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Year 2024 Coverage Letter of Support

VIA ELECTRONIC TRANSMITTAL

Medical Care Professional overseeing the care of your patient affected by (autoimmune) Pulmonary Alveolar Proteinosis (PAP),

This letter is provided to assist in your communication with insurance and other coverage providers with respect to approval of coverage/reimbursements for inhaled granulocyte-macrophage colony-stimulating factor (GM-CSF) treatment for the patient in your care who is affected by (autoimmune) Pulmonary Alveolar Proteinosis (PAP).

As you know, Pulmonary Alveolar Proteinosis (PAP) is a rare lung syndrome that affects about 7 out of every 1 million people in the global population. The PAP Foundation is on the leading edge of PAP therapies and research, and helps coordinate communication and share information by and among clinicians, researchers, practicing physicians and the PAP-patient community. As such, we have deep and unique optics into the syndrome, its treatment and the people impacted by PAP.

A simplified description of PAP and its symptoms can be found on our website: https://www.papfoundation.org/faq

Specifically as to inhaled GM-CSF therapy and those impacted by PAP, we have seen significant improvement in the quality of life of our PAP-patient population as well as a material increase in time between Whole Lung Lavage (the current standard of care for PAP treatment) for many of those who maintain properly dosed and administered GM-CSF therapy.

In the analysis directed to coverage providers, key issues to understand and consider in the context of GM-CSF treatment for PAP-patients include:

Initial Benefits to Patient

With proper GM-CSF dosing (i.e., some patients require more than 250 ug/day), after +/-3 months of treatment, the positive impact can manifest through the decrease in unabsorbed lung surfactant.

GM-CSF is understood to *differentiate* alveolar macrophages, allowing them to clear the lungs from naturally occuring lung surfactant (the *laundry detergent*-like lipids that remain in the lungs of PAP-patients.) Surfactant is not cleared in PAP-patients as their alveolar macrophages fail to *differentiate* when deprived of naturally occurring GM-CSF due to an abnormally high level of **anti GM-CSF antibodies** in their system.

With increased surfactant clearance resulting from proper GM-CSF treatment, quality of life can dramatically improve and as such helps PAP-patients' lungs function in a more normal manner, allowing for greater tolerance of physical movement, breathing and exertion with lessened levels of breathlessness and distress.

Long(er) Term Benefit to Patient

The current standard of care for PAP treatment is to conduct regularly recurring Whole Lung Lavage (WLL), a procedure that *washes out the lungs* of excess surfactant; yet this surgery does **nothing** to treat the lungs or the underlying PAP syndrome.

With increased surfactant clearance resulting from proper GM-CSF treatment, time between WLL can be dramatically increased (or in optimal circumstances, entirely eliminated) as this therapy, so long as it is maintained, is understood to allow PAP-patients' lungs to operate in a more normal manner, specifically with respect to surfactant clearance.

Without intervention, **surfactant consistently builds and festers in the lungs**, with PAP-patients being in a state of perpetual degradation, potentially causing other harmful issues and medical complications, including an elevated risk of certain life-threatening lung infections (e.g., bacterial pneumonia, mycobacterium avium-intracellulare infection, or fungal infections).

WLL itself is a highly invasive surgical procedure fraught with risk and the potential for dangerous complications. WLL involves application of paralyzing general anesthesia to the patient, often maintained for 3 to 6 hours, while a double lumen tube is inserted into the patient's lungs. One lumen is sealed into a ventilated lung while the other is inserted in the other lung that is subsequently filled (under low pressure) with a saline fluid, drained, and repeated multiple times until the drained fluid presents as clears. **The range of potential complications during and after the WLL procedure are voluminous**, and include the possibility of heart failure, saline leakage into the ventilated lung (i.e., drowning), lung

collapse, brain damage, and adverse reaction and/or complications to (immediate and prolonged) general anesthesia usage (as untreated PAP-patients can need constantly recurring WLLs for life).

Finally, by eliminating (or lessening) WLL, PAP-patients avoid numerous days in the hospital (pre and post procedure), time away from work, and standard recovery pain and complications that last for one to two weeks following each WLL.

Continuing Benefit to Insurance Provider

By coverage of inhaled GM-CSF treatment to PAP-patients, insurance providers are able to potentially avoid some or all costs and complications associated with (1) very expensive and consistently reoccuring WLL procedures (the current standard of care for PAP) and (2) potentially life threatening risks and complications from (i) consistent WLL procedures and (ii) high-levels of surfactant maintained in PAP-patients' lungs absent an effective therapy to reduce surfactant build-up. Similarly, costs could be minimized for other effects of uncontrolled PAP such as the cost of continuous oxygen supplementation therapy.

Anticipation of FDA Approval

As indicated above, we have seen significant improvements in the quality of life of our PAP-patient population as well as a material increase in time between WLL in many of those who maintain properly dosed and administered GM-CSF therapy.

Savara Pharmaceuticals [https://savarapharma.com/] has initiated and completed enrollment of its "Impala-2" Phase 3 clinical trial of inhaled GM-CSF treatment for autoimmune PAP with its drug Molgradex [with the results of an earlier Impala trial showing efficacy in terms of improvements in pulmonary gas transfer and functional health status as published in the New England Journal of Medicine on October 22, 2020] and was granted Breakthrough Therapy designation for Molgradex by the FDA. This is in addition to a number of international trials, most notably in Japan, using inhaled GM-CSF in autoimmune PAP showing significant positive response rates in at least 60% of patients. In light of Savara's efficacious clinical trial coupled with our own positive experience with GM-CSF treatment and the internationally published peer-reviewed data, we believe that FDA approval of inhaled GM-CSF is simply a matter of time. Upon FDA approval, insurance coverage should no longer be an issue.

Pending the approval of inhaled GM-CSF for use by aPAP patients in the United States by the FDA, many of our aPAP patient population utilizes **Leukine** (sargramostim) off-label[1]. The maker of Leukine, Partner Therapeutics, can provide assistance in obtaining such drug through their Leukine Direct program:

https://www.leukine.com/patient-assistance/#
Phone: 877-353-8546

The assistance provided can include benefit verification, coverage information, general inquiry assistance, and copay assistance.

*Technical Note: The FDA National Drug Codes (NDC) for **Leukine** products have recently changed:*

71837-5843-05 (package code; includes 5 vials)
71837-5843-01 (product code; single vial)

Please feel free to contact us with any questions.
We can best be reached by email at info@papfoundation.org

Sincerely,

PAP Foundation, Inc.

[1] On April 3, 2024, Partner Therapeutics, Inc. (PTx) announced that its partner Nobelpharma received approval from the Japanese Pharmaceuticals and Medical Device Agency (PMDA) for the inhaled use of Leukine (sargramostim), branded in Japan as Sargmalin, to treat aPAP.
https://www.prnewswire.com/news-releases/partner-therapeutics-leukine-sargramostim-receives-approval-in-japan-to-treat-autoimmune-pulmonary-alveolar-proteinosis-apap-302107763.html