

November 12, 2010

Anthem Blue Cross Blue Shield
Utilization Management Dept.
2000 Corporate Center Drive
Newbury Park, CA 91320

RE: Patient
Reference no. 245346346
Subscriber: ID No. ssss22222
Date of service: To be determined (prior authorization)
Service: IVIg for Complex Regional Pain Syndrome

Dear Sir or Madam:

I am writing on behalf of your insured, Patient, to appeal the noncoverage decision of intravenous immunoglobulin (IVIg) for complex regional pain syndrome. My HIPAA release and authorization is enclosed.

I. Introduction

Complex regional pain syndrome (CRPS)¹ is a debilitating disease characterized by intense pain that most often begins in an extremity and then spreads to the rest of the body. The pain that CRPS patients suffer is severe and marked by motor and functional impairment, increased or decreased sweating, allodynia (brush-evoked pain), swelling in the affected limb, and autonomic disturbances. Blaes, et al., "Autoimmunity in Complex-Regional Pain Syndrome," 1107 *Ann. N.Y. Acad. Sci.* 168-173 (2007). Other common symptoms of CRPS include visual blurring, difficulty focusing, dizziness and syncope. See Schwartzman and Popescu, "Reflex Sympathetic Dystrophy," 4 *Current Science Inc.* 165-169 (2002).

IVIg is a medically accepted treatment for CRPS and, for Patient, the only treatment that has been able to offer significant and dramatic relief from the persistent symptoms of this awful disease. As such, Anthem Blue Cross Blue Shield's ("Anthem") noncoverage decision should be overturned so that Patient may receive this medically necessary treatment.

II. INTRAVENOUS IMMUNOGLOBULIN (IVIg) IS NOT EXPERIMENTAL, INVESTIGATIONAL OR INVESTIGATIONAL FOR THE TREATMENT OF COMPLEX REGIONAL PAIN SYNDROME

Anthem has denied coverage of IVIg on the ground that it is experimental or investigational for the treatment of CRPS. However, this conclusion is contrary to the published medical literature.

Dr. Andreas Goebel recently reported that thirteen patients with long-standing, refractory CRPS experienced substantially reduced pain and improved autonomic limb symptoms when administered a low-dose treatment of intravenous immunoglobulin (IVIg). These patients were participants in a randomized, double-blinded, placebo-controlled crossover study that clearly demonstrates the effectiveness of IVIg for CRPS sufferers. Goebel, et al., "Intravenous Immunoglobulin Treatment of the Complex Regional Pain

¹ Also known as reflex sympathetic dystrophy or RSD.

Syndrome: A Randomized Trial," 152(3) *Ann. of Internal Med.* 152-158 (2010). Each patient in this study was given an infusion of IVIg at a dose of 0.5 g/kg (0.25 g/kg per day) over a period of two days. Even at this very low dosage, clear evidence of a treatment effect resulted. In the patients who received the IVIg treatment versus the saline control, there was an average decrease of 1.55 units in the pain scores they reported.² Forty-two percent of the patients (5 out of 13) had median pain scores that were at least two points lower with IVIg than with saline, and three of those patients had median pain scores that were at least 50 percent lower than it was prior to treatment. In fact, ongoing pain relief after the first infusion required a delay in administering the second infusion in three of the patients who received IVIg as opposed to saline. Two of the patients, who received IVIg as the second infusion and saline as the first, reported "much improved" or "very much improved" pain after day 28 following that second infusion. One of these patients experienced this improvement for a period of two weeks and the other for a period of three weeks. Notably, the beneficial effects of IVIg lasted over four weeks in five of the cases, but in no case did the effects last longer than three months. Goebel, et al., "Intravenous Immunoglobulin Treatment of the Complex Regional Pain Syndrome: A Randomized Trial," 152(3) *Ann. of Internal Med.* 155 (2010). See also Goebel, "Immunoglobulin Responsive Chronic Pain," 30 Supp 1 *J. Clin. Immunol.* S103-S108 (2010) (summarizing the literature).

This study built on Dr. Goebel's previous work. In 1988, Dr. Goebel discovered that the IVIg infusion he was using to treat a patient with hypogammaglobulinemia also provided the patient with unexpected and reproducible pain relief. Following this "serendipitous" finding, a prospective multiple-dose, open-label cohort study of 130 patients suffering from 12 different chronic pain syndromes was organized to evaluate the effectiveness of using IVIg to relieve pain. Good pain relief, of more than 70 percent, was reported in each of the major symptoms groups – which included CRPS, fibromyalgia, spinal pain, peripheral neuropathic pain and atypical facial pain. Overall, 20 percent of the patients had greater than 70 percent pain relief, and 27.7 percent of the patients reported pain relief between 25 percent and 70 percent. Goebel, et al., "Human Pooled Immunoglobulin in the Treatment of Chronic Pain Syndromes," 3(2) *Pain Medicine* 119-127 (2002). Significantly, "[t]he response rates were heterogeneous; for example, few patients with back pain reported good responses, whereas **those with CRPS . . . often reported exceptional benefit.**" Goebel, "Immunoglobulin Responsive Chronic Pain," 30 Supp 1 *J. Clin. Immunol.* S103-S108 (2010) (emphasis added).

Later, Dr. Goebel and his team found that IVIg provided repeated pain relief in another patient with CRPS. In this 2005 study, a patient with CRPS I reported more than 50 percent pain reduction, along with cessation of her autonomic signs, during each six weeks after three treatments of IVIg. Goebel, et al., "Intravenous Immunoglobulin Response and Evidence for Pathogenic Antibodies in a Case of Complex Regional Pain Syndrome I," 57(3) *Annals of Neurology* 463-464 (2005).

Thus, these studies conducted by Dr. Goebel – including one double-blinded, placebo-controlled study – show that IVIg provides noticeable pain relief for CRPS sufferers such as Patient.

A. Growing Medical Evidence Points to an Autoimmune Etiology of Complex Regional Pain Syndrome, Further Supporting the Efficacy of IVIg

² The Patient s rated their pain by using an 11-point numerical rating scale (0 = no pain; 10 = pain as bad as they could imagine).

Dr. Goebel's research is confirmed by many studies that conclude that there is a connection between CRPS and the immune system, which IVIg serves to strengthen. Although the exact pathophysiology of CRPS remains unclear, there is increasing evidence that the immune system is involved. Kohr, et al., "Autoantibodies in complex regional pain syndrome bind to a differentiation-dependent neuronal surface autoantigen," 143(3) *Pain* 246-251 (2009).

Evidence began to mount for the involvement of the immune system in CRPS in 2002, when researchers in the Netherlands discovered that there are increased local levels of the pro-inflammatory cytokines interleukin (IL-6) and tumor necrosis factor- α (TNF- α) in the blister fluid of patients with CRPS I.³ Such data indicated, for the first time, that inflammation plays an important role in CRPS I. Huygen, et al., "Evidence for local inflammation in complex regional pain syndrome type 1," 11(1) *Mediators of Inflammation* 47-51 (2002). Likewise, researchers then found elevated levels of the pro-inflammatory cytokines IL-6 and interleukin-1 β (IL-1 β), but not TNF- α , in the cerebrospinal fluid (CSF) of patients afflicted with CRPS. Taken together, these studies marked the, "first step[s] in discerning the involvement of the pro-inflammatory cytokines in painful disorders [which] strongly suggest that part of the process resulting in chronic pain involves central neuroimmune activation." Alexander, et al., "Changes in cerebrospinal fluid levels of pro-inflammatory cytokines in CRPS," 116(3) *Pain* 213-219 (2005).

Significantly, studies continue to confirm the suggestion that the immune system plays a role in the etiology of CRPS. For instance, one study revealed that CRPS is associated with autoantibodies against autonomic nervous system structures. Blaes, et al., "Autoimmune etiology of complex regional pain syndrome (M. Sudeck)," 63(9) *Neurology* 1734-1736 (2004). Another demonstrated that levels of interleukin-8 (IL-8), soluble tumor necrosis factor receptor I/II (sTNFR 1/II), and substance P were elevated significantly in patients with CRPS; and elevated IL-8, sTNFR 1/II, and substance P levels are indicative of an association between CRPS 1 and an inflammatory process. Schinkel, et al., "Inflammatory Mediators are Altered in the Acute Phase of Posttraumatic Complex Regional Pain Syndrome," 22(3) *Clin. J. Pain* 235-239 (2006).

Another study revealed elevated levels of pro-inflammatory cytokines, but reduced levels of anti-inflammatory cytokines in CRPS patients. This particular study compared forty patients with CRPS I and two patients with CRPS II with thirty-four controls, and found that, in the CRPS patients "mRNA levels of the pro-inflammatory cytokines TNF- α and IL-2 [interleukin-2] and serum IL-2 protein levels were elevated, and mRNA levels of the anti-inflammatory cytokines IL-4 and IL-10 were reduced." As such, the researchers concluded that their findings "show a pro-inflammatory cytokine profile in patients with CRPS." Uçeyler, et al., "Differential expression patterns of cytokines in complex regional pain syndrome," 132(1-2) *Pain* 195-205 (2007).

Further evidence of the immune system's involvement in CRPS derives from studies that demonstrate an association between the human leukocyte antigen (HLA) system,⁴

³ There are two types of CRPS. CRPS type I is the most common form, and unlike CRPS type II, it does not have demonstrable nerve lesions.

⁴ The HLA system is the name of the major histocompatibility complex (MHC) in humans. The MHC is a large genomic region, or gene family. The MHC plays an important role in the immune system. Mayer and Nyland, "Major Histocompatibility Complex (MHC) and T-Cell Receptors – Role in Immune

which is related to autoimmunity, and CRPS. For instance, one researcher found that the frequency of the HLA allele⁵ DQ1 was significantly increased in patients with CRPS as compared to those without the disease. In fact, "[t]he frequency of DQ1 was found to be increased from 42% in the normal population to 69% among patients with [CRPS]." Kemler, "HLA-DQ1 associated with reflex sympathetic dystrophy," 53 *Neurol.* 1350-1351 (1999). Another researcher found a significant elevation of the HLA allele DR13 in CRPS patients with dystonia (a movement disorder in which muscle contractions cause twisting, repetitive movements or abnormal postures) as compared to controls. Van Hilten, "Multifocal or Generalized Tonic Dystonia of Complex Regional Pain Syndrome: A Distinct Clinical Entity Associated with HLA-DR13," 48 *Ann. Neurol.* 113-116 (2000).

Still other researchers have found that some CRPS patients might be suffering from an infection-triggered autoimmune reaction. Blaes, et al., "Autoimmunity in Complex-Regional Pain Syndrome," 1107 *Ann. N.Y. Acad. Sci.* 168-173 (2007). For example, an increased incidence of *Campylobacter jejuni-IgG* (a bacteria that usually infects the bowel system) was reported in the sera of CRPS patients. Goebel, et al., "Immune responses to *Campylobacter* and serum antibodies in patients with complex regional pain syndrome," 162(1-2) *J. Neuroimmunology* 184-189 (2005). And, an increased prevalence of parvovirus B19-IgG (a single-stranded DNA virus) was reported in CRPS patients as compared to controls. Gross, et al., "Increased seroprevalence of parvovirus B19 IgG in complex regional pain syndrome is not associated with antiendothelial autoimmunity," 11 *Eur. J. Pain* 237-240 (2007). Significantly, "both [of these] infectious agents are known to induce autoimmune diseases. *Campylobacter jejuni-IgG* can induce Guillain-Barré syndrome, and parvovirus B19 infections have been linked to autoimmunity in vasculitis syndromes." Blaes, et al., "Autoimmunity in Complex-Regional Pain Syndrome," 1107 *Ann. N.Y. Acad. Sci.* 168-173 (2007).

Finally, the most recent study which tested the sera of 30 CRPS patients, 20 neuropathy Patients and 30 healthy controls for surface-binding autoantibodies to primary cultures of autonomic neurons found that "about 30-40% of CRPS Patients have surface-binding autoantibodies against an inducible autonomic nervous system autoantigen." Kohr, et al., "Autoantibodies in complex regional pain syndrome bind to a differentiation-dependent neuronal surface autoantigen," 143(3) *Pain* 246-251 (2009). Only one of the 20 neuropathy Patients had sera with specific surface binding to autonomic neurons and none of the healthy controls did. This finding "provide[s] more evidence that autoimmunity against the autonomic nervous system may be involved in the pathogenesis of CRPS." Kohr, et al., "Autoantibodies in complex regional pain syndrome bind to a differentiation-dependent neuronal surface autoantigen," 143(3) *Pain* 246-251 (2009).

Thus, medical research strongly supports an autoimmune etiology of CRPS. Because of the effectiveness in treating autoimmune disorders with IVIg, this further supports the use of IVIg in treating CRPS.

B. IVIg is an Accepted Therapy for Management of Pain with Immune Etiology

Response," Chapter 10 Microbiology and Immunology On-Line: U. of So. Carolina School of Medicine available at <<http://pathmicro.med.sc.edu/bowers/mhc.htm>> Accessed August 18, 2010.

⁵ An allele is a DNA (deoxyribonucleic acid) coding that is located on a chromosome.

IVIg also provides clear pain relief for patients suffering from a variety of diseases. These include, but are not limited to, dysautonomia, fibromyalgia, chronic fatigue syndrome, painful neuropathies, and post-polio syndrome. Below is a selection of examples that demonstrate the exceptional pain relief patients with these disorders have found with IVIg therapy.

1. Dysautonomia

Dysautonomia is an uncommon disorder characterized by acute dysfunction of the autonomic nervous system. Even though its pathogenesis remains unclear, an acute inflammatory neuropathy caused by an immune mediated mechanism may be involved – similar to Guillain-Barré syndrome.⁶ Ishitobi, et al., “Acute dysautonomia: complete recovery after two courses of IVIg,” 26(8) *Brain Dev.* 542-544 (2004). While patients with dysautonomia suffer a variety of symptoms, the most common ones are severe hypotension, abnormal sweating, blurred vision, pupillary areflexia, and pain. Recovery is usual gradual and often incomplete; yet IVIg has proven to be an effective treatment.

For example, a previously healthy 23 year-old man who began to experience abdominal pain, diarrhea, blurred vision, reduced sweating, and life-threatening postural hypotension found immediate relief after receiving IVIg. Within 36 hours of receiving the treatment, “[h]is severe and life threatening autonomic failure responded briskly . . . [and] [w]hen he relapsed 17 days later, a second course produced an equally good response.” Heafield, et al., “Idiopathic dysautonomia treated with intravenous gammaglobulin,” 71 *East Afr. Med. J.* 167-170 (1994).

Similarly, a 54 year-old man with recurrent syncope, nausea, vomiting, abdominal pain, and postural hypotension began to experience relief just six days after an IVIg dose of 1 g/kg body weight per day for two days. The patient’s postural hypotension was reduced significantly and his nausea and abdominal pains completely resolved. Repeated IVIg treatments were administered to keep his pain and other symptoms at bay. Dupond, et al., “Acute dysautonomia secondary to autoimmune diseases: Efficacy of intravenous immunoglobulin and correlation with a stimulation of plasma norepinephrine levels,” 17(6) *Clinical and Experimental Rheumatology* 733-736 (1999).

Another example comes from the treatment of a 37 year-old woman with dysautonomia who tried a two-month treatment of prednisone, hydroxychloroquine and fludrocortisone to no avail. Only when she was given an IVIg treatment every four weeks for three months did her symptoms disappear for a period of five years. When her symptoms returned, she once again “responded promptly” to IVIg. Dupond, “Five-year Efficacy of Intravenous Gammaglobulin to treat Dysautonomia in Sjögren’s Syndrome,” 106(1) *Am. J. Med.* 125 (1999); Dupond, et al., “Acute dysautonomia secondary to autoimmune diseases: Efficacy of intravenous immunoglobulin and correlation with a stimulation of plasma norepinephrine levels,” 17 *Clin. Exp. Rheumatol.* 733-736 (1999).

⁶ IVIg is a commonly accepted treatment for Guillain-Barré syndrome. Donofrio P.D., et al., “Consensus statement: the use of intravenous immunoglobulin in the treatment of neuromuscular conditions report of the AANEM ad hoc committee,” 40(5) *Muscle Nerve.* 890-900 (2009); Wiles, C.M., et al., “Intravenous immunoglobulin in neurological disease: a specialist review,” 72 *J. Neuro. Neurosurg. Psychiatry* 440-448 (2002).

A further example comes from the treatment of a 61 year-old man with dysautonomia who developed acute, lancinating pains in his arms and legs (which came and went spontaneously), difficulty urinating, constipation, fever, and orthostatic hypotension with syncope. After a 5-day course of IVIg, "[h]e improved [so] rapidly such that at the time of discharge (one week after admission), he was asymptomatic" Quan, et al., "Acute idiopathic dysautonomia: Electrophysiology and response to intravenous immunoglobulin," 54(3) *Neurology* 770-771 (2000).

Two more examples that demonstrate the effectiveness of IVIg in relieving the symptoms associated with dysautonomia come from the cases of an 11 year-old boy and a 60 year-old man. In both cases, the patients developed orthostatic hypotension so severe that they could not remain standing for more than a few minutes and were bedridden. After two high dose treatments of IVIg (400 mg/kg body weight for five consecutive days), the 11 year-old recovered completely. Ishitobi, et al., "Acute dysautonomia: complete recovery after two courses of IVIg," 26(8) *Brain Dev.* 542-544 (2004). Likewise, after two treatments of IVIg, the 60 year-old patient's orthostatic hypotension improved, along with his sensory, motor and autonomic impairments. Finally, this patient could walk by himself again. Ueda, et al., "Acute Autonomic, Sensory and Motor Neuropathy: Successful Treatment with IVIg," 48(10) *Intern. Med.* 843-846 (2009).

Thus, IVIg is an effective treatment for dysautonomia.

2. Fibromyalgia & Chronic Fatigue Syndrome

Fibromyalgia syndrome (FMS) is a condition characterized by chronic, widespread, long-term pain and allodynia. It also has been linked to debilitating fatigue, sleep problems, and joint stiffness. Caro, et al., "A subset of fibromyalgia patients have findings suggestive of chronic inflammatory demyelinating polyneuropathy and appear to respond to IVIg," 47(2) *Rheumatology* 208-211 (2008). A recent study of 58 FMS patients, 26 rheumatic non-FMS patients and 52 non-rheumatic non-FMS patients revealed that a significant subset of FMS subjects have a high prevalence of clinical and electrodiagnostic (EDX) abnormalities, which implies a demyelinating polyneuropathy, suggestive of chronic inflammatory demyelinating polyneuropathy (CIDP). Furthermore, the study also revealed that this subset appears to respond to IVIg. In fact, "[a] large percentage of this select FMS subset experienced significant short-term benefits from IVIg treatment, at least in terms of pain, tenderness and strength." *Ibid.*

Chronic fatigue syndrome (CFS) is characterized by severe fatigue that persists for longer than six months and is accompanied by symptoms such as – but not limited to – impaired concentration or memory, sore throat, headaches, unrefreshing sleep, muscle pain and multijoint pain. Kerr, et al., "Successful Intravenous Immunoglobulin Therapy in 3 Cases of Parvovirus B19-Associated Chronic Fatigue Syndrome," 36(9) *Clin. Infect. Dis.* e100-e106 (2003). Even though the causes and risk factors for CFS are not well defined, "[a] major hypothesis for the pathogenesis of CFS is that an infectious trigger, such as the persistence of an infectious agent or other immune stimulus, may lead to a chronic activation of the immune system with abnormal regulation of cytokine production." See Kerr, et al., "Successful Intravenous Immunoglobulin Therapy in 3 Cases of Parvovirus B19-Associated Chronic Fatigue Syndrome," 36(9) *Clin. Infect. Dis.* e100-e106 (2003). As such, researchers designed a study "to determine whether IVIg therapy could ameliorate the clinical symptoms and reverse the documented dysregulation in cytokine production in three cases of parvovirus B19-associated CFS." In all three cases, the answer was *yes*.

The first case involved a patient who suffered from memory and concentration loss, sore throat, painful aching muscles, new headaches, difficulty sleeping, unrefreshing sleep, postexertional malaise (general discomfort), an increased tendency to sweat, dizzy spells, blurred vision, fatigue, persistent abdominal pain and diarrhea. This 41 year-old woman took a lot of time off of work and saw her social life dwindle due to these CFS symptoms. Yet, after a treatment of IVIg – at 400mg/kg per day for five days – her symptoms resolved during the following two weeks, with a more gradual improvement during the next two months. Significantly she “subsequently returned to work without sick leave and was able to participate again in family and social activities that were not possible during her illness.” Kerr, et al., “Successful Intravenous Immunoglobulin Therapy in 3 Cases of Parvovirus B19–Associated Chronic Fatigue Syndrome,” 36(9) *Clin. Infect. Dis.* e100-e106 (2003).

The second and third cases are similar. In the second case, a 34 year-old woman suffering from CFS recovered completely only two months after her IVIg treatment. Before then, she had been suffering from fever, skin rash, pain and swelling throughout her whole body, memory loss, difficulty sleeping, new headaches, dizzy spells, blurred vision, fatigue, and painfully aching muscles. In the third case, a 46 year-old man suffering from CFS experienced relief from his persistent joint pain only three days after his IVIg treatment. His pain level continued to improve over the two weeks following the treatment, and a marked improvement occurred three months later. In fact, three months after the IVIg treatment, “his hips, knees, and ankles were virtually free of pain. This improvement continued until he achieved a complete recovery.” Both patients, like the first, were once again able to participate in work, family, and social activities that they were unable to before their treatments with IVIg. Kerr, et al., “Successful Intravenous Immunoglobulin Therapy in 3 Cases of Parvovirus B19–Associated Chronic Fatigue Syndrome,” 36(9) *Clin. Infect. Dis.* e100-e106 (2003).

IVIg also is an effective treatment for CFS even when it is not associated with parvovirus B19. For example, in a randomized, double-blinded, placebo-controlled study, researchers found IVIg to be an effective treatment for a significant number of CFS sufferers. Forty-three percent (10 out of 23) of the patients, who received IVIg instead of the control were assessed as having responded with a substantial reduction in their symptoms and were able to recommence work and leisure activities. Indeed, the “patients designated as having responded had improvement in physical, psychologic [sic], and immunologic measures.” Lloyd, et al., “A Double-Blind, Placebo-Controlled Trial of Intravenous Immunoglobulin Therapy in Patients with Chronic Fatigue Syndrome,” 89(5) *Am. J. M.* 561-568 (1990). The benefits of IVIg in CFS sufferers are two-fold: first, their symptoms, such as pain and fatigue, are relieved, and second, their ability to function again at work and in society is restored.

3. Painful Neuropathy

IVIg has been shown to relieve pain in sensory neuropathy associated with Sjögren’s syndrome⁷ in several cases. An especially notable one involves a 67 year-old man with Sjögren’s syndrome who experienced a sudden subacute onset of severe pain and dysaesthesia (a type of pain) in his fingers and extremities. The relentless pain in his feet

⁷ Sjögren’s syndrome is an autoimmune disease. Mavragani and Crow, “Activation of the type I interferon pathway in primary Sjögren’s syndrome,” *J. Autoimmun.* (2010) (Epub ahead of print).

nearly led to amputation, while the extreme pain in his hands kept him from being able to extend his fingers or touch objects. These painful symptoms dramatically were reduced after the patient was treated with IVIg. Indeed, "[t]he most striking observation in this Patient was the remarkable beneficial effect of intravenous Ig treatment on painful symptoms. Pain rated on the VAS⁸ was reduced dramatically from 10 to 2 after the first course of treatment. After the second of two courses given after relapse, the patient's ability to carry out activities of daily living was also greatly improved." Kizawa, et al., "Intravenous immunoglobulin treatment in painful sensory neuropathy without sensory ataxia associated with Sjögren's syndrome," 77(8) *J. Neurol. Neurosurg. Psychiatry* 967-969 (2006).

Likewise, in a study of five patients with sensory neuropathy associated with Sjögren's syndrome, IVIg was found to alleviate the painful symptoms of each one. Each patient previously had experienced debilitating pain that interfered with their daily activities and had not responded to conventional treatments such as, anticonvulsants, tricyclic antidepressants, or opioids. After a treatment of 0.4g/kg/day for five days of IVIg, pain rated on the VAS was reduced by 73.4% from days two to fourteen following treatment. This remarkable pain improvement lasted for two to six months. Morozumi, et al., "Intravenous immunoglobulin treatment for painful sensory neuropathy associated with Sjögren's syndrome," 279(1-2) *J. Neurol. Sci.* 57-61 (2009).

Moreover, in patients with multifocal diabetic neuropathy, IVIg has been shown to provide a "marked improvement" in severe pain. Kawagashira, et al., "Differential response to intravenous immunoglobulin (IVIg) therapy among multifocal and polyneuropathy types of painful diabetic neuropathy," 17(8) *J. Clin. Neurosci.* 1003-1008 (2010). In four out of five patients with diabetic lumbosacral radiculoplexus neuropathy (DLRPN), IVIg yielded rapid and significant pain reduction – with greater than 50% pain reduction recorded on the VAS; and only two patients required repeat infusions. Tamburin and Zanette, "Intravenous Immunoglobulin for the Treatment of Diabetic Lumbosacral Radiculoplexus Neuropathy," 10(8) *Pain Med.* 1476-1480 (2009). In a 57 year-old patient with proximal diabetic neuropathy (PDN), IVIg dramatically ameliorated severe pain and muscle weakness. In fact, pain assessed by the VAS was relieved by 80 percent after two courses of IVIg. Kawagashira, et al., "Intravenous immunoglobulin therapy markedly ameliorates muscle weakness and severe pain in proximal diabetic neuropathy," 78(8) *J. Neurol. Neurosurg. Psychiatry* 899-901 (2007).

4. Post-polio Syndrome

Similar to CRPS, IVIg also has been found to alleviate symptoms, particularly pain, associated with post-polio syndrome (PPS).⁹ PPS is a condition characterized by muscle weakness, atrophy, fatigue and pain developing several years after acute polio onset. Farbu, et al., "Post-polio syndrome Patients treated with intravenous immunoglobulin: a double-blinded randomized controlled pilot study," 14(1) *Eur. J. Neurol.* 60-65 (2007). In one randomized, double-blinded, placebo-controlled study, researchers found that a group of patients with significant pain at the start of the trial had a greater pain reduction when

⁸ The Visual Analogue Scale (VAS) is the standard tool for rating pain. Its frames measure exactly 10 cm.

⁹ Medical evidence suggests that PPS is an autoimmune disease. Gonzalez, et al., "Intravenous immunoglobulin for post-polio syndrome: a randomized controlled trial," 5 *Lancet Neurology* 493-500 (2006).

treated with IVIg, as opposed to those treated with the placebo. Gonzalez, et al., "Intravenous immunoglobulin for post-polio syndrome: a randomized controlled trial," 5 *Lancet Neurology* 493-500 (2006). In another double-blinded, randomized, controlled pilot study, post-polio sufferers who received an IVIg treatment reported a significant improvement in pain during the three months following their treatment. Farbu, et al., "Post-polio syndrome patients treated with intravenous immunoglobulin: a double-blinded randomized controlled pilot study," 14(1) *Eur. J. Neurol.* 60-65 (2007).

As such, IVIg provides pain relief for patients suffering from a variety of different diseases and in an overwhelming number of cases. IVIg provides relief to patients with CRPS; and because CRPS likely is an autoimmune disorder, it makes sense that IVIg provides such relief. IVIg also is an effective treatment for pain disorders such as fibromyalgia and dysautonomia and because CRPS is a pain disorder, it makes sense that IVIg works for CRPS as well. Therefore, although CRPS is rare and thus, there are not large studies, all of the available literature supports the use of IVIg to treat CRPS.

III. IVIg IS MEDICALLY NECESSARY TO TREAT PATIENT'S COMPLEX REGIONAL PAIN SYNDROME

Patient has been suffering from the disabling effects of complex regional pain syndrome (CRPS) ever since she was a little girl. Extreme pain, allodynia, sleepless nights and a variety of other debilitating symptoms have been a part of her daily life for more than a decade. During this time, no drug or treatment other than IVIg ever provided her lasting relief without side effects, and she has tried an overwhelming number of them. The only treatment that relieves Patient's symptoms is IVIg. As demonstrated by the following, the IVIg treatments she has had truly have been life changing and are medically necessary to treat the many incapacitating symptoms that Patient has struggled with for so long.

When she was only twelve years old, Patient was diagnosed with CRPS. (2/13/2003 Dr. Wallace office note). Patient already had been diagnosed with fibromyalgia when she was a few years younger because her ankles rolled easily and she experienced generalized body pain that no medication, including imipramine, Paxil, Flexeril, and prednisone and cortisone injections, could relieve. (12/27/2000 Dr. Wallace office note). She had found some relief with guaifenesin until a minor ankle injury left her with pain, swelling, discoloration, and hypothermia, and an inability to bear weight on her right leg that no medication or therapy could relieve. She was given lidocaine and corticosteroid injections, went through physical therapy, and massage therapy, but nothing helped. (2/13/2003 Dr. Wallace office note). Once she was given the CRPS diagnosis, she also was subscribed prednisone and Neurontin, along with Ambien for difficulty sleeping, to not avail. (*Ibid*). None of the drugs provided relief and Patient continued to be reliant on crutches and a wheelchair. (2/25/2003 Dr. Oppenheim office note).

Nevertheless, Patient underwent physical therapy at an out-of-state program, and was able to return to tennis when she returned home. She did so in pain, but "was able to keep going." (2/24/2005 Dr. Richardson CHS note). Only a year later, however, Patient could no longer ignore the persistent pain. She struggled with day-to-day activities, she could not wear shoes and she started missing a lot of school. (12/5/2007 Dr. Bursch pain evaluation). She returned to the out-of-state physical therapy program for a second time in February 2005 for another round of intensive physical therapy, but again, only enjoyed moderate functional improvement with no pain relief. (12/5/2007 Dr. Bursch pain evaluation).

In May 2006, Patient's hands began to swell and she experienced increased pain and sweating on her right side. (12/5/2007 Dr. Bursch pain evaluation). The pain, as usual, spread to the rest of her body. She had trouble wearing normal clothes and only could tolerate loose-fitting ones that barely touched her skin. Also, she could barely use her hands – for example, she could not cut apples or open jars. (6/9/2006 Dr. McCurdy note). Despite all of Patient's best efforts, such as her commitment to her at-home physical therapy exercises and her decision to stop playing tennis, she simply got worse and not better.

Throughout the next few years, Patient tried a variety of medications and treatments in an attempt to find relief. First, she was prescribed sulindac by rheumatologist Dr. Debora McCurdy, but it caused her stomach pain and was discontinued. She tried hypnosis and cold laser/electro-stimulation therapy with no relief of symptoms. (*Ibid*). She returned to CHS for another week, again, with little result. (*Ibid*). She received two lumbar nerve blocks from pain specialist Dr. Anthony Kirkpatrick. (6/8/2009 Dr. Kirkpatrick report). Neither of the blocks seemed to work; nor did Lyrica, which only caused blurry vision and dizziness with no relief of symptoms. (12/5/2007 Dr. Bursch pain evaluation).

Throughout this entire time, Patient's pain continued to disrupt her sleep schedule. She struggled to fall asleep, to stay asleep, and to wake up rested. She often was fatigued and no medication helped. For example, she tried Ambien, Lunesta, Seroquel, valerian root, melatonin, Benadryl and many more. (6/9/2006 Dr. McCurdy note). She has continued to try a number of different medications meant to treat insomnia all to no avail.

Because of the unrelenting nature of her pain, Patient consulted with neurologist Dr. Robert Schwartzman, a nationally and internationally known CRPS expert and pain management specialist. At her initial evaluation, Dr. Schwartzman noted that Patient had "generalized dynamic and static mechano allodynia, deep muscle hypersensitization, some joint pain at times, severe cold allodynia, and mechanical allodynia . . . [and] . . . episodes of dizziness." (7/5/2006 Dr. Schwartzman office note). He confirmed her CRPS diagnosis and discussed the possibility of outpatient ketamine protocol and ketamine coma. (*Ibid*).

Patient did not meet the age requirements at that time to receive the ketamine treatment and spent the next year trying a variety of "interventions" such as hypnotherapy, psychotherapy, yoga, and acupuncture to relieve her pain. (9/18/2006 Dr. Zeltzer office note). Some of these interventions were useful, but none produced any pain relief. (12/5/2007 Dr. Bursch pain evaluation).

Patient saw Dr. Schwartzman in November 2007 again and the lab report that he ordered revealed that Patient suffered from extreme allodynia and pain all over her body. (1/11/2008 Dr. Schwartzman QST lab report). Patient received two outpatient intravenous ketamine infusions, but the infusions and the nerve blocks that she received did not relieve her symptoms. Indeed, her allodynia was so painful at this point that she could not be touched and could not wear normal clothes or shoes. She had trouble eating and continued to suffer from bouts of sweating and dizziness. As such, Dr. Schwartzman referred her to undergo a ketamine coma. (10/5/2008 Dr. Schwartzman office note).

Patient underwent a ketamine coma in February 2008 and experienced significant pain relief for a short period of time. Most significantly, her allodynia subsided. (7/30/2008 Dr. Richman note). Unfortunately, the pain relief did not last even though Patient received

further low-dose ketamine infusions. (5/29/2008 and 5/30/2008 and 6/25/2008 Dr. Prager operative reports). By July 2008, Patient noted increasing pain in her right ankle, which she described as "burning, sharp, and shooting with occasional tingling." (7/30/2008 Dr. Richman note). She was treated as an outpatient and received lumbar sympathetic blocks and epidural blocks, but to no avail. (7/22/2008 Dr. Prager operative report). She was referred to pain specialist Dr. Daniel Richman who ruled out any neuromas or perineural scar tissue with an MRI of her foot and ankle. (7/30/2008 Dr. Richman office note).

By September 2008 Patient – now enrolled at college – experienced increasingly more severe and widespread pain. (9/24/2008 Dr. Schwartzman letter). As such, Patient received a series of low-dose ketamine infusions for three days. (9/22/2008 and 9/23/2008 and 9/24/2008 and Dr. Prager operative reports). Because the low-dose infusions did not provide relief, however, Patient was admitted to the hospital to receive a subanesthetic dose of ketamine around the clock. (9/24/2008 Dr. Schwartzman letter). She stayed in the ICU for two weeks and was discharged from the hospital with Motrin, Neurontin, and Medrol Dosepak. (10/5/2008 Dr. Schwartzman discharge summary). This turn of events forced Patient to take a medical leave of absence from school.

Unfortunately, Patient did not respond to the low-dose ketamine infusions. Instead, "she continue[d] to experience episodes of dizziness, nausea, as well as blurred vision . . . difficulty with sleep . . . [and] she continue[d] to experience aching, tingling, burning, as well as sharp pains to her foot and her body." (11/26/2008 Dr. Prager office note).

Other treatments that Patient tried include an Iloprost infusion. (6/8/2009 Dr. Kirkpatrick office note). She also tried Zanaflex, and baclofen, and was on Zyprexa for hallucinations caused from the ketamine. (*Ibid*). Yet, she reported in November 2008 that, "things continue to remain the same with a few changes." (11/18/2009 Dr. Prager office note). She continued to suffer increased muscle pain in her legs, increased muscle spasms, and continued difficulty sleeping. (*Ibid*). Even a five-day intravenous lidocaine infusion failed to reduce her painful symptoms. (12/5/2009 Dr. Schwartzman discharge summary).

Despite her debilitating symptoms, Patient was committed to going back to school after having taken a second leave of absence in the Fall of 2009. She struggled to get through the day from the moment she woke up in the morning until the moment she went to sleep, if she could even fall asleep. Her debilitating symptoms prevented her from being able to attend class and her sorority meetings consistently, let alone volunteer or meet new people.

After a horrible semester at school and years of trying and failing so many different medications, therapies and treatment modalities, Patient *finally* found relief with IVIg. She received her first infusion of IVIg in May 2010 inpatient and her pain not only "significantly improved during the course of the hospital stay" but also continued to improve when she returned home. (5/29/2010 Dr. Schwartzman discharge summary). In fact, to say that Patient improved barely even scratches the surface of the extraordinary effect that IVIg has had. Because of IVIg her pain along with all of her other side effects including nausea, painful periods, muscle spasms, allodynia, etc. are manageable and she gets full nights of sleep. She also is able to exercise. (7/24/2010 Dr. Schwartzman email).

However, Patient requires regular treatments of IVIg to maintain these health benefits. Several weeks after her first IVIg infusion, her symptoms started to return. Her pain, muscle spasms, shakiness and nausea all increased, while her abilities to tolerate

exercise and food decreased. She started having trouble sleeping again and her eyesight worsened. Fortunately, however, a second treatment of IVIg – on an outpatient basis – improved Patient’s symptoms once again. (7/23/2010 Dr. Church report).

Since May 2010, Patient has received five infusions of IVIg and each time, her debilitating CRPS symptoms improved. Several weeks after each treatment her symptoms do return, but they again subside once she receives another treatment. (8/31/2010 Dr. Church letter). Patient’s dramatic improvement with IVIg is the reason why she continues to receive infusions even though she has not had an EMG test, which only would increase her pain. Dr. Schwartzman notes, “I do not recommend an EMG since this type of testing is extremely painful for CRPS patients.” (10/20/2010 Dr. Schwartzman letter).

IVIg has given Patient her life back. Without IVIg she can barely function, but with it, she not only can earn her college degree but also enjoy every minute along the way. (9/29/2010 Dr. Church letter). Thus, IVIg – as the *only* treatment that works – is medically necessary to treat Patient’s debilitating chronic disease.

IV. CONCLUSION

Patient has suffered from the unrelenting effects of CRPS for far too long. The relief Patient gains from regular infusions of IVIg is supported by medical evidence. The medical evidence not only points to an autoimmune etiology of CRPS, but also to the effectiveness of treating autoimmune diseases and their painful symptoms, such as CRPS, with IVIg. Therefore, the use of IVIg for CRPS is strongly supported by the medical literature and is medically necessary to treat Patient’s disabling symptoms.

Sincerely,

Name