1 Executive summary

- This report provides relevant information for the NICE review of Technology Appraisal 85 (Renal transplantation - immunosuppressive regimens (adults)). It has been prepared in response to the final scope issued in July 2014.
- Tacrolimus, twice daily, (Prograf) has become the standard of care for renal transplantation patients in the United Kingdom (UK) since the publication of TA85 in 2004. Tacrolimus is a calcineurin inhibitor (CNI) immunosuppressant with a narrow therapeutic index. Prior to 2008, it was used at higher doses in clinical trials and clinical practice than it is today. This change in dosing practice was based on data from the landmark Symphony study, published in 2007, which compared four different regimens (1). These results indicated that target tacrolimus trough levels of 3-8 ng/mL delivered the most effective therapy, with a reduced risk of nephrotoxicity compared to the higher doses of tacrolimus used previously.
- Advagraf is a prolonged release formulation of tacrolimus that has been available since 2009. It provides an optimal tacrolimus treatment regimen, which patients find simple to adhere to; has reduced intra-patient variability in terms of drug levels; and increased graft survival compared to tacrolimus twice daily (Prograf) (2-6).
- Despite the high cost of transplant operations, transplantation is more cost-effective than dialysis from the National Health Service's (NHS) perspective and substantially improves the patient's quality of life (QOL) (7-10). Since 2003, the increasing demand for kidney transplants and the lack of high quality donors has meant that more marginally viable donor organs have been accepted for renal transplantation than previously (10). Supportive care post-transplantation is of critical importance in ensuring that the renal graft remains functional and is not rejected.
- Treatment strategies that optimise the use of CNIs are utilised to maximise the benefits of CNIs (reduced graft rejection rates), while minimising their nephrotoxic adverse effects (11).
- In both 2010 and 2012, the Medicines and Healthcare Products Regulatory Agency issued patient safety guidance requiring branded prescribing for tacrolimus (12).
- During the past decade, a number of new drugs have been approved for use in patients post-renal transplantation. The drugs have different mechanisms of action from CNIs, and each has its own advantages and disadvantages. However, there has not been significant uptake of any of the new drugs in the UK; their market shares are <5%.
- It is unlikely that new immunosuppressant agents will be approved for use in renal transplant patients over the next 5-8 years. Hence, clinicians base their therapeutic decisions on data about the existing drugs that have been available for several years. Optimising the use of the available treatments and matching the regimens to the patients' clinical needs will become increasingly important over the next few years.
- An economic model has been developed for this submission to compare the cost-effectiveness of Prograf, Advagraf, belatacept, everolimus and sirolimus,

using a UK perspective and reference case NHS list prices. The main results of the model demonstrate that:

    - Advagraf dominates Prograf, the current standard of care;
    - Prograf dominates the other comparators that are used occasionally in the UK (belatacept and sirolimus).

- This dossier summarises the evidence from a systematic review of the literature and an economic model. The major conclusion of this analysis is that Advagraf was shown to be the optimal formulation of tacrolimus and should become the standard of care immunosuppressant for renal transplant patients.