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To Whom It May Concern,

We are writing to you today to provide information about everolimus (brand name Afinitor®, Novartis) and its impact on the tuberous sclerosis complex (TSC) community. Following a series of innovative clinical trials using either everolimus or its sister compound sirolimus (brand name Rapamune®, Pfizer) published in the *New England Journal of Medicine*¹ followed by a definitive double-blind, randomized placebo-controlled trials^{2,3}, Afinitor® was approved on April 26, 2012 to treat TSC-associated kidney angiomyolipomas (AMLs). These studies, paired with our constituents' personal stories, show the global benefits of this class of compounds for kidney AMLs.

More recently, on December 9, 2019, PAR Pharmaceuticals received FDA approval through an Abbreviated New Drug Application (ANDA) to market generic everolimus.

Kidney AMLs are noncancerous growths that first appear in childhood. By 18 years of age, more than 80% of individuals with TSC will have at least one AML with many having two or more. AMLs are characterized by their eponymous amalgamation of fat, smooth muscle and abnormal blood vessels with the latter presenting the highest risk for complications. AMLs, however, continue to grow through the lifespan. If left untreated, AMLs can cause permanent, irreversible damage to the kidneys and risk death. Successful treatment with Afinitor® prevents the AMLs from further enlarging and, in many cases, induces shrinking. This mitigates many of the anticipated consequences including progressive loss of kidney function and spontaneous rupture and hemorrhage with, at the extreme, may require urgent nephrectomy.

It has come to our attention that many constituents of the TSC Alliance are unable to fill their prescriptions for Afinitor®. We would like to explain the urgency and rationale for using Afinitor® (everolimus) within the TSC community for kidney AMLs, where the benefits outweigh the risks. We will also outline the barriers to treatment facing our constituents and urge you to work with us to ensure these patients receive treatment exactly as prescribed by their physicians.

The TSC community has experienced positive outcomes and improved quality of life with the approval of Afinitor®. However, we have recently noticed barriers-to-access

Hope no matter how complex



that limit our constituents' ability to adequately manage their disease, including the following:

1. With the recent availability of generic everolimus, commercial insurance companies have begun refusing to give prior authorization (PA) on the Afinitor® brand name prescription, even of renewed prescriptions for patients currently using and being effectively treated by Afinitor®. This has interrupted the continuity of care for patients who are established users of brand everolimus (Afinitor®). Doctors are forced to hold or discontinue everolimus. Like all oral kinase inhibitors, sudden discontinuation of Afinitor® can cause rebound regrowth of the AMLs to greater than pre-treatment size with a significant risk for adverse complications as outlined above. This issue is complicated further by the fact that each state has individual regulations in place regarding formulary restrictions
2. Co-payment assistance programs limiting their support to only patients who are part of the indicated demographic as outlined on the label, despite the physician's determination that Afinitor® is the best course of treatment, at times even when a patient outside the indicated demographic has been successfully treated with brand everolimus (Afinitor®).
3. Unauthorized generic substitution, owing to subtle differences in excipient content, has the potential for unintended consequences in the management of kidney AMLs. Everolimus dosing is managed through checking levels with established on- vs. off-target effect ratios at various Afinitor® doses. Specific concerns revolve around the threshold for the emergence of side effects relative to measured drug levels with generic use.
4. General dispensing delays due to miscommunication, clerical errors and shipping errors specific to the specialty pharmacies that distribute everolimus. While some gaps related to human errors can be avoided, systems-based errors such as inclement weather affecting shipping cannot. In the past, these delays could be circumvented by distributors offering bridge supplies of Afinitor® through patient assistance programs, but due to the changing environment, there may no longer be any backup methods for patients to access their medications. As abrupt discontinuation can be accompanied by significant adverse events as described above, slight changes to distribution can have the potential to avert such complications.

In short, the TSC community depends on Afinitor® for the management of kidney angiomyolipomas. Unfortunately, with the introduction of generics, which should have improved accessibility and affordability of treatment, it has only become more difficult for our constituents to access and pay for this life-altering therapy, which is the only approved medical therapy for this indication.

We hope you will work with us to reduce the barriers facing our community. We are happy to provide you with more information and ideas for moving forward. Please do not hesitate to contact me or Jo Anne Nakagawa, Director of Clinical Projects and TSC

Clinic Liaison at the TSC Alliance, for any additional queries. Jo Anne can be reached directly at jnakagawa@tscalliance.org or 240-638-4654.

Thank you for your consideration and commitment to our community. We hope this detail clarifies both our perspective and the importance of our community's access to stable and consistent care.

In gratitude,



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¹Bissler JJ, McCormack FX, Young LR, Elwing JM, Chuck G, Leonard JM, Schmithorst VJ, Laor, T, Brody AS, Bean J, Salisbury S and Franz DN. 2008. Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangiomyomatosis. *New Engl J Med* **358(2)**: 140-151.

²Franz DN, Belousova E, Sparagana S, Bebin EM, Frost M, Kuperman R, Witt O, Kohrman MH, Flamini JR, Wu JY, Curatolo, P, de Vries PJ, Whittemore VH, Thiele EA, Ford JP, Shah G, Cauwel H, Lebwohl D, Sahnoud T and Jozwiak S. 2013. Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicenter, randomized, placebo-controlled phase 3 trial. *Lancet* **381**: 125-32.

³Bissler JJ, Kingswood JC, Radzikowska E, Zonnenberg BA, Frost M, Belousova E, Sauter M, Nonomura N, Brakemeier S, de Vries PJ, Whittemore VH, Chen D, Sahnoud T, Shah G, Lincy J, Lebwohl D and Budde K. 2013. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangiomyomatosis (EXIST-2): a multicenter, randomized, double-blind, placebo-controlled trial. *Lancet* **381**: 817-24.