HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

Opinion

16 July 2008

RAPAMUNE 1 mg, coated tablets
B/30 (CIP: 359 530-1)
RAPAMUNE 2 mg, coated tablets
B/30 (CIP: 361 568-2)
RAPAMUNE 1 mg/ml, oral solution
60 ml bottle (CIP: 356 884-7)

Applicant: WYETH PHARMACEUTICALS FRANCE

Sirolimus

List I
Medicinal product available on 6-month hospital prescription only

ATC code: L04AA10

Dates of Marketing Authorizations:
RAPAMUNE 1 mg, coated tablet – 12 April 2002
RAPAMUNE 2 mg, coated tablet – 10 January 2003
RAPAMUNE 1 mg/ml, oral solution – 13 March 2001

Reason for request: reassessment following submission of new data.

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Sirolimus

1.2. Indication

“Rapamune is indicated for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving a renal transplant. It is recommended that RAPAMUNE be used initially in combination with ciclosporin microemulsion and corticosteroids for 2 to 3 months. RAPAMUNE may be continued as maintenance therapy with corticosteroids only if ciclosporin microemulsion can be progressively discontinued.”

1.3. Dosage (see SPC)

Initial therapy (2 to 3 months post-transplantation): The usual dosage regimen for RAPAMUNE is a 6 mg oral loading dose, administered as soon as possible after transplantation, followed by 2 mg once daily. The RAPAMUNE dose should then be individualized, to obtain whole blood trough levels of 4 to 12 ng/ml (chromatographic assay). RAPAMUNE therapy should be optimized with a tapering regimen of steroids and ciclosporin microemulsion. Suggested ciclosporin trough concentration ranges for the first 2-3 months after transplantation are 150 - 400 ng/ml (monoclonal assay or equivalent technique).

Maintenance therapy: Ciclosporin should be progressively discontinued over 4 to 8 weeks, and the RAPAMUNE dose should be adjusted to obtain whole blood trough levels of 12 to 20 ng/ml 36 (chromatographic assay). RAPAMUNE should be given with corticosteroids. In patients for whom ciclosporin withdrawal is either unsuccessful or cannot be attempted, the combination of ciclosporin and RAPAMUNE should not be maintained for more than 3 months post-transplantation. In such patients, when clinically appropriate, RAPAMUNE should be discontinued and an alternative immunosuppressive regimen instituted.

2 COMPARABLE MEDICINAL PRODUCTS

2.1 Medicines in the same therapeutic category

Immunosuppressants used in combination:
Calcineurin inhibitors:
SANDIMMUN* (ciclosporin) – NEORAL* (ciclosporin microemulsion)
PROGRAF*, ADVAGRAF* (tacrolimus)
mTOR inhibitors:
CERTICAN* (everolimus)
Antimetabolics:
IMUREL* (azathioprine)
CELLCEPT* (mycophenolate mofetil)
MYFORTIC (mycophenolic acid as sodium salt)

2.2 Medicines with a similar therapeutic aim

ZENAPAX (daclizumab)
SIMULECT (basiliximab)
ORTHOCLONE OKT3* (muromonab)
LYMPHOGLOBULIN* (equine anti-human thymocyte immunoglobulin)
THYMOGLOBULIN* (rabbit anti-human thymocyte immunoglobulin)

Corticosteroids at high doses

3 SUMMARY OF THE PREVIOUS COMMITTEE OPINIONS

3.1. COMMITTEE OPINION of 28 November 2001

RAPAMUNE 1 mg/ml, RAPAMUNE 1 mg/1 ml, RAPAMUNE 2 mg/2 ml,

- Actual benefit

Immunosuppressant treatments associated with organ transplants are administered in severe clinical situations. This proprietary product is a preventive treatment combined with other immunosuppressants. Its risk-benefit ratio in combination is high. These medicinal products are first-line products. There are few alternative treatments. The actual medical benefit of these medicinal products is substantial.

- Improvement in actual benefit

In preventive induction therapy, tritherapy combining sirolimus, ciclosporin and corticosteroids is more effective than the comparator treatment including azathioprine, with no major impairment of the kidney function during a limited period of 3 months in patients presenting a low to

* broader indications than kidney transplantation

moderate immunological risk.
It should be emphasized that the comparators used in the clinical trials are not considered to be the most effective in terms of incidence of rejection.
In preventive maintenance therapy, the bitherapy RAPAMUNE - corticosteroids (after tapering and discontinuance of ciclosporin) has comparable efficacy to the tritherapy RAPAMUNE - corticosteroids - ciclosporin, while preserving the kidney function better in patients with low to moderate immunological risk and a kidney function allowing tapering of ciclosporin in maintenance therapy.

Consequently, in the case of the limited population in terms of immunological risk, RAPAMUNE:

- extends the range of available immunosuppressants
- represents an effective medicine according to the state of the art, with fewer nephrotoxic effects than ciclosporin in the context of preventive maintenance therapy for patients who can be weaned off ciclosporin.

Consequently, like other immunosuppressants, it represents an important addition to the treatment strategy.

However, in view of:

- the absence of comparative studies compared with the combinations currently used (especially CELLCEPT- PROGRAF) in preventive induction therapy

- the short follow-up period, especially in view of the possible cardiovascular complications associated with elevated cholesterol and serum triglyceride levels in the RAPAMUNE groups, it is currently difficult to position it in relation to other immunosuppressants.

On the basis of the state of the art, the Committee cannot attribute an improvement in actual benefit to it.

3.2. Committee's Opinion of 6 July 2005

RAPAMUNE 1 mg, RAPAMUNE 2 mg, RAPAMUNE 1 mg/ml

- <u>Actual benefit</u>

Immunosuppressant treatments associated with organ transplants are administered in severe clinical situations.
These proprietary products are classed as preventive treatment in combination with other immunosuppressants in adult kidney transplant recipients presenting a low to moderate immunological risk. Their risk-benefit ratio in combination is high.
These medicinal products are first-line products. There are few alternative treatments.

Public health benefit: the public health benefit burden caused by kidney transplant rejection is moderate. Preventing rejection represents an important therapeutic need. By allowing the doses of ciclosporin to be reduced (and discontinued), RAPAMUNE should reduce the adverse renal effects of preventive maintenance treatment. The expected impact on morbidity and mortality is low. Consequently, there is an expected public health benefit for the proprietary product RAPAMUNE. However, its impact will be slight.
The actual medical benefit of these medicinal products is substantial.

- <u>Improvement in actual benefit</u>

In the absence of a comparative study and having regard to its efficacy level, the Committee considers that RAPAMUNE (sirolimus) does not provide any improvement in actual benefit (IAB

V) compared with the proprietary product CERTICAN (everolimus) in preventive treatment of adult kidney transplant patients presenting a low to moderate immunological risk. It declares and confirms that RAPAMUNE (sirolimus), in combination with corticosteroids, is an effective medicine with fewer nephrotoxic effects than in combination with ciclosporin and corticosteroids in the preventive maintenance treatment of adult patients presenting a low to moderate immunological risk whose ciclosporin treatment can be discontinued.

ANALYSIS OF AVAILABLE DATA

4.1. Efficacy

On request by EMEA, trial 310 was extended (protocol amended). The 5-year data are presented here.

4.1.1 Summary of main data of pivotal trial 310 according to the opinions of the Transparency Committee dated 28 November 2001, 21 May 2003 and 6 July 2005 (extracts)

Objective: to evaluate the equivalence, in terms of organ survival, of 2 immunosuppression protocols administered as maintenance treatment: corticosteroids + sirolimus + ciclosporin A at reduced doses *vs.* corticosteroids + sirolimus without ciclosporin.

Methodology: A randomized open-label trial; 525 patients were included after a 3-month treatment period combining sirolimus + ciclosporin + corticosteroids, and divided into 2 groups of 215 patients:

Group A = continuance of treatment (tritherapy: sirolimus + ciclosporin + corticosteroids): reduced doses of ciclosporin to obtain a serum concentration of 75-200 ng/mL, and sirolimus 2 mg/day to obtain a serum concentration > 5 ng/mL.

Group B = tapering of ciclosporin over 4 to 6 weeks: dose of sirolimus increased to obtain the concentration recommended in the SPC.

In the analysis, the patients were compared on the basis of their initial randomization group, without taking account of further changes in the treatment.

Inclusion criteria:
- patients at low to moderate immunological risk
- patients who had received a kidney transplant from a dead or living donor. Patients who received a second transplant, with survival of the first organ for at least 6 months after transplantation, were also included.

Primary endpoint: 12-month organ survival rate.

Group A and group B were ruled equivalent if the 95% confidence interval of the difference (A-B) included zero, and its upper limit was ≤ 7% after 12 months and 24 months, and 10% after 36, 48 and 60 months

Secondary endpoints: the patient's survival, organ rejection confirmed by biopsy, onset of adverse events including cancer, and organ survival rate after 24, 36, 48 and 60 months.

Efficacy results: organ survival (see table 1)

Table 1: Results of overall organ survival

Primary endpoint:	**Statistical analysis**	**With ciclosporin° (group A) (n = 215)**	**Without ciclosporin (group B) (n = 215)**	**A-B% (95% CI)**
12-month organ survival	Per protocol ITT	95,3 % (205) 95,3 % (205)	97,2 % (209) 97,2 % (209)	-1,9 (-5,4 ;1,7) -1,9 (-5,4 ;1,7)
24-month organ survival	Per protocol ITT	91,6 % (197) 91,6 % (197)	94 % (202) 94 % (202)	-2,3 (-7,2 ;2,6) -2,3 (-7,2 ;2,6)
36-month organ survival	Per protocol ITT	87 % (187) 88,4 % (190)	91,6 % (197) 92,6 % (199)	-4,7 (-10,5 ; 1,2) -4,2 (-9,7 ;1,4)
48-month organ survival	Per protocol ITT	75,3 % (162) 84,2 % (181)	86 % (185) 91,2 % (196)	-10,7(-18,1;-,3) -7 (-13,2 ; -0,8)

°: ciclosporin microemulsion

Results: Impact on kidney function (glomerular filtration rate in ml/mn calculated according to the Nankivell formula)

Table 2: Kidney function (glomerular filtration rate in ml/mn):

Duration after transplant	**With ciclosporin° (group A) (n = 215)**	**Without ciclosporin (group B) (n = 215)**	**Value of p**
1 month	54.77 ± 1.37 (203)	54.69 ± 1.41 (201)	
2 months	57.85 ± 1.23 (202)	56.24 ± 1.26 (191)	
3 months	55.15 ± 1.21 (180)	55.75 ± 1.27 (182)	
6 months	55.35 ± 1.35 (189)	58.11 ± 1.31 (191)	<0.001
9 months	56.10 ± 1.20 (176)	60.28 ± 1.48 (158)	
12 months	53.17 ± 1.46 (208)	59.25 ± 1.46 (203)	<0.001
24 months	48.38 ± 1.67 (203)	58.35 ± 1.60 (201)	<0.001
36 months	47.01 ± 1.83 (196)	58.45 ± 1.89 (199)	<0.001
48 months	43.50 ± 2.00 (185)	58.06 ± 1.97 (187)	<0.001

4.1.2 - Supplementary data of pivotal trial 310 regarding preventive maintenance treatment, after 5 years (Table 3)

Organ survival

Organ survival proved non-equivalent in favour of group B (80% *vs.* 67.9%) in the per-protocol analysis, but not in the ITT analysis (88.4% *vs. 83.3%*).

A large proportion of patients were lost to follow-up after 5 years, 15.3% (33) of whom were treated with ciclosporin, and 8.4% (18) without ciclosporin.

Table 3: 5-year organ survival rate

Primary endpoint	**With ciclosporin° (group A) (n = 215)**	**Without ciclosporin (group B) (n = 215)**	**A-B% (95% CI)**
overall organ survival ℘ per protocol	67.9% (146)	80 % (172)	-12.1 (-20,3 ;-3,9)
overall organ survival in ITT	83.3% (179)	88.4% (190)	-5.1 (-11,7 ; 1,5)

℘ Organ loss was defined as physical loss of the organ (nephrectomy), loss of kidney function requiring dialysis to be maintained for over 8 weeks, re-transplant, loss to follow-up, or death.

Secondary endpoints:

- the overall survival rate of the patients was 68.8% with ciclosporin and 80.9% without ciclosporin.
- the incidence of acute rejection was 15.8% with ciclosporin and 20.5% without ciclosporin.

Kidney function

The glomerular filtration rate (in ml/mn, calculated according to the Nankivell formula) after 5 years was 42.65 $\pm$ 2.23 (n=176) with ciclosporin and 58.04 $\pm$ 2.13 (n=193) without ciclosporin. It was comparable to the rate obtained after 48 months.

4.2. Adverse effects

4.2.1 Summary of results of pivotal trial 310 according to the opinions of the Transparency Committee dated 28 November 2001, 21 May 2003 and 6 July 2005 (extracts)

Adverse effects, based on data from the clinical trials and data reported since the product was placed on the market, the frequency of which is ≥10%, are as follows:

- Hypercholesterolaemia and hypertriglyceridaemia which may require lipid-reducing treatment.
- Hypokalaemia, elevated lactic acid dehydrogenase (LDH)
- Lymphocele
- Abdominal pain, diarrhoea
- Anaemia, thrombocytopenia
- Joint pain
- Acne
- Urinary infection
- Peripheral oedema.

Other adverse effects are cited in the SPC:

- Fever, increased ASAT and ALAT, pneumopathy, venous thromboembolic events, neutropenia, tachycardia, pneumonia (≥1% and <10%)
- Pancytopenia (≥ 0.1% and < 1%)

Cases of interstitial pulmonary disease (pneumopathy, and rarely bronchiolitis obliterans and pulmonary fibrosis), some of which were fatal, with unidentified infectious aetiology, occurred in

patients receiving immunosuppressant treatments including sirolimus.
In some cases, the interstitial pulmonary disease regressed when the dose of sirolimus was reduced or withdrawn.
Cases of liver toxicity have been reported. Rare cases of fatal liver necrosis have been reported, associated with high trough concentrations of sirolimus.
Impaired healing after transplant has been reported.

4.2.2 Update
In trial 310, after 5 years, 88% of patients in the ciclosporin group and 50% in the group without ciclosporin had discontinued the treatment†. Adverse effects were the main cause of discontinuance in both groups (45% of patients treated with ciclosporin and 33% without ciclosporin).
The most frequent adverse events included herpes, in 7.9% of patients treated with ciclosporin (n=17) and 2.8% (n=6) of patients without ciclosporin.
The incidence of essential hypertension was 27% (n=58) with ciclosporin *versus* 14.4% (n=31) without ciclosporin.

The incidence of non-skin cancer was 8.37% (n=18) with ciclosporin *versus* 3.7% (n=8) without ciclosporin (p=0.04-ITT analysis); 8.8% (n=19) of patients treated with ciclosporin suffered from skin cancer against 7.4% (n=16) of patients without ciclosporin (p=0.59 - ITT analysis). The median (95% CI) time of survival of a first skin cancer was 491 days (233; 897) with ciclosporin *versus* 1126 days 629; 1459) without ciclosporin (p=0.007).

The incidence of thrombocytopenia was 13% (n=28) without ciclosporin *versus* 5.6% (n=12) with ciclosporin. The incidence of hypokalaemia was 11.2% (n=24) without ciclosporin *versus* 5.1% (n=11) with ciclosporin, while the incidence of hyperlipidaemia was 5.6% (n=12) *versus* 1.4% (n=3) with ciclosporin.
An abnormal liver function was observed in 5.1% (n=11) of patients without ciclosporin *versus* 0.9% (n=2) of patients with ciclosporin.

An increase in serum creatinine level was observed in 36.3% (n=78) of patients with ciclosporin *versus* 20.9% (n=45) without ciclosporin.
A life-threatening abnormal kidney function was observed in 6.5% (n=14) of patients with ciclosporin *versus* 1.4% (n=3) without ciclosporin.

4.3. Conclusion

The 5-year results confirm that the overall organ survival rate is greater when the combination of corticosteroids+sirolimus is administered without ciclosporin A in maintenance treatment. The high percentage of drop-outs in the two groups should be noted. As regards kidney function, the glomerular filtration rate was similar to that obtained after 48 months in both groups. The results of this trial do not allow documentation of the efficacy and tolerance of RAPAMUNE by comparison with other immunosuppressants.

† In the analysis, the patients were compared on the basis of their initial randomization group, without taking account of further changes in the treatment. Patients mainly discontinued the initial treatment due to adverse effects, protocol violation, poor response to the treatment, the patient's request, or other reasons

5 TRANSPARENCY COMMITTEE CONCLUSIONS

5.1 Actual benefit

The actual benefit of these medicinal products remains substantial.

5.2 Improvement in actual benefit

The Transparency Committee's earlier opinion of the improvement in actual benefit provided by these medicinal products does not need to be modified.

5.3 Therapeutic use

Transplants require lifelong treatment. The recommended treatment strategy for kidney transplant rejection prophylaxis is administration of bitherapy or tritherapy with or without induction therapy[‡].
The induction stage includes the use of monoclonal or polyclonal antibodies.
The immunosuppressant treatments used in maintenance therapy are grouped into four therapeutic classes:
- corticosteroids;
- calcineurin inhibitors: ciclosporin and tacrolimus;
- mTOR inhibitors: sirolimus and everolimus;
- antimetabolics: azathioprine, mycophenolate mofetil and mycophenolic acid.

The treatment protocols are under constant clinical development, and the therapeutic combinations depend to a great extent on the hospital's habits and the profiles of the recipient (age, pre-sensitization) and the donor (marginal organ, compatibility with recipient, etc.)
The place of RAPAMUNE has not been wholly formalized[§], but it can be included in the protocols used for preventive treatment:
In initial treatment (for 2-3 months after transplantation) RAPAMUNE is combined with ciclosporin microemulsion (NEORAL) and corticosteroids for the first 2-3 months after transplantation in adult patients presenting a low to moderate immunological risk.
Preventive immunosuppression in initial treatment generally includes tritherapy (or sometimes bitherapy) combining:

- tacrolimus or ciclosporin,
- mycophenolate mofetil (or azathioprine, sirolimus, everolimus)
- corticosteroids

In maintenance therapy, it is combined with corticosteroids in the population of patients whose ciclosporin treatment can be discontinued.

[‡] HAS. *Suivi ambulatoire de l'adulte transplanté rénal au-delà de 3 mois après transplantation*. Recommandations professionnelles Novembre 2007
[§] 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).

5.4. Target population

Immunosuppressant treatments associated with organ transplants are administered in serious clinical situations, which may be life-threatening.
According to the French Biomedicine Agency, 2731 kidneys were transplanted in 2006. In 2006, 6152 patients were on the kidney transplant waiting list[**].

Prevention of organ rejection after a kidney transplant is a life-long treatment, required by all transplant recipients. Some 75-80% of transplant recipients have a low to moderate immunological risk. The population suitable to receive RAPAMUNE is therefore between 2100 and 2200 patients.

5.5 Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance in the indication and the posology in the Marketing Authorisation.

5.5.2. Packaging: Appropriate for the prescription conditions

5.5.3. Reimbursement rate: 100%

[**] Agence de la Biomédecine. Bilan des activités de prélèvement et de greffe en France. Rapport d'activité de l'Etablissement Français des greffes. Année 2006