung, for the treatment of autoimmune diseases, or for any other indication. Data are limited to small studies with uncontrolled design. The role of ECP for these indications has not yet been established.

**Coding/Billing Information**

- Note:** 1) This list of codes may not be all-inclusive.  
 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

**Covered when medically necessary:**

CPT®* Codes	Description
36522	Photopheresis, extracorporeal

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