To Whom It May Concern:

I am writing to request coverage for Pegasys (peginterferon alfa-2a) for my patient \_\_\_\_\_\_\_\_\_\_. \_\_\_\_\_’s therapy would include injecting 45mg (0.25ml) subcutaneously every week. This letter documents the medical necessity for this therapy in the treatment of myelofibrosis that requires immediate treatment, and provides information about the patient’s medical history and treatment.

Pegasys (peginterferon alfa-2a) is a covalent conjugate of recombinant alfa-2a interferon. Interferons bind to specific receptors on the cell surface, initiating intracellular signaling via a complex cascade of protein-protein interactions leading to rapid activation of gene transcription. Interferon inhibits viral entry into cells and inhibits viral replication, followed by activating natural killer cells that destroy infected cells and alert others. A recent study showed that Pegasys induces complete hematologic remissions in patients with myeloproliferative neoplasms (myelofibrosis). Pegasys therapy achieves this by attaching a polyethylene glycol molecule to regular IFN-α. This significantly prolongs its presence in blood and provides extended activity over one week. It also increased participants’ compliance because it is conveniently given at home once a week by self-injection of a pre-filled syringe. It was also noted that toxicities were less pronounced and happened less often than with regular IFN-α.

Myelofibrosis (MF) is a myeloproliferative neoplasm (MPN) known to be associated with dysregulated JAK1 and JAK2 signaling.

In 1982, the FDA issued a Drug Bulletin addressing the prescribing of medication for “unlabeled” or off-label uses. The FDA itself states that the Food, Drug, and Cosmetic Act “dos not, however, limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such “unapproved” or, more precisely, “unlabeled” uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature.

The term, “unapproved uses” is, to some extent, misleading. It includes a variety of situations ranging from unstudied to thoroughly investigated drug uses. Valid new uses for drugs already on the market are often first discovered through serendipitous observations and therapeutic innovations, subsequently confirmed by well-planned and executed clinical investigations. Before such advances can be added to the approved labeling, however, data substantiating the effectiveness of a new use or regimen must be submitted by the manufacturer to the FDA for evaluation. This may take time and, without the initiative of the drug manufacturer whose product is involved, may never occur. For that reason, accepted medical practice often includes drug use that is not reflected in approved drug labeling. If the FDA itself states that its labeling is not intended to limit the prescribing of medications for off-label uses, then insurers should not be permitted to refuse coverage of off-label uses solely based on the fact that the use is off-label. Clearly, such a result would run contrary to the FDA’s own intent regarding the effect of its labeling.

With respect to its role in medical practice, the package insert is informational only.

Pegylated formulation of IFN-2α (Pegasys) appears to be a promising improvement both in potency and tolerability in the MF population [Ianotto *et al*. 2009]: an important milestone given that interferon may also be the unique conventional therapeutic agent that can reverse and/or retard progression of bone marrow fibrosis [Silver *et al*. 2011]. Pegasys appears to be a unique agent that can, over time, significantly decrease JAKV617F clonal burden and induce complete molecular responses with prolonged drug exposure [Kiladjian *et al*. 2008]. A great deal is known about the pleiotropic actions of interferons generally, but their effects on the particular pathway(s) of interest in MPN are not well understood [Kiladjian *et al*. 2011]. Interferons act directly on hematopoietic stem and progenitor cells, and are well known clinically to induce cytopenias.

In my clinical judgment, Pegasys therapy would provide significant clinical benefit for \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_. Pegasys is medically necessary and appropriate to treat \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ at this stage in his/her course of care. I am enclosing documentation supporting the medical necessity for Pegasys for this patient. I urge you to provide coverage at this time. Please contact me at (XXX) XXX-XXXX if you require additional information or would like to discuss the case in greater detail.

Sincerely,

References

Ianotto JC, Kiladijan JJ, Demory JL, et al. PEG-IFN-α-2a therapy in patients with myelofibrosis. British Journal of Haematology 2009; 146(2): 223-225. <<[Link to Article](http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2009.07745.x/full)>>

Kiladjian JJ, Cassinat B, Chevret S, et al. Pegylated interferon-alfa-2a induces complete hematologic and molecular responses with low toxicity in polycythemia vera. Blood 2008; 112(8): 3065-3071. <<[Link to Article](http://www.bloodjournal.org/content/112/8/3065.full-text.pdf+html)>>

Kiladjian JJ, Mesa RA, Hoffman R. The renaissance of interferon therapy for the treatment of myeloid malignancies. Blood 2011; 117(18): 4706-4715. << [Link to Article](http://www.bloodjournal.org/content/117/18/4706.full-text.pdf+html)>>

Silver RT, Vandris K, Goldman JJ. Recombinant interferon-α may retard progression of early primary myelofibrosis: a preliminary report. Blood 2011; 117(24): 6669-6672. << [Link to Article](http://www.bloodjournal.org/content/bloodjournal/117/24/6669.full.pdf)>>