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April 25, 2008

Customer Advocate Team  
Colorado Anthem Blue Cross Blue Shield  
700 Broadway, CAT0430  
Denver, CO 80273

RE: Patient  
Provider: Bennett Machanic  
Service: IVIg  
Date of service: Prior authorization for IVIg (proposed start date 2/19/2008)

Dear Sir or Madam:

I am writing on behalf of Patient to initiate an Independent External Review of Anthem's denial of coverage of IVIg for treatment of Relapsing Remitting Multiple Sclerosis (RRMS). The Request for Independent External Review form, a release authorizing me to represent Ms. Patient in this Independent External Review, my Blue Cross authorization and my HIPAA release is enclosed.

Anthem's initial denial was based on Anthem Clinical Guideline CG-DRUG-09. That policy does not mention multiple sclerosis, although it contains a long list of off-label uses of IVIg. In its denial letter, Anthem acknowledges that IVIg has been used to treat MS, although Anthem is critical of the published studies, without citing the studies that Anthem believes are inadequate. Anthem performed no individualized assessment of whether IVIg should be used in this particular case, but relied only on unnamed, uncited studies and a Clinical Guideline that does not mention MS.

After our second level appeal, Anthem again denied coverage, but on a different basis. Now, coverage is denied based on the fact that Ms. Patient has not tried other medications, although Anthem has not said which medications Ms. Patient would have to try in order to become eligible for IVIg. Apparently, Anthem wishes to put itself in the role of prescribing provider, not just dictating what it will cover, but also what treatment Ms. Patient's doctor should and, indeed, must prescribe instead despite the fact that Dr. Machanic participated in the level 2 appeal conference call and explained his reasons for prescribing a combination of Betaseron and IVIg – reasoning that is not addressed in the final denial letter.

As we will show, IVIg is a proven second-line therapy for RRMS. The medical literature supports this claim. A combination of Betaseron and IVIg is an entirely sensible

response to what Dr. Machanic believes is at risk of developing secondary progressive MS to attempt to stop the progression of disease. Ms. Patient's medical records support Dr. Machanic's clinical judgment that she is at risk of developing a more progressive form of the disease and, thus, that more aggressive treatment is called for. Indeed, many other insurers cover IVIg for RRMS, and we enclose a redacted copy of a Texas Independent External Appeal in which a denial of coverage by the Guardian (through a utilization review agent Medical Review Institute of America) was overturned for reasons that are present here.

Thus, for these reasons, we ask that you reverse Anthem's noncoverage decision and allow this young woman to obtain the safe and effective treatment that her treating physician has prescribed.

### **I. IVIg IS AN ACCEPTED THERAPY FOR RRMS**

First, because Anthem Clinical Guideline CG-DRUG-09 does not discuss IVIg for RRMS, and the first denial letter cites no authority for the proposition that the medical literature does not support the use of IVIg in treating RRMS, we are left trying to refute something that we have not been provided, despite our request for the materials upon which Anthem relied in reaching its denial decisions. During the second level appeal hearing, Anthem's consultant, Dr. Alexander, stated that he was relying on Hayes and Cochran, copies of which were not provided to us despite Anthem's obligation to provide us with a copy of everything on which it relies. Thus, we must base our reasoning on our best guess as to Anthem's rationale.

Indeed, Anthem verbally told Dr. Machanic's office that you were not covering the IVIg because this is an off-label use. However, the one thing that is crystal clear from Anthem Clinical Guideline CG-DRUG-09 is that you cover quite a long list of off-label uses of IVIg. Anthem's Clinical Guideline is enclosed for your reference.

Third, in fact, studies show that IVIg has several effects on the immune system that could be beneficial to RRMS. The reviewer who overturned the denial of coverage in our Texas Independent External Appeal cited Sorenson, Intravenous polyclonal human immunoglobulins in multiple sclerosis, *Neurodegenerative Dis* 2008;5:8-15. I am enclosing a copy of the full text of this article. As you can see, it reviews the major studies that have been performed to date and concludes that IVIg is appropriately used as a second-line treatment for multiple sclerosis.

The medical literature shows that IVIg 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 immunomodulators 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 measured 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).

Some detractors cite to the American Academy of Neurology Report of the Therapeutics and Technology Assessment Subcommittee from 2001, which 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 seven years old. We cite studies here that post-date that 2001 review. 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.

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 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.

## **II. IVIg IS MEDICALLY NECESSARY – INDEED, ESSENTIAL – IN THIS CASE**

Patient is a 20 year old struggling college student who was diagnosed with RRMS approximately two years ago, although she has been having symptoms since 2003. An August 10, 2006 MRI of the cervical spine showed two small oblong foci of increased signal intensity. A brain MRI dated August 9, 2006 showed several enhancing lesions. Both MRIs were considered evidence of demyelinating disease. These abnormalities were seen again on May 2007 MRIs, with new lesions appearing.

Ms. Patient's first treating neurologist was Allen Bowling, who first saw Ms. Patient on August 18, 2006, immediately after her diagnosis with MS following problems with balance, then numbness, then vision problems. She was immediately started on dexamethasone, which did not improve her symptoms. When Ms. Patient first saw Dr. Bowling, she was diagnosed with clinically isolated syndrome, which was treated with the assumption that full-blown MS could follow, as it did. Thus, Dr. Bowling administered IV Methyl Prednisone for three days followed by a Prednisone taper, and began Rebif shortly after her first visit with Dr. Bowling. Over time, Ms. Patient noted leg pain with some spasticity (1/4/07), headaches and weakness in her left leg (4/20/07). The head pain was controlled by Neurontin.

On June 25, 2007, Ms. Patient saw Dr. Bowling and complained of decreased strength and sensation in the left lower extremity which did not improve after a period of days. May 2007 MRIs showed two new lesions in the MRI of the head. Due to a new event and the fact that her MRI showed new lesions, the diagnosis of MS was made. IV Solu-Medrol was administered again.

By September 2007, the diagnosis had become MS, and Ms. Patient began seeing Dr. Machanic. Ms. Patient reported left-sided numbness and weakness, especially on hot days, and fatigue. In addition, Ms. Patient indicated that she is becoming increasingly forgetful. Romberg was positive with a tendency to fall backwards. There was diminished pin-prick sensation over the feet, becoming full at about mid-calf. Dr. Machanic noticed sensory levels over the trunk, more intense on the left than the right, and vibratory sensation reduced at the ankles. In addition, Dr. Machanic found subtle lefts upper extremity and left lower extremity hemiparesis. Dr. Machanic thought that her symptoms were consistent with RRMS in the thoracic and cervical cord, and memory deficits that suggest cognitive dysfunction.

MRIs were again obtained on August 6, 2007. The thoracic spine showed conus at the T-12-L1 level, with subtle foci of T2 prolongation, which appeared "at various levels within the cord." The brain MRI of that date found stable disease when compared with the previous study. There were several lesions, but no new or active, enhancing lesions were seen.

In October 2007, Ms. Patient reported cognitive difficulty and numbness from the left lower chest area down the left leg. At this point, Dr. Machanic referred Ms. Patient for a neuropsychological exam to test the limits of her cognitive function. Ms. Patient was found to be well below the average in processing speed, moderate difficulty in the area of mental

control on tasks that require focused attention, mildly impaired working memory, mild difficulty in auditory processing in the left ear, weakness in visual reasoning, "clear evidence of impairment in memory functioning," and impairment in cognitive flexibility and concentration.

Ms. Patient's cognitive difficulties have continued to progress to the point at which she is having increasing difficulty with her schoolwork. She went from a 4.0 cumulative grade point average in high school to less than a 3.0 average in college. The neuropsychological examination shows "[i]mpairment in information processing speed and mental control especially in the areas of concentration. Working memory also shows evidence of mild impairment."

In addition to her cognitive symptoms, Ms. Patient's MS is manifested by left or right hemiparesis associated with pain at sporadic intervals. She has had some weakness on the right side of her body and some reflex asymmetry, but her cognitive symptoms are most worrisome, especially at her young age.

In March 2008, Ms. Patient suffered a relapse – something that was entirely ignored in the second level appeal hearing, at which Anthem's consultant intimated that her cognitive problems and fatigue were psychological rather than being related to her MS. At that time, Ms. Patient's left arm had become entirely numb. This was her second relapse in the space of one year, which explains Dr. Machanic's determination that additional treatment is required. An April 21, 2008 brain MRI revealed an increase in the number of white matter foci. Dr. Machanic continues to be concerned about the risk of further relapses and deterioration of cognitive functioning.

Ms. Patient was on Rebif since just after her diagnosis until March 2008, when she was switched to Betaseron because of the side-effects of Rebif. Dr. Machanic believes that Ms. Patient should remain on an immunomodulator, but that this should be combined with IVIg to slow the progression of deterioration of cognitive function. In January 2008, Ms. Patient reported "having a real rough time trying to get her schoolwork done," and "having a real rough time with trying to organize and trying to remember. . . ." (1/14/08). Due to Ms. Patient's age and her cognitive challenges, Dr. Machanic believes "we need to get on top of this."

Dr. Machanic's treatment plan is to maintain Ms. Patient on an immunomodulator and add IVIg as a combination therapy once per month. Dr. Machanic relies on studies that show that patients with RRMS do better with combination therapy of immunomodulator and IVIg than with just a disease modifying agent. Dr. Machanic summarizes his approach as follows: "I think it is important with patients suffering from multiple sclerosis to be aggressive and stay ahead of the disease rather than to let the ravages of the disease continue to cause deterioration of the patient's clinical condition." (2/4/08).

Unfortunately, Anthem has not seen fit to tell us what medications Ms. Patient would have to try and fail before becoming eligible for coverage of IVIg. However, none of the alternatives is as safe and effective as the combination of Betaseron and IVIg.

Ms. Patient's main alternative is Tysabri. However, Tysabri's risks are well-known, and in order to try Tysabri, Ms. Patient would have to stop taking an immunomodulator since all of the known cases of progressive multifocal leukoencephalopathy (PML) "occurred in patients who were concomitantly exposed to immunomodulators (interferon beta in the patients with multiple sclerosis) or were immunocrompromized due to recent treatment with

immunosuppressants (e.g., azathioprine in the patient with Crohn's disease). Ordinarily, therefore, patients receiving chronic immunosuppressant or immunomodulatory therapy . . . should not be treated with Tysabri." (Tysabri prescribing information at p. 4). Since neutralizing antibodies are stable, Dr. Machanic believes that stopping an immunomodulator for at least six weeks would expose her to "the significant risk of an exacerbation . . . ." (February 4, 2008 letter from Dr. Machanic).

Other alternatives are sensibly rejected for similar reasons. Dr. Machanic – a Fellow of the American Academy of Neurology – explained during the second level appeal hearing that, in his view, the interferons are quite similar in effect, with the main difference being side-effects, which is why he switched Ms. Patient from Rebif to Betaseron. However, Dr. Machanic indicated that there is no reason to believe that Copaxone would be any more effective than Betaseron.

Other options include Novantrone, which can damage the heart and increase the risk of infection, as well as causing nausea, hair thinning, loss of menstrual periods, bladder infections, and mouth sores. (See enclosed prescribing information). Avonex can cause depression, liver problems, allergic reactions, blood problems, seizures, and heart problems. (Prescribing information enclosed). Methotrexate is labeled as follows: "Methotrexate should be used only in life threatening neoplastic diseases, or in patients with psoriasis or rheumatoid arthritis with severe, recalcitrant, disabling disease which is not adequately responsive to other forms of therapy." (See enclosed). Azathioprine can cause nausea and vomiting, hepatitis, pancreatitis, allergic reaction, and infection due to immune-suppression. (See enclosed). Indeed, there is no treatment available to Ms. Patient that carries with it the same promise of safety and efficacy as IVIg.

IVIg in combination with an immunomodulator provide the best option for this young woman whose cognitive difficulties are deteriorating rapidly. The medical literature supports this use of IVIg in treating RRMS. Whatever stability an immunomodulator has brought Ms. Patient should not be threatened by discontinuing it for a trial of Tysabri. Instead, IVIg is a safe and, in combination with an immunomodulator, effective medication for treating RRMS.

### **III. CONCLUSION**

Thus, there is ample medical literature upon which to base the use of IVIg in conjunction with an immunomodulator as a combination therapy for RRMS. All alternatives present significant risks that are not present with IVIg.

This is a 20 year old young woman whose physical condition and cognition are slipping away. Her doctor – a Fellow of the American Academy of Neurology with many years of treating patients with RRMS – believes that she should try a combination of Betaseron and IVIg. Anthem has not provided one iota of reasoning as to why this is not medically necessary; it simply has sought to stand in the shoes of the treating physician and demand that other, far riskier alternatives be tried instead. There is real urgency here; Dr. Machanic told Anthem's second level appeal panel that he fears that Ms. Patient will develop secondary progressive MS without more aggressive treatment. The safest alternative – and, in Dr. Machanic's experience, the most effective alternative – is a combination of Betaseron and IVIg.

For all of these reasons, we urge you to reverse Anthem's noncoverage decision and give this young woman a chance at the safe and effective treatment that her treating physician deems most appropriate. 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.