MEDICAL POLICY

Excellus
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Medical Policy Title	**Extracorporeal Photochemotherapy/Photopheresis**
Policy Number	**8.01.01**
Current Effective Date	**October 16, 2025**
Next Review Date	**October 2026**

Our medical policies are based on the assessment of evidence based, peer-reviewed literature, and professional guidelines. Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract. (Link to Product Disclaimer)

POLICY STATEMENT(S)

I. Extracorporeal photochemotherapy (ECP), or photopheresis is considered **medically appropriate** for **ANY** of the following indications:

   A. Palliative treatment of the skin manifestations of cutaneous T-cell lymphoma (CTCL) [also called mycosis fungoides (MF)] Sézary syndrome (SS) that have not responded to other therapy;

   B. Acute and chronic extensive graft-versus-host disease (GVHD) that is refractory to conventional therapy;

   C. Cardiac allograft rejection that is recurrent or refractory to immunosuppressive treatment.

II. The use of ECP (photopheresis) is considered **investigational** for **ALL** other indications, including, but not limited to, the treatment of:

   A. Acute or chronic GVHD in previously untreated patients or those responding to conventional therapy;

   B. Lyme disease;

   C. Scleroderma (a.k.a. progressive systemic sclerosis (PSS), systemic sclerosis (SS), dermatosclerosis, or CREST syndrome);

   D. Autoimmune diseases (e.g., pemphigus vulgaris, pemphigus foliaceus, psoriatic arthritis, rheumatoid arthritis, systemic lupus erythematosus, severe atopic dermatitis);

   E. Crohn's disease;

   F. Allograft rejections of solid organs other than the heart;

   G. Diabetes Mellitus.

RELATED POLICIES

Corporate Medical Policy

11.01.03 Experimental or Investigational Services

POLICY GUIDELINE(S)

Not Applicable

DESCRIPTION

ECP, or photopheresis, is an immune-modulating therapy technique used in the treatment of certain skin disorders. It involves an oral intake of 8-methoxypsoralen (8-MOP) and cytopheresis, or addition of 8-MOP to the cells after removal, followed by ultraviolet actinotherapy (UVA) irradiation and reinfusion of leukocytes into the patient.

SUPPORTIVE LITERATURE

Connelly-Smith et al (2023) states the overall response rate of CTCL to ECP is approximately 60% with complete response rates of 14% to 26%. Response to ECP correlates with short duration of disease, early use of ECP in the treatment paradigm, lower blood Sézary cell burden and significant early response of skin lesions (i.e., >50% regression within 6 months).

Sener et al (2025) noted that primary CTCLs are characterized by high relapse rates to initially highly effective therapies. Combination therapies have proven beneficial, especially if they incorporate ECP. This study investigated the synergistic effects of dimethyl fumarate (DMF) and ECP in treating CTCL, particularly SS. In vitro experiments using CTCL cell lines (HH, HuT 78, SeAx) and patient-derived SS cells demonstrated that the combination therapy significantly enhanced cell death compared to either treatment alone. Mechanistically, the combination led to increased inhibition of NF-κB signaling, elevated reactive oxygen species (ROS) production, and reduced thioredoxin reductase activity and glutathione levels—indicating oxidative stress-mediated cytotoxicity. A cell death inhibitor screen revealed that the DMF/ECP combination induced multiple cell death pathways, including apoptosis and necroptosis. Clinically, four patients with advanced CTCL were treated with this combination therapy, achieving a 100% overall response rate. Notably, the time to next treatment in skin and blood compartments extended up to 57 months, suggesting durable remission. These findings support the DMF/ECP combination as a potent and long-lasting therapeutic strategy for CTCL, warranting further clinical investigation in larger cohorts. There are several limitations to this study which suggest that, while the DMF/ECP combination is promising, larger, controlled clinical trials are needed to validate its efficacy and safety across diverse patient populations.

Evidence supporting the use of ECP for the treatment of GVHD relates to both acute GVHD (aGVHD) and chronic GVHD (cGVHD) in pediatric and adult populations. The published literature lacks randomized trials. Evidence comprises retrospective reviews and non-randomized comparisons. The data consistently show improvement in GVHD that is unresponsive to standard therapy. Additionally, there is a lack of other treatment options for these patients, and this option has the added benefit of minimal side effects from ECP, as well as the possibility of reduction and often cessation of treatment with corticosteroids and other immunosuppressive agents, if there is a response to ECP. For patients with untreated disease or those who are showing improvement on standard therapy, there is no data to support the use of ECP.

Scleroderma is the most studied of the autoimmune diseases utilizing photopheresis, but the efficacy of photopheresis for these diseases, as yet, has not been demonstrated in well-designed clinical trials.

Photopheresis alone, or in combination with immunosuppressive therapy is also being investigated in the treatment of solid organ transplant rejection. While ECP has been utilized for prevention of cardiac allograft rejection and acute rejection, the strongest evidence in cardiac transplant patients revolves around its use for recurrent and refractory allograft rejection. While the evidence consists of non-randomized studies, the outcomes from these studies provide consistent evidence of the beneficial effect of ECP for cardiac transplant patients with rejection refractory to standard therapy. There is insufficient evidence to support the use of ECP for graft rejection in other solid organs, such as lung, liver, and kidney. Though preliminary results are promising, additional studies with longer follow-up are needed, to evaluate the ultimate effect of photopheresis on patient survival.

Benazzo et al (2024) conducted a prospective randomized controlled trial that evaluated the efficacy of ECP as a prophylactic treatment to prevent rejection after lung transplantation. The study included 62 patients with COPD who underwent lung transplantation, split evenly between a treatment group receiving ECP alongside standard triple-drug immunosuppression and a control group receiving only the standard regimen. The primary composite endpoint, incidence of high-grade acute cellular rejection (ACR), cytomegalovirus (CMV) infection, or chronic lung allograft dysfunction (CLAD) within 24 months, was significantly lower in the ECP group (19.4%) compared to the control group (61.3%) ($p<0.001$). Freedom from high-grade ACR was notably higher in the ECP group ($p=0.045$), and cumulative A scores were significantly reduced at both three months (0.18 ± 0.44 vs. 0.56 ± 0.94; $p<0.05$) and 12 months (0.25 ± 0.48 vs. 1.0 ± 1.45; $p=0.002$). Additionally, the ECP group experienced fewer infections (five cases vs. 22 cases) and significantly fewer hospital days (67 vs. 309; $p=0.002$). At three years post-transplant, freedom from CLAD was also significantly greater in the ECP group ($p=0.015$). These findings suggest that adding ECP to standard immunosuppressive therapy can substantially reduce the risk of both acute and chronic rejection, improve infection outcomes, and enhance long-term transplant success. However, there are several limitations to this study including single-center design, small sample size, heterogeneous patient selection, lack of blinding, limited mechanistic insight, short follow up and need for multicenter validation.

PROFESSIONAL GUIDELINE(S)

National Comprehensive Cancer Network guidelines on primary cutaneous lymphomas (v.3.2025) 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 patients with earlier stage mycosis fungoides with Sézary syndrome involvement. The guidelines add that ECP may be more appropriate as systemic therapy in patients with or at risk of blood involvement (B1 or B2).

The terms B1 and B2 refer to levels of blood involvement as part of the TNMB staging system:

- B1 (Low blood involvement): Indicates a moderate presence of malignant T-cells in the blood. This level may occur at any disease stage except for stage IIIA. It is associated with inferior survival, even in early-stage Mycosis Fungoides.
- B2 (High blood involvement): Represents advanced disease with a high burden of malignant T-cells in the blood. It is typically seen in Sézary Syndrome and is linked to significantly worse prognosis, including a 4.6-fold increased risk of disease progression.

In 2024, the European Society for Blood and Marrow Transplantation published updated prophylaxis and management guidelines for acute and chronic GVHD. 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.

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 Sezary syndrome or erythrodermic mycosis fungoides.

REGULATORY STATUS

The U.S. Food and Drug Administration (FDA) has approved, via premarket application, two photopheresis systems manufactured by Therakos, Inc. (West Chester, PA). Both systems are approved for use in ultraviolet A (UVA) irradiation treatment, in the presence of the photoactive drug 8-methoxypsoralen (8-MOP), of extracorporeally circulating leukocyte-enriched blood, in the palliative treatment of skin manifestations of cutaneous T-cell lymphoma (CTCL), in persons who have not been responsive to other forms of treatment. The two systems are: the UVAR XTS Photopheresis System, FDA-approved in 1987, and CELLEX, FDA-approved in 2009. Treatment of GVHD is considered an off-label use of the device. Therefore, the use for treatment of autoimmune disease is considered off-label use.

The United States Food and Drug Administration (FDA) regulates photopheresis systems as medical devices. All photopheresis systems including related components require FDA approval before marketing and use in the United States to ensure they are safe and effective for human use. Refer to the FDA Medical Device website. Available from: https://www.fda.gov/medical-devices [accessed 2025 Sept 15].

The FDA lists the most serious type of medical device recalls as well as early alert communications about corrective actions being taken by companies that the FDA believes are likely to be the most serious type of recalls. Available from: Medical Device Recalls | FDA [accessed 2025 Sept 15].

CODE(S)

- Codes may not be covered under all circumstances.
- Code list may not be all inclusive (AMA and CMS code updates may occur more frequently than policy updates).
- (E/I)=Experimental/Investigational
- (NMN)=Not medically necessary/appropriate

CPT Codes

Code	Description
36522	Photopheresis, extracorporeal

HCPCS Codes

Code	Description
No Applicable	

ICD10 Codes

Code	Description
C84.00-C84.09	Mycosis fungoides (code range)
C84.10-C84.19	Sézary syndrome (code range)
D89.810-D89.813	Graft-versus-host disease (code range)
T86.00-T86.09	Complication of bone marrow transplant (code range)
T86.20-T86.39	Complications of heart transplant or heart-lung transplant (code range)

REFERENCES

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Connelly-Smith L, et al. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the writing committee for the American society for apheresis: the ninth special issue. J Clin Apher. 2023 Apr;38(2):77-278.

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National Institute for Health and Clinical Excellence (NICE) [Internet. Interventional procedure guidance 288. Extracorporeal photopheresis for Crohn's disease. 2009 Feb 25. [accessed 2025 Sept 15]. Available from: https://www.nice.org.uk/guidance/ipg288

Penack O, et al. Prophylaxis and management of graft-versus-host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation. Lancet Haematol. Feb 2024; 11(2): e147-e159.

Sener OC, et al. Dimethyl fumarate and extracorporeal photopheresis combination-therapy synergize in inducing specific cell death and long-term remission in cutaneous T cell lymphoma. Leukemia. 2025 Feb;39(2):438-450.

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SEARCH TERMS

Not Applicable

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

NCD - Extracorporeal Photopheresis (110.4) [accessed 2025 Aug 29]

PRODUCT DISCLAIMER

- Services are contract dependent; if a product does not cover a service, medical policy criteria do not apply.
- If a commercial product (including an Essential Plan or Child Health Plus product) covers a specific service, medical policy criteria apply to the benefit.
- If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.
- If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.
- If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.

POLICY HISTORY/REVISION

Committee Approval Dates

11/19/99, 01/17/02, 11/21/02, 10/15/03, 08/19/04, 06/16/05, 04/20/06, 02/15/07, 02/21/08, 01/15/09, 12/17/09, 01/20/11, 12/15/11, 12/20/12, 12/19/13, 11/20/14, 10/15/15, 10/20/16, 10/19/17, 11/15/18, 11/21/19, 11/19/20, 11/18/21, 11/17/22, 10/19/23, 10/17/24, 10/16/25

Date	Summary of Changes
10/16/25	• Annual review; policy intent unchanged.
01/01/25	• Summary of changes tracking implemented.
11/19/99	• Original effective date