

April 1, 2010

ABC Insurance Company  
4 Hill Lane  
Oshkosh, WI 12345

RE: Mr. Patient  
ID no. 1232123  
Service: Intravenous immunoglobulin  
Date of service: To be determined (prior authorization)

Dear Sir/Madam:

I am writing on behalf of your insured, Mr. Patient, to appeal your denial of coverage of intravenous immunoglobulin (IVIg) for the treatment of pemphigus vulgaris (PV).

Mr. Patient has a severe case of PV. He has been on oral steroids (prednisone) for nearly ten (10) years. As a result, he has developed both diabetes and osteoporosis. In addition, the prednisone no longer controls Mr. Patient's PV, leaving him with painful blisters on his head and in his mouth, thereby affecting his nutritional intake. He has tried azathioprine and CellCept, neither of which has generated positive results. Thus, a trial of IVIg is a sensible, conservative approach to Mr. Patient's treatment.

**I. Mr. Patient's Medical History Demonstrates That IVIg Is A Sensible, Conservative Approach**

Mr. Patient first had blisters in his mouth at age 35. His primary care physician first thought it was herpes and assumed it would pass. When blisters began to appear on Mr. Patient's scalp and spread down his throat, Dr. Jones referred him to Dr. Peters, a dermatologist. Dr. Peters examined Mr. Patient and believed the blisters to be PV. However, to be certain, Dr. Peters biopsied a sample of Mr. Patient's skin, and also tested Mr. Patient for antibody titers. Both of these tests confirmed the diagnosis of PV.

Beginning in 1999, Mr. Patient was on 80 mg. per day of prednisone. In 2003, he developed diabetes. However, because his PV flared whenever the dosage of prednisone was decreased, 80 mg. per day was maintained despite the diabetes. Dr. Jones confirmed each flare of PV with an antibody titer test, and each time the dose of prednisone was decreased, the antibody titer count increased dramatically.

In 2007, Mr. Patient broke his wrist. Because the fracture was unusual, Dr. Jones, Mr. Patient's primary care physician, sent him for a bone density test, which showed advanced osteoporosis. Dr. Jones believes that this, too, is a result of long-term use of high dose prednisone.

After consulting with Dr. Peters, Dr. Jones began to decrease Mr. Patient's dose of prednisone and to add steroid-sparing drugs to try to control the PV. Dr. Jones put Mr.

Patient on 100 mg. of azathioprine. After six months, Mr. Patient's was on only 10 mg. of prednisone per day, but his PV was "out of control," as demonstrated by very high antibody titers. Dr. Jones then tried CellCept. It, too, failed to control the PV.

During the time when the prednisone was being decreased, the PV raged so badly that it affected Mr. Patient's nutritional status. The blisters in his mouth became very painful, and extended down his throat to his vocal cords, making eating tremendously painful. Not only did this cause weight loss, but it made it more difficult to control Mr. Patient's diabetes.

By last Fall, Mr. Patient's PV was quite debilitating. Although he no longer was taking prednisone, his diabetes still posed a challenge, and the fear of further bone fracture remained. Worst of all, the PV itself was "the worst case I have ever seen," according to Dr. Peters, who states that he has seen over 50 cases of PV in his career. There are burn-like lesions on Mr. Patient's scalp, as well as in his mouth and throat. Dr. Jones agrees; something must be done. The current options are IVIg, plasmapheresis, or a biologic such as Rituxan. Dr. Peters believes that IVIg is the safest of these alternatives, all of which are equally expensive.

Dr. Peters filed a request for prior authorization with your Clinical Review Department on November 23, 2009. On January 12, 2010, you denied that request. We write now to appeal.

## **II. IVIg Is a Medically Accepted Treatment for PV**

PV once was thought to be fatal. Bystryn, et al., "IVIg Treatment of Pemphigus," *J Invest Dermatol* 125:1093-1098, 2005. It occurs when autoantibodies attack proteins known as desmogliens. Amagai, et al., "A randomized double-blind trial of intravenous immunoglobulin for pemphigus," *J Am Acad Dermatol*. 2009 April; 60(4): 595-603. It results in epithelial blistering affecting cutaneous or mucosal surfaces. Mignogna, et al., "Oral Pemphigus," *Minerva Stomatol* 2009; 58:501-18.

High doses of prednisone are the first-line treatment for PV. However, "[t]he prolonged use of systemic corticosteroids, though clinically effective in high doses, can result in multiple debilitating adverse effects. Immunosuppressive agents, used as adjuvants and as corticosteroid-sparing agents, are not effective in all patients and are contraindicated in some. Therefore, alternative treatment modalities are needed to provide effective control of PV in such patients." Sami, et al., "Corticosteroid-Sparing Effect of Intravenous Immunoglobulin Therapy in Patients With Pemphigus Vulgaris," *Arch Dermatol*. 2002; 138: 1158-1162.

Although the precise mechanism of IVIg in PV is unknown, "it seems to work by rapidly, dramatically, and selectively lowering serum levels of pemphigus antibodies. We have found that one week after a single cycle of IVIg, the average level of pemphigus antibodies decreased by an average of 70%." Bystryn, *supra*. "The rate of decrease in pemphigus antibodies is as rapid as that induced when pemphigus antibodies are removed physically by plasmapheresis, and much more rapid than with conventional treatment with high doses of steroids and cytotoxic drugs where antibody levels decrease by only 16% after 3 weeks." *Ibid*.

In another study, the antibodies that are decreased by IVIg were isolated.

Within 6 to 16 days after initiating a single cycle of intravenous immunoglobulin therapy in 9 patients, a significant decrease in serum levels of IgG4 and IgG1 antibodies against desmoglein 1 and desmoglein 3 occurred in 60% to 100% of the patients, depending on the antibody subclass and specificity. The median decrease in the antibody levels ranged from 34% to 80%. In addition, most patients (n = 6) showed clinical improvement. The decrease in IgG4 antidesmoglein 3 levels seemed to correlate with improvement in disease activity.

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Intravenous immunoglobulin therapy rapidly lowers serum levels of IgG1 and IgG4 antidesmoglein 1 and desmoglein 3 antibodies. There seems to be a stronger association between the decrease in IgG4 antidesmoglein 3 levels and improvement in clinical activity than with changes in the other antibody levels, which suggests that IgG4 antibodies have a more important role in mediating pemphigus vulgaris.

Green, et al., "Effect of Intravenous Immunoglobulin Therapy on Serum Levels of IgG1 and IgG4 Antidesmoglein 1 and Antidesmoglein 3 Antibodies in Pemphigus Vulgaris," *Arch Dermatol.* 2008;144(12):1621-1624. Similar results were found in a smaller, but equally convincing study, in which one patient with severe PV was studied in a randomized, placebo-controlled, crossover trial of IVIg. Arnold, et al., "An 'n-of-1' placebo-controlled crossover trial of intravenous immunoglobulin as adjuvant therapy in refractory pemphigus vulgaris," *Br J Dermatol.* 2009 May;160(5):1098-102. In that study, the pemphigus autoantibody titers were significantly higher when on placebo compared with IVIg treatment, as well as a significant improvement in subjective disease activity scores while on IVIg as compared with placebo. *Ibid.*

Indeed, IVIg may be more effective than other treatments. Most therapies for autoimmune diseases like PV is that they target all antibodies rather than just the pathogenic ones; however, IVIg appears to be able to selectively and markedly decrease serum levels of abnormal antibodies in PV without decreasing the levels of normal antibodies. Czernik, et al., "Intravenous immunoglobulin selectively decreases circulating autoantibodies in pemphigus," *J Am Acad Dermatol.* 2008 May;58(5):796-801. In addition, IVIg is advantageous due to its "excellent safety profile." Ruetter, et al., "Efficacy and safety of intravenous immunoglobulin for immune-mediated skin disease: current view," *Am J Clin Dermatol.* 2004;5(3):153-160.

IVIg seems particularly effective in the control of active disease unresponsive to conventional therapy. It is also useful as an adjunct to manage patients who have developed serious complications to standard therapy, or cannot be tapered off conventional therapy without a flare in disease activity.

Bystryn, *supra*. In other words, IVIg is particularly effective in cases like this one. IVIg is a safe and effective treatment of severe, recalcitrant, unresponsive PV. Mignogna, "Oral Pemphigus," *supra*; Amagai, *supra*; Mignogna, et al., "Adjuvant high-dose intravenous immunoglobulin therapy can be easily and safely introduced as an alternative treatment in patients with severe pemphigus vulgaris: a retrospective preliminary study," *Am J Clin Dermatol.* 2008;9(5):323-31.

**III. Conclusion**

In this case, Mr. Patient has few remaining alternative therapies. IVIg is the safest and most effective. Therefore, it should be covered.

Sincerely,

Patient's Representative