HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

6 February 2008

ADVAGRAF 0.5 mg prolonged-release capsule
Pack of 30 (CIP: 380 692 7)

ADVAGRAF 1 mg prolonged-release capsule
Pack of 30 (CIP: 380 696 2)

ADVAGRAF 5 mg prolonged-release capsule
Pack of 30 (CIP: 380 699 1)

Applicant: ASTELLAS PHARMA SAS

Tacrolimus

List I
ATC code: L04AA05

Initial hospital prescription for a 6-month period

Date of marketing Authorisation: 23 April 2007

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Tacrolimus.

1.2. Background

This is a new prolonged-release tacrolimus capsule formulation administered in a single daily dose. The active ingredient, tacrolimus, is currently used in the proprietary medicine PROGRAF capsule, administered in 2 daily doses, and in a solution for infusion.

1.3. Indication

- Prophylaxis of transplant rejection in adult kidney or liver allograft recipients.
- Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients.

1.4. Dosage

See the SPC

General considerations
The recommended initial doses presented below are intended to act solely as a guideline.
Advagraf is generally administered in combination with other immunosuppressive agents during the initial post-operative period.
The dose may vary according to the immunosuppressive regimen chosen. Advagraf dosing should primarily be based on the clinical assessment of signs of rejection and tolerability in each patient individually aided by blood level monitoring (see below under "Recommendations on target whole-blood trough concentrations").

If clinical signs of rejection are apparent, a change to the immunosuppressive regimen should be considered.

In *de novo* kidney and liver transplant patients, careful and frequent monitoring of tacrolimus trough levels is recommended during the first two weeks post-transplant with Advagraf to ensure adequate drug exposure in the immediate post-transplant period. As tacrolimus is a substance with low clearance, adjustments to the Advagraf dose regimen may take several days before steady state is achieved.

Conversion of Prograf-treated (twice-daily) patients to Advagraf (once daily). When converting from Prograf to Advagraf capsules, residual tacrolimus levels should be measured prior to conversion and within two weeks after conversion. Dose adjustments should be made to ensure that similar systemic exposure is maintained.

In patients unable to take oral medicinal products during the immediate post-transplant period, tacrolimus therapy can be initiated intravenously (Prograf 5 mg/ml concentrate for solution for infusion) at a dose approximately 1/5th of the recommended oral dose for this indication.

Dosing recommendations

Kidney transplantation

Prophylaxis of transplant rejection

Oral Advagraf therapy should commence at a dose of 0.20 - 0.30 mg/kg/day administered once daily in the morning. Administration should begin within 24 hours after transplantation.

Dose adjustment during the post-transplantation period

Advagraf doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to Advagraf monotherapy. Post-transplant changes in the patient's condition may alter the pharmacokinetics of tacrolimus and necessitate further dose adjustments.

Liver transplantation

Prophylaxis of transplant rejection

Oral Advagraf therapy should commence at a dose of 0.10 - 0.20 mg/kg/day administered once daily in the morning. Administration should begin approximately 12 to 18 hours after transplantation.

Dose adjustment during the post-transplantation period

Advagraf doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to Advagraf monotherapy. Post-transplant changes in the patient's condition may alter the pharmacokinetics of tacrolimus and necessitate further dose adjustments.

Conversion of Prograf-treated patients to Advagraf

Allograft transplant patients maintained on twice daily Prograf capsules dosing requiring conversion to once daily Advagraf should be converted on a 1:1 (mg: mg) total daily dose basis. Advagraf should be administered in the morning. Following conversion, tacrolimus trough levels should be monitored and if necessary dose adjustments made to maintain similar systemic exposure.

Treatment of allograft rejection

Increased doses of tacrolimus, supplemental corticosteroid therapy, and the introduction of short courses of monoclonal or polyclonal antilymphocyte antibodies have all been used to manage rejection episodes.

For more information on the conversion to Advagraf from cyclosporine, see below in the section "Dose adjustments in special patient populations".

Kidney or liver transplantation

For conversion from other immunosuppressants to once daily Advagraf, treatment should begin with the initial oral dose recommended for the prophylaxis of transplant rejection after kidney and liver transplantation, respectively.

Heart transplantation

In adult patients converted to Advagraf, an initial oral dose of 0.15 mg/kg/day should be administered once daily in the morning.

Other allografts

Although there is no clinical experience with Advagraf in lung, pancreas or intestine transplantation, Prograf has been used in lung-transplanted patients at an initial oral dose of 0.10 - 0.15 mg/kg/day, in pancreas-transplanted patients at an initial oral dose of 0.2 mg/kg/day and in intestinal transplantation at an initial oral dose of 0.3 mg/kg/day.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification:

L : Immunomodulators
L04 : Immunosuppressive agents
L04A : Immunosuppressive agents
L04AAA :Selective immunosuppressive agents
L04AAA05 :Tacrolimus

2.2. Medicines in the same therapeutic category

2.1.1 Comparator medicine

- PROGRAF (tacrolimus)*

* the indications are not identical (PROGRAF has obtained additional indications for the prophylaxis of transplant rejection in heart allograft recipients and in paediatric use).

2.1. 2 Evaluation of rival drugs (not applicable)

2.3. Medicines with a similar therapeutic aim

These are all the medicinal products used for the prophylaxis of transplant rejection in kidney and/or liver allograft recipients, and for the treatment of rejection:

2.2.1 Medicinal products with a similar therapeutic objective indicated <u>for the prophylaxis and treatment of rejection</u>:

- SANDIMMUN (cyclosporine)
- NEORAL (cyclosporine microemulsion)

2.2.2 Medicinal products with a similar therapeutic objective indicated <u>for the prophylaxis of rejection</u>:

<u>Kidney transplantation:</u> (in combination with other immunosuppressive agents)
- IMUREL* (azathioprine) CELLCEPT * (mycophenolate mofetil) - MYFORTIC (mycophenolic acid sodium salt) - RAPAMUNE (sirolimus) -
CERTICAN (everolimus):
- Corticosteroids

<u>Liver transplantation</u> (in combination with other immunosuppressive agents)
- IMUREL (azathioprine) - CELLCEPT (mycophenolate mofetil)
- Corticosteroids

3 ANALYSIS OF AVAILABLE DATA

This dossier includes in particular:

- Phase II pharmacokinetic studies (FG-506-11-01 in liver transplantation and FG-506E-12-01 in kidney transplantation) designed to compare the pharmacokinetics of ADVAGRAF with those of PROGRAF in *de novo* treated patients.
- Phase II pharmacokinetic studies in stable patients converted from PROGRAF to ADVAGRAF in kidney transplantation (FG-506E-12-02) and heart transplantation (FG-506-15-02)
- A phase III non-inferiority study versus cyclosporine in the prophylactic treatment of rejection in kidney allograft recipients (US 02-0-158)
- Interim results of a follow-up study (FG-506-14-02) of patients included in the phase II studies and in the phase III study.

3.1. Pharmacokinetic

The following phase II studies were performed:

- *De novo* in kidney (FG-506E-12-01, N=66) and liver transplantation (FG-506E-11-01, N=77)
- Conversion in kidney transplantation (FG-506E-12-02, N=60 et 02-0-131, N=67), in liver transplantation (02-0-152, N= 62) and in heart transplantation (FG-506E-15-02, N=45).
- In “de novo” kidney and liver allograft recipients, the AUC_{0-24} values for tacrolimus for ADVAGRAF on day 1 were respectively 30% and 50% lower than those obtained with equivalent doses of PROGRAF. On day 4, the systemic exposure measured from the trough levels was similar in kidney allograft recipients and in liver allograft recipients with the two formulations.
- In stable patients converted from PROGRAF (twice daily) to ADVAGRAF (once daily) on the basis of a total daily dosage of 1:1 (mg: mg), the systemic exposure to tacrolimus (AUC0-24) with ADVAGRAF was approximately 10% less than with PROGRAF.

The ratio between the trough tacrolimus levels (C24) and systemic exposure (AUC0-24) was similar for the two formulations, ADVAGRAF and PROGRAF.

3.2. Efficacy

- A phase III non-inferiority study *versus* cyclosporine in the prophylactic treatment of rejection in kidney allograft recipients (US 02-0-158)
- Interim results of a follow-up study (FG-506-14-02) grouping the patients included in the phase II studies and phase III study.

Study US 02-0-158 (prophylactic treatment of rejection in kidney allograft recipients)

A phase III, randomised, open-label, non-inferiority study conducted in kidney allograft recipients, evaluated for 12 months the efficacy and safety of AVAGRAF *versus* NEORAL and PROGRAF *versus* NEORAL (N=638 as ITT and N =629 per protocol).

Renal allograft candidates were treated with four-agent therapy comprising:

- Induction therapy with basiliximab (SIMULECT) (2 times 20 mg IV),
- A calcineurin inhibitor (ADVAGRAF, PROGRAF or NEORAL according to randomisation):

- o ADVAGRAF, instituted orally at a dose of between 0.15 and 0.20 mg/kg (the dosage recommended in the MA is 0.20 to 0.30 mg/kg once daily for kidney transplantation and recommended trough tacrolimus levels are between 7 and 16 ng/ml from D0 to D 90 then between 5 and 15 ng/ml after D90).
- o PROGRAF, instituted orally at a dose of between 0.075 and 0.10 mg/kg twice daily (the dosage recommended in the MA is 0.20 to 0.30 mg/kg in two intakes for kidney transplantation and the recommended trough tacrolimus levels are between 7 and 16 ng/ml from D0 to D 90 then between 5 and 15 ng/ml after D90).
  - ▪ or NEORAL, instituted orally at a dose between 4 to 5 mg/kg twice daily, the recommended trough cyclosporine levels being between 125 and 400 ng/ml from D0 to D 90 and then between 100 and 300 ng/ml after D90).

- In combination with mycophenolate mofetil (CELLCEPT) and corticosteroids.

Primary efficacy endpoint: percentage of patients presenting with a failure of efficacy at twelve months, corresponding to one of the following events:
- Death,
- Graft loss (return to dialysis or repeat transplantation),
- Biopsy-proven acute rejection (BPAR),
- Lost to follow-up

This primary endpoint was modified during the study. This was initially patient/graft survival at one year which was subsequently taken as a secondary endpoint.

Non-inferiority was established if the upper limit of the confidence interval of the difference between PROGRAF and NEORAL or between ADVAGRAF and NEORAL was lower than 10%.

Results:

Primary efficacy endpoint: percentage of patients presenting with a failure of efficacy at twelve months

Table 1: Results for the primary efficacy endpoint

Results for ITT population	Treatment groups		
	PROGRAF (n = 212)	ADVAGRAF (n = 214)	NEORAL (n = 212)
Death	9	3	5
Graft loss	9	5	4
BPAR	16	22	29
Lost to follow-up	4	3	1
% Patients with efficacy failure	**32 (15.1%)**	**30 (14.0%)**	**36 (17.0%)**
[95.2% CI] versus Neoral	**[-8.9%; 5.2%]**	**[-9.9%; 4.0%]**	**/**

In combination with mycophenolate mofetil (CELLCEPT) and corticosteroids, the efficacy of PROGRAF and ADVAGRAF was not inferior to that of NEORAL in terms of the percentage of patients with a failure of efficacy at 12 months (primary endpoint of the study).

Secondary endpoints, in particular:

- Patient/graft survival at 12 months

Table 2: Data on patient survival and graft survival in study 02-0-158

ITT results	Treatment groups		
	PROGRAF (n = 212)	ADVAGRAF (n = 214)	NEORAL (n = 212)
Patient Survival	199 (93.9%)	208 (97.2%)	206 (97.2%)
[95% CI] vs. Neoral	**[-7.2%; 0.6%]**	**[-3.1%; 3.2%]**	/
Graft survival	194 (91.5%)	204 (95.3%)	202 (95.3%)
[95% CI] vs. Neoral	**[-8.5%; 0.9%]**	**[-4.0%; 4.1%]**	/

The percentages of 12-month patient/graft survival in the ADVAGRAF and PROGRAF arms were in favour of non-inferiority when compared to those observed in the NEORAL group.

Long-term follow-up study FG-506-14-02

A long-term, open-label, non-comparative follow-up study (Phase III) is currently in progress. Its objective is to evaluate long-term efficacy and safety in patients who took part in the phase II studies and the phase III study:

- *de novo* in kidney transplantation (phase II study:FG-506E-12-01) and liver transplantation (phase II study: FG-506E-11-01)
- conversion in kidney transplantation (phase II study: FG-506E-12-02) and heart transplantation (phase II study: FG-506-15-02)
- *de novo* in kidney transplantation (phase III study: US 02-0-158)

3.3. Safety

The safety profile of immunosuppressive treatments is often difficult to establish because of the underlying disease and the concomitant use of many other medicinal products.

Most of the adverse reactions listed below are reversible and/or respond to a reduction in dosage. The adverse reactions with an incidence ≥10% are as follows:

- tremor, headaches
- diarrhoea, nausea
- renal function abnormalities
- hyperglycaemia, diabetes mellitus, hyperkalaemia
- hypertension
- insomnia

As with other potent immunosuppressive agents, patients receiving tacrolimus frequently present with an increased risk of infection (viral, bacterial, fungal, protozoal). The course of pre-existing infectious diseases may be worsened. Systemic or local infections may develop.

Patients receiving immunosuppressive therapy have an increased risk of developing malignant tumours. Both benign and malignant tumours, including lymphoproliferative syndromes associated with EBV and skin cancers have been described during treatment with tacrolimus (cf. SPC).

During the phase III study (US study 02-0-158) in kidney allograft recipients, the incidence of adverse reactions was similar in the 2 treatment groups (ADVAGRAF- PROGRAF) and in line with that initially observed with PROGRAF and NEORAL.

3.4. Conclusion

During the phase III study (US study 02-0-158), the efficacy of ADVAGRAF and PROGRAF was non-inferior to that of NEORAL for prophylactic treatment in kidney allograft recipients in terms of the percentage of patients presenting with a failure of efficacy at one year (primary endpoint of the study).

Although no phase III study has evaluated ADVAGRAF in the prophylaxis of rejection in liver allograft recipients, the indication was obtained in view of the similarity of the pharmacokinetic characteristics of ADVAGRAF and PROGRAF.

No data are available in patients at high immunological risk.
Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients has not been evaluated.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Immunosuppressive treatments associated with organ transplants are administered in serious clinical situations.

These medicinal products are used for prophylactic and curative treatment in combination with other immunosuppressive agents.

Their efficacy/adverse effects ratio within the context of combination therapy is high.

These proprietary products are used for first-line therapy (prophylaxis of rejection) or second-line therapy after the failure of other treatments.

There are few other treatment options.

> Public Health Benefit
> In terms of public health, the burden of liver and kidney allograft rejection may be considered to be moderate.
> An improvement in the prophylaxis and treatment of graft rejection constitutes a public health need lying within the scope of identified priorities (priorities of the *National Technical Group for Defining Public Health Goals/DGS-2003*)
>
> In view of the current preventive and curative management of graft rejection, in particular using PROGRAF, only an improvement in compliance (not demonstrated) could be expected because of the ease of use of ADVAGRAF. However, as the consequences of such an improvement have not been demonstrated (in *de novo* treatment and in patients converting from PROGRAF to ADVAGRAF), no impact in terms of morbidity and mortality is expected with this medicinal product in this indication.
> The proprietary product ADVAGRAF should not therefore provide an additional response to an identified public health need.
>
> Accordingly, taking into account the current therapeutic management of transplant rejection, ADVAGRAF is not expected to benefit public health in these indications.

The actual benefit of these medicinal products is substantial.

4.2. Improvement in actual benefit
ADVAGRAF, sustained-release capsule administered once daily, does not provide any improvement in actual benefit (IAB V) compared to PROGRAF capsule administered twice daily.
However, the Committee underlines the simplification of this dosing regimen.

4.2. Therapeutic use

Transplantation requires lifelong anti-rejection treatment by immunosuppressive agents.

Optimum immunosuppressive treatment combines several types of immunosuppressive agents with complementary pharmacotherapeutic targets, in order to reduce adverse effects without compromising efficacy by reducing their respective doses.

Induction therapy with polyclonal or monoclonal antibodies is combined during or after transplantation, in order to block lymphocyte activation and/or induce lymphocytopenia and thus reduce the risk of rejection during the equilibration phase of maintenance immunosuppression.

Treatment protocols are constantly changing and the therapeutic combinations used are mainly dependent on the practices of the centres concerned and the profiles of recipients (age, pre-sensitisation) and donors (borderline graft, compatibility with recipient etc.).

Initial preventive immunosuppression generally involves tritherapy (or sometimes bitherapy) combining:
- tacrolimus or cyclosporine,
- mycophenolate mofetil (or azathioprine, sirolimus, everolimus) in kidney transplantation and mycophenolate mofetil (or azathioprine) in liver transplantation
- corticosteroids

The administration of induction therapy depends on the centre and the profile of the recipient and/or donor.

If an episode of rejection occurs, high doses of corticosteroids are administered and monoclonal or polyclonal anti-lymphocyte antibodies are sometimes used in the case of corticosteroid-resistant rejection.

<u>Therapeutic use of ADVAGRAF</u>
ADVAGRAF is an alternative to PROGRAF in kidney and liver allograft recipients which may be prescribed preferentially because of its simplified dosing regimen for the prophylaxis and treatment of allograft rejection resistant to treatment with other immunosuppressive agents in adult patients.

Kidney and liver allograft recipients may be converted from PROGRAF to ADVAGRAF. However this involves a risk of late acute rejection inherent to any change in immunosuppression. Accordingly, conversion should be conducted with caution in these patients. After conversion, trough tacrolimus levels should be monitored and if necessary dosage adjustments made to maintain similar systemic exposure.

4.2. Target Population

The target population of ADVAGRAF is represented by kidney and liver allograft recipients. According to the data of the French Biomedecine[1] Agency, 2731 patients received a kidney grft and 1037, a liver graft in 2006.

4.3. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the indications and at the dosage in the Marketing Authorisation.

4.3.1. Packaging: Appropriate for the prescription conditions

4.3.2. Reimbursement rate: 100 %

.[1] Biomedecine Agency. Assessment of graft harvesting and transplantation activities in France. 2006 Annual Report of the French Transplant Agency.