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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 November 1, 2010 to treat TSC-associated subependymal giant cell astrocytomas (SEGAs). These studies, paired with our constituents' personal stories, show the global benefits of this class of compounds for SEGAs.

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

SEGAs are noncancerous tumors that appear on the linings of the ventricles of the brain. SEGAs typically appear in childhood or adolescence and affect up to 15% of all individuals with TSC; existing SEGAs have continued growth potential through adulthood, but new SEGAs are unlikely to develop after the age of 25. As SEGAs grow, they get intertwined with the nearby brain tissue. Untreated, SEGAs can prove fatal due to the induction of hydrocephalus through extension into and subsequent occlusion of the ventricle. SEGAs frequently can be surgically removed if caught early. But as they grow, due to being enmeshed with the nearby tissue, surgery can be risky, which can be life-ending if not impossible. In these cases, Afinitor® can mitigate further invasion as well.

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 SEGAs, 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.

Hope no matter how complex



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 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 SEGAs 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 SEGAs. 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 SEGAs. 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, 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@tsalliance.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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¹Krueger DA, Care MM, Holland K, Agricola K, Tudor, C, Mangeshkar P, Wilson KA, Byars A, Sahmoud T and Franz DN. 2010. Everolimus for subependymal giant cell astrocytomas in tuberous sclerosis. *New Engl J Med* **363(19)**: 1801-11.

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, Sahmoud 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, Sahmoud 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.