01-90919-02

Original Effective Date: 01/15/13

Reviewed: 03/27/25

Revised: 04/15/25

Subject: Extracorporeal Photopheresis

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Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions	Related Guidelines
Other	References	Updates			

DESCRIPTION:

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

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

Summary and Analysis of Evidence: For acute graft rejection after cardiac transplant, a 1992 randomized trial enrolled 16 heart transplant recipients. The use of ECP in combination with immunosuppressive therapy had efficacy similar to immunosuppressive therapy alone, with fewer infections in the ECP group. This trial was small, and time from transplantation to study entry varied (Costanzo-Nordin et al). Kirklin et al (2006) studied the use of ECP for recurrent and/or refractory cardiac allograft rejection has been the focus of most of the research on ECP. Although data are from nonrandomized studies, a comparative study of 343 cardiac transplant recipients in which 36 patients received ECP has been completed. The authors showed that at 3 months, ECP was related to a risk reduction of HC rejection or rejection death (relative risk reduction, 0.29). A reduction in HC rejection or rejection death was observed through 2 years of follow-up. Although trial results might have been confounded by improvements in immunosuppressive therapy regimens over time, they are consistent with case series for this indication, which has suggested a benefit of ECP in patients with recurrent or refractory cardiac rejection. Thus, the evidence to date provides consistent evidence for a beneficial effect of ECP for cardiac transplant patients with rejection refractory to standard therapy.

UpToDate review “Chronic lung allograft dysfunction: Bronchiolitis obliterans syndrome” (Pilewski, 2025) states, “a variety of therapies have been tried for bronchiolitis obliterans syndrome (BOS), but there are no clinical trials or well-established protocols to guide therapy. Potential treatments include adding long-term azithromycin (if not already used for prevention), changing the maintenance immunosuppressive medications, extracorporeal photopheresis, total lymphoid irradiation, plasmapheresis and other therapies to target antibodies to the allograft (immune globulin, rituximab, proteasome inhibitors), and inhaled cyclosporine. The decision among these choices depends on the severity of BOS, underlying immunosuppressive regimen, preferences of individual transplant centers, and response to treatment.” The review further states “extracorporeal psoralen photopheresis (ECP) reduced the rate of decline in lung function in the setting of BOS in single center experiences. In extracorporeal photopheresis, peripheral blood lymphocytes are collected via apheresis, treated with 8-methoxypsoralen followed by exposure to a source of ultraviolet A light, and reinfused. This process is thought to act by inducing lymphocyte apoptosis and induction of T regulatory (Treg) cells. Among 51 patients with BOS treated with ECP (two successive days every two weeks for three months and then every four weeks), the FEV1 improved or stabilized in 61 percent. Those who responded to ECP had better survival and a lower rate of retransplantation than nonresponders.” The Writing Committee of the American Society for Apheresis updated their guidelines on therapeutic use of apheresis in clinical practice in 2023 (Connelly-Smith et al, 2023), stating, “chronic lung allograft dysfunction (CLAD) includes multiple disorders, the most common being bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS). Recurrent acute cellular rejection (ACR) increases the risk of developing BOS; approximately half of lung transplant recipients develop BOS within 5 years. The Committee issued a category II, grade IC recommendation for the use of ECP for treatment of chronic lung allograft dysfunction and bronchiolitis obliterans syndrome in 2023.

Mehta et al (2021) reported findings of a single-center, open-label, randomized phase 2 trial with an adaptively randomized Bayesian design that compared prednisone with versus without ECP in patients with acute GVHD. In total, 81 patients were randomized to steroids with ECP (n=51) or steroids alone (n=30). The primary endpoint was treatment success, defined as survival and in remission without need for further therapy and on 0.80). After 81 patients were enrolled, the statistical threshold was met in favor of ECP for the primary endpoint with a probability of 81.5%. Treatment success occurred in 65% and 53% of patients treated with ECP and steroids only, respectively. Solh et al (2023) retrospectively assessed the effect of ECP on overall survival among 79 patients with steroid refractory acute GVHD. Compared to a control group (n=24) that did not receive ECP, OS and disease-free survival were higher in patients who received ECP. Hospital length of stay was significantly shorter in the ECP group. In a multivariable analysis, receipt of ECP was associated with OS and disease-free survival. Batgi et al (2021) reported results from a retrospective observational series of 75 patients with steroid refractory, acute GVHD from 4 transplant centers in Turkey who were treated with ECP. 49, Patients received ECP on 2 consecutive days every 2 weeks until resolution of signs and symptoms, and ECP was reduced to 1 treatment every 2 weeks with complete response. Most patients had grade 3 (28.0%) or grade 4 (46.7%) disease. After a median follow-up of 6 months (range, 1 to 68 months), the overall response rate was 42.7%. Median OS was 5 months for non-responders and 68 months for responders. Kansu et al (2022) reported results of a retrospective observational study that included 53 patients with steroid refractory chronic GVHD who were treated with ECP at a single-center in the US. 58, Extracorporeal photopheresis was performed using the Therakos UVAR XTS and CELLEX closed-circuit systems. All patients initiated ECP therapy with 2 treatments weekly for 4 weeks followed by 2 consecutive days every 2 weeks as a

maintenance therapy; tapering and discontinuation of ECP therapy was done at the discretion of the treating physician. Results demonstrated that after a median duration of ECP of 14 months (range, 3.0 to 56 months), CR was seen in 9 (17%) patients and PR was seen in 34 (64.2%) patients; the overall response rate was 81.2%. The OS at 1 and 3 years was 84.9% and 36.7%, respectively. Dal et al (2021) reported results from a retrospective observational series of 100 patients with steroid refractory chronic GVHD who were treated with ECP at 4 transplant centers in Turkey. 59, Patients received ECP on 2 consecutive days every 2 weeks until resolution of signs and symptoms, and ECP was reduced to 1 treatment every 2 weeks with CR. Most patients had severe (grade ≥3) disease (77%), and 50% had involvement of more than 1 organ. Overall and CR rates were 58% and 35%, respectively. After a median follow-up of 13 months (range, 1 to 261 months), OS was 41%. Median OS was 2 months for non-responders and 91 months for responders. Kitko et al (2022) evaluate the efficacy and safety of a single-device ECP (Therakos CellEx Photopheresis System) in 29 children with steroid-refractory acute GVHD. This was a prospective, single-arm, open-label, multicenter study conducted at 14 study centers in the US and Europe. During the treatment period, patients received ECP with methoxsalen in conjunction with the Therakos CellEx Photopheresis System 3 times per week for weeks 1 to 4, followed by twice weekly for weeks 5 to 12. Sixteen of the 29 patients achieved an overall response by the end of week 4 without the need for next-line systemic treatment. Similar trends were seen in 2 additional sensitivity analysis that excluded patients with incomplete organ system assessment data at baseline and incomplete organ system assessment data at baseline or week 4. The most common treatment-related adverse event was nausea. Kozlov et al (2021) performed a retrospective analysis of pediatric patients with steroid-refractory chronic GVHD (n=42). Patients received ECP for 2 consecutive days bimonthly, with a reduction in frequency according to response. Complete and partial response rates were 17% and 57%, respectively. Overall response rates by organ involvement were 75% for skin, 73% for mucous membranes, 80% for liver, 80% for gut, 22% for lungs, and 67% for joints. After a median follow-up of 774 days, 5-year OS survival was 57%, and progression-free survival were 56%.

National Comprehensive Cancer Network guidelines on primary cutaneous lymphomas (v. 1.2024) states, “ECP has been demonstrated as an effective treatment option in many retrospective studies, resulting in an overall response rate (ORR) of 42% to 74%. In a meta-analysis involving more than 400 patients with mycosis fungoides (MF) and Sézary syndrome (SS), ECP as monotherapy resulted in a 56% ORR with a 15% complete response (CR).” “ECP is generally given for at least 6 months and may be more appropriate as systemic therapy for patients with or at risk of blood involvement (B1 or B2; erythrodermic stage III disease or IVA with SS).”

Kuzmina et al (2015) reviewed the evidence of ECP use in the treatment of autoimmune disease (AID). They summarized outcomes related to the use of ECP for treatment of 9 major AID: atopic dermatitis, oral lichen planus, systemic sclerosis (SS), systemic lupus erythematous (SLE), nephrogenic systemic fibrosis (NSF), multiple sclerosis (MS), diabetic mellitus type I (DMI), rheumatoid arthritis (RA), and psoriasis. They found that existing evidence demonstrated substantial ECP feasibility, safety and in some AID also promising effectiveness. The authors concluded that the role of ECP in AID therapy is not established as most published studies were retrospective with limited number of patients and the trials were small or poorly standardized. They stated “(i)t is currently too early to draw any conclusions concerning whether long-term treatment with ECP can effectively lead to clinical benefit. The existing data after 25 years of experience clearly demonstrate safety and feasibility of ECP. However, to better

determine its role as a potential standard therapy in AID, randomized and well-planned prospective controlled trials are necessary."

POSITION STATEMENT:

Organ Rejection after Solid-Organ Transplant

Extracorporeal photopheresis **meets the definition of medical necessity** to treat cardiac allograft rejection, including acute rejection, that is either recurrent or that is refractory to standard immunosuppressive drug treatment.

Extracorporeal photopheresis **meets the definition of medical necessity** to treat lung transplant rejection (bronchiolitis obliterans syndrome, chronic lung allograft dysfunction), including acute rejection, that is either recurrent or that is refractory to standard immunosuppressive drug treatment.

Extracorporeal photopheresis is considered **experimental or investigational** for all other indications related to treatment or prevention of rejection in solid-organ transplantation.

Acute Graft-Versus-Host Disease

Extracorporeal photopheresis **meets the definition of medical necessity** as a technique to treat acute graft-versus-host disease that is refractory to medical therapy.

Extracorporeal photopheresis is considered **experimental or investigational** as a technique to treat acute graft-versus-host disease that is either previously untreated or is responding to established therapies.

Chronic Graft-Versus-Host Disease

Extracorporeal photopheresis **meets the definition of medical necessity** as a technique to treat chronic GVHD that is refractory to medical therapy.

Extracorporeal photopheresis is considered **experimental or investigational** as a technique to treat chronic GVHD that is either previously untreated or is responding to established therapies.

Cutaneous T-cell Lymphoma

Extracorporeal photopheresis **meets the definition of medical necessity** as a technique to treat:

- Late-stage (III/IV) cutaneous T-cell lymphoma, **OR**
- Early stage (I/II) cutaneous T-cell lymphoma that is progressive and refractory to established nonsystemic therapies.

Extracorporeal photopheresis is considered **experimental or investigational** as a technique to treat early stage (I/II) cutaneous T-cell lymphoma that is either previously untreated or is responding to established non-systemic therapies.

Autoimmune Diseases

Extracorporeal photopheresis is considered **experimental or investigational** as a technique to treat either the 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, or Crohn's disease.

Other

The use of extracorporeal photopheresis **for all other indications** is considered **experimental or investigational**. The clinical evidence in peer-reviewed literature is insufficient to permit conclusions on efficacy and net health outcomes for indications other than those noted above.

BILLING/CODING INFORMATION:

CPT Coding:

36522	Photopheresis, extracorporeal

ICD-10 Diagnosis Codes That Support Medical Necessity:

C84.00 – C84.09	Mycosis fungoides
C84.10 – C84.19	Sezary's disease
D89.810 – D89.813	Graft-versus-host disease
T86.00 – T86.09	Complications of bone marrow transplant
T86.21 – T86.22	Heart transplant rejection or failure
T86.290	Cardiac allograft vasculopathy

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage:

The following National Coverage Determination (NCD) was reviewed on the last guideline reviewed date: Extracorporeal Photopheresis (110.4) located at cms.gov.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

Autoimmune disease: when the body's immune system attacks the cells it is supposed to protect. This is a heterogeneous group of immune-mediated disorders, with some of the most common types being

multiple sclerosis (MS), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and systemic sclerosis/scleroderma.

Graft-versus host disease (GVHD): a rare disorder that can strike persons whose immune system is deficient or suppressed and who have received a bone marrow transplant or a non-irradiated blood transfusion. Symptoms may include skin rash, intestinal problems and liver dysfunction.

Cutaneous T-cell lymphoma (CTCL): a group of disorders characterized by abnormal accumulation of malignant T-cells in the skin, potentially resulting in the development of rashes, plaques and tumors. CTCLs belong to a larger group of disorders known as non-Hodgkin's lymphomas (NHLs).

RELATED GUIDELINES:

None applicable.

OTHER:

Index terms:

Note: The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another and is not intended to represent a complete listing of all products available.

CELLEX®
Extracorporeal photochemotherapy
UVAR® XTS Photopheresis System

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Medical Policy and Coverage Committee on 03/27/25.

GUIDELINE UPDATE INFORMATION:

01/15/13	New Medical Coverage Guideline.
12/15/13	Scheduled review. Revised description, program exceptions section and index terms. Updated references.
10/15/14	Scheduled review. Revised position statement, description section and index terms. Updated references.
10/01/15	Revision; updated ICD10 coding section.
10/15/15	Scheduled review. Position statement maintained. Updated references.
11/01/15	Revision: ICD-9 Codes deleted.
11/15/16	Scheduled review. Position statement maintained. Revised ICD10 coding section. Updated references.
11/15/17	Scheduled review. Position statement maintained. Updated references.
11/15/18	Scheduled review. Revised description section. Maintained position statement. Updated references.
10/15/19	Scheduled review. Maintained position statement and updated references.
05/15/21	Scheduled review. Revised description and maintained position statement. Updated references.

05/15/23	Scheduled review. Maintained position statement and updated references.
05/22/23	Update to Program Exceptions section.
05/15/24	Scheduled review. Revised description, maintained position statement and updated references.
04/15/25	Scheduled review. Revised description. Added coverage criteria for treatment of rejection of lung transplant. Updated references.