UNIVERSITY OF
PENNSYLVANIA
HEALTH SYSTEM

Department of Medicine

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Centers for Medicare and Medicaid Services
Mail Stop C1-09-06
7500 Security Boulevard
Baltimore, Maryland 21244

March 21, 2006

Attention: Ms. Susan Harrison, Lead Analyst

Re: NCD Reconsideration Request
Extracorporeal Photopheresis

Dear Dr. Salive:

We formally request a National Coverage Determination (NCD) Reconsideration for extracorporeal photopheresis (110.4) (Tab 1). Enclosed is a binder of supporting documentation from the peer reviewed medical literature in support of our request (Tab 2).

We request reconsideration of the NCD for extracorporeal photopheresis for the following reasons:

- This NCD was effective April 8, 1988, and has not been updated in the past 18 years.
- The technology for performance of extracorporeal photopheresis has greatly advanced in the last 18 years. Consequently, this procedure is more widely available to patients.
- Clinical investigations in the past 15 years have clearly <demonstrated the efficacy of photopheresis in two specific clinical indications: 1) cardiac transplant rejection; and 2) chronic graft-versus-host disease (cGVHD) following allogeneic hematopoietic cell transplantation. Additional evidence suggests extracorporeal photopheresisis also effective in selected patients with pemphigus vulgaris or bullous pemphigoid.
- In the setting of cardiac transplantation, administration of extracorporeal photopheresis is life-saving. Performance of extracorporeal photopheresis in patients with cGVHD vastly improves the quality of life. Similarly, extracorporeal photopheresis appears to heal mucocutaneous lesions and reduce concomitant immunosuppressive therapy in patients with pemphigus vulgaris or bullous pemphigoid.
- Extracorporeal photopheresis is not primary therapy in any of these clinical settings. Rather, extracorporeal photopheresis comprises salvage therapy, in the minority of patients refractory to standard immunosupression including high dose glucocorticoids and calcineurin inhibitors such as cyclosporin A.
- The costs of medical care for patients with continued cardiac transplant rejection prior to their demise, and likewise the costs of continued care for patients with progressive refractory cGVHD, pemphigus vulgaris or bullous pemphigoid far outweigh the costs of extracorporeaI photopheresis.

Well-documented peer-reviewed literature describes the effectiveness of photopheresis in the treatment of rejection in cardiac transplant patients, the therapy of cGVHD following allogeneic hematopoietic cell transplantation, and also management of steroid-resistant pemphigus vulgaris or bullous pemphigoid. **Tab 2** includes a compendium of pertinent clinical literature, which we would like to briefly summarize.

Role of Extracorporeal Photopheresis in Cardiac Transplant Rejection

Cardiac (both heart and heart-lung) transplantation is well established as reasonable and medically necessary therapy for a variety of cardiac disorders (Taylor et aI, 2004; Jessup and Brozena, 2003). Initial immunosupression is followed by routine surveillance with endomyocardial biopsies to diagnose episodes of acute rejection; acute rejection is typically treated with increased immunosupression (Mueller, 2004a, 2004b; Patel and Kobashigawa, 2004). A body of basic immunologic research (Gorgon et aI, 2002; Barr, 2003; Heshmati, 2003), many studies demonstrating the clinical efficacy of photopheresis in patients with a variety of disorders caused by the clonal expansion of abnormally responsive pathogenic T cell populations, and the apparent benefit of photopheresis in 4 patients with acute cardiac transplant rejection led to an international clinical trial of photopheresis in cardiac transplant recipients (Barr et aI, 1998). In this landmark study, photopheresis effectively reduced the number of subsequent acute rejection episodes. Several years later, multiple studies proved that extracorporeal photopheresis could be extremely effective at treating cardiac transplant rejection refractory to standard immunosuppressive therapy (Lehrer et aI, 2001).

Over the past 15 years, approximately 2500 cardiac transplantations have been performed annually in the United States (Taylor et aI, 2004), with little change expected in this rate of transplantation (Hosenpud, 2005). The wide variability among cardiac transplant centers in their immunosuppression regimens, the modest frequency of acute rejection episodes, the difficulty in defining appropriate endpoints in multicenter clinical trials of acute cardiac transplant rejection (Hosenpud, 2005), and the current status of extracorporeal photopheresis as salvage therapy all preclude an adequately powered clinical trial to demonstrate the efficacy of this treatment. Nonetheless, in the clinical setting of acute cardiac transplant rejection refractory to increasing doses of standard immunosuppressives, extracorporeal photopheresis is life-saving (Lehrer et al, 2001; Dall'Amico and Murer, 2005).

The costs to the Medicare trust fund following cardiac transplantation are substantial, even during just the first 90 days following transplantation. No data are available to us regarding the total costs allocable to treating individual episodes of acute cardiac transplant rejection. Similarly, the role of daclizumab in reducing the frequency and severity of these episodes (Hershberger et al, 2005), and consequently the future need for extracorporeal photopheresis in this patient population, is speculation at best. Nonetheless, for the small number of patients with refractory acute cardiac transplant rejection, photopheresis appears to be therapeutically effective, medically necessary, and life saving. Therefore, we believe the National Coverage Determination (NCD) for extracorporeal photopheresis (110.4) should be revised and updated to include this specific indication.

Role of Extracorporeal Photopheresis in cGVHD

With regard to cGVHD, allogeneic hematopoietic cell (both bone marrow and peripheral stem cell) transplantation is effective therapy for many patients with a variety of malignancies and a small number of other various conditions. Allogeneic hematopoietic cell transplantation is associated with a significant mortality. Unfortunately, following successful therapy of their underlying disorder by survival of allogeneic hematopoietic cell transplantation, between 30% and 70% of patients develop cGVHD. Primarily affecting the skin, cGVHD is a multiorgan system disease with devastating consequences to these patients. While most patients respond to increased immunosuppression,

primarily glucocorticoids and cyclosporin A, a small number of patients remain plagued by refractory cGVHD.

In the mid-1990s, a small number of case reports suggested extracorporeal photopheresis efficacious at reducing sclerodermatous skin lesions, oral mucosal ulcers, and hepatic transaminitis in patients with cGVHD previously refractory to increased immunosuppression (Foss, 2003). Subsequently, many small series have confirmed the efficacy of extracorporeal photopheresis at reducing cutaneous lesions, along with reductions in oral, hepatic, and ocular manifestations ofcGVHD (Greinix et al, 1998; Child et al, 1999; Dall'Amico and Messina, 2002; Ilhan et al, 2004; Coyle et al, 2004; Foss et al, 2005). In addition to these clinical improvements, reductions in subsequent immunosuppressive therapy were simultaneously achieved.

For the small number of patients with cGVHD, refractory to increased immunosuppressive therapy, photopheresis appears to be therapeutically effective, medically necessary, and reasonable. Therefore, we believe the National Coverage Determination (NCD) for extracorporeal photopheresis (110.4) should be revised and updated to include this specific indication.

Role of Extracorporeal Photopheresis in Pemphigus Vulgaris and Bullous Pemphigoid

Pemphigus vulgaris and bullous pemphigoid are each uncommon, autoimmune blistering diseases of the skin and mucosal surfaces. Much like acute rejection following transplantation and cGVHD, clonal expansion of abnormally responsive T cells are thought to play an important role in these disorders, typically treated successfully with glucocorticoid immunosuppression. At times, additional immunosuppression (typically azathioprine, cyclophosphamide or mycophenylate mofetil) is added for persistant disease. Despite this additional immunosupression, some patients unfortunately continue with severe and persistent mucocutaneous disease.

The initial description of extracorporeal photopheresis for patients with steroid-unresponsive pemphigus vulgaris in 1990 (Rook et al, 1990) was followed by a small number of case series (Liang et al, 1992; Gollnick et al, 1993; Wollina et al, 1999). Substantial clinical improvement in mucocutaneous lesions was achieved, generally associated with reduced immunosupression requirements.

For the small number of patients with pemphigus vulgaris or bullous pemphigoid, refractory to increased immunosuppressive therapy, photopheresis appears to be therapeutically effective, medically necessary, and reasonable. While we acknowledge that only small case series exist to demonstrate clinical efficacy, randomized clinical trials are impractical given the low prevalence of these disorders and the utility of extracorporeal photopheresis only for those few patients refractory to increased glucocorticoids and additional immunosupression. Furthermore, coverage of extracorporeal photopheresis for patients with steroid-refractory pemphigus vulgaris and bullous pemphigoid would be consonant with the existing National Coverage Decision of Intravenous Immune Globulin for Autoimmune Mucocutaneous Blistering Diseases (CAG00109N) **(Tab** 3), allowing coverage only in cases failing conventional therapy.

Summary

Specifically, we request that you consider updating NCD 110.4 (extracorporeal photopheresis) by:

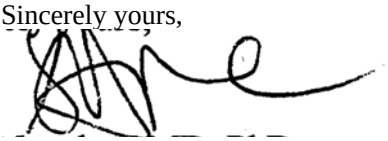
- Allowing for the additional indications for photopheresis in treating the specific disorders of acute cardiac transplant rejection, cGVHD, pemhigus vulgaris, or bullous pemphigoid refractory to conventional immunosuppressive therapy; and;

• Allowing for Medicare contractor discretion by elimination of the word "only" in the indication statement " ... extracorporeal photopheresis is covered by Medicare only when used in the palliative treatment of the skin manifestations of CTCL... ").

These two specific updates would allow coverage for patients with these four conditions in which we believe acceptable scientific evidence currently exists to support coverage by Medicare. In addition, allowing for contractor discretion would allow expansion of coverage for other conditions in which the data are too preliminary to warrant a national coverage decision, but local coverage may be appropriate. Other such condition would potentially include pemphigus foliaceus, acute GVHD, systemic sclerosis, and rejection of other solid organ transplantations.

If you have any questions or require any further information, please do not hesitate to contact any one of us.

Sincerely yours,



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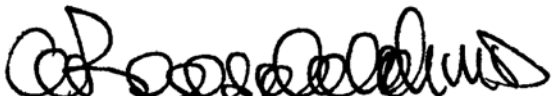

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