



18 Timberline Drive
Farmington, CT 06032
(860) 674-1370 (phone)
(860) 674-1378 (fax)
(860) 305-9835 (cell)
www.advocacyforpatients.org
patient_advocate@sbcglobal.net

March 30, 2007

AZ Benefit Options
ATTN: Appeals
PO Box 33396
Phoenix, AZ 85067

RE: Patient
ID no. Treatment: IVIg therapy
Dates of Service:

Dear Sir or Madam:

I am writing to appeal the noncoverage decision of IVIg for Patient, who suffers from relapsing, remitting multiple sclerosis (RRMS). My HIPAA release is enclosed. This is the patient's second level appeal.¹

As best we can tell from your January 22, 2007 denial letter addressed to Ms. Patient's physician, you are denying IVIg because you believe that there is no evidence of failure of standard therapies, and IVIg should be used, in your view, only when standard therapies fail. However, here, not only is there significant literature supporting the use of IVIg along with a disease-modifying agent like Copaxone, but, in fact, standard therapies have failed. Furthermore, Arizona Benefit Options paid for IVIg for this patient for a full year. This was a recognition that IVIg was a medically necessary, scientifically accepted therapy. Nothing has occurred that would cause you to change your determination regarding medical necessity, nor have you offered an explanation for this change of course.

Thus, we ask that you reverse your noncoverage decisions.

I. IVIg IS AN ACCEPTED THERAPY FOR RRMS, AND IS PRESCRIBED ALONG WITH A DISEASE-MODIFYING AGENT SUCH AS COPAXONE

First, your reviewers find that there is insufficient support in the medical research for the use of IVIg in treating relapsing remitting multiple sclerosis ("RRMS"). This is wrong.

In one 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."

¹ Although apparently the physicians filed several appeals, the patient has only filed one appeal, and has been told by telephone that she has an additional two levels of appeal remaining on these claims.

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).

Although we do not have access to a medical library, 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).

In sum, IVIg is "thought to exert a twofold effect: an immunomodulating action and a positive action on remyelination." 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 Copaxone alone.

Thus, there is both scientific evidence and clinical evidence to support the use of IVIg in treating RRMS, and there is a sufficient justification for using IVIg along with Copaxone to produce optimal results in patients.

In fact, the majority of insurance companies are covering IVIg for RRMS. We enclose policies from CIGNA, United Healthcare, Aetna, and Blue Cross Blue Shield of Texas, all of which indicate that IVIg would be covered for patients with RRMS, especially when Copaxone alone does not control symptoms, prevent flares, or cause the patient's condition to improve, as is the case here. (See Section II, below). Fisperve Health is in the minority, and the medical reviewers on this file apparently are not aware of how widespread and accepted the use of IVIg has become in the treatment of 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. MS. PATIENT'S CONDITION WORSENS WITHOUT IVIg, AND IMPROVES WITH IT, AND STANDARD THERAPIES HAVE FAILED

Your reviewer has made two very clear, and very critical, errors. First, in your January 22, 2007 letter to Ms. Patient's physician, and your February 26, 2007 letter to Ms. Patient, you state that standard therapies have not failed, and that Ms. Patient remains on Avonex. **This is false**, as documented in the enclosed records, and clearly set forth in the February 5, 2007 letter from Dr. Barry Hendin, enclosed. That letter makes clear the fact that Ms. Patient developed severe side-effects on the Avonex, so that treatment failed, and Ms. Patient was switched to Copaxone in April 2006.

In addition, we submit a January 2006 report that shows that Ms. Patient has neutralizing antibodies to beta interferon in the mild/moderately elevated range. Although not conclusive, this test suggests that there is a reduction in the clinical effectiveness of beta interferon therapy. These antibodies increased subsequent to a July 19, 2005 report of the same diagnostic test, suggesting that beta interferon is becoming less effective over time.

Second, it is equally clear that your reviewer erred yet again in stating that "the claimant had already improved substantially when examined on 8/21/2006." (11/8/2006 Peer Reviewer Final Report). The error is absolutely crystal clear: Ms. Patient **already had been on IVIg for more than a year** by 8/21/2006! IVIg was initiated in June 2005. Thus, to the extent that her condition was improved, it was **because** of the IVIg. Clearly, your reviewer did not know this, or did not appreciate it when reviewing the medical records.

What the records show is that, after starting Copaxone in April 2006, Dr. Hedlin continued IVIg for several reasons that establish medical necessity. First, Copaxone takes 8 or 9 months before it would have a therapeutic effect. Thus, during this 9-month period commencing in April 2006 and extending to January 2007, IVIg was necessary because it was the only drug Ms. Patient was taking that was having a therapeutic effect. All of the dates of service to which this appeal applies fall within that 9-month window.

Second, when attempts were made to reduce the dosage of IVIg, Ms. Patient developed "increased problems with fatigue, sensory loss, dysarthria, and increased bladder

symptoms. . . ." In fact, in July 2006 – still during that period when Copaxone was not yet at a therapeutic level – Ms. Patient developed numbness in her feet and legs, requiring five days of IV SoluMedrol, and requiring, too, that the monthly IVIg treatments be resumed. Thus, this test of decreasing the frequency of IVIg showed that the IVIg was necessary to retain stability of disease and prevent relapses.

In addition, Ms. Patient is attempting to become pregnant. If she does, she will not be able to continue Copaxone, and IVIg would be the only therapy that would be safe during pregnancy.

Ms. Patient's symptoms were greatly alleviated while she was on IVIg. The first order for IVIg was written in June 2005 (and Arizona Benefit Options covered it for a full year before changing its position without reason). A June 2005 MRI showed new lesions in the brain, and Ms. Patient was complaining of dizziness, which may have been due to the lesion in the medulla seen on MRI. Shortly thereafter, Ms. Patient suffered a flare that required five days of IV SoluMedrol.

However, by August 2005 – after three months on IVIg – Ms. Patient's symptoms had improved. By September 2005, Ms. Patient was virtually asymptomatic, with a return in energy level and general biological strength.

Unfortunately, shortly thereafter, Ms. Patient became intolerant to Avonex. At this time, her IVIg was increased to 1GM/KG/day twice a month. When her numbness progressed from the soles of her feet to her legs and she was having urological problems, her doctors moved up the IVIg treatment in July 2006. By August 2006, after a month of increased IVIg, Ms. Patient was feeling better. Her paresthesias and numbness in her feet and legs had subsided, although urological problems persisted.

Contrary to your reviewer's feeling that the IVIg had not improved Ms. Patient's condition, the medical records prove that the contrary is the case. By December 2006, Ms. Patient was doing considerably better. A December 14, 2006 MRI showed that one enhancement in the right frontal region had resolved. There still was evidence of active RRMS, but the IVIg not only helped to control Ms. Patient's symptoms, but it also seems to have restored at least the one lesion. We enclose copies of MRIs going back to 2001. The only improvement in MRI has been as a result of IVIg.

Your January 22 and February 26, 2007 letters state that Ms. Patient's neurological examination was normal before IVIg and after IVIg. It is difficult to understand how that conclusion could be drawn based on the medical records. There is no question that Ms. Patient's symptoms entirely disappeared in September 2005, after only three months of IVIg, and before she became intolerant to Avonex. When she suffered a relapse in July 2006, her IVIg treatments were moved up, and a month later, Ms. Patient was doing better.

In addition, we are submitting urodynamics studies that measure the urethral sphincter function. Before IVIg, she was retaining 300cc's in her bladder after emptying. After IVIg, this test showed only 175 ml retention – yet another improvement attributable to IVIg.

There simply is no basis in fact for the conclusion that Ms. Patient's neurological exams were normal before the IVIg, or that IVIg has not alleviated Ms. Patient's symptoms.

The facts are to the contrary. IVIg has provided a substantial benefit to Ms. Patient, and your conclusion to the contrary is not based on the medical facts before you.

In sum, in the November 8, 2006 Peer Reviewer Final Report, your reviewer states that "Milliman Guidelines suggest that [IVIg] is indicated if the patient is unwilling or unable to tolerate other remittive agents. There is not an indication of such intolerance in this case." As has been shown above, **this is false**. Ms. Patient was intolerant of Avonex. She had been started on Copaxone, but it was not at a therapeutic level. In addition, she has developed antibodies to beta interferon. Thus, according to your own reviewer's rationale, your noncoverage decision should be reversed. If one further appreciates the reviewer's error in believing that Ms. Patient was not on IVIg when he notes that she was doing better in August 2006, it is clear that the underpinnings of your reviewer's opinions are so riddled with errors that the review must be disregarded.

For all of these reasons, the noncoverage decision should be reversed.

III. ARIZONA BENEFIT OPTIONS' CHANGE OF POSITION WITHOUT GIVING A REASON IS ARBITRARY AND CAPRICIOUS AND, THUS, SHOULD BE REVERSED

Finally, Arizona Benefit Options covered IVIg for Ms. Patient for a full year. This is a clear implication that you believed this therapy was medically necessary for that year, and that you did not believe it was experimental. All of a sudden, you changed your mind. You have not provided reasons for that change of mind. You cite no new studies or other evidence that would explain this change of course. You do not rely on anything new about Ms. Patient's medical condition. In short, nothing has changed other than your position.

All you say that comes close to explaining this is that you conducted an internal audit on February 2, 2006, and decided that IVIg is "experimental." Still, you allowed claims through May 31, 2006. You do not explain why you allowed those claims but not others. Indeed, your allusion to an internal audit sounds more like selective denials of coverage than it does a genuine concern about whether IVIg is experimental when used to treat RRMS – which it is not. (See section I, above).

How can a Plan – even one not governed by ERISA – say something is medically necessary in June 2006 but not in July 2006 when nothing has changed, or that something is experimental in June 2006 but not in May 2006? This course reversal is arbitrary and capricious. As such, Arizona Benefit Options should continue to do as it did for more than a year, covering IVIg for Ms. Patient.

Indeed, even in denying coverage, Arizona Benefit Options has been inconsistent, stating that IVIg is not medically necessary in January 22 and February 26 letters, but also throwing in a claim that IVIg is experimental in the February 26, 2007 denial letter, but not in January. Your November 8, 2006 Peer Reviewer Final Report discloses absolutely nothing that would lead one to believe that IVIg is experimental. Instead, that Report states that

you have used the Milliman guidelines.² These are medical necessity guidelines that do not relate at all to the question of whether a treatment is experimental.

In short, Arizona Benefit Options' change of position without reason is arbitrary and capricious, and should be reversed.

IV. CONCLUSION

IVIg taken in conjunction with a disease-modifying agent has proven to be of benefit to Ms. Patient, and is generally accepted not only in the medical community, but also by other insurance carriers. As such, its use is not experimental, and it is medically necessary in this case. Indeed, you covered this as medically necessary for a full year, and have reversed position with no explanation. For all of these reasons, we urge you to reverse your noncoverage decision. Thank you.

Sincerely,

Jennifer C. Jaff*

² It is worth noting that, although Ms. Patient requested a copy of everything on which you relied, you have not provided the Milliman guidelines. Were this an ERISA plan, transparency would be legally required. Here, although this is a State plan and, thus, is not accountable in federal courts, one would expect the State of Arizona to demand transparency in administration of its plan.

* 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.