



HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

**TRANSPARENCY COMMITTEE**

OPINION

21 October 2009

**MODIGRAF 0.2 mg granules for oral suspension**  
**Pack of 50 single dose sachets (CIP: 395 948-2)**

**MODIGRAF 1 mg granules for oral suspension**  
**Pack of 50 single dose sachets (CIP: 395 949-9)**

**Applicant: ASTELLAS PHARMA SAS**

Tacrolimus

ATC code: L04AD02

Marketing Authorisation date: 15 May 2009

Reason for request: inclusion on the list of medicinal products reimbursed by National Health 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 granule form, specifically adapted for paediatric use, enables the administration of a more accurate dosage for a product with a narrow therapeutic window.

## 1.3. Indication

“Prophylaxis of transplant rejection in adult and paediatric, kidney, liver or heart allograft recipients.

Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult and paediatric patients”

## 1.4. Dosage

“This medicinal product should only be prescribed, and changes in immunosuppressive therapy initiated, by physicians experienced in immunosuppressive therapy and the management of transplant patients. Modigraf is a granular formulation of tacrolimus, for twice-a-day administration. Modigraf therapy requires careful monitoring by adequately qualified and equipped personnel.

### *Dosage*

The recommended initial doses presented below are intended to act solely as a guideline. Modigraf is routinely administered in conjunction with other immunosuppressive agents in the initial post-operative period. The dose may vary depending upon the immunosuppressive regimen chosen. Modigraf dosing should primarily be based on clinical assessments of rejection and tolerability in each patient individually aided by blood level monitoring (see below under “Therapeutic drug monitoring”). If clinical signs of rejection are apparent, alteration of the immunosuppressive regimen should be considered.

Careful and frequent monitoring of tacrolimus trough levels is recommended in the first 2 weeks post-transplant to ensure adequate drug exposure in the immediate post-transplant period. As tacrolimus is a substance with low clearance, it may take several days after adjustments to the Modigraf dose regimen before steady state is achieved [...]

### Prophylaxis of kidney transplant rejection

#### *Adults*

Oral Modigraf therapy should commence at 0.20-0.30 mg/kg/day administered as 2 divided doses (e.g. morning and evening). Administration should commence within 24 hours after the completion of surgery.

If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of 0.05-0.10 mg/kg/day (with Prograf 5 mg/ml concentrate for solution for infusion) should be initiated as a continuous 24-hour infusion.

#### *Paediatric patients*

An initial oral dose of 0.30mg/kg/day should be administered in 2 divided doses (e.g. morning and evening). If the clinical condition of the patient prevents oral dosing, an initial intravenous dose of 0.075–0.100 mg/kg/day (with Prograf 5 mg/ml concentrate for solution for infusion) should be administered as a continuous 24-hour infusion [...]

## Prophylaxis of liver transplant rejection

### *Adults*

Oral Modigraf therapy should commence at 0.10-0.20 mg/kg/day administered as 2 divided doses (e.g. morning and evening). Administration should commence approximately 12 hours after the completion of surgery.

If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of 0.01 – 0.05 mg/kg/day (with Prograf 5 mg/ml concentrate for solution for infusion) should be initiated as a continuous 24 – hour infusion.

### *Paediatric patients*

An initial oral dose of 0.30 mg/kg/day should be administered in 2 divided doses (e.g. morning and evening). If the clinical condition of the patient prevents oral dosing, an initial intravenous dose of 0.05 mg/kg/day (with Prograf 5 mg/ml concentrate for solution for infusion) should be administered as a continuous 24 hour infusion [...]

## Prophylaxis of heart transplant rejection

### *Adults*

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

Following antibody induction, oral Modigraf therapy should commence at a dose of 0.075 mg/kg/day administered as 2 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 (with Prograf 5 mg/ml concentrate for solution for infusion) should be initiated as a continuous 24-hour infusion [...]

### *Paediatric patients*

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

In patients without antibody induction, if tacrolimus therapy is initiated intravenously, the recommended starting dose is 0.03-0.05 mg/kg/day (with Prograf 5 mg/ml concentrate for solution for infusion) 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 Modigraf therapy is initiated orally, the recommended starting dose is 0.10 – 0.30 mg/kg/day administered as 2 divided doses (e.g. morning and evening).

### *Dose adjustment during post-transplant period in adults and paediatric patients*

Tacrolimus doses are usually reduced in the post-transplant period. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments [...].

## Dose adjustments in special populations

### *Hepatic impairment*

Dose reduction may be necessary in patients with severe liver impairment in order to maintain the blood trough levels within the recommended target range.

### *Renal impairment*

As the pharmacokinetics of tacrolimus are unaffected by renal function (see section 5.2), no dose adjustment is required. However, owing to the nephrotoxic potential of tacrolimus careful monitoring of renal function is recommended (including serial serum creatinine concentrations, calculation of creatinine clearance and monitoring of urine output).

### *Race*

In comparison to Caucasians, black patients may require higher tacrolimus doses to achieve similar trough levels.

### *Gender*

There is no evidence that male and female patients require different doses to achieve similar trough levels.

### *Paediatric patients*

In general, paediatric patients require doses 1½-2 times higher than the adult doses to achieve similar blood levels

### *Elderly patients*

There is no evidence currently available to indicate that dosing should be adjusted in elderly patients."

## 2 SIMILAR MEDICINAL PRODUCTS

### **2.1. ATC Classification (2008)**

L:	Antineoplastic and immunomodulatory agents
L04:	Immunosuppressants
L04A:	Immunosuppressants
L04AD:	Calcineurin inhibitors
L04AD02:	Tacrolimus

### **2.2. Medicines in the same therapeutic category**

Other tacrolimus-based medicinal products:

\* in the indication: "Prophylaxis of transplant rejection in adult kidney or liver transplant recipients. Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients":

- ADVAGRAF 0.5 mg prolonged release capsules
- ADVAGRAF 1 mg prolonged release capsules
- ADVAGRAF 5 mg prolonged release capsules
- ADVAGRAF 3 mg prolonged release capsules

\* in the same indications as MODIGRAF: "Prophylaxis of graft rejection in adult and paediatric kidney, liver or heart transplant recipients.

Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult and paediatric patients."

- PROGRAF 0.5 mg capsules
- PROGRAF 1 mg capsules
- PROGRAF 5 mg capsules
- PROGRAF 5 mg/1 ml concentrate for solution for infusion

### 2.3. Medicines with a similar therapeutic aim

All medicinal products used for the prophylaxis of graft rejection in kidney and/or liver and/or heart transplant recipients and for the treatment of rejection.

#### 2.3.1 Medicinal products with a similar therapeutic aim indicated for the prophylaxis and treatment of rejection:

- SANDIMMUN (ciclosporin) – adults and paediatric patients
- NEORAL (ciclosporin micro-emulsion) – adults and paediatric patients

#### 2.3.2 Medicinal products with a similar therapeutic aim indicated for the prophylaxis of rejection:

Kidney transplantation: (in combination with other immunosuppressive medicinal products)

- IMUREL (azathioprine) – adults and paediatric patients; CELLCEPT (mycophenolate mofetil) – adults and paediatric patients; MYFORTIC (mycophenolic acid in the form of a sodium salt) – adults; RAPAMUNE (sirolimus) – adults; CERTICAN (everolimus) – adults; SIMULECT (basiliximab) – adults and paediatric patients; corticosteroids – adults and paediatric patients.

Liver transplantation (in combination with other immunosuppressive medicinal products)

- IMUREL (azathioprine) adults and paediatric patients; CELLCEPT (mycophenolate mofetil) adults and paediatric patients;
- Corticosteroids – adults and paediatric patients;

Heart transplant: (in combination with other immunosuppressive medicinal products)

- IMUREL (azathioprine) - adults and paediatric patients; CELLCEPT (mycophenolate mofetil) - adults and paediatric patients; CERTICAN (everolimus) adults.
- High dose corticosteroids – adults and paediatric patients.

### 3 ANALYSIS OF AVAILABLE DATA

This application includes:

- A bioequivalence study (95-0-001): this was an open-label phase I study in four cross-over periods involving healthy adult volunteers, comparing tacrolimus granules (MODIGRAF) with tacrolimus capsules (PROGRAF). The results showed that the bioavailability of MODIGRAF exceeded that of PROGRAF by about 20%.
- Two phase III studies of tacrolimus capsules in paediatric renal transplant recipients:
  - - Study FG-506-02-03 (1999) comparing tacrolimus with ciclosporin micro-emulsion, both concomitant to azathioprine/corticosteroids. The primary endpoint was rejection after 6 months; 204 children were randomised: 196 were analysed on an ITT basis, 103 in the PROGRAF arm and 93 in the NEORAL arm. More children avoided acute rejection after 6 months (61.4% versus 34.6%,  $p=0.007$ ) in the tacrolimus arm than in the NEORAL arm. In addition, the rate of corticosteroid-resistant rejection was lower in the PROGRAF arm (7.8% versus 25.8%,  $p=0.001$ ) than in the NEORAL arm.
  - - Study FG-506-02-43 comparing daclizumab + corticosteroids over 4 days with prolonged corticosteroids, both treatments being combined with tacrolimus/MMF. The primary endpoint was the change in growth measured by changes in height according to the standard deviation score (baseline to end-of-study height). Out of 200 patients randomised, 184 were analysed on an ITT basis: 93 in the daclizumab + corticosteroid arm over 4 days and 91 in the prolonged corticosteroid arm. Because the patients included in both arms received tacrolimus, this study is not being taken into consideration in this opinion.
- A phase III comparative study (FG 506- 01-13) of tacrolimus granules given to children undergoing a liver transplant to assess the efficacy and safety of MODIGRAF (see 3.1).

#### 3.1. Efficacy

Study FG 506- 01-13

**Objective:** to compare the efficacy and safety of treatment with tacrolimus granules with that of ciclosporin micro-emulsion (ME) + azathioprine, both concomitant to corticosteroids in children receiving a first liver transplant.

**Method:** open-label randomised comparative study

#### Endpoints

Primary endpoint: incidence and time to occurrence of the first acute graft rejection after transplantation. All cases of acute rejection were confirmed by biopsy.

The secondary efficacy endpoints were:

- incidence and time to occurrence of the first acute corticosteroid-resistant rejection episode,
- graft and patient survival,
- corticosteroid dose accumulated throughout the study.

**Inclusion criteria:** To be included, the patients had to be no more than 16 years of age, with a body weight of less than 40 kg.

#### Treatment administered:

Tacrolimus was administered orally at an initial dose of 0.3 mg/kg/day in two intakes, then adjusted to obtain a blood concentration of 10 to 20 ng/ml between day 0 and day 30 then between 5 and 10 ng/ml as from day 30.

Methylprednisolone was administered at a dose of 10 mg/kg/day.

ciclosporin was administered orally at an initial dose of 10 mg/kg/day, which was then adjusted to obtain a blood concentration of 250 to 300 ng/ml during the first 6 weeks and then 100 to 200 ng/ml until the end of the study.

## Results

Out of the 185 patients randomised, 181 were analysed on an ITT basis: 91 in the tacrolimus granules arm and 90 in the ciclosporin ME arm. The mean age of patients in both treatment arms was 3 years. The proportion of patients in the ciclosporin ME arm who were positive for Epstein Barr Virus (EBV) IgG antibodies was 37/71, i.e. 52.1% compared to 24/75 (32%) in the tacrolimus arm. Six deaths occurred in the tacrolimus granules arm and seven in the arm treated with ciclosporin ME. The main reason for treatment discontinuation was the onset of adverse events, which concerned 10 patients in the tacrolimus granules arm and 35 in the ciclosporin ME arm.

### Primary endpoint

The percentage of patients not experiencing acute rejection after 12 months was statistically higher in the tacrolimus granules arm (55.5%) than in the ciclosporin arm (40.2%,  $p=0.029$ ) (see Table 1).

**Table 1:** Incidence of and time elapsing before first episode of acute rejection (Kaplan-Meier estimation)

	Tacrolimus granules N=91		Ciclosporin ME N=90		p‡
	Acute rejections	Incidence (%)	Acute rejections	Incidence (%)	
Week 1	10		21		
Week 2	17		9		
Week 3	4		6		
Week 4	1		2		
Month 2	3		5		
Month 3	1		2		
Months 4-6	0		3		
Months 7-9	1		1		
Months 10-12	1		0		
> month 12 to end of study	0	0.555	0	0.402	0.029

Intention-to-treat population

p‡ Wilcoxon test for the difference in time until onset of the event between treatment arms during the 12 months of the study

All episodes of acute rejection were confirmed by biopsy.

### Secondary endpoints

The incidence of the first episode of acute corticosteroid-resistant rejection after 12 months was 94% in the tacrolimus granules arm and 70.4% in the ciclosporin ME arm ( $p<0.001$ ).

The incidence of corticosteroid-resistant graft rejections was higher in the ciclosporin ME arm (26.7%) than in the tacrolimus arm (5.5%) after 12 months ( $p<0.001$ ).

The rate of patient survival after 12 months was 93.4% in the tacrolimus granules arm and 92.2% in the ciclosporin ME arm ( $p=0.773^1$ ).

After one year, graft survival rates were 92.3% in the tacrolimus granules arm and 85.4% in the ciclosporin ME arm ( $p=0.555^1$ ).

There was no significant difference between the tacrolimus granules and ciclosporin arms regarding the accumulated dose of corticosteroids after 12 months.

<sup>1</sup> Wilcoxon test

### 3.2. Tolerance

The overall incidence of adverse events was similar in both treatment arm; in study FG-506-01-13, 97.8% of patients in both the tacrolimus granules arm and ciclosporin ME arm experienced at least one adverse event; 94.4% of patients in the tacrolimus granules arm experienced an adverse event deemed by the investigators to be ascribable to treatment during the study and 90% in the ciclosporin emulsion arm.

The most common adverse effects occurring during the study (hypertension, fever and acidosis) are summarised in Table 2. Significantly more patients in the tacrolimus granules arm experienced EBV infection and acidosis, while a greater number of patients in the ciclosporin emulsion arm suffered from hirsutism and gingival hyperplasia (0% compared to 8.9%,  $p=0.003$  according to Fisher's exact test).

**Table 2:** summary of most common AE considered as ascribable\* to study treatment – number of patients (%)

Adverse effects	Tacrolimus granules N=91 (%)	Ciclosporin ME N=90 (%)
Hypomagnesaemia	33 (36.3)	23 (25.6)
Hypertension	30 (33.0)	37 (41.1)
Fever	30 (33.0)	32 (35.6)
Hepatic function test anomalies	27 (29.7)	21 (23.3)
EBV infection**	23 (25.3)	9 (10.0)
Infection	16 (17.6)	17 (18.9)
Acidosis**	14 (15.4)	3 (3.3)
CMV infection	13 (14.3)	21 (23.3)
Sepsis	13 (14.3)	14 (15.6)
Hirsutism**	0	24 (26.7)

Intention-to-treat population

\* Causal relationship with the study treatment very probable, probable, possible, unknown or missing

\*\* ( $p<0.05$ ), according to Fisher's exact test

Two patients (2.2%) died during the study in the tacrolimus arm (N=91) and three (3.3%) in the ciclosporin ME arm (N=90).

In terms of infectious complications, out of the 181 patients in the ITT population, 154 (85.1%) experienced at least one infection during the study. There was a higher number of EBV infections ( $p=0.013$ , Fishers' exact test) in the tacrolimus granules arm (25.3%) than in the ciclosporin ME arm (10%). At inclusion, 32% of patients in the tacrolimus granules arm and 52.1% of those in the ciclosporin ME arm were positive for EBV-VCA IgG. Patients in the tacrolimus granules arm were therefore more likely to acquire new EBV infections during the study.

Post-transplant lymphoproliferative syndromes associated with EBV were detected in 2/91 (2.2%) and 0/90 patients in the tacrolimus granules and ciclosporin arms, respectively. Post-transplant lymphoproliferative syndromes associated with EBV were suspected in 3/91 (3.3%) and 1/90 (1.1%) patients in the tacrolimus granules and ciclosporin arms, respectively.

### 3.3. Conclusion

During a phase III study of 181 liver transplant recipients under the age of 16, tacrolimus granules combined with corticosteroids were more effective than ciclosporin ME combined with azathioprine and corticosteroids in terms of the number of patients avoiding acute rejection evidenced by biopsy (55.5% with tacrolimus granules versus 40.2% with ciclosporin ME;  $p=0.029$ ).



In terms of safety, the numbers of patients experiencing adverse events considered to be ascribable to treatment were similar in the two treatment arms. The most common adverse effects were fever and hypertension. More cases of EBV infection and acidosis were observed in the tacrolimus arm than in the arm treated with ciclosporin. MODIGRAF displayed a similar safety profile to ciclosporin ME.

## 4 TRANSPARENCY COMMITTEE CONCLUSIONS

### 4.1. Actual benefit

Organ transplantation is a clinical situation of a particularly serious nature.

These proprietary medicinal products come within the scope of prophylactic and curative treatment combined with other immunosuppressive medicinal products.

The efficacy/adverse effects ratio of these medicinal products in the context of combined therapy is high.

These proprietary medicinal products are used in first-line treatment.

There are few alternative treatments available.

Public health benefit: in terms of public health, the burden of rejection following liver, kidney and heart transplantation can be considered to be moderate. The burden of the condition corresponding to the population likely to benefit specifically from treatment with Modigraf (children, adults with difficulty in swallowing or in the event of concomitant prescription with liver enzyme inhibitors/inducers, protease inhibitors, antifungal triazoles, etc.) is nonetheless thought to be low given the limited number of patients concerned.

An improvement in the prevention of graft rejections is a public health need that falls within the scope of identified priorities (GTNDO chronic renal impairment-related priorities - 2003).

Given the narrow therapeutic window of tacrolimus and the precise dose adjustments enabled by the oral suspension formulation, Modigraf can be expected to improve dosage adjustments, especially in low-weight children. Modigraf should limit the variability between individuals and the potential risks of under- or overdosing with the capsule form and may, in the longer term, contribute to an impact on the risk of graft rejection.

However, as the consequences of any variability have not been demonstrated, and given the small number of patients concerned, Modigraf is not expected to have any impact on morbidity and mortality in population terms.

Consequently, Modigraf is not expected to have an impact on public health.

The actual benefit of these proprietary medicinal products is substantial.

### 4.2. Improvement in actual benefit

Thanks to the improvement in the methods of administration that this granule form of tacrolimus is likely to procure in terms of more accurate dosing and the clinical consequences thereof, it provides a minor improvement in actual benefit (level IV) in its therapeutic use for the prevention of graft rejection and the treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in the context of paediatric transplantation.

In terms of the indications for adults stipulated in the MA, this granule form of tacrolimus does not provide any improvement in actual benefit (level V).

#### 4.3. Therapeutic use

Transplantation requires lifelong anti-rejection treatment with immunosuppressive medicinal products.

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.).

Optimum immunosuppressive therapy combines several types of immunosuppressive medicinal products with complementary pharmacotherapeutic targets, aimed at reducing adverse effects without compromising efficacy because of a reduction in their respective doses.

##### Heart transplants:

Calcineurin inhibitors (CNIs) (tacrolimus and ciclosporin) are the first immunosuppressive medicinal products to be used in such combined therapies. The CNI + mycophenolate mofetil (MMF) combination is currently the combined therapy of choice, even if azathioprine is still used to a lesser extent.

Polyclonal or monoclonal antibodies combined in per/post-transplant induction therapy are used to induce lymphopenia to further reduce the risk of rejection.

Preventive immunosuppression generally includes triple therapy combining:

- a calcineurin inhibitor (tacrolimus or ciclosporin),
- a cell proliferation inhibitor (mycophenolate mofetil or azathioprine),
- tapering doses of corticosteroids (then discontinuation when possible).

If rejection occurs, further doses of corticosteroids can be administered and brief courses of monoclonal or polyclonal antibodies introduced.

##### Liver and kidney transplants<sup>23</sup>

Induction therapy with polyclonal or monoclonal antibodies, administered during or after transplantation, serve to block lymphocyte activation and/or induce lymphopenia so as to reduce the risk of rejection during the stabilisation phase of maintenance immunosuppression.

Initial preventive immunosuppression generally involves triple therapy (or sometimes dual therapy) combining:

- calcineurin inhibitors: tacrolimus or ciclosporin,
- mycophenolate mofetil (or azathioprine, sirolimus, everolimus) in kidney transplantation and mycophenolate mofetil or azathioprine in liver transplantation,
- a glucocorticoid

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

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

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<sup>2</sup> HAS. Outpatient monitoring of adult kidney transplant patients more than 3 months after transplantation. Professional guidelines November 2007

<sup>3</sup> Woodroffe R, Yao GL, Meads C, Bayliss S, Ready A, Raftery J, et al. Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study. Health Technol Assess 2005;9(21) :1-179, iii-iv.

The two populations likely to benefit most from tacrolimus granules, because of its pharmaceutical form which enables a more accurate dosage adjustment, are children and adults prescribed tacrolimus metabolism inhibitors concomitantly: for example, antifungal triazoles and protease inhibitors.

#### **4.4. Target population**

The target population for MODIGRAF corresponds to adults and children who have received a heart, liver or kidney transplant and thus require prophylactic graft rejection therapy. The target population also comprises adults and children suffering from allograft rejection that is resistant to treatment with other immunosuppressive medicinal products.

The two populations likely to benefit most from tacrolimus granules, because of its pharmaceutical form which enables a more accurate dosage adjustment, are children and adults prescribed tacrolimus metabolism inhibitors concomitantly: antifungal triazoles and protease inhibitors.

According to the Biomedicine Agency (ABM)<sup>4</sup>, there were 360 heart, 1,011 liver and 2,937 kidney adult transplant recipients in 2008. For information, on January 1, 2009, 300 adult patients were on the heart transplant waiting list, 669 on the liver transplant list and 6,859 on the kidney transplant list.

It is currently impossible to quantify the target population of adults most likely to benefit from MODIGRAF.

In 2008, the maximum number of new adult patients able to benefit from MODIGRAF was 3,900. It is impossible to estimate accurately the adult target population as immunosuppressive therapy is life-long and therefore concerns all heart, liver and kidney transplant recipients (missing data).

As for the paediatric population, which could especially benefit from tacrolimus granules for oral suspension, 18 children received a heart transplant in 2008, 71 a liver transplant and 71 a kidney transplant. For information, on January 1, 2008, 12 children were on the heart transplant waiting list, 39 on the liver transplant list and 61 on the kidney transplant list.

In 2008, the maximum number of new paediatric patients able to benefit from MODIGRAF was 160. Similarly, it is impossible to estimate accurately the target paediatric population as immunosuppressive therapy is life-long and therefore concerns all heart, liver and kidney transplant recipients (missing data).

#### **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 indications and dosages of the MA.

4.5.1. Packaging: appropriate for the prescription requirements.

4.5.2. Reimbursement rate: 100%.

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<sup>4</sup> Biomedicine Agency. Overview of graft harvesting and transplantations in France. Biomedicine Agency Annual Report for 2008 available on website: <http://www.agence-biomedecine.fr/annexes/bilan2008/accueil.htm>. Access August 31 2009