Medical Coverage Policy

Effective Date.....8/15/2023
Next Review Date.....8/15/2024
Coverage Policy Number..... 0320

Extracorporeal Photopheresis

Table of Contents

Related Coverage Resources

Heart, Lung and Heart-Lung Transplantation
Plasmapheresis

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy addresses the use of extracorporeal photopheresis (ECP) (CPT® 36522).

Coverage Policy

Extracorporeal photopheresis is considered medically necessary for ANY of the following indications:

- erythrodermic cutaneous T-cell lymphoma (CTCL) (e.g., mycosis fungoides and Sézary syndrome)
- acute or chronic graft-versus-host disease (GVHD)
- cardiac transplantation (rejection prophylaxis or cellular/recurrent rejection)
- lung transplantation (bronchiolitis obliterans syndrome, chronic lung allograft dysfunction)

Extracorporeal photopheresis is considered experimental, investigational or unproven for ANY other indication, including ANY of the following:

- 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
- eosinophillic 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 ECP, is a type of apheresis. It is a cell-based immunomodulatory therapy that removes blood via a machine and isolates white blood cells. Then, these white blood cells are exposed to a photoactive compound called 8-methoxypsoralen followed by exposure to ultraviolet A light before returning the blood to the patient. The mechanism of action of ECP remains elusive. ECP produces a number of immunological changes and in some patients produces immune homeostasis with clinical improvement. 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, graft-versus-host disease, solid organ graft rejection, and several autoimmune disorders and dermatologic conditions.

U.S. Food and Drug Administration (FDA)
ECP was first approved by the FDA for the treatment of advanced cutaneous T-cell lymphoma (CTCL) in 1988.
A number of open and closed systems exist. In the United States, only closed systems have been FDA approved. Therakos (Exton, PA) has developed several generations of closed systems. The closed system CELLEX has recently replaced the UVAR XTS®.

Professional Societies/Organizations

The Writing Committee of the American Society for Apheresis (ASA) updated their Guidelines on the Use of Therapeutic Apheresis in Clinical Practice in 2023 (Connelly-Smith, et al., 2023). Using an evidence-based approach, the ASA developed Category Definitions for Therapeutic Apheresis as follows:

- Category I: Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.
- Category II: Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.
- Category III: Optimum role of apheresis therapy is not established. Decision making should be individualized.
- Category IV: Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful.

and evidence grading 'Grade' descriptions as follows:

- Grade 1A: Strong recommendation, high-quality evidence
- Grade 1B: Strong recommendation, moderate quality evidence
- Grade 1C: Strong recommendation, low-quality or very low-quality evidence
- Grade 2A: Weak recommendation, high-quality evidence
- Grade 2B: Weak recommendation, moderate-quality evidence
- Grade 2C: Weak recommendation, low-quality or very low-quality evidence

The ASA defines ECP as a therapeutic procedure in which the buffy coat is separated from the patient's blood, treated extracorporeally with a photoactive compound (e.g., psoralens) and exposed to ultraviolet A light then subsequently reinfused to the patient during the same procedure.

The ASA addressed these following indications specific to ECP (organized by Category and Grade):

Indication	Category	Grade
Cutaneous T-cell lymphoma; mycosis fungoides; Sezary syndrome (Erythrodermic)	I	IB
Cardiac transplantation, Cellular/recurrent rejection	II	IB
Graft-versus-host disease, (Chronic)	II	IB
Graft-versus-host disease, (Acute)	II	IB
Lung transplantation, Chronic lung allograft dysfunction	II	IC
Lung transplantation, Bronchiolitis obliterans syndrome	II	IC
Cardiac transplantation, Rejection prophylaxis	II	2A
Systemic sclerosis	III	2A
Atopic dermatitis, recalcitrant	III	2B
Psoriasis, Disseminated pustular	III	2B
Transplantation, liver, Antibody mediated rejection/Immune suppression withdrawal	III	2B
Cutaneous T-cell lymphoma; Non-erythrodermic mycosis fungoides	III	2B
Transplantation, liver, Desensitization, ABOi	III	2C
Inflammatory bowel disease, Crohn's Disease	III	2C
Nephrogenic systemic fibrosis	III	2C
Pemphigus vulgaris, Severe	III	2C

National Comprehensive Cancer Network Guidelines™ ([NCCN Guidelines™]): The Primary Cutaneous Lymphoma guideline (Version 1.2023 — January 5, 2023) notes that ECP is one of several suggested treatment regimens for patients with mycosis fungoides/Sezary syndrome.

Literature Review
ECP has been used for over 35 years in the treatment of erythrodermic CTCL and over 20 years for chronic and acute GvHD and solid organ transplant rejection. ECP is also used in bronchiolitis obliterans syndrome, the most common form of chronic lung allograft dysfunction (CLAD).

In a retrospective review of all patients treated for mycosis fungoides (MF) at a single US facility between 1999 and 2011, 65 patients with stage III or IV disease were identified including 20 Black and 45 Caucasian individuals (Agi, et al., 2014). Results of the retrospective review demonstrated these racial disparities:

- Only 7 of 20 Black patients (35%) compared with 30 of 45 (66%) of Caucasian patients were treated with ECP (p=0.029).
- In addition, ECP was discussed as an option for 45% of Blacks compared to 82% of Caucasians (p=0.007).
- When discussed as an option, Blacks and Caucasians had identical rates of ECP use (78% vs 81%, p=0.841).

Use of ECP in the following proposed indications (organized by American Society for Apheresis Category and Grade) is not considered standard of care:

- Systemic sclerosis (SSc) is a systemic connective tissue disorder of unknown etiology characterized by the accumulation of collagen and other extracellular matrix proteins, in skin and other organs. Antinuclear antibodies are present in more than 95% of patients with SSc. Identifying disease subtype, stage, and involved organs is very important in determining the best course of action for treatment. Current therapies use medications that focus on the four main features of the disease: inflammation, autoimmunity, vascular disease, and tissue fibrosis.

- Psoriasis is a chronic skin disorder with high genetic predisposition. Plaques and papules are result of hyperproliferation and abnormal differentiation of epidermis which leads to its thickening (acanthosis). There are topical and systemic therapies. Systemic therapies include methotrexate, retinoids, systemic immunosuppression (cyclosporine). Recently, biologic agents are used more frequently.

- Atopic dermatitis (AD), or eczema, is the most common chronic relapsing skin disease seen in infancy and childhood. It affects 10–30% of children worldwide and frequently occurs in families with other atopic diseases. The treatment of AD requires a systematic, multifaceted approach that incorporates skin hydration, topical anti-inflammatory therapy (including tacrolimus), identification, and elimination of flare factors (especially foods), and, if necessary, systemic therapy. In refractory disease phototherapy (UVA-1, UVB, or PUVA) are used.

- Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory diseases of the gastrointestinal tract and are collectively known as inflammatory bowel disease (IBD). First-line therapies for IBD include anti-inflammatories, steroid, and immunosuppressive medications. Both corticosteroids and 5- aminosalicylic acids (5-ASAs) are effective in achieving remission. In addition, 5-ASAs and immunosuppressant drugs reduce the risk of subsequent relapse of activity in quiescent disease. Unfortunately, complications from

chronic steroid administration include steroid resistance, dependency, and the sequelae of long-term steroid use. For those with refractory disease thiopurines, such as azathioprine and 6- mercaptopurine are used. In CD specifically, infliximab, monoclonal antibody to anti-tumor necrosis factor, may induce remission and has been FDA cleared for this purpose.

- Nephrogenic systemic fibrosis (NSF), formerly called nephrogenic fibrosing dermopathy, is a rare but severe systemic disorder in patients with acute or chronic kidney disease (CKD), almost exclusively associated with the administration of gadolinium (Gd) containing contrast agents. Avoidance of Gd administration, if possible, has been recommended for patients with GFR <30 mL/min; resulting in decreased reports of new cases. Replacement of renal function through renal transplant has been associated with cessation of progression and reversal in some patients. It should be noted that dialysis has not been associated with improvement once symptoms are established. Initiation of prophylactic hemodialysis shortly after exposure to Gd may decrease the likelihood of the harmful effect.

- Pemphigus vulgaris is a rare, potentially fatal, autoimmune mucocutaneous blistering disease. Introduction of corticosteroids reduced the mortality rate from 70 to 100% to 30%. However, long-term administration of high dose corticosteroids can be associated with severe adverse effects. Other therapeutic options include dapsone, gold, and systemic antibiotics, which are often used in combination with other immunosuppressant agents (azathioprine, methotrexate, and cyclophosphamide).

- Dermatomyositis (DM)/polymyositis (PM) are forms of idiopathic inflammatory myopathy, with significant morbidity and mortality even with standard treatments. Muscle weakness, usually insidious at onset but worsening over time, is characteristic of both. Severity is variable. Most patients respond to corticosteroid therapy initially. Recurrent or resistant disease may require higher corticosteroid doses, azathioprine, methotrexate, rituximab, or intravenous immune globulin. Remission occurs in most of the patients after months of immunosuppressive and intensive supportive therapy, especially in juvenile DM.

Use Outside of the US
The UK Photopheresis Society updated their consensus statement on the role of extracorporeal photopheresis in the management of cutaneous T-cell lymphoma, graft-versus-host disease and organ transplant rejection (Alfred, et al., 2017). The Consensus Statements address patient selection, treatment schedules, monitoring protocols and patient assessment criteria for ECP

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	Extracorporeal PHOTOPHERESIS (110.4)	4/20/2012
LCD		No Determination found	

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Coding Information

Notes:
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.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
36522	Photopheresis, extracorporeal

***Current Procedural Terminology (CPT®) ©2022 American Medical Association: Chicago, IL.**

References

1. Agi C, Kuhn D, Chung J, Zampella J, Hinds G. Racial differences in the use of extracorporeal photopheresis for mycosis fungoides. J Dermatolog Treat. 2015 Jun;26(3):266-8.

2. Alfred A, Taylor PC, Dignan F, El-Ghariani K, Griffin J4, Gennery AR. The role of extracorporeal photopheresis in the management of cutaneous T-cell lymphoma, graft-versus-host disease and organ transplant rejection: a consensus statement update from the UK Photopheresis Society. Br J Haematol. 2017 Apr;177(2):287-310.

3. Benden C, Haughton M, Leonard S, Huber LC. Therapy options for chronic lung allograft dysfunction-bronchiolitis obliterans syndrome following first-line immunosuppressive strategies: A systematic review. J Heart Lung Transplant. 2017 Sep;36(9):921-933.

4. Buder K, Zirngibl M, Bapistella S, Meerpohl JJ, Strahm B, et al. Extracorporeal photopheresis versus alternative treatment for chronic graft-versus-host disease after haematopoietic stem cell transplantation in children and adolescents. Cochrane Database Syst Rev. 2022 Jun 9;6(6):CD009898.

5. Buder K, Zirngibl M, Bapistella S, Meerpohl JJ, Strahm B, et al. Extracorporeal photopheresis versus standard treatment for acute graft-versus-host disease after haematopoietic stem cell transplantation in children and adolescents. Cochrane Database Syst Rev. 2022 Sep 27;9(9):CD009759.

6. Centers for Medicare and Medicaid Services (CMS). National Coverage Determination (NCD) for Extracorporeal Photopheresis (110.4). 2012. Accessed June 2023. Available at URL address: https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=113&ncdver=3&SearchType=Advanced&CoverageSelection=Both&NCSelection=NCA%7cCAL%7cNCD%7cMEDCAC%7cTA%7cMCD&ArticleType=SAD%7cEd&PolicyType=Both&s=All&KeyWord=Extracorporeal+Photopheresis&KeyWordLookUp=Title&KeyWordSearchType=Exact&kq=true&bc=IAAAACAAAAAAAA%3d%3d&

7. Connelly-Smith L, Alquist CR, Aqui NA, Hofmann JC, Klingel R et al. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice - Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Ninth Special Issue. J Clin Apher. 2023 Apr;38(2):77-278.

8. Du AX, Osman M, Gniadecki R. Use of Extracorporeal Photopheresis in Scleroderma: A Review. Dermatology. 2020;236(2):105-110.

9. Jagasia M, Scheid C, Socié G, Ayuk FA, Tischer J, et al. Randomized controlled study of ECP with methoxsalen as first-line treatment of patients with moderate to severe cGVHD. Blood Adv. 2019 Jul 23;3(14):2218-2229.

10. Knobler R, Arenberger P, Arun A, Assaf C, Bagot M, et al. European dermatology forum - updated guidelines on the use of extracorporeal photopheresis 2020 - part 1. J Eur Acad Dermatol Venereol. 2020 Dec;34(12):2693-2716.

11. Knobler R, Berlin G, Calzavara-Pinton P, Greinix H, Jaksch P, Laroche L, et al. Guidelines on the use of extracorporeal photopheresis. J Eur Acad Dermatol Venereol. 2014 Jan;28 Suppl 1:1-37.

12. Malik MI, Litzow M, Hogan W, Patnaik M, Murad MH, Prokop LJ, et al. Extracorporeal photopheresis for chronic graft-versus-host disease: a systematic review and meta-analysis. Blood Res. 2014 Jun;49(2):100-6..

13. Mayo Clinic. Disease and Conditions. Accessed June 2023. Available at URL address: https://www.mayoclinic.org/diseases-conditions

14. National Comprehensive Cancer Network ® (NCCN). NCCN GUIDELINES™ Clinical Guidelines in Oncology™. Primary Cutaneous Lymphomas. Version 1.2023 — January 5, 2023. ©National Comprehensive Cancer Network, Inc 2023 All Rights Reserved. Accessed June 2023. Available at URL address: https://www.nccn.org/professionals/physician_gls/pdf/primary_cutaneous.pdf

15. Reinisch W, Knobler R, Rutgeerts PJ, Ochsenkühn T, Anderson F, et al. Extracorporeal photopheresis (ECP) in patients with steroid-dependent Crohn's disease: an open-label, multicenter, prospective trial. Inflamm Bowel Dis. 2013 Feb;19(2):293-300.

16. U.S. Food and Drug Administration. Center for Devices and Radiological Health (CDRH). PMA Approval. THERAKOS CELLEX PHOTOPHERESIS SYSTEM. 1987. Accessed June 2023. Available at URL address: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P860003S083 http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?start_search=1&sortcolumn=do_desc&PAGENUM=500&pmanumber=P860003

17. Valipour A, Jäger M, Wu P, Schmitt J, Bunch C, Weberschock T. Interventions for mycosis fungoides. Cochrane Database Syst Rev. 2020 Jul 7;7(7):CD008946