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August 4, 2009

CIGNA National Appeals Unit  
ATTN: Level 2 Appeals  
PO Box 5225  
Scranton, PA 18505-5225

RE: Patient  
ID no.  
Service: Gamunex (IVIg)  
Date of service: To be determined (prior authorization)

Dear Sir or Madam:

I am writing on behalf of Patient to request a second-level review of your noncoverage decision of Gamunex (IVIg treatment) for the treatment of overlap syndrome (lupus, scleroderma, and Sjogren's). My HIPAA release and authorization is enclosed.

You have denied coverage of Gamunex on the ground that such therapy is "unproven or experimental" when it comes to treating Ms. Patient's clinically diagnosed autoimmune disorders. However, you have not done an individualized consideration of her request in the context of her medical history and the reasons why her physicians, Drs. Makris, Bryan, and Bockenstedt, believe that IVIg treatment is the best treatment for her symptoms. IVIg is one of only two medications that has proven effective for her, and of those two, it is the safest. IVIg was demonstrated to be effective for Ms. Patient in the trial period previously covered by CIGNA. Further, there is ample support in the medical literature for the use of IVIg under these circumstances. Thus, we ask that you reverse your noncoverage decision and permit Ms. Patient to obtain IVIg treatments to allow her to achieve remission, before prolonged inflammation and medication side-effects result in more serious – and costly – deleterious effects.

#### **I. Use of IVIg Treatment is Medically Necessary in this Case**

Patient suffers from an overlap syndrome (Systemic Lupus Erythematosus [SLE], Sjogren's Syndrome, and scleroderma). (Dr. Bryan 5/18/2009 office note). Over the years, she has presented with a number of symptoms. Regarding her mixed connective tissue disease, her symptoms most often manifest as recurring episodes of joint pain and inflammation. Other recurring issues include abdominal pain, nausea, vomiting, lack of appetite, skin tightness and lesions, as well as dry eyes and mouth. Some of which are inherent to the diseases themselves, such as the skin lesions and dry eyes, while others developed from the direct side-effects of medications or their interactions with one another.

Ms. Patient has used a number of medications and therapies over the years, most of which have not effectively treated her symptoms. According to her medical records, these therapies have included prednisone, Methotrexate (both orally and subcutaneously), Cellcept, Arava, Plaquenil, gold injections, and multiple doses of rituximab (Rituxan). (Dr. Makris, 6/17/2009). As often is the case with cytotoxic agents and immunosuppressant agents, she has been refractory to most of the treatments mainly due to gastrointestinal or other toxicity, and for some time it appeared that Rituxan was the only medication capable of relieving her SLE symptoms.

Ms. Patient received rituximab infusions approximately every 3-4 months leading up to her trial of IVIg. She responded well, but after 8 courses<sup>1</sup> her doctors began to worry about giving her so many doses because rituximab has highly toxic side-effects. (Dr. Makris, 6/17/2009). Rituximab treatments are known to deplete the B cell line of the immune system, which is exactly what Ms. Patient experienced. Knowing this, the doctors feared uncontrollable infections that might have resulted from her compromised immune system and the periodic malnourishment she experienced from her inability to keep food down. The inherent toxicity of rituximab led Ms. Patient's doctors to discontinue the therapy, and they began seeking an alternative treatment for her SLE.

CIGNA initially approved coverage of a 3 month trial of IVIg, which worked as well as, if not better than, the rituximab treatments. (Dr. Makris, 6/17/2009). Ms. Patient received two rounds of monthly infusions for three days at a time in February and March 2009 – all that CIGNA would approve. (Dr. Bryan, 5/18/2009 office note; Dr. Evans, 3/16/2009 office note). She experienced no side-effects or adverse reactions to the treatment. Her doctors were able to decrease her prednisone down to her baseline dose. But the effects of the first IVIg treatment wore off, and she quickly began to experience increases in her joint symptoms. In particular, problems reappeared in her wrists, hands, and feet. These symptoms necessitated higher doses of Prednisone, which in turn aggravates her gastrointestinal system (Scleroderma manifestation) despite her use of Reglan and Nexium to control such GI symptoms. When receiving IVIg, Ms. Patient's symptoms were alleviated; when treatment was withheld, her symptoms returned. After her second round of IVIg in March wore off, she required increased dosing of prednisone as her symptoms again worsened. (Dr. Bockenstedt, 5/18/2009).

In another effort to find a less potent and toxic alternative to Rituxan when CIGNA denied coverage of further IVIg treatment, Ms. Patient was started on gold injections, which lead to severe pain at the injection site as well as nausea/vomiting. (Dr. Bryan, 5/18/2009 office note addendum). Her doctors were quick to take her off the injections.

Thus, at this point, Ms. Patient is left with no alternatives. The only other medication that has been at all successful in controlling her diseases is Rituxan, and Ms. Patient's doctors are concerned that further administration of Rituxan would be dangerous because it destroys B cells, leaving Ms. Patient susceptible to infection.

In addition to the prednisone, Ms. Patient's symptoms currently are being managed with Plaquenil, although she reports that she is experiencing increasingly severe pain while waiting to see if she will be permitted further IVIg treatments.

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<sup>1</sup> Some of the records reflect 11 courses of Rituxan. (See, e.g., Drs. Bryan and Bockenstedt, 5/18/2009).

The pattern demonstrated by her past experiences is rather clear. Ms. Patient has tried every available medication and therapy. With the exception of the IVIg treatment, every other alternative has led to either a severely compromised immune system (as in the case of Rituxan) or severe gastrointestinal issues (as in the case of every other medication listed above). Without IVIg, her conditions require a higher dose of prednisone, which in turn requires a higher dose of Reglan and Nexium to combat her nausea, and even then is not always successful at achieving that end, especially because, at times, Ms. Patient has difficulty swallowing pills. (Dr. Makris, 12/8/2009 office note).

IVIg is the only suitable treatment that avoids all complications. No matter how one chooses to look at her scenario, not using IVIg will be detrimental to Ms. Patient's health. Treating her with the best available therapy now will act preventatively to take care of her current diseases, likely lead to fewer complications in the future, and eliminate the need for "damage control," thereby saving CIGNA more money in the long run. Thus, IVIg is medically necessary in this case.

## **II. IVIg Treatment for SLE and other Connective Tissue Diseases is Supported by the Medical Literature**

CIGNA denied coverage of IVIg on the ground that it is experimental. However, the medical literature documents twenty years of successful use of intravenous immunoglobulin (IVIg) in the treatment of SLE.

Indeed, CIGNA's own clinical policy on lupus states that IVIg "may be used to treat lupus that is associated with destruction of blood platelets."

<<http://www.cigna.com/healthinfo/hw123404.html>> (Citing Petri, M., Systemic lupus erythematosus (including pregnancy and antiphospholipid antibody syndrome), in MH Weisman et al., eds., *Treatment of the Rheumatic Diseases: Companion to Kelley's Textbook of Rheumatology*, pp. 274–288. Philadelphia: W.B. Saunders (2<sup>nd</sup> ed. 2001). In and of itself, this statement recognizes that IVIg is a viable solution to treating lupus.

One of the first reported uses of IVIg was a case study of three patients with life-threatening manifestations of SLE who were unresponsive to conventional high-dose corticosteroid and/or immunosuppressive therapy. Corvetta, et al., "Use of high-dose intravenous immunoglobulin in systemic lupus erythematosus: report of three cases," *Clin Exp Rheumatol* 1989; 7: 295-299. In this case study, one patient with lupus encephalitis quickly resolved. A second patient with SLE-associated leuko- and thrombocytopenia experienced an increase in leukocyte and platelet counts as well as a decrease in anti-DNA antibody levels and an increase in total complement hemolytic activity. The third patient with lupus encephalitis and nephritis was suspended from treatment due to renal complications. However, in two of the three cases, IVIg was found to be of great use in treating SLE.

Another case study was reported in 1993, this time documenting the effect on lupus pneumonitis as well. Following IVIg therapy, the lupus pneumonitis and encephalitis in one patient, and the lupus nephritis in a second patient, resolved. "Continuous treatment with IVIg, every 5 weeks for up to 20 months induced a prolonged clinical and laboratory remission." Winder, et al., "Treatment of Systemic Lupus Erythematosus by Prolonged Administration of High Dose Intravenous Immunoglobulin: Report of 2 Cases," *Journal of Rheumatology* 1993; 20(3): 495-498. Consistent with Ms. Patient's course of treatment, the doctors in this trial were able to stop treatment with cytotoxic agents, and the dosages of corticosteroids were lowered significantly. The researchers effectively found that IVIg is

a means of treating life threatening cases of SLE, maintaining remission longer than any conventional immunosuppressive therapy. *Ibid.*

Between 1989 and 1999, there were approximately five other case studies of patients receiving IVIg for treatment of SLE. Each study ranged from 3-12 patients, and all but one documented positive results. Levy, et al., "A study of 20 SLE patients with intravenous immunoglobulin – clinical and serologic response," *Lupus* 1999; 8: 705-712 (citing Lin, et al., "Improvement of histological and immunological change in steroid and immunosuppressive drug-resistant lupus nephritis by high-dose intravenous gamma globulin," *Nephron*, 1989; 53: 303-310; Schroeder, et al., "High dose intravenous immunoglobulin's in systemic lupus erythematosus: clinical and serological results of a pilot study," *J Rheumatol*, 1996; 23: 71-75; Francioni, et al., "Long term IVIg treatment in systemic lupus erythematosus," *Clin Exp Rheum*, 1994; 12: 163-168; Maier, et al., "Intravenous immunoglobulin therapy in systemic erythematosus-associated thrombocytopenia," *Arthritis Rheum*, 1990; 33: 1233-1239; and De Pita, et al., "Intravenous immunoglobulin therapy is not able to efficiently control cutaneous manifestations in patients with lupus erythematosus," *Lupus*, 1997; 6: 415-417.)

These early case studies have given way to larger case series and the strong desire to pursue further research. The largest study involved 20 SLE patients, in which there was an "impressive clinical response." Levy, et al., *supra*, at 707. In 9 patients evaluated before and after the IVIg, mean Systemic Lupus Activity Measure (SLAM) scores decreased in every patient. *Ibid.* In all, IVIg treatment was found to be beneficial in 17 out of the 20 patients, or 85 percent. *Ibid.* Thirteen patients showed near complete resolution; four patients had partial or temporary relief of symptoms; and only three patients did not see a response. *Ibid.*

Several other researchers have lauded the effects of IVIg in treating SLE. For example, in patients with cutaneous lupus erythematosus, IVIg was found to be useful. Goodfield, "Intravenous immunoglobulin (IVIg) for therapy-resistant cutaneous lupus erythematosus (LE)," *J. of Dermatological Treatment* 2004; 15: 46-50. IVIg has beneficial effect on lupus nephritis. Rauova, et al., "High-dose intravenous immunoglobulins for lupus nephritis – a salvage immunomodulation," *Lupus* 2001; 10: 209-213; Meissner, et al., "Intravenous immunoglobulin therapy in a patient with lupus serositis and nephritis," *Rheumatol Int* 2000; 19: 199-201. IVIg is helpful in treating neuropsychiatric lupus, as well. Sherer, et al., "Successful Treatment of Systemic Lupus Erythematosus Cerebritis with Intravenous Immunoglobulin," *Clin Rheumatol* 1999; 18: 170-173. And paper after paper concludes that IVIg has a beneficial effect on SLE. Zandman-Goddard, et al., "Novel approaches to therapy for systemic lupus erythematosus," *Euro J. of Int. Med.* 2000; 11: 130-134; Kamali, et al., "Experience with monthly, high-dose, intravenous immunoglobulin therapy in patients with different connective tissue diseases," *Rheumatol Int* 2001; 25: 211-214; Sherer, et al., "Intravenous immunoglobulin for immunomodulation of systemic lupus erythematosus," *Autoimmunity Reviews* 2006; 5: 153-155; Zandman-Goddard, et al., "Intravenous Immunoglobulin Therapy and Systemic Lupus Erythematosus," *Clinical Reviews in Allergy & Immunology* 2005; 29: 219-228.

An advantage of using IVIg over conventional treatments (i.e., high-dose steroids and immunosuppressants) in patients with active SLE, is that IVIg has not been found to increase the risk of opportunistic infections, and it obviates ovarian toxicity, hemorrhagic cystitis, and carcinogenicity caused by cyclophosphamide. E. Toubi, et al., "High-dose intravenous immunoglobulins: An option in the treatment of systemic lupus erythematosus,"

*Human Immunology* 2005; 66: 395-402, 398 (citing Schroeder, et al., *supra*). Similarly, Ms. Patient's GI symptoms subsided in much the same way when she was on IVIg.

IVIg is a standard therapeutic modality for a number of autoimmune diseases, including immune thrombocytopenic purpura, Kawasaki disease, Guillain-Barre syndrome, and polymyositis. More specific to Ms. Patient, IVIg has been demonstrated as effective in SLE patients manifesting anything from neuropsychiatric disturbances to cardiopulmonary issues, renal issues, and to bone marrow complications. Schoenfeld, et al., "IVIg therapy in autoimmunity and related disorders: our experience with a large cohort of patients," *Autoimmunity* 2005; 38(2): 123-137 (citations omitted). A recent article even documented the efficacy of IVIg treatment on maternal and fetal outcome in pregnant patients affected with SLE. Perricone, R., "Intravenous immunoglobulin therapy in pregnant patients affected with systemic lupus erythematosus and recurrent spontaneous abortion," *Rheumatology* 2008; 47: 646-651. The mechanisms of action of IVIg in autoimmune diseases are diverse and include all arms of the immune system including enhanced suppressor activity, Fc receptor blockage, complement regulation, T-cell regulation, idiotype network regulation, and other mechanisms that can be attributed to the presence of 'contaminating' molecules in IVIg, such as solubilized membrane products and HLA determinants. See Levy, Y., et al., *supra* at 710 (citing Ballow, M., "Mechanisms of action of intravenous immunoglobulin: clinical implications in autoimmune and inflammatory diseases," in: Kazatchkine, Morell, A. (eds), *Intravenous Immunoglobulin Research and Therapy*. Parthenon Publishing: New York, 1996, pp. 123-128.). See also Ballow, M., "Mechanisms of Action of Intravenous Immunoglobulin Therapy and Potential use in Autoimmune Connective Tissue Diseases," *Cancer* 1991; 68 (15 Supp) 1430-1436.

IVIg would likely be helpful in the treatment of Ms. Patient's scleroderma as well, saving CIGNA additional costs related to the medications she is using to control its symptoms. In a study of mice with excessive fibrosis due to increased synthesis and accumulation of collagen in the skin, IVIg treatment in the experimental condition decreased collagen expression after treatment. Shoenfeld, et al., IVIg therapy in autoimmunity and related disorders: our experience with a large cohort of patients, *Autoimmunity* 2005; 38(2): 123-127 (citing Blank, M., et al., "The role of intravenous immunoglobulin therapy in mediating skin fibrosis in tight skin mice," *Arthritis Rheum*, 2002; 46: 1689-1690).

Finally, it should be noted that usage of rituximab in the treatment of Ms. Patient's overlap syndrome is, in itself, an off-label usage. Your coverage policy does not indicate that coverage of rituximab is available for patients suffering from either SLE, Sjogren's Syndrome, or scleroderma. Your policy only indicates that rituximab is medically necessary for the treatment of non-Hodgkin's lymphoma (NHL), treatment of relapsed/refractory chronic lymphocytic leukemia, treatment of relapsed/refractory Waldenstrom's macroglobulinemia, treatment of immune or idiopathic thrombocytopenic purpura, and treatment of active rheumatoid arthritis (RA). <[http://www.cigna.com/customer\\_care/healthcare\\_professional/coverage\\_positions/pharmacy/ph\\_5108\\_coveragepositioncriteria\\_rituximab\\_rituxan.pdf](http://www.cigna.com/customer_care/healthcare_professional/coverage_positions/pharmacy/ph_5108_coveragepositioncriteria_rituximab_rituxan.pdf)> (last accessed 6/26/09). There is absolutely no justification for denying coverage of one medication on grounds that it is unproven or experimental while approving the usage of a different medication which also being used off-label, as indicated by your very own published coverage documentation.

### III. Conclusion

There has been a large amount of data collected over the past 20 years suggesting that IVIg should be considered a standard therapy for those suffering from SLE and overlap disorders involving multiple connective tissue diseases. Studies show that IVIg is effective as a treatment for SLE as both a salvage immunotherapy as well as in control of disease activity in general and amelioration of classical disease manifestations. At this point, further research is being conducted not to determine whether IVIg is an acceptable treatment for SLE, but only to determine the appropriate therapeutic dosage and the clinical manifestations that can be best treated with IVIg. The literature establishes that IVIg is effective.

Taken as a whole, it seems that IVIg therapy in most patients with SLE can achieve at least partial or temporary clinical improvement. Given Ms. Patient's clear success in her trial of IVIg, we know she would achieve clinical improvement if given the opportunity, so there is no need to speculate on the efficacy of the treatment for her as an individual. Nor is there any reason to suspect she would encounter one of the few complications that occasionally accompany the usage of IVIg, such as rashes, headaches, arthralgias, or a decline in renal function.

Rather than abandon a medication that has been so successful for this patient, CIGNA ought to permit Ms. Patient to receive IVIg treatment to re-establish remission quickly, without the need for complex medication changes and trials which would likely have a deleterious effect on her health. Thus, the noncoverage decision should be reversed.

Thank you.

Sincerely,

Jennifer C. Jaff\*

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\* Admitted to practice law in Connecticut, New York and the District of Columbia. Advocacy for Patients is a 501(c)(3) tax-exempt organization and does not charge patients for its services. Advocacy for Patients is funded by, among other sources, grants from foundations and companies that engage in health care-related advocacy, manufacturing, delivery and financing. A list of grantors will be furnished upon request.