19 January 2016

Dr Margaret Helliwell
Vice chair
National Institute for Health and Care Excellence
10 Spring Gardens
London SW1A 2BU

Dear Dr Helliwell,

**Re: Final Appraisal Determination – Multiple Technology Appraisal**
**Immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85) (ID 456)**

Astellas wishes to appeal against the above FAD, in relation to prolonged-release tacrolimus, which concludes that:

*1.4 Rabbit anti-human thymocyte immunoglobulin, prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept are not recommended to prevent organ rejection in adults having a kidney transplant.*
*The Appraisal Committee was unable to make recommendations on these technologies to prevent organ rejection in adults having a kidney transplant who have:*

- *biopsy-proven nephrotoxity associated with calcineurin inhibitors or*
- *biopsy-proven thrombotic microangiopathy.*

Astellas appeals under two grounds:
Ground 1a: In making the assessment that preceded the recommendation, NICE has failed to act fairly and
Ground 2 The recommendation is unreasonable in the light of the evidence submitted to NICE.

The supporting case for each ground is set out as follows:

**Ground 1a: In making the assessment that preceded the recommendation, NICE has: failed to act fairly**
**1a.1 Inconsistent selection of study populations during systematic review biases the results of the AG model unfairly against prolonged release tacrolimus contrary to section 3.5.3 of NICE Process Guide**

- Astellas contends that the Assessment Group (AG) failed to consistently apply selection criteria (as outlined in section 3.2.1 of NICE's *Guide to the Methods of Technology Appraisal* (2013) [Methods Guide]), specifically in relation to study populations during the systematic review of data for prolonged-release tacrolimus and, as a consequence, relevant studies were excluded without proper reasoning and not considered by the Appraisal Committee (AC). This led to the evidence not being synthesised in a transparent way.
    - In considering the evidence the AG excluded two key studies (Silva et al 2007 and Albano et al 2013), citing both as being unrepresentative of the NHS

population, which recruited patients from Canada, North America, Brazil and Europe, yet included a study (Tsuchiya 2013) which recruited predominantly Japanese patients. At the first AC meeting, it was communicated that the 11 remaining studies were representative of the NHS population; however, Astellas would contend that exclusion of Silva and Albano is unfounded, based on an unfair application of the selection criteria.

- Due to the procedurally unfair approach taken to selecting evidence by the AG, the AC has failed adhere to Section 3.7.25 of the Process Guide and by exclusion of data to Section 3.1.1 of the Methods Guide which states '*Consideration of a comprehensive evidence base is fundamental to the appraisal process.* As a consequence, the conclusion reached by the AG regarding the efficacy of prolonged-release tacrolimus and considered by the AC is biased and misleading. Inclusion of Tsuchiya and the exclusion of Silva and Albano also questions the external validity/generalisability of the AC's recommendations to the UK population, within the context of NICE's methods guide.
- It is important to note that had appropriate consistent selection criteria been applied and studies with populations relevant to the NHS patient population included (e.g. Silva and Albano) different clinical and economic outcomes would have resulted, showing clinical and cost effectiveness for prolonged-release tacrolimus.

**1a.2 Inconsistent calculation of price of tacrolimus formulations in the AG model that does not represent the true cost of tacrolimus to the NHS (NICE Process Guide 3.5.3)**

- The AG assumed that tacrolimus was prescribed only in secondary care and has unfairly failed to acknowledge that the majority of tacrolimus is prescribed in primary care. The use of eMIT data to determine drug prices for the AG reference case was therefore inappropriate. NICE's own Methods Guide recommends in Section 5.5.3 that "*For medicines that are predominantly prescribed in primary care, prices should be based on the Drug Tariff*."
- Astellas acknowledges that a proportion of prescribing is through the hospital at Commercial Medicines Unit (CMU) agreed discounted prices; however, these were also not fairly reflected in the reference case (issues raised in the process in relation to omissions in outsourced pharmacy, homecare and incomplete hospital data and not addressed by AG) or the scenario analyses.
- In the List price scenario the AG used the lowest possible per mg price for a single dose pack combination (50 pack of 5mg Adoport). This is clinically inappropriate given that, as a narrow therapeutic index medication with 'prescribe by brand' mandated by MHRA and requirement for therapeutic drug monitoring, tacrolimus dose can only be titrated to a target exposure on a per-patient basis using the variety of dose forms available. Therefore any calculation must reflect all the dose forms used in clinical practice, as reflected in the eMIT calculation.
- Had the Drug Tariff prices (April 2015, reported in prescription cost analysis (PCA)) been used, weighted by the proportions of the dose/pack forms actually used in practice (the method used by AG for the reference case) the per mg price for immediate-release tacrolimus can be observed as £1.51 whereas that for prolonged-release tacrolimus is £1.24.

Without prejudice to the specific clinical efficacy objections raised here, application of Drug Tariff reference pricing would have led to a deterministic ICER for prolonged-release tacrolimus of £1615 per QALY, from which a substantially different conclusion is likely to have been drawn by the AC. This inconsistency of approach is manifestly unfair and has led to a flawed assessment.

**Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE**

**2.1 Failure by the AC to appropriately handle the available data leading to a manifestly wrong conclusion being drawn that prolonged-release tacrolimus is inferior to immediate release tacrolimus.**

Astellas contends that there is no proper evidentiary basis for the AC's conclusion that prolonged release tacrolimus is inferior to immediate release tacrolimus.

- This conclusion is in sharp contrast with the position provided in FAD section 4.62 to the effect that there '*were no consistent differences between immediate and prolonged-release tacrolimus'.* This is in contrast with the point estimates used in the model, leading to an apparent difference.
- A meta-analysis using only the efficacy results from a single RCT (Kramer) is inappropriate, invalid and cannot be classed as meta-analysis, a statistical technique for combining data from multiple studies.
- Inappropriate interpretation of data derived from the Kramer study which underpinned the numerical (but not statistically significant) differences in the AG model is unreasonable as no RCT evidence has shown superiority in graft survival for either immediate-release tacrolimus or prolonged-release tacrolimus.
- It is inappropriate to extrapolate data from a single RCT of 24 weeks' duration (Kramer et al 2010) to a model horizon of 50 years including extrapolation of statistically insignificant efficacy data to infer a clinically and economically significant difference.
- Use of numerically different secondary endpoints for safety extrapolation out to the same 50 year time point and emphasis on those safety endpoints for 49 years out of 50 in the model is also inappropriate.
- Regulatory Authorities consider efficacy and safety profile of these products to be therapeutically equivalent, as specified in the products' SmPCs. Were the safety profile for Advagraf (prolonged-release tacrolimus) to be considered unfavourable as compared with the immediate release tacrolimus, the Committee for Medicinal Products for Human Use ("CHMP") would not have adopted a favourable scientific opinion. The AC/AG assessment appears to be diametrically opposed to the available evidence and the informed assessment already made by the CHMP. As Pill LJ articulated in paragraph 62 the Court of Appeal judgment in *R (Servier Laboratories Ltd) v NICE* [2010] EWCA Civ 346, it is not suggested that NICE are bound by EMA's decision or its reasoning but the applicants are entitled to expect any decision against them to be properly reasoned, especially when it is contrary to the reasoned decision of an equally eminent body.

Astellas Pharma Ltd.
2000 Hillswood Drive, Chertsey, KT16 0RS.
Tel: +44 (0) 203 379 8000 Fax: +44 (0) 203 379 8703
Registered in England & Wales number 00787610
Registered office as above

The AG and AC have used a modelling approach that suggested that prolonged-release tacrolimus was dominated by the immediate-release formulation in the absence of any RCT evidence to support this position, a conclusion based on use of efficacy data from a single short term RCT (Kramer et al 2010). All evidence from RCTs comparing immediate-release tacrolimus with prolonged-release tacrolimus shows statistically significant non-inferiority in terms of clinical efficacy and side effect profile. Should Kramer have been excluded or one of the excluded studies mentioned above in point 1a.1 have been included in the analyses then the opposite conclusion would have been reached and prolonged-release tacrolimus would have been superior to immediate-release tacrolimus, following NICE methods Guide 5.8.6.

**2.2 The AC and AG dismissed other relevant evidence, resulting in unreasonably restrictive recommendations**

- Failure by AC and AG to regard the evidence derived from the relevant RCT of non-adherence based on Kuypers et al 2013, which demonstrates an improvement in adherence for prolonged release tacrolimus against immediate release tacrolimus, a well–established risk factor for graft survival, as acknowledged by the AG in its response to the ACD consultation. Astellas contends that some patients are at risk of poor adherence and consequent tacrolimus blood-level variability, as evidenced by the Kuypers 2013 RCT, and also UK observational data from Oxford, Hammersmith and Glasgow. The AC's dismissal that "*It would be difficult to identify a subgroup of patients likely to benefit from prolonged-release tacrolimus*" (FAD section 4.65) is erroneous. Within clinical practice there are a range of validated clinical tools (both subjective and objective measures) which are routinely used to identify patients at high risk of poor adherence.
- Complete disregard of non RCT evidence with no proper justification despite the recognition that RCT evidence was limited. Section 3.1.1 of the NICE Methods Guide states '*Consideration of a comprehensive evidence base is fundamental to the appraisal process. Evidence of various types and from multiple sources may inform the appraisal. …..'* as shown in Section 5.2.3
    - Further non-RCT evidence was submitted by Astellas, from the independent European Liver Transplant Registry, which demonstrated an 8% better graft survival (P=0.01) at three years for patients on prolonged-release tacrolimus (Advagraf) compared to those on immediate release formulations. It should be noted that graft survival benefit was observed in a less immunogenic allograft (liver), and therefore should be considered as relevant to kidney allograft. Additionally, in response to the ACD consultation, evidence demonstrating advantages in patients treated with prolonged-release tacrolimus in regards to adherence and serum tacrolimus variability issues was disregarded, both factors shown to impact graft survival in renal transplant patients.
- Failure of the AC to take proper account of advice from professional and patient groups. Within the responses to the ACD consultation, a number of professional and patient groups challenged recommendation 1.4, highlighting the reliance on RCTs and the resulting restrictive nature of the recommendation. Whilst the AC has responded, these do not clearly justify how the AC can on one hand state (FAD Section 4.56)

Astellas Pharma Ltd.
2000 Hillswood Drive, Chertsey, KT16 0RS.
Tel: +44 (0) 203 379 8000 Fax: +44 (0) 203 379 8703
Registered in England & Wales number 00787610
Registered office as above

'...*The Committee acknowledged that immunosuppressive therapies are chosen based on a number of factors, and that some treatments may be particularly beneficial for individual people or groups of people*.' and then not recommend a number of technologies including prolonged-release tacrolimus.

Had the submitted evidence been properly taken into account according to NICE Methods Guide and given due weight by the AC, it is clear that NICE would have reached the decision to recommend prolonged release tacrolimus.

**Conclusion**

It is Astellas' considered submission that the FAD seeking to exclude prolonged release tacrolimus from being prescribed in NHS England is manifestly wrong. NICE has failed to follow its processes by acting unfairly, in that it excluded evidence of relevance to a UK population and used an erroneous methodological approach, compounded by unrepresentative pricing in the health economic model. NICE has acted unreasonably by basing its recommendations on a health economic model that is fundamentally flawed in its treatment of evidence for prolonged release tacrolimus due to the over-reliance on one RCT. In addition, NICE failed to consider the wealth of relevant real-world evidence, including that from the UK clinical community. Prolonged release tacrolimus has robust evidence for clinical effectiveness relevant to UK clinical practice. The decision for not recommending prolonged release tacrolimus is unreasonable, based on an appropriate assessment of available data and conveys no healthcare value to the NHS, but will adversely affect kidney transplant patients and dialysis services.

Astellas requests an oral hearing for the determination of this Appeal.

Yours sincerely

[redacted]
Medical Director

Astellas Pharma Ltd.
2000 Hillswood Drive, Chertsey, KT16 0RS.
Tel: +44 (0) 203 379 8000 Fax: +44 (0) 203 379 8703
Registered in England & Wales number 00787610
Registered office as above