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December 15, 2008

Aetna
Customer Resolution Team
PO Box 14002
Lexington, KY 40512

RE: Patient
Type of service: IVIg
Dates of service: To be determined (prior authorization)

Dear Sir or Madam:

I am writing on behalf of your insured, Patient, to request a second level appeal of Aetna's noncoverage decision of IVIg to treat transverse myelitis. My HIPAA release and authorization to represent Ms. Patient in this appeal is enclosed.

In sum, this is a young patient with progressive transverse myelitis (TM), which has not responded to either IV Solu-Medrol or plasma exchange (plasmapheresis). The only other treatment suggested by her doctors is IVIg. If it works, it will allow Ms. Patient to continue to live independently and productively despite her quickly progressing and debilitating TM.

Aetna takes the position that IVIg to treat transverse myelitis is experimental. However, the use of IVIg in this case is supported by the medical literature. Ms. Patient's policy provides that the exclusion of allegedly experimental or investigational treatments will not apply when the "HMO has determined that available scientific evidence demonstrates that the drug is effective or ***the drug shows promise of being effective*** for the disease." (December 5, 2008 Denial Letter, p. 3) (emphasis added). Thus, Aetna has the discretion to cover IVIg in this case based on the medical literature submitted along with extensive clinical records. Aetna should exercise this discretion in this case, in which a very young woman's life hangs in the balance, and no alternative treatments are available.

I. Ms. Patient Suffers Devastating Symptoms of TM that Demand Treatment

Patient, who is 33 years of age, became acutely ill in the Fall of 2008. Her symptoms have progressed over slightly more than three months to include urinary incontinence, a band-like back pain, spasticity, acute weakness on her right side and partial weakness on her left, numbing on the left side of her face, numbness and tingling in various

locations in her body, occasional partial paralysis of the right leg, cognitive issues including mixing words and having trouble with verbal expression, blurry vision, double vision, and floaters, decreased memory, severe myoclonus, and loss of balance and resulting falls. All of these symptoms are typical in TM. (See 10/28/2008 discharge summary).

Ms. Patient is being treated by a neurologist, a rheumatologist and immunologist, and a nephrologist. In addition to TM, she suffers from systemic illnesses including herpes (see 9/22/2008 letter from Dr. Schwartzman to Dr. Huppert), psoriasis and psoriatic arthritis and chronic kidney disease. (See 10/2/2008 discharge summary). She also has a history of shingles and Raynaud's Phenomenon. (See 9/23/08 Initial History and Physical Exam). All of her physicians believe that her underlying autoimmune illnesses have triggered the TM. Dr. Huppert, the rheumatologist and immunologist, believes that the current onset of TM is a precursor of multiple sclerosis.

Treatment to date has proven to be ineffective. While in the hospital in September 2008, Ms. Patient was given IV Solu-Medrol 1 g for each of three days, followed by oral prednisone taper starting at 100 mg and decreasing every three days. (See 10/2/2008 discharge summary). When her symptoms became more severe, Dr. Schwartzman increased the dosage to 100 mg per day again, with a much slower taper. She is still on 20 mg per day. See also instructions from Dr. Huppert on dosage of prednisone dated November 11, 2008. These months of steroid therapy did not alleviate her symptoms or slow the progression of her disease.¹

In addition, Ms. Patient has undergone two rounds of five treatments each plasma exchange or plasmapheresis. These treatments have failed to have any lasting benefit.

The only other treatment Ms. Patient's doctors have suggested is IVIg. (See December 5, 2008 note by Dr. Schwartzman requesting authorization for IVIg therapy). Ms. Patient did have five days of IVIg during the October hospitalization, as follow up to her first round of plasmapheresis. She did report some relief of her symptoms during the first 10 days or so after this treatment. She has not felt this same relief after subsequent trials of plasmapheresis, leading Dr. Schwartzman to believe that the IVIg was the contributing factor in her improvement. It is on this basis that Dr. Schwartzman has prescribed further trial of IVIg.

II. The Use of IVIg Is Supported by the Medical Literature

Aetna has denied coverage of IVIg for TM on the ground that it is experimental or investigational. However, Ms. Patient's policy provides that the exclusion of allegedly experimental or investigational treatments will not apply when the "HMO has determined that available scientific evidence demonstrates that the drug is effective or ***the drug shows promise of being effective*** for the disease." (December 5, 2008 Denial Letter, p. 3) (emphasis added). There is ample scientific evidence to support the exercise of this discretion to grant coverage in this case, even if IVIg is experimental in treating TM (which we do not concede it is).

In some sense, every treatment for TM other than IV solumedrol, which was tried and failed, is experimental. TM is so rare that there is no consensus approach to treatment

¹ In the December 5, 2008 denial letter, Aetna questions whether Ms. Patient has been tried on high doses of steroids. The enclosed clinical records establish that she has, in fact, had both IV Solu-Medrol and high doses of oral prednisone, neither of which provided relief.

when IV solumedrol fails to alleviate symptoms. C. Krishnan, et al., "Transverse Myelitis: pathogenesis, diagnosis and treatment," *Frontiers in Bioscience* 2004; 9:1483-1499. However, this is not an argument for denying all other forms of treatment. A trial of IVIg is supported by the medical literature.

First, it goes without saying, as recognized in Aetna's policy on IVIg, that IVIg is an entirely accepted treatment of other demyelinating diseases such as relapsing remitting multiple sclerosis, as well as other neurological diseases causing symptoms similar to those Ms. Patient is experiencing, like Guillain-Barre syndrome. Aetna Clinical Policy Bulletin no. 0206. In addition, IVIg is often used to treat a whole host of immune-related diseases like systemic lupus erythematosus, immune related blistering diseases; indeed, the list of accepted uses is quite long, and dances all around the fringes of TM. The entirely accepted use of IVIg for these somewhat overlapping illnesses supports the use of IVIg in this case.

TM is a devastating, progressive illness that begins with "symptoms and signs of neurological dysfunction in motor, sensory and autonomic nerves and nerve tracts of the spinal cord," and, when maximal deficit is reached, "approximately 50% of patients have lost all movement of their legs, virtually all patients have some degree of bladder dysfunction, and 80-94% of patients have numbness, paresthesias or band-like dysesthesias." D.A. Kerr, et al., Immunopathogenesis of acute transverse myelitis, *Curr Opin Neurol* 2002; 15:339-347; C. Krishnan, et al., "Transverse Myelitis: pathogenesis, diagnosis and treatment," *Frontiers in Bioscience* 2004; 9:1483-1499. TM is thought to fall into two main categories: cases in which there is an antecedent illness or infection, ranging from lupus to MS to "[s]everal of the herpes viruses" – and Ms. Patient does have herpes and recurring herpes zoster – and cases that are considered idiopathic. (Kerr, *supra*; Krishnan, *supra*) (emphasis added). The "presence of rashes, night-sweats, **oral or genital ulcers**, sicca symptoms, shortness of breath, pleuritic pain or hematuria" all are indicators of TM, and Ms. Patient has suffered from rashes and night sweats. Krishnan, *supra* (emphasis added). "Researchers believe that transverse myelitis often occurs when your body's immune system mistakenly attacks its own tissues, resulting in inflammation and injury to the myelin within your spinal cord." *Transverse Myelitis*, Mayo Clinic <<http://www.mayoclinic.com/health/transverse-myelitis/DS00854>> (accessed December 4, 2008). TM "can be the presenting feature of MS," as Ms. Patient's rheumatologists believes it is in her case. Transverse Myelitis Consortium Working Group, "Proposed diagnostic criteria and nosology of acute transverse myelitis," *Neur* 2002; 59: 499-504.

The weight of authority holds that, because "[t]here is currently no treatment that has been clearly shown to modulate the outcome" of TM, due to the "varied immunopathogenesis, it may be that distinct treatment options need to be employed for different subsets of ATM patients." Kerr, *supra*. The Mayo Clinic cautions that treatment may depend on the patient's specific complications and symptoms; "[t]reatment can be tailored to fit your needs," *Transverse Myelitis*, Mayo Clinic <<http://www.mayoclinic.com/health/transverse-myelitis/DS00854>> (accessed December 4, 2008). The National Institutes of Health state that, because there is no effective cure, "[f]ollowing initial therapy, the most critical part of the treatment for this disorder consists of keeping the patient's body functioning while hoping for either complete or partial spontaneous recovery of the nervous system." National Institute of Neurological Disorders and Stroke, NINDS Transverse Myelitis Information Page, <http://www.ninds.nih.gov/disorders/transversemyelitis/transversemyelitis.htm?css=print> (accessed December 4, 2008).

IVIg is considered by some to be an equally useful alternative to IV steroids or plasmapheresis. See, e.g., *Acute Transverse Myelitis*, Children's Hospital Boston

<http://www.childrenshospital.org/az/Site794/printerfriendlypageS794PO.html> (accessed on December 2, 2008). Thus, Marchioni, et al. found that several forms of myelitis "showed a good response to intravenous immunoglobulin (IVIg) after steroid treatment failure." E. Marchioni, et al., "Effectiveness of intravenous immunoglobulin treatment in adult patients with steroid-resistant monophasic or recurrent acute disseminated encephalomyelitis," *J. Neurol* 2002; 249:100-104. Similarly, Yuichiro, et al. concluded that a patient with TM "excellently responded to IVIg while methylprednisolone pulse therapy was not effective." I. Yuichiro, et al., "Reversible stenosis of large cerebral arteries in a patient with combined Sjogren's syndrome and neuromyelitis optical spectrum disorder," *Rheumatol Int* 2008; 28:1277-1280. IVIg has proven to be effective in treating TM accompanied by mixed connective tissue disease. S. Bhinder, et al., "Transverse myelitis, a rare neurological manifestation of mixed connective tissue disease – a case report and a review of literature," *Clin Rheumatol* 2007; 26: 445-447. And IVIg along with IV methylprednisolone was effective in treating a severe case of TM in a child. LF Fonseca, et al., "Early-onset acute transverse myelitis following hepatitis B vaccination and respiratory infection: case report," *Arq Neuropsiquiatr* 2003; 61(2A):265-268. Finally, a large study showed that, although IVIg alone was not more effective than steroids or plasma exchange, plasma exchange followed by IVIg is quite effective in treating TM. H. Murai, et al., "Effect of immunotherapy in myelitis with atopic diathesis," *J. Neurol Sci* 2004; 227: 39-47. Indeed, in Ms. Patient's case, the only real (albeit temporary) relief she has felt was during the 10 days or so following five days of IVIg after plasmapheresis during the October hospitalization.

Time is very much of the essence for treating TM. "Recovery from transverse myelitis usually begins within 2 to 12 weeks of the onset of symptom and may continue for up to 2 years. However, if there is no improvement within the first 3 to 6 months, significant recovery is unlikely." National Institute of Neurological Disorders and Stroke, NINDS Transverse Myelitis Information Page, <http://www.ninds.nih.gov/disorders/transversemyelitis/transversemyelitis.htm?css=print> (accessed December 4, 2008). Ms. Patient's case is progressing rapidly, beginning in September with slight symptoms – primarily, urinary incontinence – that have become increasingly severe and disabling. Since the only other treatments suggested for TM – steroids and plasmapheresis – have been tried and failed, Aetna should allow a trial of IVIg in an effort to stem the progression of this disease.

In short, since everything that has been tried has failed, and everything that has not been tried would be considered experimental by Aetna, the literal application of Aetna's policy regarding IVIg would mean denying Ms. Patient any treatment at all. This is unacceptable. Ms. Patient is 33 years old. If IVIg were to work, she would retain her ability to walk and engage in the activities of daily living. Without the IVIg, we know that her condition will worsen and, as is the case in TM patients who are not treated successfully, she will develop some degree of paralysis. Since "the pathogenesis of TM is believed to be immune-mediated," "in TM patients, it is likely that there is abnormal activation of the immune system" Krishnan, *supra*. Thus, it is equally likely that normalization of the immune system may well resolve Ms. Patient's symptoms and stem the tide of disease progression.

In sum, there is ample scientific evidence to support the conclusion that IVIg "shows promise of being effective" in this case. Not only has Ms. Patient already been shown to respond to a combination of plasmapheresis and IVIg, but there is ample medical literature to support the use of IVIg in treating steroid-resistant TM. Therefore, the noncoverage decision should be reversed.

III. Conclusion

In sum, IVIg should be covered. Steroid therapy has been tried and failed. Plasmapheresis alone has been tried and failed. The only relief Ms. Patient has experienced was during approximately 10 days after treatment with IVIg after plasmapheresis. This empirical evidence, when taken with the medical literature cited above, establishes that IVIg "shows promise of being effective." Under the terms of Ms. Patient's policy, Aetna has the discretion to approve the use of IVIg here. Without effective treatment, Ms. Patient's medical bills for rehabilitation, physical therapy, and other needs will skyrocket far beyond the cost of IVIg. Thus, it is in both Aetna's interest and Ms. Patient's to try further IVIg therapy.

Of course, if you would like any additional information, please do not hesitate to contact me. Thank you.

Sincerely,

Jennifer C. Jaff*

* Admitted to practice law in Connecticut, New York and the District of Columbia. Advocacy for Patients is a 501(c)(3) tax-exempt organization and does not charge patients for its services. Advocacy for Patients is funded by, among other sources, grants from foundations and companies that engage in health care-related advocacy, manufacturing, delivery and financing. A list of grantors will be furnished upon request.