1 Executive summary

- This report provides relevant information for the NICE review of Technology Appraisal 99 (TA99) (Renal transplantation - immunosuppressive regimens (children and adolescents)). It has been prepared based on the final scope issued in July 2014.
- Tacrolimus is the only licensed product for paediatric transplant recipients; in the economic model, Prograf™ dominates all other relevant comparators. Advagraf™ is not licensed for paediatric transplant recipients but is widely used in clinical practice and may be more cost-effective than Prograf™.
- The number of paediatric, kidney only transplants in the UK rose from 119 in 2012-13 to 124 in 2013-14 (1).
- Between 2002 and 2012, there has been a statistically significant improvement in graft survival in paediatric kidney transplant recipients (KTRs) but no corresponding improvement in patient survival (1).
- Maintenance immunosuppression post kidney transplantation consists of calcineurin inhibitors (CNIs), mammalian target of rapamycin (mTOR) inhibitors, antimetabolites and corticosteroids. Most children in the UK receive triple immunosuppression therapy with a CNI (ciclosporin or tacrolimus), a DNA proliferation inhibitor (usually azathioprine), and a corticosteroid following kidney transplantation. Currently, tacrolimus is the most commonly used CNI in England and Wales (2).
- Since the publication of TA99 in 2006, a number of new immunosuppressive therapies have been developed for the management of children and adolescents post-transplantation.
- Astellas markets tacrolimus (Prograf™) a CNI, which has a UK marketing authorisation for use in children for primary immunosuppression in kidney allograft recipients and the treatment of kidney allograft rejection resistant to conventional immunosuppressive regimens. It is recommended as a treatment option within current NICE appraisals TA99 (3), and TA85 (4). In one of the few paediatric trials reported, tacrolimus therapy resulted in a significantly lower incidence of acute rejection (36.9%) compared with ciclosporin (59.1%, $p = 0.003$) in paediatric KTRs (5, 6). The incidence of corticosteroid-resistant rejection was also significantly lower during tacrolimus therapy (7.8% vs. 25.8%, $p = 0.001$).
- Modigraf™ (tacrolimus granules for oral solution) is a formulation of tacrolimus that is licensed for use in adult and paediatric patients who have received a kidney, liver or heart allograft for the prophylaxis of transplant rejection (7). It has not previously been considered by NICE for the management of paediatric KTRs. Modigraf™ was designed for use in patients who cannot swallow capsules; its comparator is ‘special’ tacrolimus liquid preparations that are available via the NHS, specials manufacturers, or are prepared by parents/caregivers.
- Although Advagraf™ (once-daily, prolonged release tacrolimus) does not currently have a licence for use in children and adolescents, anecdotal evidence suggests that it has been used in this patient group as part of routine clinical

practice. Following NICE's advice that Advagraf™ will be considered in TA99, this dossier includes relevant data on Advagraf™.

- The dossier describes the results of a literature review and an economic model that has been developed to compare Prograf™ with comparator immunosuppressive therapies.
- The economic model compared Prograf™ with Modigraf™, Advagraf™, belatacept, everolimus and sirolimus (note: the last four drugs are not currently licensed for use in paediatric KTRs).
- The lowest initial age in the model is two years because there were no paediatric renal transplants in infants under 2 years of age in 2012 (8). The maximum time horizon was 16 years. In the base case analysis, the starting age was 8 years, with a time horizon of 10 years, since the median age when paediatric patients receive a transplant is between 8 and 11.99 years (8).
- The base case analysis assumed that the initial age of the KTR was 8 years. The time horizon was 10 years, and the discount rate was 3.5%. The model included adverse events and a half-cycle correction was applied.
- Prograf™ was cost-effective when compared with belatacept, everolimus and sirolimus (sirolimus II: CNI avoidance) since the incremental cost-utility ratio is below the generally accepted threshold value of £20,000-30,000/QALY.
- Prograf™ was not cost-effective when compared with sirolimus I in a CNI minimisation strategy. It should be noted that sirolimus I is used in very small and specific patient groups rather than the general paediatric transplant population.
- Prograf™ is the gold standard immunosuppressant for the management of paediatric transplant recipients.
- Advagraf™ is both less expensive and more effective than Prograf™ in the model. Its once-daily dosing regimen may assist children and adolescents to adhere better to their immunosuppressive regimen, thus improving their clinical outcomes. Advagraf™ is not yet approved for use in paediatric KTRs but data from ongoing clinical trials will be submitted to the regulatory authorities as soon as they are available.
- Although several assumptions have had to be made to construct a paediatric model, Prograf™ maintains its status as the standard of care for the immunosuppression of paediatric kidney transplant recipients against relevant comparators.