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Preauthorization is not required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

DESCRIPTION

Extracorporeal photopheresis (ECP) is a leukapheresis-based immunomodulatory procedure that involves the following three steps: (1) the patient's 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 is added to the lymphocyte fraction, which is then exposed to ultraviolet-A (320-400 nm wavelength) light at a dose of one to two J/cm²; and (3) 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.

SUMMARY OF EVIDENCE

GRAFT 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 randomized controlled trial (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 bronchiolitis obliterans syndrome (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 immune-suppressive 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.

Autoimmune Disease

For individuals who have autoimmune diseases (e.g., 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) cutaneous T-cell lymphoma (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.

POLICY

ORGAN REJECTION AFTER SOLID-ORGAN TRANSPLANT

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.

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

GRAFT-VERSUS-HOST DISEASE

Acute

Extracorporeal photopheresis may be considered **medically necessary** as a technique to treat acute graft-versus-host disease (GVHD) that is refractory to medical therapy.

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

Chronic

Extracorporeal photopheresis may be considered **medically necessary** as a technique to treat chronic GVHD that is refractory to medical therapy.

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

AUTOIMMUNE DISEASES

Extracorporeal photopheresis is considered **investigational** as a technique to treat either 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 disease.

CUTANEOUS T-CELL LYMPHOMA

Extracorporeal photopheresis may be considered **medically necessary** as a technique to treat late-stage (III or IV) cutaneous T-cell lymphoma.

Extracorporeal photopheresis may be considered **medically necessary** as a technique to treat early stage (I or II) cutaneous T-cell lymphoma that is progressive and refractory to established nonsystemic therapies.

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

OTHER

Extracorporeal photopheresis is considered **investigational** for all other indications.

POLICY GUIDELINES

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 respond adequately to a standard regimen of immunosuppressive therapy.

Recurrent allograft rejection is defined as having at least two rejection episodes after standard immuno-suppressive 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 one, followed by biweekly therapy on two consecutive days in months two and three, then monthly on two consecutive days in months four through six.

GRAFT-VERSUS-HOST DISEASE

Methylprednisolone is considered first-line treatment of acute 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 one cycle (i.e., ECP on two consecutive days) weekly for acute GVHD and every two weeks for chronic GVHD. Treatment duration is based on clinical response; 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 PG1).

Table PG1. 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

Stage Tumor T, N, and M Categories

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 1,000 cells per cubic millimeter, in the presence of immunophenotypical abnormalities (CD4/CD8 ratio greater than 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.

MEDICARE ADVANTAGE

Extracorporeal photopheresis may be considered **medically necessary** for:

- Palliative treatment of skin manifestations of cutaneous T-cell lymphoma that has not responded to other therapy
- Patients with acute cardiac allograft rejection whose disease is refractory to standard immunosuppressive drug treatment; and
- Patients with chronic graft versus host disease whose disease is refractory to standard immunosuppressive drug treatment.

Use for all other conditions would be **investigational**.

MEDICARE ADVANTAGE POLICY GUIDELINES

Extracorporeal photopheresis for the treatment of bronchiolitis obliterans syndrome (BOS) following lung allograft transplantation may have potential to be a benefit for Medicare Advantage members, but only when extracorporeal photopheresis is performed under coverage with evidence development (CED).

BACKGROUND**ORGAN REJECTION TREATMENT AFTER SOLID ORGAN TRANSPLANT**

The standard treatment of 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), 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 an 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 the 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 the 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 (8-MOP). 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 (i.e., 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 protocol, 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 neoplasia 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, which should be 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), or 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. 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 of time (mean, two to 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 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 five 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.

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®; Therakos; now Mallinckrodt) 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.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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