Protocol

Extracorporeal Photopheresis

(80136)

Medical Benefit		**Effective Date**: 01/01/15	**Next Review Date**: 09/17
Preauthorization	Yes	**Review Dates**: 05/09, 03/10, 09/10, 03/11, 03/12, 03/13, 03/14, 09/14, 09/15, 09/16	

Preauthorization is 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 steps:

1. Patient 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/cm^2.
3. The light-sensitized lymphocytes are reinfused into the patient.

ECP has been investigated for the treatment of patients with a variety of autoimmune diseases, graft-versus-host disease (GVHD), T-cell lymphoma (TCL), treatment for and prevention of organ rejection after solid organ transplant, and other miscellaneous conditions.

Summary of Evidence

Organ Rejection After Solid Organ Transplant

Heart

Evidence for the use of extracorporeal photopheresis (ECP) in cardiac transplant recipients relates to three indi-cations: acute rejection; recurrent, multiple and/or refractory rejection; and prevention of rejection. For acute rejection and for prevention of rejection, two small randomized trials provide insufficient evidence to permit conclusions concerning the effect of ECP on net health outcome. Therefore, ECP is considered investiga-tional for the treatment and prevention of acute rejection in cardiac transplant recipients. Studies with more patients and longer follow-up are needed. For recurrent, multiple and/or refractory cardiac allograft rejection, evidence to date provides consistent evidence for a beneficial effect of ECP for cardiac transplant patients with rejection refractory to standard therapy. Therefore, ECP is considered medically necessary for the treatment of recurrent, multiple and/or refractory cardiac rejection.

Lung

Evidence for the use of ECP in lung transplant recipients relates to two indications: acute rejection and chronic

rejection refractory to corticosteroids/refractory bronchiolitis obliterans syndrome (BOS). For acute rejection, data are very limited and do not permit any conclusions. This area needs a prospective, randomized, clinical trial focused specifically on the treatment of patients with acute rejection. For treatment of refractory BOS, data are nonrandomized and uncontrolled and show inconsistent results across BOS grades. Prospective, randomized controlled trials (RCTs) are necessary with analyses stratified by BOS grade. Therefore, ECP is considered investigational when used in lung transplantation.

Liver

In liver transplantation, evidence to date has focused on prevention of rejection with ECP. This evidence is insufficient to permit conclusions concerning the effect of ECP on net health outcome. There is a need for RCTs comparing immunosuppressive therapy alone to immunosuppressive therapy with ECP. Therefore, ECP is considered investigational in liver transplant patients for any indication.

Kidney

For renal transplant recipients, evidence comprises small case series in patients with refractory rejection. This evidence is insufficient to permit conclusions concerning the effect of ECP on net health outcome. RCTs comparing immunosuppressive therapy with immunosuppressive therapy with ECP and examining histologic confirmation of treatment response are needed. Therefore, ECP is considered investigational in renal transplant patients for any indication.

Graft-Versus-Host Disease

Evidence for the use of ECP for the treatment of graft-versus-host disease (GVHD) relates to both acute GVHD (aGVHD) and chronic (cGVHD) in pediatric and adult populations. Evidence comprises retrospective reviews and nonrandomized comparisons and consistently shows improvement in GVHD that is unresponsive to standard therapy. Additionally, there is a lack of other treatment options for these patients; adverse effects of 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. Clinical input unanimously supported the use of ECP in patients with refractory aGVHD. Therefore, treatment of refractory aGVHD or cGVHD with ECP is considered medically necessary.

For patients with untreated disease or those who are showing improvement on standard therapy, there is no data to support the use of ECP. Therefore, ECP is considered investigational in these settings.

Autoimmune Disease

Evidence for the use of ECP for the treatment of autoimmune diseases including multiple sclerosis and cutaneous or visceral manifestations of autoimmune diseases, including but not limited to scleroderma, systemic lupus erythematosus, rheumatoid arthritis, pemphigus, psoriasis, autoimmune bullous disorders, severe atopic dermatitis, Crohn disease, and diabetes, is sparse and insufficient to permit conclusions. Therefore, treatment of autoimmune diseases with ECP is considered investigational.

T-Cell Lymphoma

Cutaneous T-Cell Lymphoma

Evidence from small case series has shown a response to ECP in patients with advanced stage cutaneous T-cell lymphoma (CTCL), as well as prolongation of survival in a proportion of patients. Therefore, ECP may be considered medically necessary as a technique for the treatment of patients with stages III/IV CTCL.

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, ECP may be considered medically necessary as a technique for the treatment of patients with refractory or progressive early stage CTCL.

In contrast, when early stage CTCL does respond to less-invasive, topical therapies, patients whose disease remains quiescent under such treatments usually experience near-normal life expectancy. As a consequence, ECP is considered investigational as a technique for the treatment of patients with stage I/II CTCL that is either previously untreated or is responding to established therapies.

Non-CTCL/Leukemia

Data from one small case series showed at least a partial response to extracorporeal photopheresis in some patients with refractory noncutaneous T-cell malignancies. More data from larger studies are needed to determine the role of ECP in the treatment of these diseases.

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.

Acute GVHD

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 GVHD

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 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 disease.

Cutaneous T-cell Lymphoma

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

Extracorporeal photopheresis may be considered **medically necessary** as a technique to treat early stage (I/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/II) cutaneous T-cell lymphoma that is either previously untreated or is responding 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 that recurred after standard immunosuppressive therapy.

There is no standard schedule for extracorporeal photopheresis, and reported schedules vary by the organ type. However, most reported cardiac and lung schedules initiate therapy with two consecutive days of extracorporeal photopheresis 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

Methlyprednisolone is considered first-line treatment of acute GVHD. For chronic GVHD, an alternating regimen of cyclosporine and prednisolone 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 generally recommend 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 (based on the TNM classification system)

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 (WHO-EORTC), Sezary syndrome is defined by the triad of erythroderma, generalized lymphadenopathy, and the presence of neoplastic T-cells (Sezary cells) in skin, lymph nodes, and peripheral blood. The International Society of Cutaneous Lymphomas recommends an absolute Sezary cell count of at least 1,000 cells per cubic mm, 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

Treatment for and Prevention of Organ Rejection After Solid Organ Transplant

The standard of care for 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 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 to specifically 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]

Treatment of GVHD

ECP as a treatment of GVHD after a prior allogeneic stem cell transplant is based on the fact that GVHD is an immunologically mediated disease. GVHD can be categorized into acute disease, occurring within the first 100 days after infusion of allogeneic cells, or 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 aGVHD 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 aGVHD.

Treatment of 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 UV light in the presence of 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.

Treatment of 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 panniculitic T-cell lymphoma. In addition, a number of benign or very indolent conditions can be confused with mycosis fungoides, further complicating diagnosis. See the Policy Guidelines for the current staging classification of CTCL using the tumor, node, metastasis (TNM) classification system.

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 (mean, two to 10 years) as waxing and waning cutaneous eruptions before biopsy confirmation. The prognosis of patients with mycosis fungoides/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 to 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 through stage 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, possibly excepting ones in the earliest stages, is not curable. 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.

Peripheral T-Cell Lymphoma

Peripheral T-cell lymphoma (PTCL) is a group of rare and usually aggressive non-Hodgkin lymphomas that develop from mature T cells. PTCL comprises approximately 10% to 15% of all cases of non-Hodgkin lymphoma in the United States and generally occurs in adults 60 years of age or older. Standards of care are evolving, including the use of hematopoietic stem cell transplantation.[6]

Regulatory Status

FDA has approved via premarket application for two photopheresis systems manufactured by Therakos™ Inc. (West Chester, PA). Both systems are approved for use in ultraviolet A (UVA) irradiation treatment, in the presence of the photoactive drug 8-MOP, 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.

8-MOP (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 that is unresponsive to other forms of treatment.

The use of either Therakos Photopheresis System or UVADEX® for other conditions is an off-label use of an FDA-approved device/drug. 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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