HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

9 May 2007

PROGRAF 0.5 mg, hard capsules
B/50 (CIP: 358 958 8)

PROGRAF 1 mg, hard capsules
B/50 (CIP: 358 957 1)

PROGRAF 5 mg, hard capsules
B/50 (CIP: 358 757 2)

PROGRAF 5 mg/ml, concentrate for solution for infusion
B/10 1-ml glass ampoules (CIP: 558 874 2)

Applicant: ASTELLAS PHARMA SAS

Tacrolimus
List I
Initial hospital prescription for a period of 6 months

Dates of Marketing Authorisations:
PROGRAF 0.5 mg, hard capsules: February 24, 1998
PROGRAF 1 mg, hard capsules: August 21, 1995
PROGRAF 5 mg, hard capsules: August 21, 1995
PROGRAF 5 mg/1 ml, concentrate for solution for infusion: August 21, 1995
Variation to the extension of indication: July 7, 2006 (mutual recognition procedure)

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the extension of indication: “Prophylaxis of transplant rejection in heart allograft recipients; extension of indication of treatment of corticosteroid-resistant rejection to forms resistant to other immunosuppressive medicinal products”.

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Tacrolimus

1.2. Indication

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

1.3. Dosage

Dosage recommendations - Heart transplantation

Prophylaxis of transplant rejection - Adults

Prograf can be used with antibody induction (allowing for delayed start of Prograf therapy) or alternatively in clinically stable patients without antibody induction.

Following antibody induction, oral Prograf therapy should be initiated at a dose of 0.075 mg/kg/day administered as two divided doses (e.g. morning and evening). Administration should commence within 5 days after the completion of surgery as soon as the patient's clinical condition is stabilised. If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of 0.01 to 0.02 mg/kg/day should be initiated as a continuous 24-hour infusion.

An alternative strategy was published, where oral tacrolimus was administered within 12 hours post transplantation. This approach was reserved for patients without organ dysfunction (e.g. renal dysfunction). In that case, an initial oral tacrolimus dose of 2 to 4 mg per day was given in combination with mycophenolate mofetil and corticosteroids, or in combination with sirolimus and corticosteroids.

Prophylaxis of transplant rejection - Children

Prograf has been used with or without antibody induction in paediatric heart transplantation.

In patients without antibody induction, if Prograf therapy is initiated intravenously, the recommended starting dose is 0.03 - 0.05 mg/kg/day as a continuous 24-hour infusion targeted to achieve tacrolimus whole blood concentrations of 15 - 25 ng/ml. Patients should be converted to oral therapy as soon as clinically practicable. The first dose of oral therapy should be 0.30 mg/kg/day starting 8 to 12 hours after discontinuing intravenous therapy.

Following antibody induction, if Prograf therapy is initiated orally, the recommended starting dose is 0.10 - 0.30 mg/kg/day administered as two divided doses (e.g. morning and evening).

Dosage adjustment

During post-transplant period in adults and children in general, Prograf doses are usually reduced. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.

Rejection therapy – adults and children

Increased Prograf doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes.

In adult patients converted to Prograf, an initial oral dose of 0.15 mg/kg/day should be administered in two divided doses (e.g. morning and evening).

In paediatric patients converted to Prograf, an initial oral dose of 0.20 - 0.30 mg/kg/day should be administered in two divided doses (e.g. morning and evening).

For more information, see the SPC.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

L ANTINEOPLASIC DRUGS AND IMMUNOMODULATING AGENTS

L04 IMMUNOSUPPRESSIVE AGENTS

L04A IMMUNOSUPPRESSIVE AGENTS

L04AA SELECTIVE IMMUNOSUPPRESSIVE AGENTS

L04AA05 Tacrolimus

2.2. Medicines in the same therapeutic category

SANDIMMUN (ciclosporin)
NEORAL (ciclosporin microemulsion)

SANDIMMUN (ciclosporin), NEORAL (ciclosporin microemulsion): “Prophylaxis of transplant rejection. Treatment of transplant rejection, in patients previously receiving other immunosuppressive protocols (to avoid the risks associated with excessive immunodepression).”

2.3. Medicines with a similar therapeutic aim

These are all medicinal products used in prophylaxis of transplant rejection after heart transplantation:

IMUREL (azathioprine): “Organ transplantation: Prophylaxis of transplant rejection in combination with corticosteroids or other immunosuppressive agents.”

CELLCEPT (micophenolate mofetil): “CellCept is indicated, in combination with ciclosporin and corticosteroids, for the prophylaxis of acute organ rejection in kidney, heart or liver allograft recipients.”

CERTICAN (everolimus): “Certican is indicated for the prophylaxis of organ rejection in adult kidney or heart allograft recipients with a low to moderate immunological risk. Certican must be used in combination with ciclosporin in microemulsion form and corticosteroids.”

High-dose corticosteroids

3 ANALYSIS OF AVAILABLE DATA

Data provided by the company concern the use of PROGRAF in adult and paediatric heart allograft recipients.

Prophylaxis of transplant rejection – Adults and children

In adults:

Phase II studies:

- A pilot study (FG-506-05-01) performed to obtain preliminary data on the efficacy and safety of tacrolimus *vs* ciclosporin and to determine the optimum doses of tacrolimus in heart transplantation.
- Two dose-finding studies (FG-506-05-03 and FG-506-05-04).

These phase II studies were not taken into account by the Transparency Committee.

Phase III studies:

The pivotal study (FG-506-05-02)[1] compared the efficacy of tacrolimus with that of micronised ciclosporin as concomitant treatments with azathioprine, corticosteroids and an induction therapy, in heart transplant candidates.

Phase IV studies, an American study (US 20-01-003)[2] compared after one year the efficacy of tacrolimus with that of micronised ciclosporin in combination with mycophenolate mofetil, in adult heart transplant recipients.

In children: the company submitted several publications in support of its application. Eight retrospective studies concerning the use of the tacrolimus in paediatric heart transplantation. Most studies involved between 10 and 127 children. Three prospective studies[3,4,5] were also provided.

The clinical report of the Hrc/Hrc1 study, a preliminary American study, was presented to the CHMP with a view to extending the indication of tacrolimus to the prophylaxis of heart transplant rejection (1989-1992) with historical controls under ciclosporin (1982-1989).

Only the 2 prospective studies are discussed in this opinion.

[1] Grimm M et al. Superior prevention of acute rejection by tacrolimus vs. cyclosporine in heart transplant recipients – A large European trial. *Am J Transplant* 2006; 6 (6): 1387-97

[2] Kobashigawa JA et al. Tacrolimus with mycophenolate mofetil (MMF) or sirolimus vs. cyclosporine with MMF in cardiac transplant patients: 1-year report. *Am J Transplant* 2006; 6(6): 1377-86

[3] Pollock-Barziv SM et al. Randomised clinical trial of tacrolimus vs cyclosporine-based immunosuppression in pediatric heart transplantation: Preliminary results at 15-month follow-up. J Heart Lung Transplant 2005; 24(2): 190-4

[4] Herzberg GZ et al. The effects of HLA mismatching and immunosuppressive therapy on early rejection - outcome in paediatric heart transplant recipients. *J Heart Lung Transplant* 1998; 17(12):1195-200

[5] West LJ et al. ABO-incompatible heart transplantation in infants. *N Engl J Med* 2001; 344(11): 793-800

Rejection therapy - adults and children

The efficacy of tacrolimus in the treatment of transplant rejection was evaluated in allograft recipients failing under ciclosporin. The company provided the studies submitted to the CHMP in March 2005 in the context of the harmonisation procedure.

Studies analysed	*Number of patients converted to tacrolimus because of rejection*
Study FG-506-05-02	14 patients
Report FG95-506-10[6]	38 patients (24 adults and 14 children)
Study 93-0-003[7]	12 patients
Report FG94-506-09[8] (Report on tacrolimus for compassionate use in England)	10 patients

3.1. Efficacy

Prophylaxis of transplant rejection in adults

Study FG-506-05-02:

Randomised, open-label, parallel-group study comparing tacrolimus (Tac) with micronised ciclosporin (CyA) in 2 groups of 157 patients who had all received antilymphocyte induction therapy and were treated with corticosteroids and azathioprine (Aza).

- Study duration: 18 months.
- Main inclusion criteria: Patients aged from 18 to 65 years requiring heart transplantation *(de novo).*
- Main exclusion criteria:
  - History of malignant disease
  - Systemic infection
  - Pulmonary vascular resistance > 4 Wood units.
- Dosing regimen: all patients received an induction therapy (polyclonal or monoclonal antibodies) within 24 hours of transplantation for a period of not more than 3 to 7 days. Oral treatment with Tac (0.075 mg/kg/day) or CyA (4-6 mg/kg/day) was initiated within 5 to 10 days of transplantation, once normal gastric motility and renal function had been restored, overlapping the induction treatment by 1 to 2 days. The IV route was only used when oral administration was impossible.
- Primary efficacy endpoint: incidence at 6 months of the first biopsy-proven acute rejection (BPAR) ≥1B (according to the ISHLT grading system[9]). Endomyocardial biopsies were read locally at each centre and a blinded centralised reading was then made by 2 independent experts

[6] Report Number FG95-506-10 - Updated "rescue" experience in adult and paediatric heart transplant recipients treated with FK506 at the University of Pittsburgh - Wolfgang Meyer ? August 16, 1995 – Document interne

[7] Mentzer RM et al. Tacrolimus as a rescue immunosuppressant after heart and lung transplantation. *Transplantation* 1998; 65(1): 109-113

[8] Report Number FG-94-506-09 - Tacrolimus (FK506) rescue therapy in heart transplant recipients failing conventional therapy. *Fujisawa GmbH*, 16 March 1994

[9] Stewart S et al. Part 1: Endomyocardial biopsies for heart and heart-lung transplant recipients based on International Society for Heart Lung Transplantation ISHLT) grading system. In: Atlas of biopsy pathology for heart and lung transplantation (1st edition), page 1-53 (Arnold Publishers 2000)

N.B.:
ISHLT rejection grading system (2000):
Grade 1B (mild): Diffuse but limited infiltration, without necrosis
Grade 3A (moderate): Highly active multifocal infiltrates and/or necrosis of myocytes

- Safety endpoints: patient and graft survival, overall incidence of adverse events, clinical and laboratory safety data with specific monitoring of kidney and carbohydrate-lipid metabolism disorders and blood pressure.

Results:
The principal analysis was carried out at 6 months on the ITT population i.e. 314 patients (157 in each group).
Eight patients (5.1%) in the Tac group had to switch to the CyA group (1 because of rejection, 6 for poor safety and 1 case decided by the physician), whereas 16 (10.2%) patients in the CyA group had to switch to the Tac group (14 for rejection, 2 for poor safety). This difference (5.1% vs. 10.2%) was significant ($p<0.001$)
Induction therapy and treatments with corticosteroids and azathioprine were similar in the 2 groups (dosing regimen, duration etc.).

Efficacy:
Local reading of biopsies: 93/150 (62.0%) of patients in the Tac group and 120/148 (68.9%) of patients in the CyA group experienced an episode of acute grade ≥1B rejection, confirmed by local reading of a biopsy within the first 6 months post-transplantation ($p=0.327$, Cochran-Mantel-Haenszel test stratified for donor age and centre).

Centralised reading of biopsies: 81/150 (54.0%) of patients in the Tac group and 97/146 (66.4%) of patients in the CyA group experienced an episode of acute grade ≥1B rejection, confirmed by centralised reading of a biopsy within the first 6 months post-transplantation ($p=0.029$, Cochran-Mantel-Haenszel test stratified for donor age and centre).

Safety:
Adverse events at 18 months, were:

- Post-transplantation hypertension (Tac: 55.6% vs. CyA: 73.2%, $p=0.009$),
- Hyperlipidaemia (Tac: 24.8% vs. CyA: 41.9%, $p=0.004$),
- Diabetes: based on the adverse events reported by the investigators (Tac: 20.3% vs. CyA:10.5%, $p=0.038$). Based on two fasting blood glucose values ≥126 mg/dl (ADA/WHO criteria), no statistically significant difference was observed between the two groups (for the whole study, 32.8% vs. 26.3%; from the 7th month, 7.6% vs. 6.7%)

Study US 20-01-003:

This American, randomised, open-label phase IV study, compared 3 parallel groups:

- Oral tacrolimus in combination with mycophenolate mofetil (CELLCEPT) and corticosteroids (CS): Tac/MMF
- Oral micronised ciclosporin (NEORAL) in combination with MMF and corticosteroids: CyA/MMF,
- Oral tacrolimus in combination with sirolimus (RAPAMUNE) and corticosteroids: Tac/SIR. This combination is not validated in the respective MAs of the two products for heart transplantation.

The primary objective was to test the efficacy of the Tac/MMF combination vs. CyA/MMF in the ITT population in terms of patient/graft survival, biopsy-proven acute rejection (BPAR) ≥3A, and BPAR ≥3A with haemodynamic repercussions.
The main inclusion criteria for this study were: patients aged 18 and older with heart disease requiring a first heart transplantation.

A population of 343 randomised patients was studied for 1 year: 113 were treated with Tac/MMF, 117 with CyA/MMF and 113 with Tac/SIR.

The primary efficacy endpoints (evaluated at 6 and 12 months) were:

- Graft and patient survival at 1 year,
- Incidence of biopsy-proven acute rejection (BPAR) ≥3A,
- Incidence of BPAR ≥3A associated with haemodynamic repercussions.

Safety was assessed from the documented adverse effects of both products: renal safety, high blood pressure, lipid assessment, diabetes, serious bacterial, viral or fungal infections.

Results:
No statistically significant difference was observed between the Tac/MMF and CyA/MMF groups regarding the 3 efficacy parameters.
The Tac/MMF combination was characterised by a better renal and lipid safety profile. At 1 year, serum creatinine levels were significantly lower (1.38 mg/dl) in the Tac/MMF group than in the CyA/MMF group (1.52 mg/dl, p = 0.046).
No significant difference was observed between the Tac/MMF and CyA/MMF groups regarding the incidence of *de novo* diabetes or other adverse events. In the Tac group, fewer patients presented hypercholesterolaemia or hypertriglyceridaemia.

Prophylaxis of transplant rejection - Children
Pollock-Barziv *et al.*[3]: a prospective, randomised, open-label comparative study conducted in 26 paediatric heart transplant recipients followed between 2000 and 2002 at Toronto University Hospital. These children received either tacrolimus (n = 14, average age: 4.2 years) or ciclosporin microemulsion (n = 12, average age: 5.8 years), combined in the two groups having induction therapy comprising azathioprine and corticosteroids.
The collected data suggested that the 2 treatments had a similar efficacy in terms of patient survival, transplant rejection after 15 months of follow-up, the incidence and severity of acute rejection as well as the time to onset of rejection episodes.

Herzberg *et al.*[4]: a prospective study comparing the effects of recipient/donor HLA incompatibility on transplant rejection as a function of the treatments used (ciclosporin or tacrolimus) in 38 children. The study showed that HLA-A and HLA-B incompatibility had no effect on the incidence of rejection, whatever the treatment used. On the other hand, the presence of two HLA-DR incompatibilities increased the risk of severe rejection in children treated with ciclosporin compared to children treated with tacrolimus (p=0.01).

West *et al.*[5]: this study was not taken into account, as it evaluated the feasibility of ABO-incompatible heart transplantation in children. The results were compared with those of children with an ABO-compatible heart transplant.

Rejection therapy - Adults and children
Study FG-506-05-02:
During this prospective study, some patients were converted to the anticalcineurin of the other group. Eight patients (5.1%) in the Tac group had to switch to the CyA group (1 for rejection, 6 for toxicity and 1 case decided by the physician), whereas 16 (10.2%) patients in the CyA group had to switch to the Tac group (14 for rejection, 2 for poor safety). This difference (5.1% vs. 10.2%) was significant.

Of the 14 patients switching from the CyA group to the Tac group because of rejection, 12 were still receiving Tac + CS + AZA or MMF at 18 months post-transplantation (2 died: 1 with myocardial ischaemia and 1 with acute renal failure).

Study 93-0-003[10]:

This prospective study evaluated the efficacy of tacrolimus in 16 heart allograft recipients in whom tacrolimus replaced ciclosporin because of recurrent acute rejection (n = 12), humoral rejection (n = 1), and serious adverse effects (n = 3).

Of the 16 patients who switched to tacrolimus, 3 presented a biopsy-proven acute rejection during follow-up, 6 patients had no or only one episode of rejection, 2 patients had 2 episodes of rejection and 4 patients all presented with more than 2 rejections.

Because the data were collected retrospectively during study FG95-506-10[6], as during study FG94-506-09[8] they are not discussed in this opinion.

The FG94-506-09 study report presented data collected in 10 patients who received tacrolimus under ATU conditions (before its marketing in 1994) for the treatment of rejection. This study is not discussed because of the small number of patients involved and especially because of the wide variety of anti-rejection treatments used before switching to tacrolimus in each patient: corticosteroids, anti-CD3 antibodies, polyclonal antibodies (antilymphocyte immunoglobulins).

3.2. Conclusion

Prophylaxis of transplant rejection – Adults and children

In the submitted, studies, PROGRAF was used in heart allograft recipients, in combination with other immunosuppressive medicinal products. The comparator was the other available calcineurin inhibitor, ciclosporin. The doses specified in the MA were used in these studies.

The primary endpoint was the occurrence of episodes of rejection diagnosed by endomyocardial biopsy (BPAR) ≥1B after 6 months of treatment.

A difference was noted between the 2 treatment groups (Tac and CyA) in favour of tacrolimus, compared to ciclosporin (after antilymphocyte induction therapy and treatment with corticosteroids and azathioprine), with a centralised and blinded reading of biopsies.

In the American study, no significant difference was observed between the Tac /MMF and CyA/MMF groups regarding 1-year graft and patient survival, the incidence of biopsy-proven acute rejections (BPAR) ≥3A and, the incidence of BPAR ≥3A associated with haemodynamic repercussions.

In paediatric heart transplantation, most of the studies were open-label retrospective studies on very small populations. The control groups were historical series of paediatric heart transplant patients treated with ciclosporin. No clear conclusions could be drawn from these studies regarding the relative efficacy of the two types of treatment.

Rejection therapy - Adults and children

The studies provided analyzed the conversion rates from one immunosuppressive agent to the other, in particular after rejection. The reasons for converting to PROGRAF were mainly due to refractory rejection whereas conversions away from PROGRAF were mainly due to its adverse effects. In terms of safety, tacrolimus had a better profile than ciclosporin.

[10] Mentzer RM et al. Tacrolimus as a rescue immunosuppressant after heart and lung transplantation. *Transplantation* 1998; 65(1): 109-113

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual Benefit

Immunosuppressive treatments associated with organ transplants are administered in serious clinical situations.
These products are intended for prophylactic and curative treatment combined with other immunosuppressive agents.
Their efficacy/safety ratio in the context of combination therapy is high.
These medicinal products can be 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 transplant rejection (after heart transplantation) is low.

An improvement in the prophylaxis and treatment of transplant rejection constitutes a public health need lying within the scope of identified priorities (GTNDO priorities).

In view of the current management of transplant rejection, the improved cardiac safety compared to ciclosporin and a probable improvement in treatment compliance, this product may be expected to have a small benefit in terms of morbidity and mortality in the indication prophylaxis of heart transplant rejection.

Moreover, as PROGRAF is already used for the curative management of transplant rejection (organ allografts), it is not expected to have an additional benefit in terms of morbidity and mortality for the indication treatment of transplant rejection.

PROGRAF should therefore provide an additional response to an identified public health need.

Accordingly, in view of the current therapeutic management of transplant rejection, PROGRAF is expected to benefit public health. This benefit is small.

The actual benefit of PROGRAF is substantial.

4.2. Improvement in actual benefit:

In this new indication and therapeutic situation, PROGRAF provides a moderate improvement in actual benefit (IAB III), in terms of efficacy and safety, compared to ciclosporin.

4.3. Therapeutic use

Transplantation requires lifelong anti-rejection treatment with immunosuppressive agents.
Optimum immunosuppressive treatment requires a combination of several types of immunosuppressive agents with complementary pharmacotherapeutic targets, in order to reduce adverse effects without compromising efficacy by reducing their respective doses.
The pivotal immunosuppressive agents are the anticalcineurins (ICNs) (tacrolimus and ciclosporin), which are the first to be used in these combinations. Initially, before mycophenolate mofetil (MMF) became available, azathioprine (an antiproliferative drug) was used as adjuvant therapy. The ICN + MMF combination is currently the first line combination, even if, to a lesser extent, azathioprine is still used.

Induction therapy with polyclonal or monoclonal antibodies may be combined during or after transplantation, in order to induce lymphopenia and further reduce the risk of rejection.

There is no consensus about the best prophylactic or curative treatment for heart transplant rejection. Treatment protocols are constantly changing and the therapeutic combinations used mainly depend on the practices of the centres concerned and the profiles of recipients (age, pre-sensitisation) and donors (borderline graft, compatibility with recipient etc.).

Prophylactic immunosuppression usually involves tritherapy combining:

- A calcineurin inhibiter (PROGRAF or NEORAL),
- An antiproliferative agent (CELLCEPT or IMUREL),
- Tapered doses of corticosteroids (which are discontinued when possible).

Induction therapy (quadruple therapy) may be added in some centres.

The administration of additional doses of corticosteroids, and the institution of short courses of monoclonal or polyclonal antibodies, may be used when episodes of rejection occur.

4.4. Target population

The target population of PROGRAF in the new indication is represented by heart allograft recipients.
According to the data of the French Biomedecine Agency[11], 339 heart transplants were performed in 2005, including 13 in paediatric patients.

4.5. 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 extensions of indications and posology of the Marketing Authorisation.

4.5.1. Packaging: Appropriate to the conditions of prescription.

4.5.2. Reimbursement rate: 100 %

[11] Agence de Biomedecine. Activity Report of the French Transplantation Agency. 2005 Accessible on the website: http://www.efg.sante.fr/fr/doc/rapp_synt2005.pdf. Viewed on 10 October 2006