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Subject: Extracorporeal Photopheresis

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

[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.

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 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
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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.

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

REFERENCES:

1. Afram G, Watz E, et al. Higher response rates in patients with severe chronic skin graft-versus-host disease treated with extracorporeal photopheresis. *Cent Eur J Immunol.* 2019;44(1):84-91. doi: 10.5114/ceji.2018.75831. Epub 2019 Apr 15.
2. Agency for Healthcare Research and Quality (AHRQ). Guideline Summary NGC-9103: Diagnosis and management of acute graft-versus-host disease. British Committee for Standards in Haematology - British Society of Blood and Marrow Transplantation. *Br J Haematol* 2012 Jul;158(1):30-45.
3. Agency for Healthcare Research and Quality (AHRQ). Guideline Summary NGC-9104: Diagnosis and management of chronic graft-versus-host disease. Haemato-oncology Task Force of the British Committee. *Br J Haematol.* 2012 Jul;158(1):46-61.
4. Agency for Healthcare Research and Quality (AHRQ). Guideline Summary NGC-9106. Organ-specific management and supportive care in chronic graft-versus-host disease. British Committee for Standards in Haematology - British Society of Blood and Marrow Transplantation. *Br J Haematol* 2012 Jul;158(1):62-78.
5. Agency for Healthcare Research and Quality (AHRQ). Guideline Summary NGC-10034: Extracorporeal photopheresis in the management of graft-versus-host disease in patients who have received allogeneic blood or bone marrow transplants: recommendations. Stem Cell Transplant Steering Committee. Toronto (ON): Cancer Care Ontario (CCO); 2013 Aug 29.
6. Alfred A, et al. 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.
7. Barr ML, Meiser BM, Eisen HJ et al. Photopheresis for the prevention of rejection in cardiac transplantation. Photopheresis Transplantation Study Group. *N Engl J Med* 1998; 339(24):1744-51.
8. Belizaire R, Kim HT, et al. Efficacy and immunologic effects of extracorporeal photopheresis plus interleukin-2 in chronic graft-versus-host disease. *Blood Adv.* 2019 Apr 9;3(7):969-979. doi: 10.1182/bloodadvances.2018029124.
9. Berger M, Albiani R, Sini B, Fagioli F. Extracorporeal photopheresis for graft-versus-host disease: the role of patient, transplant, and classification criteria and hematologic values on outcome-results from a large single-center study. *Transfusion.* 2014 Oct 29.
10. Blue Cross Blue Shield Association Evidence Positioning System®. 8.01.36 - Extracorporeal Photopheresis, 11/20.
11. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Extracorporeal photopheresis for autoimmune disease. TEC Assessments 2001; Volume 16, Tab 10.
12. Bredeson C, Rumble RB, Varela NP, Kuruvilla J, Kouroukis CT; Stem Cell Transplant Steering Committee. Extracorporeal photopheresis in the management of graft-versus-host disease. *Curr Oncol.* 2014 Apr;21(2):e310-25.
13. Brown TJ, Gentry C, et al. Novel Application of Extracorporeal Photopheresis as Treatment of Graft-versus-Host Disease Following Liver Transplantation. *ACG Case Rep J.* 2017 Mar 29;4:e48.
14. Centers for Medicare and Medicaid Services. National Coverage Determination (NCD) for Extracorporeal Photopheresis (110.4). 04/30/12.
15. Cho A, et al. Extracorporeal Photopheresis-An Overview. *Front Med (Lausanne).* 2018 Aug 27;5:236. doi: 10.3389/fmed.2018.00236. eCollection 2018.
16. Cid J, Carbassé G, et al. Efficacy and safety of one-day offline extracorporeal photopheresis schedule processing one total blood volume for treating patients with graft-versus-host disease. *Transfusion.* 2019 Aug;59(8):2636-2642. doi: 10.1111/trf.15384. Epub 2019 May 28. PMID: 31135994.

17. ClinicalTrials.gov. NCT00054600. Safety and Efficacy Study of Photopheresis With UVADEX to Prevent Graft-versus-Host Disease. Therakos: last updated 04/07/10.
18. ClinicalTrials.gov. NCT00157001. Feasibility Study of Photopheresis Post Angioplasty. Therakos: last updated 03/29/11.
19. ClinicalTrials.gov. NCT00609609. Photopheresis for the Treatment of Acute Graft Versus Host Disease. M.D. Anderson Cancer Center: last updated 09/06/12.
20. ClinicalTrials.gov. NCT01174940. Test Extracorporeal Photopheresis (ECP) Treatment Before/After Allogeneic Bone Marrow Transplant (BMT) or Peripheral Blood Stem Cell (PBSC) Transplant to Prevent Graft Versus Host Disease. University of Kansas: last updated 08/14/12.
21. ClinicalTrials.gov. NCT02226068: Photopheresis Versus Ciclosporine in Severe Atopic Dermatitis. University of Aarhus (March 2015).
22. ClinicalTrials.gov. NCT03500575: Extracorporeal Photopheresis in Lung Transplant Rejection for Cystic Fibrosis (CF) Patients (PHORLUCY). Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico (May 2018).
23. Das-Gupta E, et al. Extracorporeal photopheresis as second-line treatment for acute graft-versus-host disease: Impact on six month freedom from treatment failure. *Haematologica* January 2014.
24. Das-Gupta E, Dignan F, Shaw B, et al. Extracorporeal photopheresis for treatment of adults and children with acute GVHD: UK consensus statement and review of published literature. *Bone Marrow Transplant*. Oct 2014;49(10):1251-1258.
25. De Waure C, et al. Extracorporeal Photopheresis for Second-Line Treatment of Chronic Graft-versus-Host Diseases: Results from a Health Technology Assessment in Italy. *Value Health*. 2015 Jun;18(4):457-66. doi: 10.1016/j.jval.2015.01.009. Epub 2015 Apr 16.
26. Du AX, Osman M, Gniadecki R. Use of Extracorporeal Photopheresis in Scleroderma: A Review. *Dermatology*. 2019 Jul 30:1-6. doi: 10.1159/000501591.
27. Fernández EJ, López C, Ramírez A, Guerra R, López L, Fernández F, Tapia M, García-Cantón C. Role of photopheresis in the treatment of refractory cellular rejection in kidney transplantation. *Nefrologia*. 2016 May-Jun;36(3):327-8.
28. Flinn AM, Gennery AR. Extracorporeal photopheresis treatment of acute graft-versus-host disease following allogeneic haematopoietic stem cell transplantation. *F1000Res*. 2016 Jun 27;5. pii: F1000 Faculty Rev-1510.
29. Flinn AM, Gennery AR. Treatment of Pediatric Acute Graft-versus-Host Disease-Lessons from Primary Immunodeficiency? *Front Immunol*. 2017 Mar 21;8:328.
30. Greer M, et al. Phenotyping established chronic lung allograft dysfunction predicts extracorporeal photopheresis response in lung transplant patients. *Am J Transplant*. 2013 Apr;13(4):911-8.
31. Greinix HT, Knobler RM, Worel N, Schneider B, Schneeberger A, Hoecker P, Mitterbauer M, Rabitsch W, Schulenburg A, Kalhs P. The effect of intensified extracorporeal photochemotherapy on long-term survival in patients with severe acute graft-versus-host disease. *Haematologica*. 2006 Mar;91(3):405-8.
32. Hart JW, Shiue LH, Shpall EJ, Alousi AM. Extracorporeal photopheresis in the treatment of graft-versus-host disease: evidence and opinion. *Therapeutic Advances in Hematology* 4 (5).
33. Hassani J, Feldman SR. Phototherapy in Scleroderma. *Dermatol Ther (Heidelb)*. 2016 Dec;6(4):519-553.
34. Hautmann AH, Wolff D, Hahn J et al. Extracorporeal photopheresis in 62 patients with acute and chronic GVHD: results of treatment with the COBE Spectra System. *Bone marrow transplantation* 2013; 48(3):439-45.

35. Jagasia MH, et al. Classic and Overlap Chronic Graft-versus-Host Disease (cGVHD) Is Associated with Superior Outcome after Extracorporeal Photopheresis (ECP). *Biol Blood Marrow Transplant*. 2009 October; 15(10): 1288–1295.
36. Jagasia M, Greinix H, Robin M et al. Extracorporeal photopheresis versus anticytokine therapy as a second-line treatment for steroid-refractory acute GVHD: a multicenter comparative analysis. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation* 2013; 19(7):1129-33.
37. Klassen J. The role of photopheresis in the treatment of graft-versus-host disease. *Current Oncology—Volume 17, Number 2*. 2010.
38. Knobler R, Arenberger P, 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. doi: 10.1111/jdv.16890. Epub 2020 Oct 6.
39. Knobler R, Arenberger P, et al. European dermatology forum: Updated guidelines on the use of extracorporeal photopheresis 2020 - Part 2. *J Eur Acad Dermatol Venereol*. 2021 Jan;35(1):27-49. doi: 10.1111/jdv.16889. Epub 2020 Sep 22.
40. Koppelhus U, Poulsen J, Grunnet N, Deleuran MS, Obitz E. Cyclosporine and Extracorporeal Photopheresis are Equipotent in Treating Severe Atopic Dermatitis: A Randomized Cross-Over Study Comparing Two Efficient Treatment Modalities. *Front Med (Lausanne)*. 2014 Oct 1;1:33.
41. Lee G, Arepally GM. Anticoagulation techniques in apheresis: from heparin to citrate and beyond. *J Clin Apher*. 2012;27(3):117-25.
42. Ludvigsson J et al. Photopheresis at onset of type 1 diabetes: a randomised, double blind, placebo controlled trial. *Archives of disease in childhood* 85.2 (2001): 149-154.
43. Malik MI, Litzow M, Hogan W, Patnaik M, Murad MH, Prokop LJ, Winters JL, Hashmi S. Extracorporeal photopheresis for chronic graft-versus-host disease: a systematic review and meta-analysis. *Blood Res*. 2014 Jun;49(2):100-6.
44. Margaix-Muñoz M, Bagán JV, Jiménez Y, Sarrión MG, Poveda-Roda R. Graft-versus-host disease affecting oral cavity. A review. *J Clin Exp Dent*. 2015 Feb 1;7(1):e138-45.
45. Martin PJ, et al. First- and second-line systemic treatment of acute graft-versus-host disease: recommendations of the American Society of Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2012 Aug;18(8):1150-63.
46. McGirt LY, et al. Predictors of response to extracorporeal photopheresis in advanced mycosis fungoides and Sézary syndrome. *Photodermatol Photoimmunol Photomed*. 2010 August; 26(4): 182–191.
47. Miguel D, et al. Treatment of Scleroedema Adultorum Buschke: A Systematic Review. *Acta Derm Venereol*. 2018 Mar 13;98(3):305-309. doi: 10.2340/00015555-2846.
48. National Cancer Institute: PDQ® Mycosis Fungoides and the Sézary Syndrome Treatment. Bethesda, MD: National Cancer Institute. Date last modified 08/12/13. Available at: <http://cancer.gov/cancertopics/pdq/treatment/mycosisfungoides/HealthProfessional>. Accessed 11/01/13.
49. National Comprehensive Cancer Network (NCCN). National Comprehensive Cancer Network (NCCN). Non-Hodgkin's Lymphoma. V.3.2012.
50. National Institute for Health and Clinical Excellence (NICE). Interventional procedure guidance 288. Extracorporeal photopheresis for Crohn's disease. February 2009. (Accessed 09/03/14).
51. Oldham M, et al. X-Ray Psoralen Activated Cancer Therapy (X-PACT). *PLoS One*. 2016 Sep 1;11(9):e0162078.
52. Perfetti P, Carlier P, Strada P et al. Extracorporeal photopheresis for the treatment of steroid refractory acute GVHD. *Bone marrow transplantation* 2008; 42(9):609-17.

53. Robinson CA, et al. Cessation of extracorporeal photopheresis in chronic lung allograft dysfunction: effects on clinical outcome in adults. *Swiss Med Wkly*. 2017 May 10;147:w14429.
54. Schwartz J, Padmanabhan A, Aqui N, Balogun RA, 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 Seventh Special Issue. *J Clin Apher*. 2016 Jun;31(3):149-62.
55. Sung AD, Chao NJ. Concise review: acute graft-versus-host disease: immunobiology, prevention, and treatment. *S Stem Cells Transl Med*. 2013 Jan;2(1):25-32.
56. Szczepiorkowski ZM, et al. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice—Evidence-Based Approach from the Apheresis Applications Committee of the American Society for Apheresis. *Journal of Clinical Apheresis* 25:83–177 (2010).
57. Shaughnessy PF et al. Extracorporeal Photopheresis for the Prevention of Acute GVHD in Patients Undergoing Standard Myeloablative Conditioning and Allogeneic Hematopoietic Stem Cell Transplantation. *Bone Marrow Transplant*. 2010 June ; 45(6): 1068–1076.
58. Trautinger F, Knobler R, Willemze R et al. EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome. *Eur J Cancer* 2006; 42(8):1014-30.
59. UpToDate. Treatment of acute graft-versus-host disease. 2020. Accessed at uptodate.com.
60. UpToDate. Treatment of advanced stage (IIB to IV) mycosis fungoides. 2020. Accessed at uptodate.com.
61. UpToDate. Treatment of chronic graft-versus-host disease. 2020. Accessed at uptodate.com.
62. UpToDate. Treatment of Sézary syndrome. 2020. Accessed at uptodate.com.
63. U.S. Food and Drug Administration, UVAR XTS PHOTOPHERESIS SYSTEM- P860003 S047 (02/01/08); THERAKOS UVAR XTS PHOTOPHERESIS SYSTEM- P860003 S049; UVAR XTS PHOTOPHERESIS SYSTEM- P860003 S050.
64. Willemze R. Primary cutaneous lymphomas. *Annals of Oncology* 22 (Supplement 4): iv72–iv75, 2011.
65. Willemze R, Jaffe ES, Burg G et al. WHO-EORTC classification for cutaneous lymphomas. *Blood* 2005; 105(10):3768-85.
66. Worel N, Leitner G. Clinical Results of Extracorporeal Photopheresis. *Transfus Med Hemother*. 2012 Aug;39(4):254-262.
67. Zic JA. Extracorporeal Photopheresis in the Treatment of Mycosis Fungoides and Sézary Syndrome. *Dermatol Clin*. 2015 Oct;33(4):765-76.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Medical Policy & Coverage Committee on 04/22/21.

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.