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May 21, 2021

Dr Benedikt Huttner,
The Secretary of the Expert Committee on the Selection and Use of Essential Medicines
Medicines Selection, IP and Affordability (MIA)
Department of Health Products Policy and Standards (HPS)
20 Avenue Appia
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Sent via email: emlsecretariat@who.int

Re: Comments on the application for the inclusion of tacrolimus in the WHO (World Health Organization) model list of essential medicines entitled "Review of the Available Evidence on Tacrolimus in Adults and Children for the Prevention and Treatment of Transplant Rejection, and Proposal for Inclusion."

Dear Dr Huttner:

Astellas Pharma, Inc. (Astellas) is dedicated to improving the health of people around the world through the provision of innovative and reliable pharmaceutical products. As a manufacturer and distributor of tacrolimus, Astellas appreciates the opportunity to submit comments to the review document recommending the inclusion of tacrolimus in the class of immunomodulators in the WHO Model List of Essential Medicines for the therapeutic indication, prophylaxis of transplant rejection in adults and children allograft recipients.

Astellas believes that the WHO Essential Medicines List should continue to be used for the purpose it was originally created for; to serve as a guide for countries in making their own decisions about the medicines in their own formularies and appropriate procurement of those medicines.

Tacrolimus is available in differing formulations in over 100 countries and has been available for use for 28 years. Our comments today focus on providing the Expert Committee with additional information regarding the use, effectiveness and potential benefit of tacrolimus, while also further clarifying some of the statements contained within in the application.

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Calcineurin inhibitors (CNIs) and long-term outcome:

With the introduction of CNIs, patient and graft survival rates have improved. 1-year graft survival currently exceeds 80%. Whilst survival rates do gradually decline over the long term, in kidney transplant, 5- and 10-year graft survival rates in Europe are 77% and 56%, and for liver transplant, 64% and 54% (Neuberger et al[1]). "These survival rates are affected by and vary with patient non-adherence[1], intra-patient variability of exposure[2,3], anti-body mediated rejection (ABMR)[4], and sub-optimal immunosuppression[5]. Thus, although consideration has been given to clinical trials and systematic reviews, we would recommend including additional review of published data from long-term follow up, e.g., registry data[6].

Tacrolimus as a CNI

In current clinical practice ≈ 90% of indicated transplant recipients are treated with tacrolimus based immunosuppression[7,8]. Although, tacrolimus is a core component of immunosuppressive (IS) therapy, during the early post-transplant period, it is combined with other IS medications e.g., mycophenolate mofetil, azathioprine, mTORS, and/or steroids and/or an induction agent (either basiliximab or anti-thymocyte globulin).

Indications and Formulations

Tacrolimus is available in various formulations such as immediate release capsules, immediate release granules for pediatric use, and prolonged release tablets and capsules. All these formulations are available in varying dose strengths or patients with unique needs.

The approved indications for different formulations vary in different regions. Immediate release (IR) tacrolimus is approved for; prophylaxis of transplant rejection in liver, kidney or heart allograft recipients (adult and children) and treatment of allograft rejection resistant to treatment with other IS medicinal products.

Prolonged releases (PR) tacrolimus is approved for: Prophylaxis of transplant rejection in adult kidney or liver allograft recipients and treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients.

It is also important to know that in some regions, PR tacrolimus have the same indication as IR tacrolimus i.e., adults and paediatrics (e.g., Australia).

Multiple formulations of tacrolimus are necessary to enable optimisation of therapy on an individual patient basis e.g., IR granules fulfil an unmet medical need for patients with inability to swallow intact capsules, such children. Alternatively, PR capsules would be an option to decrease intra-patient variability and non-adherence in specific patient population.

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It should be noted that prescribing information needs to be carefully referenced before prescribing tacrolimus, as the risks and benefits of individual indications should be carefully weighed by the prescribing medical professional.

Dosing guidelines

Tacrolimus is classified as a narrow therapeutic index (NTI) medication[9]. Comparatively slight differences in tacrolimus dose or concentration may result in decreased efficacy (e.g., rejection episodes[10-11]) or increased side effects (e.g., nephrotoxicity[12], risk of malignancy[13] and infection, including viral reactivation[14]). Therefore, tacrolimus therapy requires careful monitoring to maintain systemic exposure in a narrow therapeutic range. This means that tacrolimus is not a dose-based therapy but a concentration-controlled drug. It is therefore important to point out that the recommended doses are only initial starting doses, all subsequent doses are individualised based on target trough levels. Furthermore, the initial dosing recommendations vary in different region and clinical practice. It is also important to state that low exposure (<5 ng/mL) is usually associated with increased risk of graft loss and dnDSA development[15,5]

2017 NICE guidance for kidney transplant in adults

The application references a 2017 NICE guidance which evaluated, in part, the perceived clinical and cost-effectiveness between IR and PR tacrolimus. It should be noted that several clinical studies demonstrating the superiority of PR tacrolimus capsules in reduced intra-patient variability[16,17], improved adherence[18], improved long-term renal function[19,20] the long-term graft survival is not included in this review. We would recommend these additional data be considered.

Cost effectiveness of tacrolimus

A number of publications on better graft function/survival with PT tacrolimus capsules are missing from the narratives[6,16-20]. Absence of discussion on these data may present an incomplete picture when evaluating cost-effectiveness.

Summary of regulatory status and market availability of tacrolimus

In the European region tacrolimus was first approved in 1994 (UK, MHRA for liver and kidney transplantation). In 2007, PR tacrolimus capsules were approved, whereas in 2009 the IR tacrolimus granules were approved. The use of tacrolimus ointment (Protopic) in 2002 was for a non-transplant indication.

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Astellas hopes these comments will be useful to the WHO EML Expert Committee on the Selection and Use of Essential Medicines as it evaluates the application for inclusion of tacrolimus on the WHO Model List of Essential Medicines. We would welcome the opportunity to discuss these comments with the Expert Committee should that be required.

Sincerely,

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References

1. Neuberger et al, Transplantation, April 2017, Volume 101, Number 4
2. Süsal et al, Am J Transplant. 2019;1–9.
3. Del Bello A, et al World J Gastroenterol. 2018 Apr 28;24(16):1795–1802
4. Sellarés J et al. Am J Transplant 2012;12;388–399
5. Wiebe et at, Am Soc Nephrology, 2017
6. Adam R, Transplantation 2019, online DOI: 10.1097/TP.0000000000002700
7. Kim WR, et al. OPTN/SRTR 2013 Annual Data Report: Liver. Am J Transplant. 2015;15 Suppl 2:1-28; 2:
8. Matas AJ, et al. OPTN/SRTR 2013 Annual Data Report: Kidney. Am J Transplant. 2015;15 Suppl 2:1-34
9. EMA/618604/2008 Rev. July 2010, EWP of the CHMP.
10. Hricik DE et al, Journal of the American Society of Nephrology : JASN. 2015.
11. Israni AK, et al.: official journal of the European Society for Organ Transplantation. 2013;26(10):982-989.
12. Randhawa PS, et al The American journal of surgical pathology. 1993;17(1):60-68.
13. Carenco C, et al. Am J Transplant. 2015;15(3):678-686.
14. Cosio FG, et al Transplantation. 2007;83(4):411-416.
15. Opelz G, Tacrolimus trough levels and kidney graft survival. Newsletter 1: 2014. Available at: www.ctstransplant.org/public/newsletters/2014/png/2014 Accessed October 2015
16. Wu MJ, et al. Transplantation 2011;92(6):648–52
17. Stifft F, et al. Transplantation 2014;97(7):775–80
18. Kuypers DRJ et al. Transplantation 2013;95:333–340.
19. Spagnoletti G, et al. Transplant Proc 2014;46(7):2224–7
20. Silva et at, Transplantation 2014

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