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April 28, 2008

Office of Personnel Management
Insurance Services Program Health Insurance Group 1
1900 E Street, NW
Room 3435
Washington, DC 20415

RE: Patient
ID No.
Group (federal employee plan)
Service: IVIg
Date of service: Prior authorization of extended care benefits for 1/17 to 3/30/2008

Dear Sir or Madam:

I am writing on behalf of Patient to appeal Blue Cross Blue Shield of Texas's (BCBS of TX) denial of extended care benefits covering of IVIg for treatment of Relapsing Remitting Multiple Sclerosis (RRMS). My HIPAA release is enclosed.

I. Introduction

The Blue Cross Blue Shield of Texas federal employee plan has been paying for IVIg for Ms. Patient's RRMS for years. All of a sudden, it stopped covering this treatment. On January 22, 2008, BCBS of TX sent Ms. Patient a letter stating as follows:

The request for intravenous immune globulin therapy for the diagnosis of relapsing-remitting multiple sclerosis is denied as not medically necessary as the Blue Cross Association medical policy 8.01.05 considers IVIG therapy to no longer be a drug of choice for the treatment of relapsing-remitting multiple sclerosis.

We appealed on February 26, 2008 and received a decision dated April 28, 2008 – two full months later – upholding the denial on the same grounds.

However, based on a review of the medical literature, this simply is false. In addition, when given individualized consideration, you will see that, for this patient, IVIg is medically necessary. Thus, we ask that you reverse your noncoverage decision.

II. IVIg IS AN ACCEPTED THERAPY FOR RRMS

Blue Cross policy 8.01.05 at page 6 of 15 states that the previous policy statement regarding IVIg for MS was based on a 1998 TEC assessment. However, your policy goes on to state that, in 2002, the American Academy of Neurology published a technology assessment on therapies for MS and did not recommend IVIg. Thus, we begin with an analysis of this technology assessment.

The American Academy of Neurology Report of the Therapeutics and Technology Assessment Subcommittee from 2001 states that the studies of IVIg to date "have generally involved small numbers of patients, have lacked complete data on clinical and MRI outcomes, or have used methods that have been questioned. It is, therefore, only possible that IVIg reduces the attack rate in RRMS." *Neurology* 2002; 58(2): 169-78. However, there are several aspects in which this report is lacking.

First, it is nearly six years old. We cite studies here that post-date that 2001 review that should be considered. Indeed, how can a 2002 technology assessment be the reason for a 2008 change in your policy? The AAN technology assessment was available to you when you updated policy 8.01.05 between 2002 and 2008, and yet you never before relied upon it as a basis for denying coverage. It strains credulity for you to claim that this is the sole reason for your change in policy.

Second, the published article does not contain any of the analysis of IVIg studies; that analysis is found in a far longer document that contains the full report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. The entire consideration of IVIg is reduced to less than one page and considers only three studies from 1997 to 1999, the abstracts of some of which are enclosed herein. The authors of the report state that the first of these studies "reported that treatment with IVIg reduced the clinical attack rate," and the "difference in final unconfirmed proportion with 1- point EDSS progression was also reduced although this outcome was not significant." The second study generated "mixed" results. "For patients who completed both treatment arms . . . the total number of enhancing lesions seen on MRI . . . and the number of new lesions . . . were reduced in patients treated with IVIg." The third study also reported significant reductions in the clinical attack rate. Thus, reliance on this Report, which considers only three studies conducted in the late 1990s, is entirely misplaced.

IVIg has several effects on the immune system that could be beneficial to RRMS. It may help treat acute relapses, prevent new relapses, and promote remyelination. Sorenson PS. The role of intravenous immunoglobulin in the treatment of multiple sclerosis. *J. Neuro. Scien* 2003 Feb 15; 206(2): 123-130. That article goes on to state that IVIg also has been proven to be beneficial in treating secondary progressive MS. Thus, "IVIg is a valuable alternative for treatment of relapsing-remitting MS . . ." The same author found, too, that IVIg "exerts a number of effects that may be beneficial in multiple sclerosis: reduction of inflammation, inhibition of macrophages, and promotion of remyelination." Sorenson PS. Treatment of multiple sclerosis with intravenous immunoglobulin: review of clinical trials. *J Neurol Sci*, 2003 Oct; 24 Suppl 4: S227-30.

IVIg is "thought to exert a twofold effect: an immunomodulating action and a positive action on remyelization." Valiat, JM, et al., "Inflammation and demyelination: IgIV mode of action," *Rev Neurol* (Paris), 2006 Jun; 162 Spec. No. 1: 3S12-3S16. This result is not achieved with Betaseron alone.

There is much additional support in the literature for the use of IVIg in treating RRMS. In the first study to test the assumption that IVIg might be effective for the interval treatment of MS, beneficial effects were seen within 6 months of treatment and did not appear to depend on the severity of baseline disability. "IVIg treatment also had a positive effect on daily and social living according to patient self rating on the Incapacity Status and Environmental Status Scales and was associated with a lower, though not significantly different number of hospital admissions and days spent in hospital. These data support IVIg as an alternative treatment option for relapsing-remitting MS" Strasser-Fuchs, S., et al., "The Austrian Immunoglobulin in MS (AIMS) study: Final analysis." *Multiple Sclerosis* 2000; 6(Suppl 2): S9-S13.

In 2004, a randomized, placebo-controlled double-blind study in 91 patients were studied after the first neurological event suggestive of demyelinating disease. Achiron, A., et al., "Intravenous immunoglobulin treatment following the first demyelinating event suggestive of multiple sclerosis: a randomized, double-blind, placebo-controlled trial." *Arch Neurol.* 2004 Oct; 61(10):1515-20. That study showed that IVIg treatment for the first year from onset of the first neurological event suggestive of demyelinating disease significantly lowers the incidence of a second attack and reduces disease activity as measure by brain MRI.

In another double-blind placebo-controlled study of 40 patients with RRMS found that IVIg "may be safe and effective in reducing the frequency of exacerbations in RR-MS." Achiron, A., et al., "Intravenous Immunoglobulin treatment in multiple sclerosis. Effect on relapses," *Neurology* 1998 Feb; 50(2); 398-402. See also Achiron, A., et al., "Intravenous gammaglobulin treatment in multiple sclerosis and experimental autoimmune encephalomyelitis: delineation of usage and mode of action," *J. Neurol. Neurosurg Psychiatry*, 1994 Nov; 57 Suppl: 57-61 ("IVIg treatment significantly reduced the number and severity of acute exacerbations and resulted in a lesser neurological disability.").

In addition, IVIg's use was heralded in Fazekas, F., "Randomised placebo-controlled trial of monthly intravenous immunoglobulin therapy in relapsing-remitting multiple sclerosis," *Lancet* 1997 Mar 1; 349 (9052): 589-93. The EDSS score decreased in the IVIg-treated patients and increased in the placebo group in significant numbers. The authors conclude that "[m]onthly IVIg is an effective and well-tolerated treatment for patients with relapsing-remitting multiple sclerosis." That same year, a study was published that showed that "IVIg treatment was associated with a significant reduction in relapses. . . ." Fazekas, F., et al., "Treatment effects of monthly intravenous immunoglobulin on patients with relapsing-remitting multiple sclerosis," *Mult Scler*, 1997 Apr; 3(2); 137-141.

Other studies have found IVIg to be beneficial in treating RRMS. For example, Sorensen, P.S., et al., "Intravenous Immunoglobulin G reduces MRI activity in relapsing multiple sclerosis," *Neurology*, 1998 May; 50(5): 1273-81. In that study, 26 patients in a randomized, double-blind, crossover study were studied, and the results showed that, with IVIg therapy, there were fewer lesions on MRI than in the placebo treatment. In another study, IVIg was found to be "beneficial for prevention of exacerbations in patients with relapsing MS." Sorensen, PS, et al., "A double-blind cross-over trial of intravenous immunoglobulin G in multiple sclerosis," *Mult Scler*, 1997 Apr; 3(2): 145-8. "The ability of intravenous immunoglobulin (IVIg) to restore visual acuity and/or muscle strength is also being investigated." "Multiple Sclerosis: Hope Through Research," National Institute of Neurological Disorders and Stroke, p. 9 (last updated February 2007). Both clinical evidence and MRI show that IVIg has beneficial effects on relapse rate and neurological

disability, decreasing both the "disease burden" and the appearance of new lesions. Achiron, A., et al. Use of intravenous immunoglobulin in multiple sclerosis. BioDrugs, 1998 Jun;9(6): 465-75.

Although we have been unable to locate a published report of this study, we enclose a Science Daily report of a Chicago study that found that IVIg reduces the risk of a second attack of MS, and that IVIg may, in fact, reduce the number of lesions on MRI. IVIg not only improves the course of the disease, but also repairs "the damage to the myelin sheath by enhancing remyelination." Advances in Multiple Sclerosis, <<http://www.msadvances.com.faq.php3>> (last accessed on 3/14/2007). The National Multiple Sclerosis Society reports on these studies, stating that studies show that IVIg both decreases the rate of relapse and decreases the number of lesions shown on MRI.

Nor is there reason to worry about the safety of IVIg. A group in Israel administered more than 10,000 infusions for more than 200 patients for various autoimmune disease, including MS. Katz, U., et al., "Safety of intravenous immunoglobulin therapy," Autoimmune Rev. 2007 Mar; 6(4): 257-9. See also Katz, U., et al., "Long term safety of IVIg therapy in multiple sclerosis: 10 years experience," Autoimmunity, 2006 Sep; 39(6): 513-7 (showing that IVIg has a beneficial effect in patients with RRMS and that it is safe); Poehlau D. Treatment of chronic progressive multiple sclerosis with intravenous immunoglobulins – interim results on drug safety of an ongoing study. IVIg study group. Mult. Scler, 2000; 6 Suppl 2:S21-3 (IVIg is safe therapy even for severely disabled multiple sclerosis patients).

In fact, the majority of insurance companies are covering IVIg for RRMS. We enclose policies from CIGNA, United Healthcare, and Aetna, all of which indicate that IVIg would be covered for patients with RRMS.

In addition, we filed and won an independent review for another patient in Texas with precisely the same diagnosis and treatment. A redacted copy of that decision is enclosed. This external review explains in detail why the decision to use IVIg should be upheld based both on medical need and on the medical literature.

In sum, IVIg is not experimental or without significant support in the literature. The fact that it is covered by insurance companies quite widely shows that this is the standard of care.

III. IVIg IS MEDICALLY NECESSARY – INDEED, ESSENTIAL – IN THIS CASE

An excellent summary of the early phases of Patient's illness is found in a July 27, 2004 consult written by Dr. Kathleen Hawker, a neurologist at the University of Texas Southwestern Medical Center. Ms. Patient's illness started with a short-lived vision problem, then fatigue, then stumbling and falling, until she was diagnosed with RRMS in May 2003. Initially, she was started on Avonex. (5/30/2003 O'Brien office note). She then had an attack in August 2003 which included incontinence and numbness and weakness in her legs. (8/8/2004 O'Brien office note). She then underwent a course of IV Solumedrol followed by a course of prednisone. (8/29/2003 home health certification and plan of care). However, she never derived any benefit from steroids. (11/20/2003 O'Brien office note). At this point, Ms. Patient became disabled, and her treating neurologist, Dr. Cherie O'Brien, told her that it was unlikely that she would ever work again.

In September 2003, Ms. Patient was started IVIg in addition to Avonex. (9/8/2003 and 9/15/2003 O'Brien office notes). Dr. O'Brien notes that the IVIg was necessary despite receiving five days of high-dose steroids. (9/15/2003 O'Brien office note). She had five days of IVIg, ending on September 19, 2003. A September 22, 2003 MRI shows abnormalities, but the enhancement in the left parietal lobe was gone. Dr. O'Brien stated that, "with the IVIG she is no longer experiencing enhancing lesions or active multiple sclerosis." (10/9/2003 O'Brien office note).

Still, Ms. Patient's MS continued to progress. After a sprained ankle, she received rehabilitation, and Dr. O'Brien recommended additional physical therapy for deficits in gait, balance and lower extremity strength. (September and October 2003 physical therapy notes). October 1, 2003 auditory and visual evoked potentials revealed vision problems due to MS, as well. In early October 2003, Dr. O'Brien decided to switch Ms. Patient from Avonex to Rebif, although it took several weeks to obtain insurance company approval. (10/9/2003, 10/17/2003, 11/20/2003 O'Brien office notes).

In the interim, Dr. O'Brien noted that Ms. Patient was doing far worse without the IVIg. She had no energy and was struggling with the activities of daily living. (10/16/2003 office note). Ms. Patient was then switched to a maintenance dose of IVIg 0.5 g/kg for two days in a row once a month. By the third month of this maintenance dose of IVIg, Ms. Patient was doing much better. (12/11/2003 O'Brien office note). She had more energy and no longer was dropping things. There was a jerk in her right leg and her left eye had significant blind spots, as well as some spasticity in her legs. However, the improvement in her energy level was accompanied by dramatically improved proprioception. Dr. O'Brien attributed this improvement to the IVIg since Ms. Patient had only had three doses of Rebif by this time.

In December 2003, Dr. O'Brien documented the fact that Ms. Patient's symptoms were worse before her IVIg treatment and better after it. (12/18/2003 O'Brien office note). In the second day of her monthly maintenance dose of IVIg, her gait was much improved. (12/19/2003 O'Brien office note).

In January 2004, Ms. Patient suffered another relapse manifested by dizziness, bumping into things, blurry vision, fecal incontinence, and some spasticity, although her gait was improved. (1/19/2004 O'Brien office note). Dr. O'Brien then initiated an increased dose of IVIg. In a matter of days, Ms. Patient had more energy and was walking better. (1/22/2004 O'Brien office note). Dr. O'Brien believed Ms. Patient's condition had improved since August 2003. An April 28, 2004 MRI showed no significant change in the appearance of lesions, and a previously seen left basal ganglion enhancement no longer was visualized. Thus, both clinical symptoms and MRI showed the positive effects of the IVIg.

Indeed, at this point, a fairly clear pattern emerged. Ms. Patient missed her IVIg treatments for two months and her gait became more unstable, and she had increased urinary and fecal incontinence. (7/12/2004 O'Brien office notes). Dr. O'Brien administered a full dose of IVIg that week and then returned to a maintenance dose. On only her second day of the full IVIg induction, Ms. Patient's gait was improved, she was less unsteady and less stiff, her balance was improved, she had more energy, and her cognition had improved. (7/13/2004 O'Brien office note).

Ms. Patient again missed her IVIg treatment because she had a hysterectomy, which led to increased vision problems in her left eye and increased urinary incontinence, as well as other symptoms. (9/27/2004 O'Brien office note). Dr. O'Brien again initiated a full

induction of IVIg. By the last day of the IVIg induction, Ms. Patient's symptoms "clearly improved after reinduction with IVIG." (9/30/2004 O'Brien office note). Her gait was better, she was walking better, and the blind spot in her left eye was smaller.

At the time of her October 2004 monthly maintenance dose of IVIg, Ms. Patient was having vision problems with her left eye. (10/25/2004 O'Brien office note). Dr. O'Brien increased the IVIg dose to be administered over 3 days, and then scheduled maintenance doses every 3 weeks instead of every 4 weeks. In only a matter of days, there was some improvement in the left eye. (10/28/2004 O'Brien office note).

The pattern that emerged was clear: Ms. Patient was better when she was on IVIg and worse when she was not. This pattern has continued.

After Dr. O'Brien found worsening left optic neuritis, she increased the IVIg dosage over the next week. (11/17/04 O'Brien office notes). However, three weeks after an IVIg induction, her eyesight was worse and Dr. O'Brien decided to give three back-to-back treatments of IVIg at 2g/kg. In December 2004, Dr. O'Brien said that the improvement from the IVIg treatments did not work and Rebif had plateaued, and Dr. O'Brien decided to try Tysabri. (12/6/04 O'Brien office notes).

However, despite two Tysabri infusions, there was noted deterioration since stopping the IVIg. (3/15/2005 O'Brien office notes). Ms. Patient was experiencing extreme fatigue, unsteadiness, falling, increased cognitive deficits, urinary incontinence, rightness in her left leg. Dr. O'Brien decided to resume IVIg beginning with a full induction followed by a maintenance dosage. Dr. O'Brien states that IVIg helped Ms. Patient to avoid falling, and her left eye had stabilized.

On May 9, 2005, the IVIg dose was increased. By August 1, 2005 MRI, Ms. Patient's disease was stable, with no new lesions or abnormal enhancement.

On December 6, 2005 and February 22, 2006, Dr. O'Brien noted that Ms. Patient's condition was improved by the IVIg. She had improved eyesight, energy and stamina. However, Ms. Patient suffered a relapse in May 2006; she lost the vision in her left eye, was off-balance and bumping into things, and had no energy. (5/9/06 O'Brien office note). Dr. O'Brien again increased her IVIg to 120g/day for two days each month. Her motor strength increased and her vision was stable. (8/16/2006, 9/20/2006 O'Brien office note). Dr. O'Brien stated that Ms. Patient was consistently doing better at the higher dose of IVIg; she no longer deteriorates while waiting for the next infusion, and her energy is increased and her vision stable. (9/20/2006, 3/22/2007 O'Brien office notes). It seems that, whenever Ms. Patient suffers a set-back, the one thing that has brought her out of it is IVIg.

Based on the severity and frequency of Ms. Patient's relapses, the ability to cut a relapse short and return Ms. Patient to her base level is derived only from IVIg. Avonex and Rebif have not gotten the same results. Tysabri carried with it no great promise, but was pulled from the market before Ms. Patient had had more than 2 infusions. Steroids by IV and by mouth have been ineffective. Only IVIg helps when Ms. Patient suffers a relapse. Taking the only tool that works away from her is tantamount to consigning her to an existence marked by blindness, falling, dropping things, no energy, and ever-progressing disease. Since the objective medical evidence shows clearly that Ms. Patient benefits from IV more than anything else, we ask that you grant coverage.

IV. CONCLUSION

For all of these reasons, we urge you to reverse BCBS of TX's noncoverage decision.

Thank you.

Sincerely,

Jennifer C. Jaff*

* 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.