# AWMSG Secretariat Assessment Report – Advice no. 0811
# Tacrolimus (Advagraf®) for the prophylaxis of transplant rejection in adult kidney or liver allograft recipients and the treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients

This assessment report is based on evidence submitted by Astellas Pharma Ltd. on 18 January 2010.

## 1.0 PRODUCT DETAILS

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| **Licensed indication** | Tacrolimus (Advagraf®) for the prophylaxis of transplant rejection in adult kidney or liver allograft recipients and the treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients[1]. |
| **Dosing** | Advagraf® is administered orally once daily (in the morning) on an empty stomach. For kidney transplant rejection prophylaxis, the dose is 0.2–0.3 mg/kg/day, starting within 24 hours of surgery. The dose for liver transplant rejection prophylaxis is lower at 0.1–0.2 mg/kg/day, and should commence within 12–18 hours following surgery. Careful and frequent monitoring of tacrolimus trough levels in patients treated with Advagraf® is recommended in the first two weeks post-transplant to ensure adequate drug exposure.<br><br>Further dosing guidance, including conversion from Prograf®, is available in the Summary of Product Characteristics (SPC)[1]. |
| **Marketing authorisation date** | 23 April 2007[1] |
| **UK launch date** | June 2007[2] |

## 2.0 DECISION CONTEXT

### 2.1 Background

Organ transplantation is the most appropriate therapy for patients with end-stage organ failure, including renal and hepatic failure[3]. In the UK (2009-2010), 3,706 organ transplants were performed with a success rate higher than 90% at 1-year post-transplant, regardless of organ type[3,4]. Of the 2,694 kidney transplants undertaken in the UK during 2009–2010, 92 were performed in the University Hospital of Wales, Cardiff[4]. During the same period, 707 patients underwent liver transplantation in the UK, which is not currently performed in Wales[4]. However, the applicant company estimates that of these new liver transplant patients, 28 per year will be Welsh residents[5]. Data obtained from NHS Blood and Transplant identified 22 liver transplants and 30 kidney transplants performed on Welsh residents outside of Wales during 2010[6].

Tacrolimus exerts its immunosuppressive action by inhibiting the activated serine threonine phosphatase, calcineurin, in T-lymphocytes. Tacrolimus particularly inhibits

the formation of cytotoxic lymphocytes, which are mainly responsible for graft rejection[3]. To maintain a graft, treatment will continue long-term and will probably be life-long. There is evidence that non-adherence to therapy increases the risk of graft failure in kidney transplant patients[7,8], which can result in increased economic burden due to the need for dialysis treatment[9]. A meta-analysis in kidney transplant patients found that non-adherence rates range from 20% to 50%[8]. A similar meta-analysis in liver recipients found the rate of non-adherence to immunosuppressant medication to be 6.7 cases per 100 patients per year[10]. Another study demonstrated that approximately 15% of liver recipients exhibited low blood immunosuppressant levels on more than a quarter of occassions[11]. Reasons for non-adherence are multifactorial and individualised.

Tacrolimus is available as a twice daily (Prograf®) and a once daily prolonged-release formulation (Advagraf®). Prograf® is licensed in adults and children for the prophylaxis of transplant rejection in liver, kidney or heart allograft recipients and the treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products[12]. Advagraf® is not currently licensed for use in children or as prophylaxis in heart allograft recipients[1].

The applicant company have restricted their submission to tacrolimus (Advagraf®) for the prophylaxis of transplant rejection in adult kidney or liver allograft recipients and have not included data on the treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients, as they assert that use for this indication will be minimal[5,13].

### 2.2 Comparators

The comparator requested by the Welsh Medicines Partnership (WMP) was immediate-release tacrolimus capsules (Prograf®). In 2010, a branded generic immediate-release tacrolimus product (Adoport®) was licensed for the 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[14].

### 2.3 Guidance and related advice

- National Institute for Health and Clinical Excellence (NICE). Technology Appraisal 85. Immunosuppressive therapy for renal transplantation in adults (2004)[15].

The All Wales Medicines Strategy Group (AWMSG) has previously issued recommendations for the use of Advagraf®:

- Tacrolimus prolonged-release (Advagraf®) is not recommended for use within NHS Wales for the prophylaxis of transplant rejection in adult kidney or liver allograft recipients and the treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients (2008)[16].
- Tacrolimus prolonged-release (Advagraf®) is not recommended for use within NHS Wales for the prophylaxis of transplant rejection in adult kidney or liver allograft recipients and the treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients. (2009)[17].

## 3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFICACY

The company submission is based upon comparisons of Prograf® and Advagraf® treatment and includes several studies, including six phase II and five phase III studies in both liver and kidney transplant patients. The company concludes that all studies

support the efficacy of Advagraf® as an alternative to Prograf® in patients who have *de novo* kidney or liver transplants, and in stable kidney or liver recipients converted to Advagraf®-based immunosuppression[5]. Due to the wealth of trial data provided by the company submission, the phase II studies will not be discussed further in this section[5,18–23]. Additionally, the company submission includes two phase III studies in stable kidney and liver transplant recipients converted from Prograf® treatment to an Advagraf®-based regimen, which demonstrate that the two therapeutic regimens are broadly comparable[24,25]. These studies will also not be discussed further in this section.

## 3.1 Kidney and liver *de novo* transplant recipients commenced on Advagraf®

### 3.1.1 Phase III study (02-0-158) in *de novo* kidney transplant recipients

This was a phase III, open-label, multi-centre, non-inferiority study in *de novo* kidney transplant recipients. Patients (over the age of 12 years) were randomised (1:1:1) to receive one of three treatment regimens: Advagraf®, Prograf® or ciclosporin. The starting dose for both tacrolimus formulations was 0.15–0.20 mg/kg/day. All patients also received basiliximab induction therapy and administration of corticosteroids and mycophenolate mofetil (MMF)[26].

The primary efficacy endpoint was a composite endpoint of efficacy failure at one year, comprising of any patient who died, experienced graft failure, had a biopsy-proven acute rejection (BPAR) or was lost to follow-up. Although 668 patients were randomised into the study, only 638 patients received at least one dose of study drug and were included in the efficacy analysis. Both tacrolimus groups were compared separately with ciclosporin but not with each other. At one year post-transplant, efficacy failure rates in the tacrolimus treatment arms were statistically non-inferior to that in the ciclosporin group. Kaplan-Meier estimates for patient and graft survival one year post-transplant were also similar between treatment groups[26].

### 3.1.2 Phase III study (FG-506E-12-03) in *de novo* kidney transplant recipients

This was a multi-centre, 24-week, parallel-group, double-blind, double-dummy study in *de novo* kidney transplantation adult patients (n = 676) randomised to receive either Prograf® or Advagraf® (both 0.2 mg/kg/day). All patients also received MMF and corticosteroids as part of their immunosuppressive regimen, but without antibody induction. Key donor and recipient demographics were not significantly different except for mean human leukocyte antigen DR-1 (HLA-DR) mismatch with higher risk for Advagraf® versus Prograf® ($p < 0.01$)[27].

The primary endpoint was the event rate for BPAR within 24 weeks using data from the per-protocol-set (PPS; n = 571). Locally reviewed BPAR event rates were 15.8% for Prograf® and 20.3% for Advagraf® ($p = 0.182$), a treatment difference of 4.5% (95% confidence interval (CI): -1.8 to 10.9); non-inferiority was not met as the upper limit of the CI fell outside the pre-specified figure of 10%. However, histological grade of BPAR and efficacy failure rates were comparable between treatment arms, as were Kaplan-Meier patient and graft survival rates at 24 weeks and 12 months[27].

### 3.1.3 Phase III study (FG-506E-11-03) in *de novo* liver transplant recipients

This was a multi-centre, 24-week, double-blind, double-dummy, parallel-group study in *de novo* liver transplantation patients (n = 475) randomised to receive either Prograf® or Advagraf®. All patients received corticosteroids as the only other primary immunosuppressant[28]. The initial dose of Advagraf® was double that of Prograf® due to the lower tacrolimus exposure levels observed in the early stages of pharmacokinetic studies in *de novo* liver transplant recipients[19,28]. After the first three days, both formulations were titrated to achieve pre-defined tacrolimus trough concentrations[28].

The primary endpoint of the study was the event rate for BPAR within 24 weeks post-transplantation. BPAR event rates in the PPS population (n = 360) were 33.7% for Prograf® versus 36.3% in patients receiving Advagraf® (p = 0.512); treatment difference was 2.6% (95% CI: -7.3% and 12.4%, which falls within the predefined 15% non-inferiority margin). The 12-month BPAR frequency and event rates confirmed the non-inferiority of Advagraf® to Prograf®. Additionally, Kaplan-Meier patient and graft survival and renal function measurements were comparable between treatment arms[28].

## 4.0 SUMMARY OF EVIDENCE ON COMPARATIVE SAFETY

At the time of licensing Advagraf®, the Committee for Medicinal Products for Human Use (CHMP) concluded that "the safety of the prolonged-release formulation of tacrolimus is consistent with that known for the Prograf® formulation"[3]. In January 2009, the Medicines and Healthcare products Regulatory Agency (MHRA) issued advice following reports, mostly from the UK, of serious medication errors with Prograf® and Advagraf®[29]. Reports documented prescribing errors by hospital doctor or GP (six reports), dispensing errors by pharmacist related to generic or brand prescribing (41 reports) or administration errors by doctor, nurse or patient (eight reports). Some of these cases led to serious adverse events (AEs), such as BPAR or other side effects which could be a consequence of under- or over-exposure to tacrolimus[29]. By the end of February 2010, the MHRA had received 12 reports involving prescribing or dispensing errors associated with oral tacrolimus, including four cases of acute rejection, three cases of increased drug levels and two cases of increased creatinine levels[30]. In response, the company has instigated a comprehensive risk minimisation plan, which is detailed in the submission[5]. This includes artwork change on the Advagraf® packaging and amendment of the tacrolimus SPCs to include a statement advising against errors in substitution of Advagraf® and Prograf®[1,12]. The MHRA report provides the following advice to healthcare professionals[29]:

- Prograf® is an immediate-release formulation that must be taken twice a day: once in the morning and once in the evening.
- Advagraf® is a prolonged-release formulation that must be taken once a day in the morning.
- The indications for Advagraf® and Prograf® are not identical. Advagraf® is licensed for use in adults only.
- Care should be taken to ensure the correct brand of tacrolimus is prescribed and dispensed.

The company submission includes several studies comparing the safety profile of Prograf® and Advagraf® in patients with kidney and liver transplants[5]. The incidence of AEs and serious AEs was found to be comparable between the Prograf® and Advagraf® treatment arms in *de novo* kidney and liver recipients[27,28]. Metabolism disorders and infections were the most commonly reported AEs in *de novo* kidney recipients, while renal insufficiency/impairment, hypertension, tremor and hyperglycaemia were the most frequent AEs in *de novo* liver transplant patients. Prograf®-treated kidney and liver recipients exhibited significantly more bacterial infection and hyperglycaemia respectively when compared with those receiving Advagraf®-based therapy[27,28]. By contrast, the incidence of pharyngitis, gastroenteritis and cytomegalovirus infection was significantly greater in Advagraf®-treated kidney recipients when compared with those receiving Prograf®. Serious AEs reported in kidney transplant patients included bacterial pyelonephritis and unclassified haemorrhages, the incidences of which were statistically greater for Advagraf® recipients when compared with Prograf®-treated patients (3.6% versus 0.9% and 1.5% versus 0.0% respectively)[27].

Patient withdrawal was slightly more frequent in liver recipients receiving Advagraf®, which the investigators conclude was for a variety of reasons rather than a consistent pattern[28]. Treatment discontinuation due to AEs was comparable between the two treatment arms in both kidney and liver recipients[27,28]. In the long-term study FG506E-14-02, 20% of Advagraf®-treated transplant recipients discontinued treatment; this was mainly attributed to AEs. Additionally, during the four-year study period there were 13 deaths, of which five were considered by the investigators to be possibly or probably linked to the study drug[22].

## 5.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

- The applicant company have not included data on the treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients, as they assert that use for this indication will be minimal[5,13]. When the company applied for marketing authorisation, no studies had been performed with prolonged-release tacrolimus for this indication, but CHMP have acknowledged that this data is available for Prograf® and therefore expect Advagraf® to be therapeutically equivalent for this indication at similar doses[3].
- The indications for Advagraf® and Prograf® are not identical; Advagraf® is not licensed for use in children or as prophylaxis in heart allograft recipients.
- Medication errors resulting from incorrect dispensing, prescribing or administration of tacrolimus, including Advagraf® and Prograf®, have resulted in patients being under or over exposed to tacrolimus. These have led to serious adverse reactions including BPAR; see Section 4.0 for further information, including the steps taken to minimise risk.
- Improved adherence to once daily Advagraf® compared to twice daily Prograf® has not been investigated. A number of studies have tried to identify potential reasons for non-adherence, but conclusions are variable. A study designed to assess poor adherence in black patients demonstrated that once daily dosing significantly improved adherence when compared with twice daily dosing. However, only 10.1% of the 278 patients considered eligible for the analysis were receiving once daily medication compared with 70.5% receiving twice daily dosing[31]. Data obtained on the effect of adherence on transplant outcome are questionable, mainly due to the lack of standardisation for assessment of adherence and use of retrospective studies. Consideration to start a once daily formulation is likely to most benefit those patients who receive other medications that are administered as a once daily dose. Reasons for non-adherence are multifactorial and it is important to identify what these are on an individual patient basis. As transplant recipients in Wales will need to take an evening dose of MMF[32], it is debatable how a once daily tacrolimus regimen will improve adherence.
- The possibility that patients referred to English hospitals may be commenced on Advagraf® before returning to Wales should be considered.
- High intra-patient variability in tacrolimus clearance has previously been associated with poor long-term outcomes in transplant patients receiving Prograf®[33]. Whilst pharmacokinetic studies suggest that Advagraf® may offer benefits to intra-patient variability when compared with Prograf®[3,18–21], to date this has not been demonstrated to improve patient outcomes in randomised clinical trials[5].
- CHMP considers that non-Caucasian patients were under-represented in the clinical trials presented in the marketing authorisation application[3] and the company acknowledges that black patients can require increased doses of tacrolimus compared to Caucasian patients[5].

- In the phase III study FG-506E-11-03, Advagraf® was considered non-inferior to Prograf® using predefined CI margins in *de novo* liver transplant recipients[28]. However, these margins were greater than that used for the study FG-506E-12-03 in *de novo* kidney transplant recipients[27]. If the stricter margin had been used in the liver study, non-inferiority would not have been met. Additionally, PPS data was analysed for the primary endpoint in phase III studies, excluding a large proportion of the population[5].
- The number of high risk patients, such as those undergoing re-transplantation, was very low in the phase III study 02-0-158 in *de novo* kidney recipients. Additionally, the initial doses of both Prograf® and Advagraf® in this study were lower than the licensed recommended dosage of 0.2–0.3 mg/kg/day[26]. However, studies FG-506E-12-03 and FG-506E-11-03 used an initial dose of 0.2 mg/kg/day for both tacrolimus formulations[27,28].

## 6.0 SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

### 6.1 Cost-effectiveness evidence

#### 6.1.1 Context

The company submission describes a cost-minimisation analysis (CMA) of once daily tacrolimus prolonged-release capsules (Advagraf®) in comparison with twice daily tacrolimus immediate-release capsules (Prograf®) for the prophylaxis of transplant rejection in *de novo* adult kidney recipients[5]. Treatment of allograft rejection resistant to treatment with other immunosuppressive agents is not considered.

The basis of the CMA approach is presumed therapeutic equivalence in terms of effectiveness, safety and AEs and adherence, based on a range of pharmacokinetic studies and clinical trials[18–28,34]. The two tacrolimus regimens are assumed to differ only with respect to dose differences observed in the phase III 02-0-158 trial[26], and acquisition costs. No switching of treatments is permitted.

A state transition model has been developed in which patients with a functioning graft may proceed to a BPAR state and then to dialysis, or to return to a functioning graft state with previous BPAR experience. Alternatively, from each health state patients may proceed to dialysis and death. After 12 months, BPAR is assumed not to occur. Re-transplantation is not considered as an option. A 10-year time horizon of analysis has been selected for the base case analysis (see Appendix 1 for further details).

#### 6.1.2. Results

Results for time horizons of 1, 5, 10 and 15 years, as reported in the company submission, are shown in Table 1.

**Table 1. Company-reported base case acquisition costs for Prograf® and Advagraf® over the different time horizons[5]**

| Year | Prograf® | Advagraf® | Difference |
|---|---|---|---|
| 1 | £3,871 | £3,434 | -£437 |
| 5 | £14,993 | £12,900 | -£2,093 |
| 10 | £25,306 | £21,678 | -£3,628 |
| 15 | £32,708 | £27,978 | -£4,730 |

A wide range of one-way sensitivity analyses were conducted and demonstrated that the Prograf® and Advagraf® doses post 12 months were the most influential parameters. The Prograf® dose would need to decrease by 22% or the Advagraf® dose would need to increase by 10% (all else being equal) for the 10-year cost savings reported above to be lost. In addition, the acquisition costs of Advagraf® 1mg capsules

would need to increase by 24%, or Prograf® 1mg capsule costs decrease by 19% for the cost savings reported above to be lost (all else being equal). Acquisition costs of other dose strengths would need to vary by in excess of 50% for the reported cost savings to be lost. Use of Welsh patient-level dosing data and Welsh market share data resulted in similar cost savings to those reported in the 10-year base case analysis.

Probabilistic sensitivity analysis is reported to have been conducted and to have found a mean difference in cost between Advagraf® and Prograf® over the 10-year time horizon of -£4,688 (95% CI -£31,612 to £16,610), with 64.6% of 10,000 simulations demonstrating cost savings (not verified).

### 6.1.3 WMP critique

Strengths of the economic evidence presented by the company include:

- A reasonable assumption of therapeutic equivalence between Advagraf® and Prograf®, supported by a wide range of pharmacokinetic and clinical studies[18–28,34].
- A wide range of sensitivity analyses have been conducted to explore key areas of uncertainty.

Limitations of the economic evidence presented by the company include:

- Exclusion of branded generic immediate-release tacrolimus (Adoport®)[14] from the analysis as a relevant comparator. This product is considered bioequivalent to Prograf® (notwithstanding current advice to minimise the risk of medication errors relating to tacrolimus products)[14], and has a lower list price.
- The CMA presented by the company relates to the use of tacrolimus in *de novo* renal transplant patients only. The company suggests that the results of this analysis may be applied to the use of Advagraf® in liver transplant recipients, but expected costs will be different.

## 7.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

### 7.1 Budget impact evidence

### 7.1.1 Context and methods

The budget impact analysis relates to kidney and liver transplant recipients[5]. Based on communications with University Hospital of Wales, the company reports that 1,406 people live with transplants in Wales, of which around 1,000 are kidney recipients and 300 are liver recipients. Reports claim that approximately 140 kidney transplants are expected in each of the next five years. Incidence of liver transplants is assumed to be 28 per year, based on UK figures scaled down to the Welsh population size. These numbers are assumed to remain constant over the next five years. About 10% of patients are expected to lose the graft or to die each year. The company assumes that 80% of all kidney and liver transplant patients are currently treated with tacrolimus and 20% with ciclosporin. It is also assumed that switching from Prograf® to Advagraf® or to alternative therapy in future years will be negligible. Among *de novo* transplanted patients, 95% are expected to be treated with Advagraf®, resulting in an uptake that represents 12% of tacrolimus in year 1, rising to 47% in year 5. The daily dose of tacrolimus assumed in the analysis is 4.5 mg, rounded up from a reported mean of 4.3 mg received by 575 Welsh patients based on company-obtained data from University Hospital of Wales[5].

### 7.1.2 Results

The estimated numbers of tacrolimus patients and total cost savings over five years are shown in Table 2.

**Table 2. Company-reported cost savings associated with Advagraf®[5]**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Total tacrolimus patients | 1,285 | 1,317 | 1,345 | 1,370 | 1,393 |
| Prograf® | 1,125 | 1,013 | 911 | 820 | 738 |
| Advagraf® | 160 | 304 | 434 | 550 | 655 |
| Annual Prograf® costs | £3,153,600 | £2,839,642 | £2,553,715 | £2,298,624 | £2,068,762 |
| Annual Advagraf® costs | £376,096 | £714,582 | £1,020,160 | £1,292,830 | £1,539,643 |
| Total costs after introduction of Advagraf® | £3,529,696 | £3,554,224 | £3,573,876 | £3,591,454 | £3,608,405 |
| Total cost if all patients are on Prograf® | £3,602,112 | £3,691,814 | £3,770,304 | £3,840,384 | £3,904,858 |
| Net saving (Prograf®-Advagraf®) | £72,416 | £137,590 | £196,428 | £248,930 | £296,453 |
| No differences in net cost implications for Advagraf®/Prograf® beyond the drug acquisition costs are considered. The mean daily cost for Advagraf® (4.5 mg once a day) is £ 6.44, and for Prograf® (2.5 mg am and 2 mg pm) is £7.68. | | | | | |

Sensitivity analysis of budget impact was conducted using data on Welsh patient Prograf® doses provided by the University Hospital of Wales. Taking into account individual dose requirements for 575 Prograf® recipients, the mean dose equivalent annual Advagraf® cost is reported to be £1,981 per year compared to £2,577 for Prograf®[5]. This is reported to result in a net cost saving of £95,360 in year 1, rising to £390,380 in year 5 (data not verified).

A scenario analysis was conducted using the same Welsh patient-level data on tacrolimus dosing, but assuming the costs of the branded generic immediate-release tacrolimus capsules (Adoport®) compared against Advagraf®. Across the range of doses reported for all 575 patients, treatment with Advagraf® is estimated, on average, to be around 6% lower than with Adoport®, due to a non-linear pricing structure[5].

### 7.1.3 WMP critique of the company's budget impact estimates

The company has adopted a pragmatic approach to estimating budget impact, assuming 10% of patients stop tacrolimus treatment due to graft loss and death, and 0% conversion from Prograf® to Advagraf® for existing patients. Budget implications address current dose requirements for patients in Wales. However, estimated patient numbers are based on the total number of transplant patients in Wales (1,406), which includes 106 transplant patients other than kidney and liver recipients.

### 7.2 Comparative unit costs

According to NICE guidance on immunosuppressive therapy for renal transplantation in adults[15], several primary immunosuppressive regimens are available for kidney transplant patients. These include calcineurin-inhibitor-based treatments with ciclosporin, or tacrolimus as an alternative. The initial choice of tacrolimus or ciclosporin should be based on the relative importance of their side-effect profiles for individual patients. Sirolimus (macrolide immunosuppressant) is recommended in cases of proven intolerance to calcineurin inhibitors (including nephrotoxicity)[15]. Some examples of acquisition costs for initial immunosuppressive therapy in a 70 kg kidney transplant patient are shown in Table 3.

**Table 3. Examples of immunosuppressant acquisition costs for the prophylaxis of allograft rejection in adult kidney recipients**

| Regimen | Example of daily initial dose* | Cost per day** |
|---|---|---|
| Ciclosporin (Deximune®) capsules 25, 50 and 100 mg | 10–15 mg/kg | £12.18–£18.19 |
| Ciclosporin (Neoral®) capsules 10, 25, 50 and 100 mg | 10–15 mg/kg | £16.25–£24.28 |
| Sirolimus (Rapamune®) tablets 1 and 2 mg | 6 mg | £17.30 |
| Tacrolimus (Advagraf®) capsules 0.5, 1, 3 and 5 mg | 0.2–0.3 mg/kg | £16.41–£22.79 |
| Tacrolimus (Prograf®) capsules 0.5, 1 and 5 mg | 0.2–0.3 mg/kg | £18.29–£25.34 |
| Tacrolimus (Adoport®) capsules 0.5, 1 and 5 mg | 0.2–0.3 mg/kg | £14.92–£20.67 |
| *Maintenance doses should be adjusted according to blood concentration and renal function.<br>**Costs are based on British National Formulary[35] and/or Monthly Index of Medical Specialities (MIMS)list prices[36] and calculated for a 70 kg adult.<br>This table does not imply therapeutic equivalence of drugs or the stated doses. | | |

## 8.0 ADDITIONAL INFORMATION

### 8.1 Shared care arrangements

- Tacrolimus (Prograf®) for renal transplantation is currently available under shared care agreements within some areas of NHS Wales. If recommended for use within NHS Wales, WMP is of the opinion that Advagraf® may also be suitable for shared care. Consideration should be given to reviewing the shared care arrangements for tacrolimus.
- Consideration needs to be given to potential risks associated with the availability of two different dosage formulations being prescribed in primary and secondary care.
- Prograf® and Advagraf® should not be interchanged without careful therapeutic monitoring and should be carried out only under the close supervision of a transplant specialist.

### 8.2 Ongoing studies

The company submission highlighted the following ongoing studies[5]:

- Study PMR-EC-1205 in stable kidney transplant patients has been submitted for publication[37].
- Study PMR-EC-1105 in stable liver transplant patients is about to be submitted for publication[38].
- Study 12-10 in kidney transplant patients to investigate the optimal suppression of immunity to prevent kidney rejection (OSAKA) has been completed and the company anticipates the presentation of data within the next 12 months[39].

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## Appendix 1. Additional Health Economic Analysis Information

### Table 1A. Health economic analysis detail[5]

| | Base Case Model | Appropriate? |
|---|---|---|
| **Comparator(s)** | Advagraf® (tacrolimus prolonged-release hard capsules) once a day *versus* Prograf® (tacrolimus immediate-release hard capsules) twice a day. | Immediate-release tacrolimus is the appropriate comparator, as agreed with WMP. The company's basis for excluding Adoport®, a branded-generic immediate-release capsule version of tacrolimus, is that this is not currently used in Wales, and that there are no data to support the equivalence of Adoport® and Advagraf®. However, the MHRA issued a Drug safety update in May 2010[30] which noted that Prograf® and Adoport® are bioequivalent and are interchangeable formulations, notwithstanding the recommendations for prescribing by brand and the need for careful specialist monitoring should switching between formulations be undertaken. A comparison of Advagraf® against Adoport® would therefore seem to be feasible and of value, given its current list price is lower than that of Prograf®[36]. |
| **Population** | Adult kidney transplant recipients. The model applies to *de novo* transplant patients with an assumed body mass of 64 kg. | The CMA was performed for kidney transplant recipients only. Treatment of allograft rejection resistant to treatment with other immunosuppressive agents is not considered. The company assumes that the analysis presented for renal transplant recipients also applies to patients with liver transplants. Under the assumption of equivalence in outcomes, actual cost differences may differ between indications. |
| **Analysis type** | CMA was performed using a state-transition Markov model, which assumes five health states: two states with functioning graft (with and without previous BPAR experience), state with BPAR, state with non-functioning graft (dialysis), and death state. | CMA would be appropriate under the assumption of equivalence in efficacy (see Efficacy section below). |
| **Perspective** | Considers direct medical costs only, from the perspective of NHS Wales | Yes, appropriate to consider direct costs from the perspective of NHS Wales. |
| **Time horizon** | A 10-year time horizon is used in the base case analysis, with 1, 5 and 15 years explored in sensitivity analyses. | Ten years was chosen as it is claimed to reflect the approximate duration of graft survival. The company notes that 50% of kidney grafts function after 10–12 years and 58% of liver grafts function at 15 years. |
| **Discount rate** | 3.5% applied to both costs and outcomes | Yes. |

**Table 1A. Continued**

| | Base Case Model | Appropriate? |
|---|---|---|
| **Efficacy** | Pharmacokinetic studies demonstrated bioequivalence of Advagraf® and Prograf®[18–21]. Transition probabilities between health states were calculated from the phase III trial 02-0-158[26] for the first 12 months post-transplantation. After 12 months BPAR is assumed not to occur. From year 2 onwards transitions between health states were modelled using data on graft survival for patients with and without previous BPAR. Two functioning graft states were assumed since previous BPAR experience may increase the probability of graft loss. Probabilities on patient and graft survival were derived from NHS Blood and Transplant[40] and UK Renal Registry data[41]. | It is reasonable to assume equivalence in efficacy. |
| **Adverse effects** | AEs assumed to be the same as for Prograf®, since Advagraf® and Prograf® are considered to be clinically equivalent. | Yes. Comparison of AEs for Prograf® and Advagraf® patients in clinical trials showed comparable profiles for both formulations, as discussed in Section 5 of this report. |
| **Utility values** | Since this is a CMA, utility values were not used, | Yes. Implicit assumption of CMA is no difference in any domains of health outcomes, so utility values would be the same for Prograf® and Advagraf®. |
| **Resource use and costs** | The base case analysis assumes a starting daily dose of 11.2 mg for both Prograf® and Advagraf®, which is reduced linearly over 12 months to 5.7 mg for Prograf® and 6.1 mg for Advagraf®, based on data from trial 02-0-158[26]. These doses at 12 months are assumed to remain constant throughout the remaining graft lifetime.<br><br>As the cost per mg of the available doses of both formulations differ, the company used 2009 English prescribing costs data to establish the market share of each available dose with which to estimate an average cost per mg. Welsh prescribing data are reportedly not used in the base case analysis due to negligible current use of Advagraf® in Wales.<br><br>A range of sensitivity and scenario analyses have been conducted to address the uncertainty in Advagraf®/Prograf® acquisition costs associated with differences in daily dose, unit costs and market share distribution. Welsh patient-level dosing data have been calculated using Prograf® data for 575 patients provided by the University Hospital of Wales. The mean daily dose for Welsh patients was 4.3 mg, which has been used in a scenario analysis.<br><br>The modes include other immunosuppressive agents and AE costs, including antibody induction (basiliximab), MMF (Cellcept®), corticosteroids (Medrone®), antibiotic (ampicillin) and dehydration therapy (Dioralyte®). Costs were taken from the latest BNF[35].<br><br>Costs for haemodialysis and peritoneal dialysis for inpatient and outpatient treatments were derived from NHS reference costs (2008-2009)[42]. | Appropriate sources of resource use and costs have been identified and used, although more recent data are available. |

**Table 1A. Continued**

| | Base Case Model | Appropriate? |
|---|---|---|
| **Uncertainty and scenario analyses** | Parameter uncertainty was addressed by deterministic sensitivity analyses using distributions (where available), and a value range of ±25% for point estimates. Analysis acknowledges uncertainty in: doses of Advagraf®/Prograf®; antibody induction and corticosteroids; treatment of AEs and acute rejection episodes; patient and graft survival rates; Advagraf®/Prograf® market share[5].<br><br>Threshold sensitivity analyses were conducted on the most sensitive parameters (as identified by deterministic analysis) in order to identify threshold values for cost-saving.<br><br>Scenario analysis included market share estimates from Welsh prescription cost analysis[43].<br><br>Joint parameter uncertainty was assessed using probabilistic analysis using 10,000 Monte Carlo simulations. | Yes, a wide range of sensitivity analyses have been conducted to explore key areas of uncertainty. |
| **Model Provided?** | Yes | Yes. |

AE: adverse events; BNF: British National Formulary; BPAR: biopsy-proven acute rejection; CMA: cost-minimisation analysis; MHRA: Medicines and Healthcare products Regulatory Agency; MMF: mycophenolate mofetil.