

MEDICAL POLICY – 8.01.36

Extracorporeal Photopheresis

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Replaces: 8.01.501

RELATED MEDICAL POLICIES:

5.01.532 Cutaneous T-Cell Lymphomas (CTCL): Systemic Therapies

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Introduction

Extracorporeal photopheresis is a treatment of white blood cells. Blood is withdrawn and a specialized machine separates the whole blood into its different components — red blood cells, white blood, cells, platelets, and plasma. White blood cells are kept back and the rest of the blood is returned to the patient. The white blood cells are mixed with medication that makes them sensitive to ultraviolet light. After being exposed to ultraviolet light, the white blood cells are returned to the patient. White blood cells are part of the immune system, and treating them in this way stimulates the immune system. High quality medical studies have shown this technique is successful in treating a number of conditions. These include organ rejection after a heart transplant, graft-versus-host disease, and cutaneous T-cell lymphoma in certain situations. It has also been proposed to treat a number of autoimmune conditions, like Crohn disease or multiple sclerosis. Because more medical studies are needed to show if it works for other conditions, using this technique for autoimmune conditions is investigational (unproven).

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Indication	Medical Necessity
Organ rejection after solid organ transplant	<p>Extracorporeal photopheresis may be considered medically necessary to treat cardiac allograft rejection, including acute rejection, that is either recurrent or that is refractory to standard immunosuppressive drug treatment.</p> <p>Extracorporeal photopheresis is considered investigational in all other situations related to treatment or prevention of rejection in solid organ transplantation.</p>
Graft-versus-host disease	<p>Extracorporeal photopheresis may be considered medically necessary as a technique to treat:</p> <ul style="list-style-type: none"> • Acute graft-versus-host disease (GVHD) that is refractory to medical therapy • Chronic GVHD that is refractory to medical therapy <p>Extracorporeal photopheresis is considered investigational as a technique to treat acute GVHD or chronic GVHD that is either previously untreated or is responding to established therapies.</p>
Cutaneous T-cell lymphoma	<p>Extracorporeal photopheresis may be considered medically necessary as a technique to treat:</p> <ul style="list-style-type: none"> • Late stage (III/IV) cutaneous T-cell lymphoma • Early stage (I/II) cutaneous T-cell lymphoma that is progressive and refractory to established nonsystemic therapies <p>Extracorporeal photopheresis is considered investigational as a technique to treat early stage (I/II) cutaneous T-cell lymphoma that is either previously untreated or responsive to established nonsystemic therapies.</p>

Indication	Investigational
Autoimmune diseases	<p>Extracorporeal photopheresis is considered investigational as a technique to treat either the cutaneous or visceral manifestations of autoimmune diseases, including but not limited to:</p>



Indication	Investigational
	<ul style="list-style-type: none"> • Autoimmune bullous disorders • Crohn disease • Diabetes • Multiple sclerosis • Pemphigus • Psoriasis • Rheumatoid arthritis • Scleroderma • Severe atopic dermatitis • Systemic lupus erythematosus
Other	Extracorporeal photopheresis is considered investigational for all other indications.

Documentation Requirements
<p>The patient’s medical records submitted for review should document that medical necessity criteria are met. The record should include clinical documentation of:</p> <ul style="list-style-type: none"> • Diagnosis/condition • History and physical examination documenting the severity of the condition • The medical therapy that has been attempted

Coding

Code	Description
CPT	
36522	Photopheresis, extracorporeal

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information



Organ Rejection after Solid Organ Transplant

A regimen of immunosuppressive therapy is standard of care for the treatment of solid organ rejection. Therefore, refractory rejection is defined as rejection that fails to adequately respond to a standard regimen of immunosuppressive therapy.

Recurrent allograft rejection is defined as having at least 2 rejection episodes after standard immunosuppressive therapy.

There is no standard schedule for extracorporeal photopheresis (ECP) and reported schedules vary by the organ type. However, most reported cardiac and lung schedules initiate therapy with two consecutive days of ECP in month 1, followed by biweekly therapy on two consecutive days in months 2 and 3, then monthly on two consecutive days in months 4 through 6.

Graft-Versus-Host Disease

Methylprednisolone is considered first-line treatment of acute graft-versus host disease (GVHD). For chronic GVHD, an alternating regimen of cyclosporine and prednisone is commonly used; other therapies include antithymocyte globulin, corticosteroid monotherapy, and cytotoxic immunosuppressive drugs such as procarbazine, cyclophosphamide, or azathioprine. Therefore, refractory disease is defined as GVHD that fails to respond adequately to a trial of any of these therapies.

Treatment schedule and duration of ECP for GVHD have not been optimally defined. Guidelines and consensus statements have generally recommended 1 cycle (ie, ECP on two consecutive days) weekly for acute GVHD and every 2 weeks for chronic GVHD. Treatment duration is based on clinical response (see [Practice Guidelines and Position Statements](#) section); discontinuation is generally recommended for no or minimal response.

Cutaneous T-Cell Lymphoma Staging

Cutaneous T-cell lymphoma staging is based on the tumor, node, metastases (TNM) classification system (see [Table 1](#)).



Table 1. Cutaneous T-cell Lymphoma Staging

Stage	Tumor T, N, and M Categories
IA	T1N0M0
IB	T2N0M0
IIA	T1-2N1M1
IIB	T3N0-1M0
III	T4N0-1M0
IVA	T1-4N2-3M0
IVB	T1-4N0-3M1

Sézary Syndrome

According to the World Health Organization–European Organization for Research and Treatment of Cancer, Sézary syndrome is defined by the triad of erythroderma, generalized lymphadenopathy, and the presence of neoplastic T cells (Sézary cells) in the skin, lymph nodes, and peripheral blood. The International Society of Cutaneous Lymphomas recommends an absolute Sézary cell count of at least 1000 cells per cubic millimeter, in the presence of immunophenotypical abnormalities (CD4/CD8 ratio >10; loss of any or all of the T-cell antigens CD2, CD3, CD4, and CD5; or both), or the demonstration of a T-cell clone in the peripheral blood by molecular or cytogenetic methods.

Benefit Application

Refer to contract or benefit language for specific language regarding extracorporeal photopheresis and chronic graft versus host disease.

Evidence Review



Description

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

- Patient blood is collected into a centrifuge system that separates the leukocyte-rich portion (buffy coat) from the rest of the blood.
- The photosensitizer agent 8-methoxypsoralen is added to the lymphocyte fraction, which is then exposed to ultraviolet A (320-400 nm wavelength) light at a dose of 1-2 J/cm².
- The light-sensitized lymphocytes are reinfused into the patient.

The use of ECP has been investigated for patients needing treatment for organ rejection after solid organ transplant, graft-versus-host disease (GVHD), autoimmune diseases, and T-cell lymphoma.

Background

Organ Rejection Treatment after Solid Organ Transplant

The standard treatment for organ transplant rejection is immunosuppression, with the particular regimen dictated by the organ being transplanted. As organ transplantation success rates have improved, more patients are facing the morbidity and mortality associated with immunosuppressive therapies developed to prevent rejection of the transplanted organ. Immunosuppressive therapies are used to lower the responsiveness of the recipient's immune system, decreasing the chance of rejection. Unfortunately, portions of the immune system responsible for the prevention of viral, fungal, and bacterial infection also are affected. This can, in turn, lead to serious infections, including opportunistic infections.

Although first approved for the treatment of cutaneous T-cell lymphoma (CTCL), extracorporeal photopheresis (ECP) has more recently been used as a supplement to conventional therapies in the area of solid organ transplantation.¹ Reports of the successful use of ECP in human cardiac transplant recipients were published in 1992^{2,3} and use in other transplant patients followed. Although the specific mechanism of action of ECP is unknown, the reinfusion of treated leukocytes seems specifically to suppress the patient's immune response to the donor organ, although maintaining the body's ability to respond to other antigens.⁴ The specificity of ECP to target the immune response to the transplanted organ allows ECP to decrease organ rejection without the increased risk of infection, common with immunosuppressive drugs.⁵



Graft-Versus-Host Disease

Given that graft-versus-host disease (GVHD) is an immune mediated disease, ECP can be used to treat GVHD after a prior allogeneic cell transplant. In fact, GVHD can be categorized in two ways: (1) as an acute disease, occurring within the first 100 days after infusion of allogeneic cells; or (2) as a chronic disease, which develops sometime after 100 days. Acute GVHD is commonly graded from I to IV, ranging from mild disease, which is characterized by a skin rash without involvement of the liver or gut, to grades III and IV, which are characterized by generalized erythroderma, elevated bilirubin levels, or diarrhea. Grade III acute GVHD is considered severe, and grade IV is considered life-threatening. Chronic GVHD typically presents with more diverse symptomatology resembling autoimmune diseases such as progressive systemic sclerosis, systemic lupus erythematosus, or rheumatoid arthritis. Chronic GVHD may affect the mouth, eyes, respiratory tract, musculoskeletal system, and peripheral nerves, as well as the skin, liver, or gut — the usual sites of acute GVHD.

Autoimmune Disease

The use of ECP as a treatment of autoimmune disease is based on the premise that pathogenic lymphocytes form an expanded clone of cells, which are damaged when exposed to ultraviolet light in the presence of agent 8-methoxypsoralen. It is hypothesized that the resulting damage induces a population of circulating suppressor T-cells targeted against the light-damaged cells. It is further hypothesized that these suppressor T-cells are targeted at a component of the cell that is common to the entire clone of abnormal cells (ie, not just the light-sensitized cells), thus inducing a systemic effect. However, although scleroderma and other autoimmune diseases are associated with the presence of circulating autoantibodies, it is unknown how these antibodies are related to the pathogenesis of the disease. As discussed in this policy, photopheresis is not associated with consistent changes in autoantibody levels.

T-Cell Lymphoma

Cutaneous T-Cell Lymphoma

According to the National Cancer Institute, CTCL is a neoplasm of malignant T lymphocytes that initially presents as skin involvement. CTCL is extremely rare, with an estimated incidence of approximately 0.4 per 100,000 annually, but because most are low-grade malignancies with long



survival, overall prevalence is much higher. Two CTCL variants, mycosis fungoides and the Sézary syndrome, account for approximately 60% and 5% of new cases of CTCL, respectively.

CTCL is included in the Revised European-American Lymphoma classification as a group of low-grade T-cell lymphomas. They are distinguished from other T-cell lymphomas that involve the skin such as anaplastic large cell lymphoma, peripheral T-cell lymphoma, adult T-cell leukemia/lymphoma (usually with systemic involvement), and subcutaneous panniculitis T-cell lymphoma. In addition, a number of benign or very indolent conditions can be confused with mycosis fungoides, further complicating diagnosis.

Mycosis fungoides typically progresses from an eczematous patch/plaque stage, covering less than 10% of the body surface (T1), to a plaque stage, covering 10% or more of the body surface (T2), and finally to tumors (T3) that frequently undergo necrotic ulceration. Sézary syndrome is an advanced form of mycosis fungoides with generalized erythroderma (T4) and peripheral blood involvement (B1) at presentation. The cytologic transformation from a low-grade lymphoma to a high-grade lymphoma sometimes occurs during the course of these diseases and is associated with poor prognosis. A common cause of death during the tumor phase is sepsis from *Pseudomonas aeruginosa* or *Staphylococcus aureus* caused by chronic skin infection with staphylococcus species and subsequent systemic infections.

The natural history of mycosis fungoides is typically indolent. Symptoms may present for long periods (mean, 2-10 years) as waxing and waning cutaneous eruptions. The prognosis of patients with mycosis fungoides or Sézary syndrome is based on the extent of disease at presentation and its stage. Lymphadenopathy and involvement of peripheral blood and viscera increase in likelihood with worsening cutaneous involvement and define poor prognostic groups. Median survival after diagnosis varies according by stage. Median survival in patients with stage IA disease exceeds 20 years, with most deaths in this group typically unrelated to mycosis fungoides. In contrast, median survival in patients with stage III or IV disease is less than 5 years; more than 50% of these patients die of their disease.

Appropriate therapy of CTCL depends on a variety of factors, including stage, the patient's overall health, and the presence of symptoms. In general, therapies can be categorized into topical and systemic treatments that include ECP. In contrast to more conventional lymphomas, CTCL is usually not curable (unless caught in its earliest stages). Thus, systemic cytotoxic chemotherapy is avoided except for advanced stage cases. Partial or complete remission is achievable, although most patients require lifelong treatment and monitoring.



Summary of Evidence

Organ Rejection after Solid Organ Transplant

Heart Transplant

For individuals who are heart transplant recipients who experience acute graft rejection refractory to immunosuppression who receive ECP, the evidence includes a small RCT. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. The small RCT, while suggesting similar outcomes for ECP and corticosteroids, is insufficient to permit conclusions on the utility of ECP. Studies with more patients and longer follow-up are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are heart transplant recipients who experience recurrent and/or refractory graft rejection who receive ECP, the evidence includes a comparative study and small case series. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Current evidence is consistent on the beneficial effect of ECP for cardiac transplant patients with graft rejection refractory to standard therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are heart transplant recipients who require prophylaxis to prevent graft rejection who receive ECP, the evidence includes a small RCT. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. The small randomized trial is insufficient to permit conclusions on the utility of ECP. Studies with more patients and longer follow-up are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Lung Transplant

For individuals who are lung transplant recipients who experience acute graft rejection who receive ECP, the evidence includes a small retrospective study and small case series. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Current evidence is very limited and any conclusions drawn lack certainty. A prospective, randomized trial is needed specifically evaluating the treatment of patients with acute graft rejection. The evidence is insufficient to determine the effects of the technology on health outcomes.



For individuals who are lung transplant recipients with BOS refractory to corticosteroids who receive ECP, the evidence includes a prospective study and numerous retrospective analyses. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Studies have shown inconsistent results across BOS grades. Prospective, RCTs are necessary with analyses stratified by syndrome grade. The evidence is insufficient to determine the effects of the technology on health outcomes.

Liver Transplant

For individuals who are liver transplant recipients who experience graft rejection and receive ECP, the evidence includes a small nonrandomized study, a retrospective study, and a case series. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Current evidence does not permit conclusions on the utility of ECP in this population. There is a need for RCTs comparing immunosuppressive therapy alone with immunosuppressive therapy with ECP. The evidence is insufficient to determine the effects of the technology on health outcomes.

Kidney Transplant

For individuals who are kidney transplant recipients who experience recurrent graft rejection who receive ECP, the evidence includes a small prospective study and numerous case reports. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Current evidence does not permit conclusions on the effect of ECP on net health outcome. RCTs, comparing immunosuppressive therapy with immunosuppressive therapy using ECP and examining histologic confirmation of treatment response, are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Graft-Versus-Host Disease

For individuals who have acute or GVHD refractory to medical treatment who receive ECP, the evidence includes systematic reviews, retrospective studies, and case series. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Current evidence has consistently shown that ECP reduces the incidence of GVHD that is unresponsive to standard therapy. Additionally, there is a lack of other treatment options for these patients; adverse events related to ECP are minimal; and, if there is a response to ECP,



patients may be able to reduce or discontinue treatment with corticosteroids and other immunosuppressive agents. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Clinical input obtained in 2014 supported the use of ECP in patients with refractory acute GVHD.

Autoimmune Disease

For individuals who have autoimmune diseases (eg, 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, and Crohn disease) who receive ECP, the evidence includes isolated RCTs, small prospective and retrospective studies, and case reports. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. The current literature assessing the various autoimmune diseases is not sufficiently robust to support conclusions. The evidence is insufficient to determine the effects of the technology on health outcomes.

T-Cell Lymphoma

For individuals who have advanced-stage (stage III or IV) CTCL who receive ECP, the evidence includes a systematic review and numerous small case series. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Evidence from these small case series has shown a favorable response to ECP treatment and an increase in survival in a proportion of these patients. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have refractory or progressive early-stage (stage I or II) CTCL who receive ECP, the evidence includes a systematic review. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Given the unfavorable prognosis for patients with early-stage CTCL that progresses on nonsystemic therapies, the relative lack of adverse events with ECP compared with other systemic treatments, and the good response rates often observed with ECP, this therapy is an option for those with refractory or progressive early-stage CTCL. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.



Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this policy are listed in [Table 2](#).

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
Graft-versus-host disease			
NCT00637689	Improving Outcomes Assessment in Chronic GVHD	601	Feb 2020
NCT01460914	Outcomes of Cutaneous T-Cell Lymphoma and Chronic Graft-Versus-Host Disease in Patients Treated with Extracorporeal Photopheresis	100	Oct 2050
Autoimmune disorders			
NCT02296346^a	Open-Label Study to Evaluate the Efficacy of ECP in Secondary Progressive Multiple Sclerosis	66	Oct 2017 (suspended)
T-cell lymphoma			
NCT01460914	Outcomes of Cutaneous T-Cell Lymphoma and Chronic Graft-Versus-Host Disease in Patients Treated with Extracorporeal Photopheresis	100	Oct 2050
Unpublished			
Solid organ transplants			
NCT01824368	Extracorporeal Photopheresis in Liver Transplantation. Phase 2 Clinical Trial in Safety and Efficacy in Patients With Gradual Decrease of Immunosuppression (FEC-TH)	10	Apr 2016 (completed)
Graft-versus-host disease			
NCT01380535^a	A Randomized Controlled Study of Extracorporeal Photopheresis (ECP) Therapy With UVADEX for the Treatment of Patients With Moderate to Severe Chronic Graft-versus-Host Disease (cGvHD)	60	Mar 2017 (completed)
NCT00609609	A Randomized Phase 2 Study for the Evaluation of Extracorporeal Photopheresis (ECP) in Combination With Corticosteroids for the Initial Treatment of Acute Graft-Versus-Host Disease (GVHD)	81	Jan 2016 (completed)

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.



Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received through two academic medical centers and 5 Blue Distinction Centers for Transplant when this policy was under review in 2014. Respondents agreed unanimously that extracorporeal photopheresis should not be medically necessary for previously untreated acute graft-versus-host disease but should be medically necessary for acute graft-versus-host disease that is refractory to medical therapy.

Practice Guidelines and Position Statements

Graft Versus Host Disease

Acute GVHD

UK Photopheresis Society

An evidence-based consensus statement from the UK Photopheresis Society (2014) recommended ECP as second-line therapy in combination with other agents for patients with steroid-refractory, steroid-dependent, or steroid-intolerant grade II, III, or IV acute graft-versus-host disease (GVHD).⁷⁵

American Society of Blood and Marrow Transplantation

Evidence-based recommendations from the American Society of Blood and Marrow Transplantation (2012) advised that ECP cannot be considered superior to horse antithymocyte globulin for treatment of acute GVHD.⁷⁶ This conclusion was based on older studies.^{43,77}



Acute GVHD and Chronic GVHD

British Committee for Standards in Haematology et al

Evidence-based guidelines from the British Committee for Standards in Haematology and the British Society for Bone Marrow Transplantation (2012) recommend ECP in acute GVHD as a second-line treatment for steroid-refractory disease⁷⁸ and in chronic GVHD as a second-line treatment for skin, oral, or liver involvement.⁷⁹

Italian Society of Hemapheresis and Cell Manipulation et al

A nine-member panel representing the Italian Society of Hemapheresis and Cell Manipulation and the Italian Group for Bone Marrow Transplantation (2013) published consensus recommendations for ECP in adults and children with acute GVHD or chronic GVHD.⁸¹ The panel recommended ECP for treatment of acute GVHD in adults and children who are nonresponsive to steroids or calcineurin inhibitors or have contraindications to immunosuppressive therapy because of viral reactivation or other infectious complication (“better results are expected in patients with isolated skin involvement”) and for treatment of chronic GVHD in adults and children who are steroid-resistant or steroid-dependent.

National Cancer Institute

In its guideline on childhood hematopoietic cell transplantation, the National Cancer Institute listed ECP as a second-line treatment for patients with acute GVHD resistant to first-line methylprednisolone.⁸² For chronic GVHD therapy, the guidelines recommended that steroids are first-line therapy, but steroid-sparing approaches, including ECP, are being developed. In this setting, ECP has shown “some efficacy in a percentage of patients.”

Cancer Care Ontario

Cancer Care Ontario (2014) published evidence-based consensus guidelines on ECP for GVHD.⁸³ ECP was recommended as “an acceptable therapy for the treatment of steroid-dependent or refractory acute GVHD in adult and pediatric patients” and for “steroid-dependent or refractory chronic GVHD in adult and pediatric patients.” The strength of the recommendations was not graded.



T-Cell Lymphoma

National Comprehensive Cancer Network

National Comprehensive Cancer Network guidelines on T-cell lymphomas (v.5.2018) lists the use of ECP as a category A 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 either earlier stage mycosis fungoides with Sézary syndrome involvement.⁸⁴

Medicare National Coverage

Solid-Organ Transplants

Effective 2006, the Centers for Medicare and Medicaid Services (CMS) concluded that ECP is reasonable and necessary for persons with “acute cardiac allograft rejection whose disease is refractory to standard immunosuppressive drug treatment”.⁸⁵

Effective 2012, CMS also provided coverage for ECP for the treatment of “bronchiolitis obliterans syndrome (BOS) following lung allograft transplantation only when extracorporeal photopheresis is provided under a clinical research study” that meets certain conditions.⁸⁵

Graft Versus Host Disease

Effective 2006, CMS provided coverage of ECP for patients with chronic GVHD “whose disease is refractory to standard immunosuppressive drug treatment.”⁸⁵

Autoimmune Disorders

There are no national coverage decisions on the use of ECP for the treatment of autoimmune disease.

T -Cell Lymphoma

Effective 1988, CMS provided coverage for ECP as “palliative treatment of skin manifestations of cutaneous T-cell lymphoma that has not responded to other therapy.”⁸⁵



Regulatory Status

Two photopheresis systems (Therakos; now Mallinckrodt) were approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process. Both systems are approved for use in ultraviolet-A irradiation treatment, in the presence of the photoactive drug 8-methoxypsoralen, of extracorporeally circulating leukocyte-enriched blood, in the palliative treatment of skin manifestations of CTCL, in persons who have not been responsive to other forms of treatment. The two systems are:

- UVAR® XTS Photopheresis System (FDA-approved in 1987)
- CELLEX® (FDA approved in 2009)

Photoactive 8-methoxypsoralen (UVADEX®) is FDA-approved for extracorporeal administration with the UVAR® XTS or CELLEX® Photopheresis System in the palliative treatment of the skin manifestations of CTCL unresponsive to other forms of treatment.

The use of either Therakos photopheresis system or UVADEX® for other conditions is off-label.

FDA product code: LNR.

References

1. Marques MB, Tuncer HH. Photopheresis in solid organ transplant rejection. *J Clin Apher.* Apr 2006;21(1):72-77. PMID 16619230
2. Costanzo-Nordin MR, Hubbell EA, O'Sullivan EJ, et al. Photopheresis versus corticosteroids in the therapy of heart transplant rejection. Preliminary clinical report. *Circulation.* Nov 1992;86(5 Suppl):II242-250. PMID 1424007
3. Rose EA, Barr ML, Xu H, et al. Photochemotherapy in human heart transplant recipients at high risk for fatal rejection. *J Heart Lung Transplant.* Jul-Aug 1992;11(4 Pt 1):746-750. PMID 1498142
4. Hivelin M, Siemionow M, Grimbert P, et al. Extracorporeal photopheresis: from solid organs to face transplantation. *Transpl Immunol.* Jul 2009;21(3):117-128. PMID 19409991
5. Szczepiorkowski ZM, Bandarenko N, Kim HC, 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. *J Clin Apher.* Jun 2007;22(3):106-175. PMID 17394188
6. Carlo WF, Pearce FB, George JF, et al. Single-center experience with extracorporeal photopheresis in pediatric heart transplantation. *J Heart Lung Transplant.* Jun 2014;33(6):624-628. PMID 24661684
7. Kirklin JK, Brown RN, Huang ST, et al. Rejection with hemodynamic compromise: objective evidence for efficacy of photopheresis. *J Heart Lung Transplant.* Mar 2006;25(3):283-288. PMID 16507420



8. Maccherini M, Diciolla F, Laghi Pasini F, et al. Photopheresis immunomodulation after heart transplantation. *Transplant Proc.* Feb-Mar 2001;33(1-2):1591-1594. PMID 11267432
9. Dall'Amico R, Montini G, Murer L, et al. Extracorporeal photochemotherapy after cardiac transplantation: a new therapeutic approach to allograft rejection. *Int J Artif Organs.* Jan 2000;23(1):49-54. PMID 12118837
10. 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.* Dec 10 1998;339(24):1744-1751. PMID 9845709
11. Villanueva J, Bhorade SM, Robinson JA, et al. Extracorporeal photopheresis for the treatment of lung allograft rejection. *Ann Transplant.* Mar 2000;5(3):44-47. PMID 11233043
12. Benden C, Speich R, Hofbauer GF, et al. Extracorporeal photopheresis after lung transplantation: a 10-year single-center experience. *Transplantation.* Dec 15 2008;86(11):1625-1627. PMID 19077900
13. Salerno CT, Park SJ, Kreykes NS, et al. Adjuvant treatment of refractory lung transplant rejection with extracorporeal photopheresis. *J Thorac Cardiovasc Surg.* Jun 1999;117(6):1063-1069. PMID 10343253
14. Jaksch P, Scheed A, Keplinger M, et al. A prospective interventional study on the use of extracorporeal photopheresis in patients with bronchiolitis obliterans syndrome after lung transplantation. *J Heart Lung Transplant.* Sep 2012;31(9):950-957. PMID 22884382
15. Greer M, Dierich M, De Wall C, et al. Phenotyping established chronic lung allograft dysfunction predicts extracorporeal photopheresis response in lung transplant patients. *Am J Transplant.* Apr 2013;13(4):911-918. PMID 23406373
16. Lucid CE, Savani BN, Engelhardt BG, et al. Extracorporeal photopheresis in patients with refractory bronchiolitis obliterans developing after allo-SCT. *Bone Marrow Transplant.* Mar 2011;46(3):426-429. PMID 20581885
17. Morrell MR, Despotis GJ, Lublin DM, et al. The efficacy of photopheresis for bronchiolitis obliterans syndrome after lung transplantation. *J Heart Lung Transplant.* Apr 2010;29(4):424-431. PMID 19853479
18. Urbani L, Mazzoni A, Catalano G, et al. The use of extracorporeal photopheresis for allograft rejection in liver transplant recipients. *Transplant Proc.* Dec 2004;36(10):3068-3070. PMID 15686696
19. Urbani L, Mazzoni A, De Simone P, et al. Avoiding calcineurin inhibitors in the early post-operative course in high-risk liver transplant recipients: The role of extracorporeal photopheresis. *J Clin Apher.* 2007;22(4):187-194. PMID 17294458
20. Urbani L, Mazzoni A, Colombatto P, et al. Potential applications of extracorporeal photopheresis in liver transplantation. *Transplant Proc.* May 2008;40(4):1175-1178. PMID 18555142
21. Jardine MJ, Bhandari S, Wyburn KR, et al. Photopheresis therapy for problematic renal allograft rejection. *J Clin Apher.* Jun 2009;24(4):161-169. PMID 19536814
22. Kumlien G, Genberg H, Shanwell A, et al. Photopheresis for the treatment of refractory renal graft rejection. *Transplantation.* Jan 15 2005;79(1):123-125. PMID 15714180
23. Dall'Amico R, Murer L. Extracorporeal photochemotherapy: a new therapeutic approach for allograft rejection. *Transfus Apher Sci.* Jun 2002;26(3):197-204. PMID 12126206
24. Dall'Amico R, Murer L, Montini G, et al. Successful treatment of recurrent rejection in renal transplant patients with photopheresis. *J Am Soc Nephrol.* Jan 1998;9(1):121-127. PMID 9440096
25. Baron ED, Heeger PS, Hricik DE, et al. Immunomodulatory effect of extracorporeal photopheresis after successful treatment of resistant renal allograft rejection. *Photodermatol Photoimmunol Photomed.* Apr 2001;17(2):79-82. PMID 11338406
26. Sunder-Plassman G, Druml W, Steininger R, et al. Renal allograft rejection controlled by photopheresis. *Lancet.* Aug 19 1995;346(8973):506. PMID 7637500
27. Abu-Dalle I, Reljic T, Nishihori T, et al. Extracorporeal photopheresis in steroid-refractory acute or chronic graft-versus-host disease: results of a systematic review of prospective studies. *Biol Blood Marrow Transplant.* Nov 2014;20(11):1677-1686. PMID 24867779



28. Flowers ME, Apperley JF, van Besien K, et al. A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease. *Blood*. Oct 1 2008;112(7):2667-2674. PMID 18621929
29. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Extracorporeal photopheresis for graft-versus-host disease. *TEC Assessments*. 2001;Volume 16:Tab 9.
30. 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 Transplant*. Mar 2013;48(3):439-445. PMID 22922407
31. Ussowicz M, Musial J, Mielcarek M, et al. Steroid-sparing effect of extracorporeal photopheresis in the therapy of graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. *Transplant Proc*. Nov 2013;45(9):3375-3380. PMID 24182819
32. Weitz M, Strahm B, Meerpohl JJ, et al. Extracorporeal photopheresis versus standard treatment for acute graft-versus-host disease after haematopoietic stem cell transplantation in paediatric patients. *Cochrane Database Syst Rev*. 2014;2:CD009759. PMID 24569960
33. Weitz M, Strahm B, Meerpohl JJ, et al. Extracorporeal photopheresis versus alternative treatment for chronic graft-versus-host disease after haematopoietic stem cell transplantation in paediatric patients. *Cochrane Database Syst Rev*. Feb 25 2014;2(2):CD009898. PMID 24569961
34. Perotti C, Del Fante C, Tinelli C, et al. Extracorporeal photochemotherapy in graft-versus-host disease: a longitudinal study on factors influencing the response and survival in pediatric patients. *Transfusion*. Jun 2010;50(6):1359-1369. PMID 20113452
35. Halle P, Paillard C, D'Incan M, et al. Successful extracorporeal photochemotherapy for chronic graft-versus-host disease in pediatric patients. *J Hematother Stem Cell Res*. Jun 2002;11(3):501-512. PMID 12183835
36. Salvaneschi L, Perotti C, Zecca M, et al. Extracorporeal photochemotherapy for treatment of acute and chronic GVHD in childhood. *Transfusion*. Oct 2001;41(10):1299-1305. PMID 11606832
37. Berger M, Pessolano R, Albiani R, et al. Extracorporeal photopheresis for steroid resistant graft versus host disease in pediatric patients: a pilot single institution report. *J Pediatr Hematol Oncol*. Oct 2007;29(10):678-687. PMID 17921848
38. Zhang H, Chen R, Cheng J, et al. Systematic review and meta-analysis of prospective studies for ECP treatment in patients with steroid-refractory acute GVHD. *Patient Prefer Adherence*. Feb 2015;9:105-111. PMID 25653504
39. Greinix HT, Knobler RM, Worel N, et al. The effect of intensified extracorporeal photochemotherapy on long-term survival in patients with severe acute graft-versus-host disease. *Haematologica*. Mar 2006;91(3):405-408. PMID 16531267
40. 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. *Biol Blood Marrow Transplant*. Jul 2013;19(7):1129-1133. PMID 23623892
41. Rubegni P, Feci L, Poggiali S, et al. Extracorporeal photopheresis: a useful therapy for patients with steroid-refractory acute graft-versus-host disease but not for the prevention of the chronic form. *Br J Dermatol*. Aug 2013;169(2):450-457. PMID 23534380
42. Shaughnessy PJ, Bolwell BJ, van Besien K, 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*. Jun 2010;45(6):1068-1076. PMID 19915634
43. Perfetti P, Carlier P, Strada P, et al. Extracorporeal photopheresis for the treatment of steroid refractory acute GVHD. *Bone Marrow Transplant*. Nov 2008;42(9):609-617. PMID 18660840
44. Malik MI, Litzow M, Hogan W, et al. Extracorporeal photopheresis for chronic graft-versus-host disease: a systematic review and meta-analysis. *Blood Res*. Jun 2014;49(2):100-106. PMID 25025011
45. Ontario Health Technology Advisory Committee. OHTAC Recommendation: Extracorporeal Photopheresis. 2006; http://www.hqontario.ca/english/providers/program/ohtac/tech/recommend/rec_ecp_032806.pdf. Accessed December 2018.



46. Foss FM, DiVenuti GM, Chin K, et al. Prospective study of extracorporeal photopheresis in steroid-refractory or steroid-resistant extensive chronic graft-versus-host disease: analysis of response and survival incorporating prognostic factors. *Bone Marrow Transplant.* Jun 2005;35(12):1187-1193. PMID 15852025
47. Dignan FL, Aguilar S, Scarisbrick JJ, et al. Impact of extracorporeal photopheresis on skin scores and quality of life in patients with steroid-refractory chronic GVHD. *Bone Marrow Transplant.* May 2014;49(5):704-708. PMID 24566709
48. Greinix HT, Volc-Platzer B, Knobler R. Criteria for assessing chronic GVHD. *Bone Marrow Transplant.* Mar 2000;25(5):575. PMID 10713639
49. Rubegni P, Cuccia A, Sbano P, et al. Role of extracorporeal photochemotherapy in patients with refractory chronic graft-versus-host disease. *Br J Haematol.* Jul 2005;130(2):271-275. PMID 16029456
50. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Extracorporeal photopheresis for autoimmune disease. *TEC Assessments.* 2001;Volume 16:Tab 10.
51. Rook AH, Freundlich B, Jegasothy BV, et al. Treatment of systemic sclerosis with extracorporeal photochemotherapy. Results of a multicenter trial. *Arch Dermatol.* Mar 1992;128(3):337-346. PMID 1550365
52. Fries JF, Seibold JR, Medsger TA, Jr. Photopheresis for scleroderma? No! *J Rheumatol.* Jul 1992;19(7):1011-1013. PMID 1512753
53. Melski JW. Price of technology. A blind spot. *JAMA.* Mar 18 1992;267(11):1516-1518. PMID 1538542
54. Trentham DE. Photochemotherapy in systemic sclerosis. The stage is set. *Arch Dermatol.* Mar 1992;128(3):389-390. PMID 1550373
55. Papp G, Horvath IF, Barath S, et al. Immunomodulatory effects of extracorporeal photochemotherapy in systemic sclerosis. *Clin Immunol.* Feb 2012;142(2):150-159. PMID 22036269
56. Cavaletti G, Perseghin P, Dassi M, et al. Extracorporeal photochemotherapy: a safety and tolerability pilot study with preliminary efficacy results in refractory relapsing-remitting multiple sclerosis. *Neurol Sci.* Apr 2006;27(1):24-32. PMID 16688596
57. Ludvigsson J, Samuelsson U, Ernerudh J, et al. Photopheresis at onset of type 1 diabetes: a randomised, double blind, placebo controlled trial. *Arch Dis Child.* Aug 2001;85(2):149-154. PMID 11466190
58. Sanli H, Akay BN, Ayyildiz E, et al. Remission of severe autoimmune bullous disorders induced by long-term extracorporeal photochemotherapy. *Transfus Apher Sci.* Dec 2010;43(3):353-359. PMID 21035398
59. Rubegni P, Poggiali S, Cevenini G, et al. Long term follow-up results on severe recalcitrant atopic dermatitis treated with extracorporeal photochemotherapy. *J Eur Acad Dermatol Venereol.* Apr 2013;27(4):523-526. PMID 22540319
60. Wolf P, Georgas D, Tomi NS, et al. Extracorporeal photochemotherapy as systemic monotherapy of severe, refractory atopic dermatitis: results from a prospective trial. *Photochem Photobiol Sci.* Jan 2013;12(1):174-181. PMID 22948099
61. Reinisch W, Knobler R, Rutgeerts PJ, et al. Extracorporeal photopheresis (ECP) in patients with steroid-dependent Crohn's disease: an open-label, multicenter, prospective trial. *Inflamm Bowel Dis.* Feb 2013;19(2):293-300. PMID 22573600
62. Edelson R, Berger C, Gasparro F, et al. Treatment of cutaneous T-cell lymphoma by extracorporeal photochemotherapy. Preliminary results. *N Engl J Med.* Feb 5 1987;316(6):297-303. PMID 3543674
63. Knobler R, Duvic M, Querfeld C, et al. Long-term follow-up and survival of cutaneous T-cell lymphoma patients treated with extracorporeal photopheresis. *Photodermatol Photoimmunol Photomed.* Oct 2012;28(5):250-257. PMID 22971190
64. Freiman A, Sasseville D. Treatment of mycosis fungoides: overview. *J Cutan Med Surg.* Sep-Oct 2006;10(5):228-233. PMID 17234106
65. Keehn CA, Belongie IP, Shistik G, et al. The diagnosis, staging, and treatment options for mycosis fungoides. *Cancer Control.* Apr 2007;14(2):102-111. PMID 17387295
66. Knobler E. Current management strategies for cutaneous T-cell lymphoma. *Clin Dermatol.* May-Jun 2004;22(3):197-208. PMID 15262305



67. Scarisbrick JJ. Staging and management of cutaneous T-cell lymphoma. *Clin Exp Dermatol*. Mar 2006;31(2):181-186. PMID 16487086
68. Whittaker SJ, Foss FM. Efficacy and tolerability of currently available therapies for the mycosis fungoides and Sezary syndrome variants of cutaneous T-cell lymphoma. *Cancer Treat Rev*. Apr 2007;33(2):146-160. PMID 17275192
69. Scarisbrick JJ, Taylor P, Holtick U, et al. U.K. consensus statement on the use of extracorporeal photopheresis for treatment of cutaneous T-cell lymphoma and chronic graft-versus-host disease. *Br J Dermatol*. Apr 2008;158(4):659-678. PMID 18241274
70. Trautinger F, Knobler R, Willemze R, et al. EORTC consensus recommendations for the treatment of mycosis fungoides/Sezary syndrome. *Eur J Cancer*. May 2006;42(8):1014-1030. PMID 16574401
71. Whittaker SJ, Marsden JR, Spittle M, et al. Joint British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T-cell lymphomas. *Br J Dermatol*. Dec 2003;149(6):1095-1107. PMID 14696593
72. National Cancer Institute. Mycosis Fungoides (Including Sézary Syndrome) Treatment (PDQ®)—Health Professional Version. 2018; <https://www.cancer.gov/types/lymphoma/hp/mycosis-fungoides-treatment-pdq?redirect=true>. Accessed December 2018.
73. Miller JD, Kirkland EB, Domingo DS, et al. Review of extracorporeal photopheresis in early-stage (IA, IB, and IIA) cutaneous T-cell lymphoma. *Photodermatol Photoimmunol Photomed*. Oct 2007;23(5):163-171. PMID 17803594
74. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood*. May 15 2005;105(10):3768-3785. PMID 15692063
75. 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. PMID 24887389
76. Martin PJ, Rizzo JD, Wingard JR, 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*. Aug 2012;18(8):1150-1163. PMID 22510384
77. Messina C, Locatelli F, Lanino E, et al. Extracorporeal photochemotherapy for paediatric patients with graft-versus-host disease after haematopoietic stem cell transplantation. *Br J Haematol*. Jul 2003;122(1):118-127. PMID 12823353
78. Dignan FL, Clark A, Amrolia P, et al. Diagnosis and management of acute graft-versus-host disease. *Br J Haematol*. Jul 2012;158(1):30-45. PMID 22533831
79. Dignan FL, Amrolia P, Clark A, et al. Diagnosis and management of chronic graft-versus-host disease. *Br J Haematol*. Jul 2012;158(1):46-61. PMID 22533811
80. Das-Gupta E, Watson LB, J., Russell N. Physicians Poster Sessions. P503: a single-centre experience of the efficacy of extracorporeal photopheresis in the treatment of steroid-refractory acute graft-versus-host disease. *Bone Marrow Transplant*. 2011;46(S1):S114.
81. Pierelli L, Perseghin P, Marchetti M, et al. Extracorporeal photopheresis for the treatment of acute and chronic graft-versus-host disease in adults and children: best practice recommendations from an Italian Society of Hemapheresis and Cell Manipulation (SIdEM) and Italian Group for Bone Marrow Transplantation (GITMO) consensus process. *Transfusion*. Oct 2013;53(10):2340-2352. PMID 23305044
82. National Cancer Institute. Childhood Hematopoietic Cell Transplantation (PDQ®)—Health Professional Version. 2018; Available at: <https://www.cancer.gov/types/childhood-cancers/child-hct-hp-pdq/> Accessed December 2018.
83. Bredeson C, Rumble RB, Varela NP, et al. Extracorporeal photopheresis in the management of graft-versus-host disease. *Curr Oncol*. Apr 2014;21(2):e310-325. PMID 24764713
84. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines on oncology: T-cell lymphomas. Version 5.2018. https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf. Accessed December 2018.



85. Center for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for Extracorporeal Photopheresis (110.4). 2012; <https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=113&ncdver=3&bc=AAAAgAAAAAAAAA%3d%3d&>. Accessed December 2018.

History

Date	Comments
11/16/00	Add to Therapy Section - New Policy.
01/08/02	Replace Policy - Revised; added information on photopheresis for graft vs. host disease; considered medically necessary for chronic disease.
05/11/04	Replace Policy - Policy reviewed; literature updated; no change in policy statement.
06/14/05	Replace Policy - Policy reviewed with literature search; no change in policy statement.
06/16/06	Replace Policy - Policy updated with literature search; policy statement unchanged. Scope and Disclaimer updated.
01/08/08	Replace Policy - Policy updated with literature search; no change in policy statement. "Extracorporeal" added to the title. References and code added.
12/16/08	Minor Updates - Spelling Corrected.
06/09/09	Replace Policy - Policy updated with literature search. Three new policy statements for CTCL added (two medically necessary statements). Title changed to reflect cutaneous T-cell lymphoma (CTCL) indication. References added. Policy reviewed and recommended by Oncology Advisory Panel on May 21, 2009. OAP recommended removing chronic from first policy statement.
02/09/10	Replace Policy - Policy updated with literature search. Policy statement minor update "chronic" added to medically necessary statement, no other changes. References added.
06/10/10	Delete Policy - Policy deleted from active status.
11/09/10	Reinstate Policy - Policy reinstated. Requests are being received.
03/08/11	Replace Policy - Policy updated with literature search; reference numbers 8, 9 and 17 added; autoimmune bullous disorders added as investigational. No other changes to policy statements.
05/12/11	Reviewed by OAP - No changes recommend to the policy.
04/10/12	Replace policy. Policy updated with literature search; reference numbers 8, 9, 17 and 28 added; autoimmune bullous disorders added as investigational; no other changes to policy statements. Policy 8.01.51 (Extracorporeal Photopheresis as Treatment for and Prevention of Organ Rejection after Solid-Organ Transplant) combined with this policy; 8.01.51 deleted as a separate policy. Title changed to reflect combined policies



Date	Comments
	and coding updated.
09/10/12	Update Coding Section – ICD-10 codes are now effective 10/01/2014.
09/21/12	Update Related Policy, add 5.01.532.
02/12/13	Update Related Policies, change title on Policy 8.02.02.
04/08/13	Replace policy. Policy updated with literature search; policy statement added that ECP is investigational for any other indications; references 6, 15, 60, 61, 62 added. Title changed to “Extracorporeal Photopheresis”.
03/11/14	Coding Update. Code 99.88 was removed per ICD-10 mapping project; this code is not utilized for adjudication of policy.
07/14/14	Annual Review. Policy updated with literature review through April 16, 2014; references 15, 35-36, 39, 43-45, 51-56, 65-68, 70, and 84 added; references 6, 29, 37, and 78 updated. Clinical input reviewed. New policy statement added that ECP is medically necessary in refractory acute graft-versus-host disease. For autoimmune diseases, Investigational policy statement updated to include severe atopic dermatitis and Crohn disease; no other changes to policy statements.
06/17/15	Annual Review. Policy updated with literature review through March 2, 2015; references 11, 39-40, 43, 49, 54, and 63 added. Policy statements unchanged. Benefit Application clarified. ICD-9 and ICD-10 diagnosis and procedure codes removed; these do not facilitate adjudication.
12/01/16	Annual Review, approved November 8, 2016. Policy updated with literature review. Added reference 38. No changes to policy statements.
01/01/18	Annual Review, approved December 6, 2017. Policy updated with literature review through August 2017; no references added. Policy statement unchanged.
11/01/18	Minor update, removed 8.02.02 from related policies as it was archived.
01/01/19	Annual Review, approved December 19, 2018. Policy updated with literature review through August 2018; no references added. Policy statement unchanged.
04/01/19	Minor update, added Documentation Requirements section.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2019 Premera All Rights Reserved.

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Tsab ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb. Tej zaum tsab ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb txog koj daim ntawv thov kev pab los yog koj qhov kev pab cuam hnu ntawm Premera Blue Cross. Tej zaum muaj cov hnu tseem ceeb uas sau rau hauv daim ntawv no. Tej zaum koj kuj yuav tau ua qee yam uas peb kom koj ua tsis pub dhau cov caij nyuog uas teev tseg rau hauv daim ntawv no mas koj thiaj yuav tau txais kev pab cuam kho mob los yog kev pab them tej nqi kho mob ntawd. Koj muaj cai kom lawv muab cov ntshiab lus no uas tau muab sau ua koj hom lus pub dawb rau koj. Hu rau 800-722-1471 (TTY: 800-842-5357).

Iloko (Ilocano):

Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabalin nga adda ket naglaon iti napateg nga impormasion maipanggep iti aplikasyonyo wenno coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a petsa iti daytoy a pakdaar. Mabalin nga adda rumbeng nga aramidenyo nga addang sakbay dagiti partikular a naituding nga aldaw tapno mapagtalinaedyo ti coverage ti salun-atyto wenno tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong iti bukodyo a pagsasao nga awan ti bayadanyo. Tumawag iti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):

Questo avviso contiene informazioni importanti. Questo avviso può contenere informazioni importanti sulla tua domanda o copertura attraverso Premera Blue Cross. Potrebbero esserci date chiave in questo avviso. Potrebbe essere necessario un tuo intervento entro una scadenza determinata per consentirti di mantenere la tua copertura o sovvenzione. Hai il diritto di ottenere queste informazioni e assistenza nella tua lingua gratuitamente. Chiama 800-722-1471 (TTY: 800-842-5357).

日本語 (Japanese):

この通知には重要な情報が含まれています。この通知には、Premera Blue Cross の申請または補償範囲に関する重要な情報が含まれている場合があります。この通知に記載されている可能性がある重要な日付をご確認ください。健康保険や有料サポートを維持するには、特定の期日までに行動を取らなければならない場合があります。ご希望の言語による情報とサポートが無料で提供されます。800-722-1471 (TTY: 800-842-5357)までお電話ください。

한국어 (Korean):

본 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지서는 귀하의 신청에 관하여 그리고 Premera Blue Cross 를 통한 커버리지에 관한 정보를 포함하고 있을 수 있습니다. 본 통지서에는 핵심이 되는 날짜들이 있을 수 있습니다. 귀하의 귀하의 건강 커버리지를 계속 유지하거나 비용을 절감하기 위해서 일정한 마감일까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하의 이러한 정보와 도움을 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 800-722-1471 (TTY: 800-842-5357) 로 전화하십시오.

ລາວ (Lao):

ແຈງການນີ້ມີຂໍ້ມູນສໍາຄັນ. ແຈງການນີ້ອາດຈະມີຂໍ້ມູນສໍາຄັນກ່ຽວກັບຄໍາຮ້ອງສະໝັກ ຫຼື ຄວາມຄົມຄອງປະກັນໄພຂອງທ່ານຜ່ານ Premera Blue Cross. ອາດຈະມີວັນທີ່ສໍາຄັນໃນແຈງການນີ້. ທ່ານອາດຈະຈໍາເປັນຕ້ອງດໍາເນີນການຕາມກຳນົດ ເວລາສະເພາະເພື່ອຮັກສາຄວາມຄົມຄອງປະກັນສະພາບ ຫຼື ຄວາມຊ່ວຍເຫຼືອເວັ້ນເວີ້ ຄ່າໃຊ້ຈ່າຍຂອງທ່ານໄດ້. ທ່ານມີສິດໄດ້ຮັບຂໍ້ມູນນີ້ ແລະ ຄວາມຊ່ວຍເຫຼືອເປັນພາສາຂອງທ່ານໂດຍບໍ່ເສຍຄ່າ. ໃຫ້ໃບທາ 800-722-1471 (TTY: 800-842-5357).

ភាសាខ្មែរ (Khmer):

សេចក្តីជូនដំណឹងនេះមានព័ត៌មានយ៉ាងសំខាន់។ សេចក្តីជូនដំណឹងនេះប្រហែលជាមានព័ត៌មានយ៉ាងសំខាន់អំពីទម្រង់បែបបទ ឬការរៀបចំរបស់អ្នកកាមរយ: Premera Blue Cross ។ ប្រហែលជាមាន កាលបរិច្ឆេទសំខាន់នៅក្នុងសេចក្តីជូនដំណឹងនេះ។ អ្នកប្រហែលជាត្រូវការបញ្ជាក់សមត្ថភាព ដល់កិច្ចការផ្ទៃក្នុងរបស់នានា ដើម្បីនឹងរក្សាទុកការធានារ៉ាប់រងអនាគតរបស់អ្នក ឬប្រាក់ដុល្លារចេញផ្លូវ។ អ្នកមានសិទ្ធិទទួលបានព័ត៌មាននេះ និងដុល្លារនៅក្នុងភាសារបស់អ្នកដោយមិនអស់លុយឡើយ។ សូមទូរស័ព្ទ 800-722-1471 (TTY: 800-842-5357)។

ਪੰਜਾਬੀ (Punjabi):

ਇਸ ਨੋਟਿਸ ਵਿਚ ਖਾਸ ਜਾਣਕਾਰੀ ਹੈ. ਇਸ ਨੋਟਿਸ ਵਿਚ Premera Blue Cross ਵਲੋਂ ਤੁਹਾਡੀ ਕਵਰੇਜ ਅਤੇ ਅਰਜੀ ਬਾਰੇ ਮਹੱਤਵਪੂਰਨ ਜਾਣਕਾਰੀ ਹੋ ਸਕਦੀ ਹੈ . ਇਸ ਨੋਟਿਸ ਨਵ ਖਾਸ ਤਾਰੀਖਾਂ ਹੋ ਸਕਦੀਆਂ ਹਨ. ਜੇਕਰ ਤੁਸੀਂ ਜਸਰਤ ਕਵਰੇਜ ਰਿੱਖਣੀ ਹੋਵੇ ਜਾਂ ਓਸ ਦੀ ਲਾਗਤ ਜਵਿੱਚ ਮਦਦ ਦੇ ਇਕੱਠ ਹੋ ਤਾਂ ਤੁਹਾਨੂੰ ਅੰਤਮ ਤਾਰੀਖ ਤੋਂ ਪਹਿਲਾਂ ਢੁੱਝ ਖਾਸ ਕਰਮ ਚੁੱਕਣ ਦੀ ਲੋੜ ਹੋ ਸਕਦੀ ਹੈ ,ਤੁਹਾਨੂੰ ਮੁਫਤ ਵਿੱਚ ਤੋਂ ਅਪਣੀ ਭਾਸ਼ਾ ਵਿੱਚ ਜਾਣਕਾਰੀ ਅਤੇ ਮਦਦ ਪ੍ਰਾਪਤ ਕਰਨ ਦਾ ਅਧਿਕਾਰ ਹੈ ,ਕਾਲ 800-722-1471 (TTY: 800-842-5357).

فارسی (Farsi):

این اعلامیه حاوی اطلاعات مهم میباشد. این اعلامیه ممکن است حاوی اطلاعات مهم درباره فرم تقاضا و یا پوشش بیمه ای شما از طریق Premera Blue Cross باشد. به تاریخ های مهم در این اعلامیه توجه نمایید. شما ممکن است برای حفظ پوشش بیمه تان یا کمک در پرداخت هزینه های درمانی تان، به تاریخ های مشخصی برای انجام کارهای خاصی احتیاج داشته باشید. شما حق این را دارید که این اطلاعات و کمک را به زبان خود به طور رایگان دریافت نمایید. برای کسب اطلاعات با شماره 800-722-1471 (کلیر بران TTY تماس باشماره 800-842-5357) تماس برقرار نمایید.

Polskie (Polish):

To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje odnośnie Państwa wniosku lub zakresu świadczeń poprzez Premera Blue Cross. Prosimy zwrócić uwagę na kluczowe daty, które mogą być zawarte w tym ogłoszeniu aby nie przekroczyć terminów w przypadku utrzymania polisy ubezpieczeniowej lub pomocy związanej z kosztami. Macie Państwo prawo do bezpłatnej informacji we własnym języku. Zadzwońcie pod 800-722-1471 (TTY: 800-842-5357).

Português (Portuguese):

Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde ou ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

Română (Romanian):

Prezenta notificare conține informații importante privind cererea sau acoperirea asigurării dumneavoastră de sănătate prin Premera Blue Cross. Pot exista date cheie în această notificare. Este posibil să fie nevoie să acționați până la anumite termene limită pentru a vă menține acoperirea asigurării de sănătate sau asistența provizorie la costuri. Aveți dreptul de a obține gratuit aceste informații și ajutor în limba dumneavoastră. Sunați la 800-722-1471 (TTY: 800-842-5357).

Русский (Russian):

Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Fa'asamoa (Samoan):

Atonu ua iai i lenei fa'asilasilaga ni fa'amatalaga e sili ona taua e tatau ona e malamalama i ai. O lenei fa'asilasilaga o se fesoasoani e fa'amatala atili i ai i le tulaga o le polokalame, Premera Blue Cross, ua e tau fia maua atu i ai. Fa'amolemole, ia e iloilo fa'alelei i aso fa'apitoa olo'o iai i lenei fa'asilasilaga taua. Masalo o le'a iai ni feau e tatau ona e faia ao le'i aulia le aso ua ta'ua i lenei fa'asilasilaga ina ia e iai pea ma maua fesoasoani mai ai i le polokalame a le Malo olo'o e iai i ai. Olo'o iai iate oe le aia tatau e maua atu i lenei fa'asilasilaga ma lenei fa'matalaga i legagana e te malamalama i ai aunoa ma se togiga tupe. Vili atu i le telefoni 800-722-1471 (TTY: 800-842-5357).

Español (Spanish):

Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Tagalog (Tagalog):

Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue Cross. Maaaring may mga mahalagang petsa dito sa paunawa. Maaring mangailangan ka na magsagawa ng hakbang sa ilang mga itinakdang panahon upang mapanatili ang iyong pagsakop sa kalusugan o tulong na walang gastos. May karapatan ka na makakuha ng ganiitong impormasyon at tulong sa iyong wika ng walang gastos. Tumawag sa 800-722-1471 (TTY: 800-842-5357).

ไทย (Thai):

ประกาศนี้มีข้อมูลสำคัญ ประกาศนี้อาจมีข้อมูลที่สำคัญเกี่ยวกับกาการสมัครหรือขอบเขตประกันสุขภาพของคุณผ่าน Premera Blue Cross และอาจมีกำหนดการในประกาศนี้ คุณอาจจะต้องดำเนินการภายในกำหนดระยะเวลาที่แน่นอนเพื่อจะรักษาการประกันสุขภาพของคุณหรือการช่วยเหลือที่มีค่าใช้จ่าย คุณมีสิทธิที่จะได้รับข้อมูลและความช่วยเหลือในภาษาของคุณโดยไม่มีค่าใช้จ่าย โทร 800-722-1471 (TTY: 800-842-5357)

Український (Ukrainian):

Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страховального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дзвоніть за номером телефону 800-722-1471 (TTY: 800-842-5357).

Tiếng Việt (Vietnamese):

Thông báo này cung cấp thông tin quan trọng. Thông báo này có thông tin quan trọng về đơn xin tham gia hoặc hợp đồng bảo hiểm của quý vị qua chương trình Premera Blue Cross. Xin xem ngày quan trọng trong thông báo này. Quý vị có thể phải thực hiện theo thông báo đúng trong thời hạn để duy trì bảo hiểm sức khỏe hoặc được trợ giúp thêm về chi phí. Quý vị có quyền được biết thông tin này và được trợ giúp bằng ngôn ngữ của mình miễn phí. Xin gọi số 800-722-1471 (TTY: 800-842-5357).