Medical Policy

Extracorporeal Photopheresis

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Policy Number: 248
BCBSA Reference Number: 8.01.36
NCD/LCD: National Coverage Determination (NCD) for Extracorporeal Photopheresis (110.4)

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.

### Medicare HMO Blue℠ and Medicare PPO Blue℠ Members

#### Indications and Limitations of Coverage

**Nationally Covered Indications**

The Centers for Medicare & Medicaid Services has determined that extracorporeal photopheresis is reasonable and necessary under §1862(a)(1)(A) of the Social Security Act (the Act) under the following circumstances:

1. **Effective April 8, 1988,** Medicare provides coverage for:
   - Palliative treatment of skin manifestations of cutaneous T-cell lymphoma that has not responded to other therapy.

2. **Effective December 19, 2006,** Medicare also provides coverage for:
   - 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.

3. **Effective April 30, 2012,** Medicare also provides coverage for:
   - Extracorporeal photopheresis 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 the following conditions:
     - The clinical research study meets the requirements specified below to assess the effect of extracorporeal photopheresis for the treatment of BOS following lung allograft transplantation. The clinical study must address one or more aspects of the following question:
       - Prospectively, do Medicare beneficiaries who have received lung allografts, developed BOS refractory to standard immunosuppressive therapy, and received extracorporeal photopheresis experience improved patient-centered health outcomes as indicated by:
         a. improved forced expiratory volume in one second (FEV1);
         b. improved survival after transplant; and/or,
         c. improved quality of life?
     - The required clinical study must adhere to the following standards of scientific integrity and relevance to the Medicare population:
       a. The principal purpose of the research study is to test whether extracorporeal photopheresis potentially improves the participants’ health outcomes.
       b. The research study is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
       c. The research study does not unjustifiably duplicate existing studies.
       d. The research study design is appropriate to answer the research question being asked in the study.
       e. The research study is sponsored by an organization or individual capable of successfully executing the proposed study.
       f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it must also be in compliance with 21 CFR parts 50 and 56.
       g. All aspects of the research study are conducted according to appropriate standards of scientific integrity (see http://www.icmje.org).
       h. The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare requirements for coverage with evidence development.
       i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the...
objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.

j. The clinical research study is registered on the ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.

k. The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors (http://www.icmje.org).

l. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.

m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Act, the Agency for Healthcare Research and Quality supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

Any clinical study under which there is coverage of extracorporeal photopheresis for this indication pursuant to this national coverage determination (NCD) must be approved by April 30, 2014. If there are no approved clinical studies on this date, this NCD will expire and coverage of extracorporeal photopheresis for BOS will revert to the coverage policy in effect prior to the issuance of the final decision memorandum for this NCD.

Nationally Non-Covered Indications
All other indications for extracorporeal photopheresis not otherwise indicated above as covered remain non-covered.

National Coverage Determination (NCD) for Extracorporeal Photopheresis (110.4)
http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=113&ncdver=3&bc=AgAAgAAAAAgAA&

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required for outpatient services.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Commercial Managed Care (HMO and POS)</th>
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<tr>
<td>Commercial PPO and Indemnity</td>
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<tr>
<td>Medicare HMO Blue℠</td>
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<tr>
<td>Medicare PPO Blue℠</td>
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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**

<table>
<thead>
<tr>
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<th>Code Description</th>
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<tr>
<td>36522</td>
<td>Photopheresis, extracorporeal</td>
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**ICD-9 Diagnosis coding**

<table>
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<th>Code Description</th>
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<tr>
<td>202.10</td>
<td>Mycosis fungoides, unspecified site, extranodal and solid organ sites</td>
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<tr>
<td>202.11</td>
<td>Mycosis fungoides of lymph nodes of head, face, and neck</td>
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<tr>
<td>202.12</td>
<td>Mycosis fungoides of intrathoracic lymph nodes</td>
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<td>202.13</td>
<td>Mycosis fungoides of intra-abdominal lymph nodes</td>
</tr>
<tr>
<td>202.14</td>
<td>Mycosis fungoides of lymph nodes of axilla and upper limb</td>
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<td>202.15</td>
<td>Mycosis fungoides of lymph nodes of inguinal region and lower limb</td>
</tr>
<tr>
<td>202.16</td>
<td>Mycosis fungoides of intrapelvic lymph nodes</td>
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<td>202.17</td>
<td>Mycosis fungoides of spleen</td>
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<td>202.18</td>
<td>Mycosis fungoides of lymph nodes of multiple sites</td>
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<td>Sezary’s disease, unspecified site, extranodal and solid organ sites</td>
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<td>202.22</td>
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<td>202.28</td>
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<td>279.52</td>
<td>Chronic graft-versus-host disease</td>
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<td>Acute or chronic graft-versus-host disease</td>
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<td>996.83</td>
<td>Complications of transplanted organ, heart</td>
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<tr>
<td>996.85</td>
<td>Complications of transplanted bone marrow</td>
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<td>996.88</td>
<td>Complications of stem cell transplant</td>
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**ICD-10 Diagnosis Codes**

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<th>ICD-10-CM Diagnosis codes:</th>
<th>Code Description</th>
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<td>C84.00</td>
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<td>C84.01</td>
<td>Mycosis fungoides, lymph nodes of head, face, and neck</td>
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<tr>
<td>C84.02</td>
<td>Mycosis fungoides, intrathoracic lymph nodes</td>
</tr>
<tr>
<td>C84.03</td>
<td>Mycosis fungoides, intra-abdominal lymph nodes</td>
</tr>
<tr>
<td>C84.04</td>
<td>Mycosis fungoides, lymph nodes of axilla and upper limb</td>
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<tr>
<td>C84.05</td>
<td>Mycosis fungoides, lymph nodes of inguinal region and lower limb</td>
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</tbody>
</table>
Description
Extracorporeal photopheresis (ECP) is a leukapheresis-based immunomodulatory procedure that involves the following 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 (8-MOP) 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 per square cm AND
- The light-sensitized lymphocytes are re-infused into the patient.

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

Treatment for and Prevention of Organ Rejection after Solid-Organ Transplant
Immunosuppression is the standard of care for treatment of organ transplant rejection, with the particular regimen dictated by the organ being transplanted. Immunosuppressive therapies are used to lower the responsiveness of the recipient’s immune system, decreasing the chance of rejection.
ECP has more recently been used as a supplement to conventional therapies in the area of transplantation.

Summary—Solid Organ Rejection
The evidence for the use of ECP in cardiac transplant patients relates to 3 indications: acute rejection; recurrent, multiple and/or refractory rejection; and prevention of rejection. Studies with more patients and longer follow-up are needed. Therefore, ECP is considered investigational for the treatment and prevention of acute rejection in cardiac transplant recipients.
ECP for recurrent, multiple and/or refractory cardiac allograft rejection has been the focus of most of the research on ECP. The 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.

The bulk of the ECP in lung transplant literature focuses on treatment of refractory bronchiolitis obliterans syndrome (BOS). The evidence to date, which consists of small case series, is insufficient to permit conclusions concerning the effect of this procedure on health outcomes in lung transplant. Studies with larger numbers of subjects and longer follow-up are needed. Therefore, ECP is considered investigational when used in lung transplantation.

In liver transplantation, the evidence for the use of ECP is limited and is insufficient to permit conclusions concerning the effect of ECP on net health outcome for liver transplant patients. Therefore, ECP is considered investigational in liver transplant patients for any indication.

For renal transplant recipients, the evidence for the use of ECP is sparse and is insufficient to permit conclusions concerning the effect of ECP on net health outcome for renal transplant patients. Therefore, ECP is considered investigational in renal transplant patients for any indication.

**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 after 100 days.

**Summary – Graft-versus-Host Disease (GVHD)**

Evidence for the use of ECP for the treatment of GVHD relates to both aGVHD and cGVHD in pediatric and adult populations. The published literature lacks randomized trials. Evidence comprises retrospective reviews and nonrandomized comparisons. These data consistently show improvement in GVHD that is unresponsive to standard therapy and are consistent with conclusions from the 2001 TEC Assessment. Additionally, there is a lack of other treatment options for these patients, with the added benefit of minimal side effects from ECP, as well as the possibility of reduction and often cessation of treatment with corticosteroids and other immunosuppressive agents if there is a response to ECP. 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.

**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.

**Summary – Treatment of Autoimmune Disease**

Evidence for the use of ECP for the treatment of autoimmune diseases including 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, is sparse and insufficient to permit conclusions. There are randomized trials for 2 indications: scleroderma and type 1 diabetes. Methodologic flaws in the scleroderma trial limit applicability of the data. In the type 1 diabetes trial, no difference in hemoglobin A1C was observed between those treated with and without ECP. Therefore, treatment of autoimmune diseases with ECP is considered investigational.
Treatment of Cutaneous T-Cell Lymphoma (CTCL)
CTCL is a neoplasia of malignant T lymphocytes that initially presents as skin involvement. CTCL is included in the Revised European-American Lymphoma classification as a group of low-grade T-cell lymphomas.

Summary – Treatment of Cutaneous T-Cell Lymphoma (CTCL)
Numerous small, nonrandomized studies have been generally consistent with an initial trial that showed that ECP treatment can produce clinical improvement and may prolong survival in a substantial proportion of patients with advanced-stage CTCL. The National Cancer Institute recommends ECP as first-line treatment for patients with stage III/IV CTCL. Therefore, ECP may be considered medically necessary as a technique for the treatment of patients with stages III/IV CTCL.

While the literature on ECP as a technique to treat early stage (I/II) cutaneous T-cell lymphoma that is progressive and refractory to established nonsystemic therapies is limited, given the unfavorable prognosis for patients with early-stage CTLC that progresses while receiving nonsystemic therapies, the relative lack of adverse events with ECP compared to other systemic treatments, and the good response rates often associated with ECP, ECP may be considered medically necessary as a technique for the treatment of patients with refractory or progressive early-stage CTCL.

By contrast, because early-stage CTCL typically responds to less-invasive, topical therapies, patients whose disease remains quiescent under such treatments usually experience a 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.

Examples of photopheresis systems include the UVAR® XTS Photopheresis System and the UVADEX®. All photopheresis systems are considered investigational regardless of the commercial name, the manufacturer or FDA approval status except when used for the medically necessary indications that are consistent with the policy statement.

Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>6/2015</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>5/2014</td>
<td>Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.</td>
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<tr>
<td>2/2013</td>
<td>BCBSA National medical 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.</td>
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No changes to commercial policy statements.
Coverage for Medicare HMOBlue, Medicare PPO Blue for therapeutic pheresis clarified based on CMS' NCD.

2/2008  BCBS Association National Policy Review
No changes to policy statements.

1/2008  Reviewed - Medical Policy Group - Neurology
No changes to policy statements.

No changes to policy statements.

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

References


