

December 28, 2010

Blue Cross Blue Shield of New Jersey
1900 Elm Street
Newark, New Jersey 07101

RE: Patient
ID No. 1111189
Service: IVIg
Date of service: Prior authorization of extended care benefits for 1/17 to 3/30/2010

Dear Sir or Madam:

I am writing on behalf of Patient to appeal Blue Cross Blue Shield of New Jersey's (BCBSNJ) denial of extended care benefits covering intravenous immune globulin (IVIg) for treatment of Multifocal Motor Neuropathy (MMN). My HIPAA release and authorization is enclosed.

I. INTRODUCTION

Blue Cross Blue Shield of New Jersey has been paying for IVIg to treat Mr. Patient's MMN for years. All of a sudden, it stopped covering this treatment. On January 22, 2010, BCBSNJ sent Mr. Patient a letter stating as follows:

The request for therapy for Multifocal Motor Neuropathy is denied as not medically necessary as the BCBSNJ Policy 016 considers IVIG therapy to no longer be a drug of choice for the long-term treatment of MMN.

We appealed on February 26, 2010 and received a decision dated April 28, 2010 – two full months later – upholding the denial on the same grounds. However, based on a review of the medical literature, including a position taken by the National Institutes of Health, this position is unfounded. In addition, when given individualized consideration, there is no question that, for this patient, IVIg is medically necessary. Thus, we ask that you reverse your noncoverage decision.

II. IVIg for MULTIFOCAL MOTOR NEUROPATHY IS NOT EXPERIMENTAL or INVESTIGATIONAL

Multifocal Motor Neurology (MMN) was first described more than twenty years ago. MMN is:

characterised [sic] by slowly progressive, asymmetric, distal weakness of one or more limbs with no objective loss of sensation. It may cause prolonged periods of disability. The treatment options for multifocal motor neuropathy are sparse. Patients with multifocal motor neuropathy do not usually respond to steroids or plasma exchange, and may even worsen with these treatments. Many uncontrolled studies have suggested a beneficial effect of intravenous immunoglobulin. Multifocal motor

neuropathy is a rare, probably immune mediated disorder

Van Schaik, et al., "Intravenous Immunoglobulin for Multifocal Motor Neuropathy," 1 *The Cochrane Library* 2009.

The National Institutes of Health report that treatment of MMN generally consists of intravenous immunoglobulin (IVIg) or immunosuppressive therapy with cyclophosphamide, and that the prognosis for patients who receive early treatment is good, albeit with a slow progression over time. <http://www.ninds.nih.gov/disorders/multifocal_neuropathy/multifocal_neuropathy.htm>. Thus, IVIg is a first-line therapy for MMN.

The positive effect of IVIg on a majority of patients with MMN has been established by both double-blinded placebo-controlled trials and retrospective studies.

A long-term study was conducted on ten patients with MMN who received IVIg for an average of 7.25 years. Muscle strength as measured by MRC scores¹ improved on average from 69.3 before treatment to 75.7 after the first three courses of treatment. At the last follow up (average 7.25 years later), the average MRC score was 75.2. Functional assessment as measured by Modified Rankin Disability (MRD)² scores improved from an average of 2.3 before treatment to 1.0 after one year of treatment. Upon final examination, the MRD score was unchanged from the score after one year score. The researchers found "significant long-term clinical and neurophysiologic improvement in 10 patients with MMN on maintenance IVIg therapy followed for an average period of 7.25 years (range, 3.5 to 12 years)." The researchers also "documented that long-term monthly IVIg therapy produced stable clinical improvement, a significant reduction in the number of [conduction blocks], degree of axonal degeneration (AD), and development of reinnervation. However, all but one patient remained IVIg dependent." Vucic, et al., "Decrease in Conduction Blocks and Reinnervation with Long-Term IVIg," 63 *Neurology* 1264-1265 (2004).

In another large study, a diligent attempt was made to locate every MMN patient in the Netherlands. Ninety-seven patients were identified and eighty-eight participated in the study. Ninety-four percent responded to IVIg therapy. The non-responders had longer disease duration before the first treatment than those who responded. Seventy-six percent of the patients were receiving IVIg treatment at the time of the study (median duration 6 years; range 0 to 17 years). Seventeen patients did not receive IVIg maintenance because: (1) five patients experienced no beneficial effect; (2) eight patients were stable without treatment; and (3) others had a concomitant disorder. The researchers concluded "that an early start of IVIg, followed by maintenance treatment, is at present the only intervention that may

¹ An MRC score of 0 indicated no movement; 1. slight movement; 2. movement with gravity eliminated; 3. movement against gravity; 4. movement against gravity and resistance; and 5. normal power.

² MRD score of 0 indicated no symptoms; 1. non disabling symptoms which did not interfere with daily activities; 2. slight disability, not all activities but self care; 3. moderate disability, requires assistance with some activities of daily living; 4. moderately severe disability, unable to walk without assistance; 5. severe, constant nursing care.

prevent axonal degeneration and a more severe outcome." Cats, et al., "Correlates of Outcome and Response to IVIg in 88 Patients with Multifocal Motor Neuropathy," 75 *Neurology* 818-25 (2010).

In a controlled clinical trial of 16 patients who had exhibited symptoms for 0.5 to 12 years, five patients initially were given a placebo, and 11 received IVIg. Subjective functional improvement with IVIg treatment was rated as dramatic or very good in nine patients, moderate in one, mild in one, and absent in five patients. This improvement was absent after placebo. The neurologic disability score improved by 6.7+/-3.3 points with IVIg, whereas it decreased by 2.1+/-3.0 with placebo ($p = 0.038$). Grip strength on the weaker side was increased by 6.4+/-1.9 kg with IVIg treatment; it decreased by 1.0+/-0.8 kg with placebo ($p = 0.0021$). Conduction block worsened by 12.98+/-6.52 percent with placebo, but improved by 12.68+/-5.62 percent with IVIg ($p = 0.037$). Conduction block was reversed in five patients with IVIg but in none with placebo. Thus, this controlled clinical trial provided evidence that IVIg improves weakness, disability and conduction block in patients with MMN. Federico, et al., "Multifocal Motor Neuropathy Improved by IVIg: Randomized, Double-Blind, Placebo-Controlled Study," 55 *Neurology* 1256-62 (2000).

Similarly, six patients who previously had responded to IVIg were enrolled in a double-placebo trial. Four patients received two IVIg treatments and two placebo treatments, and two patients received one IVIg and one placebo treatment in a randomized order. Five out of six patients responded to IVIg but not to placebo. One patient responded to IVIg in the same manner as to placebo. Thus, IVIg treatment can lead to improvement of muscle strength in patients with MMN. Van de Berg, et al., "Treatment of Multifocal Motor Neuropathy with High Dose Intravenous Immunoglobulins: a Double Blind, Placebo Controlled Study," 59 *Neurological Neurosurgical Psychiatry* 248-52 (1995).

In another report, nineteen patients with MMN, of whom ten patients had never been treated with IVIg and nine patients previously had been treated but had recurring symptoms, were studied. Forty-four percent of the first group and 80 percent of the previously treated group showed a therapeutic benefit and a self assessment benefit. IVIg treatment remained efficacious over the six month treatment period. Treatment did not affect a cure, and continued treatment was required to maintain benefits. However, IVIg was found to be effective. Leger et al., "Intravenous Immunoglobulin Therapy in Multifocal Motor Neuropathy: A Double-Blind Controlled Study," 124 *Brain* 145-53 (2001).

However, treatment with IVIg cannot be discontinued after achieving short-term relief of symptoms. A retrospective study was conducted of 40 patients with MMN of which 18 had been treated previously. The MRC scores significantly improved in 14 of the 20 previously untreated patients. The study confirmed a significantly high short-term response to IVIg therapy for patients with MMN. However, at the end of follow-up (2.2 +or - 2.0 years), only eight patients had significant remission, whereas 25 patients were dependent on periodic IVIg infusions. Leger, et. al. "Intravenous immunoglobulin as short- and long-term therapy of multifocal motor neuropathy: a retrospective study of response to IVIg and of its predictive criteria in 40 patients," 79 *Journal Neurological Neurosurgical Psychiatry* (93-96) 2008.

Similarly, researchers at the University of Oxford, Radcliff Infirmary, conducted a retrospective study of forty seven patients with MMN. Twenty-four patients were treated with IVIg over a 2 to 12 year period of time, compared with twenty-three patients who were not treated. Of the patients who were treated with IVIg, only five were not responsive to IVIg. However, "the majority of patients report improved long term function with maintenance treatment for as long as 10 years." Dr Slee recommended "an IVIg regimen that pre-empts rather than awaits clinical deterioration as the valid approach to the long-term management of patients with MMN requiring treatment." Mark Slee, et al., "Multifocal Motor Neuropathy: The Diagnostic Spectrum and Response to Treatment," *69 Neurology* 1680 -87 (2007).

Thus, study after study – both randomized and open-label – shows that IVIg is a safe and effective long-term treatment for MMN. No reports in the literature contradict this conclusion. No other treatment for MMN has produced these same results. A recent Cochrane study concluded, after a sophisticated statistical analysis of all reports found on Medline and Cochrane, including those cited above, that IVIg is superior to placebo in inducing an improvement in muscle strength in patients with MMN. Muscle strength improved spontaneously in 4 percent of patients, but treatment with IVIg increased the chance of improvement to 78 percent. Open and uncontrolled studies show IVIg treatment effective in improving muscle strength in 81 percent of cases. Van Schaik, *supra*. There simply is no question that IVIg is the appropriate treatment for MMN.

Several large medical societies agree. For example, in the only work which addresses MMN referenced in BCBSNJ Policy No. 016, Canadian agencies desiring to ensure that IVIg use is in keeping with an evidence-based approach to the practice of medicine convened a panel of experts to develop an evidence-based guideline for the use of IVIg in the treatment of neurologic conditions, including MMN.³ Recommendations were based on interpretation of the available evidence and, where evidence was lacking, consensus of expert clinical opinion was relied upon. For many of the diseases addressed in this publication, the panel did not recommend IVIg treatment. However, the expert panel agreed that IVIG is the only treatment demonstrated by clinical trial to be effective for MMN, and it is widely accepted as first-line therapy for this condition. Based on clinical experience, members of the panel noted that the effect of IVIG is variable, and over time, the interval between treatments may shorten as the therapeutic benefit of IVIG declines. The panel emphasized the importance of continuing regular IVIG maintenance therapy to avoid secondary axonal degeneration. Feasby, et al. "Guidelines on the Use of Intravenous Immune Globulin for Neurologic Conditions," *Transfusion Medicine Reviews* 2007 21(2 Suppl 1):S57-S107 (emphasis added).

Similarly, the European Federation of Neurological Societies issued their guideline for MMN treatment after retrieving all relevant material from Medline and Cochrane Library in July 2004. The principal recommendations⁴ and good practice points⁵ were:

³ The publication of this study appears as reference 46 in Horizon BCBSNJ Uniform Policy Manual (Policy No. 016).

⁴ Recommendations were identified as level A, level B or level C. A Level A recommendation was defined as one that is established as effective, ineffective, or harmful, and requires at least one convincing class I study or at least two consistent, convincing class II studies. A

- (i) IVIg (2 g/kg given over 2-5 days) should be considered as the first line treatment (level A recommendation) when disability is sufficiently severe to warrant treatment;
- (ii) corticosteroids are not recommended (good practice point);
- (iii) if initial treatment with IVIg is effective, repeated IVIg treatment should be considered (level C recommendation); the frequency of IVIg maintenance therapy should be guided by the individual response (good practice point). Typical treatment regimens are 1 g/kg every 2-4 weeks or 2 g/kg every 4-8 weeks (good practice point);
- (iv) if IVIg is not or not sufficiently effective, then immunosuppressive treatment may be considered. Cyclophosphamide, cyclosporin, azathioprine, interferon beta 1a, or rituximab are possible agents (good practice point); and
- (v) toxicity makes cyclophosphamide a less desirable option (good practice point).

The recommendations clearly suggest the use of IVIg as the first line treatment and the continuation on a regular basis if the initial treatment is successful. Van Schaik, et al., "European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of Multifocal Motor Neuropathy," *13 European Journal of Neurology* (802-808) 2006.

In sum, MMN has been recognized as a distinct disease for over twenty years. IVIg is an effective treatment in a majority of the patients identified with MMN. No other treatment is as effective, and some of the other treatments for neuromuscular diseases such as corticosteroids are contraindicated. The effectiveness of IVIg has been verified by both double-blind placebo and retrospective studies. IVIg is considered the standard treatment for MMN by the NIH. Canadian and European guidelines support this conclusion. Thus, IVIg for the treatment of MMN is not experimental or investigational; instead, it is the first line therapy for this chronic illness.

Level B recommendation is one that is probably effective, ineffective, or harmful, and requires at least one convincing class II study or overwhelming class III evidence. A level C recommendation is one is possibly effective, ineffective, or harmful, requiring at least two convincing class III studies. Class I studies were adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. Class II studies were prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e. Class III studies were other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment. The article also refers to class IV evidence, which was defined as evidence from uncontrolled studies, case studies, case reports or expert opinion.

⁵ When only class IV evidence was available but consensus could be reached, the Task Force offered advice as "good practice points."

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

In 2002, Mr. Patient began experiencing a tremor in the fingers of his right hand. He then had difficulty moving one finger at a time. He could not type or write. Mr. Patient, who was 29 years old at the time, waited almost a year before visiting a physician. The initial diagnosis was ALS. However, Mr. Patient was not satisfied with that diagnosis and received a second opinion recommending nerve surgery. (7/15/2002 Dr. Smith office note). Reluctant to undergo the surgery, Mr. Patient visited a neurologist who diagnosed him with MMN. (9/4/2002 Dr. Neuro office note). He then went to the Mayo Clinic, which confirmed the MMN diagnosis. (11/4/2002 Mayo Clinic summary report). By this time, Mr. Patient had an odd sensation in his wrist and atrophy between his thumb and forefinger. IVIg therapy was begun immediately. (12/1/2002 Dr. Neuro office note). The tremors and sensation in the wrist went away. (12/29/2002 Dr. Neuro office Note).

Initially, Mr. Patient received 160 grams of IVIg (2 grams/kg of body weight per month). After six months of treatment, a weaning process was begun. Dr. Neuro's plan was to reduce the amount of IVIg by 10 percent each month until Mr. Patient began experiencing tremors before the 26th day, at which time, he would restore the previous month's dosage level. (6/1/2003 Dr. Neuro office note). Mr. Patient, fortunate to be diagnosed soon after the onset of the disease, had his IVIg intake dramatically reduced. Mr. Patient was stabilized at a dosage of 34 grams of IVIg every 30 days. No further atrophy was found after the initial treatment. (2/12/2005 Dr. Neuro patient note).

Every month, some time between the 27th day and the 30th day after treatment, Mr. Patient begins to experience tremors. (6/12/2006; 12/12/2006; 6/19/2007; 12/12/2007; 6/12/2008; 1/6/2009 Dr Neuro office notes). These tremors are so significant to make sleeping difficult at times. Dr. Neuro is confident that Mr. Patient is receiving the minimum dosage necessary to control symptoms and prevent further deterioration. Mr. Patient still has atrophy between his right thumb and forefinger, but has experienced no further loss of strength. (12/15/2009 Dr. Neuro office note).

Mr. Patient clearly needs continued treatment to avoid both the immediate tremors upon cessation of treatment and to prevent further deterioration. This is Dr. Neuro's recommendation and is amply substantiated by the medical literature presented above.

After seven years, BCBSNJ decided not to authorize further treatments as not medically necessary. There is nothing in the medical literature to suggest a reason for discontinuing IVIg treatment for a MMN patient like Mr. Patient. In fact, literature published in the last year supports IVIg treatment for MMN. Cats, *supra*. The Canadian paper referenced on BCBSNJ Policy No. 016 strongly recommends that IVIg treatment for MMN should not be interrupted. Feasby, *supra*. In light of the fact that Dr. Neuro did wean Mr. Patient down to the lowest effective dosage, BCBSNJ should be confident that Mr. Patient is receiving not only the right treatment, but the right amount. Thus, the noncoverage decision should be reversed.

IV. CONCLUSION

For all of these reasons, we urge you to reverse the noncoverage decision and restore the treatment that has controlled Mr. Patient's disease for seven years.

Thank you.

Sincerely,

Jennifer C. Jaff