

Protocol

Extracorporeal Photopheresis

(80136)

Medical Benefit		Effective Date: 07/01/13	Next Review Date: 03/15
Preauthorization	Yes	Review Dates: 05/09, 03/10, 09/10, 03/11, 03/12, 03/13, 03/14	

*The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. **Preauthorization is required.** 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 per square cm.
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.

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 are also affected. This can, in turn, lead to serious infections, including opportunistic infections.

While 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 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, while 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 immunosuppressant drugs. (5)

Treatment of Graft-versus-Host Disease (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–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, while 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.

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 antibodies, it is not certain how these antibodies are related to the pathogenesis of the disease, and, as discussed in this Protocol, photopheresis is not associated with consistent changes in autoantibody levels.

Treatment T-Cell Lymphoma

Cutaneous T-Cell Lymphoma (CTCL)

According to the National Cancer Institute (NCI), CTCL is a neoplasia of malignant T lymphocytes that initially present 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, the overall prevalence is much higher. Two CTCL variants, mycosis fungoides and the Sezary 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 progress 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. Sezary 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 a 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, an average of two to 10 years, as waxing and waning cutaneous eruptions prior to biopsy confirmation. The prognosis of patients with mycosis fungoides/Sezary 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. The median survival following diagnosis varies according to stage. Patients with stage IA disease have a median survival of 20 or more years, with the majority of deaths for this group typically unrelated to mycosis fungoides. In contrast, more than 50% of patients with stage III through stage IV disease die of their disease, with a median survival of less than five years.

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 the majority of patients require lifelong treatment and monitoring.

Peripheral T-Cell Lymphoma (PTCL)

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

Regulatory Status

In the U.S., the UVAR® XTS Photopheresis System was approved via premarket application (PMA) by the U.S. Food and Drug Administration (FDA) for use in the ultraviolet-A (UVA) irradiation (in the presence of the photoactive drug, methoxsalen) of extracorporeally circulating leukocyte-enriched blood in the palliative treatment of the skin manifestations of cutaneous T-cell lymphoma (CTCL) in persons who have not been responsive to other therapy.

8-MOP (UVADEX®) is approved by the FDA for use in conjunction with UVAR XTS Photopheresis System for use in the UVA irradiation in the presence of the photoactive drug methoxsalen of extracorporeally circulating leukocyte-enriched blood in the palliative treatment of the skin manifestations of CTCL in persons who have not been responsive to other therapy.

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

Policy (Formerly Corporate Medical Guideline)

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

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

Extracorporeal photopheresis is considered **investigational** as a technique to treat acute graft-versus-host disease or chronic graft-versus-host disease 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 or autoimmune bullous disorders.

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 Guideline

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 for one month, followed by biweekly therapy on two successive days for months two and three, then monthly on two consecutive days for months four–six.

An alternating regimen of cyclosporine and prednisone is commonly used to treat chronic graft-versus-host disease. Other therapies include antithymocyte globulin, corticosteroid monotherapy, and cytotoxic immunosuppressive drugs such as procarbazine, cyclophosphamide, or azathioprine. Therefore, refractory disease is defined as chronic graft-versus-host disease that fails to respond adequately to a trial of any of the above therapies.

CTCL 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

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 CTCL 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.

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 provided under a valid clinical trial (billed to original fee-for-service-Medicare not Medicare Advantage).

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

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.**

References

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

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