



MASSACHUSETTS

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Medical Policy

Extracorporeal Photopheresis

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Policy Number: 248

BCBSA Reference Number: 8.01.36 (For Plans internal use only)

Related Policies

None

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

Extracorporeal photopheresis may be considered **MEDICALLY NECESSARY** to treat the following conditions:

- Cardiac allograft rejection, including acute rejection, that is either recurrent or that is refractory to standard immunosuppressive drug treatment
- Acute graft-versus-host disease or chronic graft-versus-host disease that is refractory to medical therapy
- Late-stage (III/IV) cutaneous T-cell lymphoma, or
- Early stage (I/II) cutaneous T-cell lymphoma that is progressive and refractory to established non-systemic therapies.

Refractory rejection is defined as rejection that fails to respond adequately to a standard regimen of immunosuppressive therapy.

Extracorporeal photopheresis is considered **INVESTIGATIONAL** for the following conditions:

- Treatment or prevention of rejection in solid-organ transplantation except for rejection that is recurrent or refractory to standard immunosuppressive drug treatment
- Acute graft-versus-host disease or chronic graft-versus-host disease, that is either previously untreated or is responding to established therapies
- 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, severe atopic dermatitis, or Crohn disease.
- Early stage (I/II) cutaneous T-cell lymphoma that is either previously untreated or is responding to established nonsystemic therapies.

Extracorporeal photopheresis is [INVESTIGATIONAL](#) for all other indications.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is not required .
Commercial PPO and Indemnity	Prior authorization is not required .

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

CPT Codes

CPT codes:	Code Description
36522	Photopheresis, extracorporeal

ICD-10 Diagnosis Codes

ICD-10-CM Diagnosis codes:	Code Description
C84.00	Mycosis fungoides, unspecified site
C84.01	Mycosis fungoides, lymph nodes of head, face, and neck
C84.02	Mycosis fungoides, intrathoracic lymph nodes
C84.03	Mycosis fungoides, intra-abdominal lymph nodes
C84.04	Mycosis fungoides, lymph nodes of axilla and upper limb
C84.05	Mycosis fungoides, lymph nodes of inguinal region and lower limb
C84.06	Mycosis fungoides, intrapelvic lymph nodes
C84.07	Mycosis fungoides, spleen
C84.08	Mycosis fungoides, lymph nodes of multiple sites
C84.09	Mycosis fungoides, extranodal and solid organ sites
C84.10	Sézary disease, unspecified site
C84.11	Sézary disease, lymph nodes of head, face, and neck
C84.12	Sézary disease, intrathoracic lymph nodes
C84.13	Sézary disease, intra-abdominal lymph nodes
C84.14	Sézary disease, lymph nodes of axilla and upper limb
C84.15	Sézary disease, lymph nodes of inguinal region and lower limb
C84.16	Sézary disease, intrapelvic lymph nodes
C84.17	Sézary disease, spleen
C84.18	Sézary disease, lymph nodes of multiple sites
C84.19	Sézary disease, extranodal and solid organ sites
D89.810	Acute Graft-Versus-Host Disease
D89.811	Chronic graft-versus-host disease

D89.812	Acute on chronic graft-versus-host disease
D89.813	Graft-versus-host disease, unspecified
T86.00	Unspecified complication of bone marrow transplant
T86.01	Bone marrow transplant rejection
T86.02	Bone marrow transplant failure
T86.03	Bone marrow transplant infection
T86.09	Other complications of bone marrow transplant
T86.21	Heart transplant rejection
T86.31	Heart-lung transplant rejection
T86.5	Complications of stem cell transplant

DESCRIPTION

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 infections 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 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 2 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. 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 evidence review, 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, the 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.

Cutaneous T-cell lymphoma 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. 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 of time (mean, 2 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 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

Description

Extracorporeal photopheresis (ECP) is a leukapheresis-based immunomodulatory procedure that involves the following 3 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 1 to 2 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.

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 extracorporeal photopheresis (ECP), the evidence includes a small randomized controlled trial (RCT). Relevant outcomes are overall survival (OS), 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 that the technology results in an improvement in the net health outcome.

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 OS, 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 an 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 and a prospective pilot study. Relevant outcomes are OS, change in disease status, and treatment-related mortality and morbidity. The small randomized trial is insufficient to permit conclusions on the utility of ECP. The pilot study was non-comparative and evaluated outcomes in high-risk cardiac transplant patients. Studies with more patients and longer follow-up are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 OS, 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 that the technology results in an improvement in the net health outcome.

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 OS, 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 that the technology results in an improvement in the net health outcome.

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 OS, 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 that the technology results in an improvement in the net health outcome.

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 OS, 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. There is a need for RCTs comparing immunosuppressive therapy with and without the use of ECP and examining histologic confirmation of

treatment response. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Graft-Versus-Host Disease

For individuals who have acute or chronic graft-versus-host disease (GVHD) refractory to medical treatment who receive ECP, the evidence includes systematic reviews, a randomized study, retrospective studies, and case series. Relevant outcomes are OS, 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 an improvement in the net health outcome.

Other Indications, Not Related To Solid Organ Transplant

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's disease) who receive ECP, the evidence includes isolated RCTs, small prospective and retrospective studies, and case reports. Relevant outcomes are OS, 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 that the technology results in an improvement in the net health outcome.

Cutaneous 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 OS, 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 an 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 OS, 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 an improvement in the net health outcome.

Policy History

Date	Action
12/2023	Annual policy review. References updated. Policy statements unchanged.
12/2022	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
12/2021	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
1/2021	Medicare information removed. See MP #132 Medicare Advantage Management for local coverage determination and national coverage determination reference.
12/2020	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
11/2019	Annual policy review. Description, summary, and references updated. Policy statements unchanged.

11/2018	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
6/2015	Annual policy review. New references added.
10/2014	Annual policy review. New medically necessary and investigational indications described. Clarified Coding information. Effective 10/1/2014.
5/2014	Updated Coding section with ICD10 procedure and diagnosis codes. Effective 10/2015.
8/2013	Annual policy review. New investigational indications described. Title changed. Effective 8/1/2013.
2/2013	Annual policy review. No change in medical policy statement. Investigational statement clarified to apply to acute cardiac transplant rejection that is not recurrent or refractory. Effective 2/4/2013.
11/2011-4/2012	Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements.
4/2011	Medical Policy 248 created. No changes to policy statements from source medical policy 071: Pheresis.
11/2010	Reviewed - Medical Policy Group- Gastroenterology, Nutrition and Organ Transplantation No changes to policy statements.
9/2010	Reviewed - Medical Policy Group -Hematology and Oncology No changes to policy statements.
6/2010	Annual policy review. No changes to policy statements.
4/2010	Reviewed - Medical Policy Group -Cardiology. No changes to policy statements.
9/2009	Reviewed - Medical Policy Group -Hematology and Oncology. No changes to policy statements.
2/2008	Annual policy review. No changes to policy statements.
1/2008	Reviewed - Medical Policy Group – Neurology. No changes to policy statements.
9/2007	Reviewed - Medical Policy Group - Hematology/Oncology. No changes to policy statements.
4/2007	Reviewed - Medical Policy Group Cardiology. No changes to policy statements.
1/2007	Reviewed - Medical Policy Group Neurology. No changes to policy statements.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

[Medical Policy Terms of Use](#)

[Managed Care Guidelines](#)

[Indemnity/PPO Guidelines](#)

[Clinical Exception Process](#)

[Medical Technology Assessment Guidelines](#)

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