

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

PID# D040771

DATE: February 17, 2006

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SUBJECT: ODS POSTMARKETING SAFETY REVIEW  
Consult: One-Year Post Pediatric Exclusivity Postmarketing  
Adverse Events Review  
Drug: Sirolimus Oral Solution and Tablets  
NDA: 21-110, 21-083  
Pediatric Exclusivity Approval Date: November 17, 2004

**1. EXECUTIVE SUMMARY**

The AERS database was searched for reports of adverse events (serious and non-serious) occurring with the use of sirolimus in pediatric patients. Up to the "data lock" date of December 18, 2005, AERS contained 3172 cases for sirolimus (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent approximately 2.8% of the total (88/3172).

DDRE was asked to focus on the 1-year period following the approval of pediatric exclusivity, November 17, 2004 to November 17, 2005. We used an AERS data lock date of December 18, 2005, to allow time for reports received up to November 17, 2005, to be entered into AERS. During the first 13 months after pediatric exclusivity was

granted, AERS received a total of 862 cases (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent approximately 2.2% of the total number of cases (19/862). We will refer to this 13-month interval as the pediatric exclusivity period in the remainder of this review. Individual review of the 19 unique cases retrieved from AERS on January 13, 2006, indicated that all had a serious outcome although there were no fatalities. The AERS database shows that sirolimus is used in patients as young as 14 months of age, with the majority of the patients in this case series being under 12 years of age (sirolimus is indicated for patients 13 years and older). In both US and foreign patients sirolimus was used almost exclusively as prophylaxis for renal transplants (RTP). Few cases clearly indicated the duration of therapy; where stated, the majority of patients received between 1 and 8 months of therapy.

Seventeen of the 19 cases indicated that patients were hospitalized. Admissions were associated with the reported symptoms or events (ex. pericardial effusion, neurotoxicity, etc.), altered laboratory values (ex. increased creatinine, increased drug levels, etc.) and procedures (ex. renal biopsy, pericardiocentesis). In the two cases where it was reported that patients experienced a disability, such disability was not described. Where stated (17/19) the majority of the patients (n=13) recovered from the adverse events.

The most frequently reported adverse events are labeled events. Of the unlabeled events reported in this population during the exclusivity period, two reports of pericardial effusion and one case of cerebral bleeding were of particular interest due to the young age of the children and the seriousness of the events. However, given the confounding of the pericardial effusion cases with viral infections and the cerebral bleeding episodes occurring after sirolimus was discontinued, it is premature to determine if sirolimus use played a clear role in these adverse events.

We will continue to monitor adverse events in the pediatric population and communicate any emerging signal to the review division. We will also discuss the need for the further evaluation of the specific drug interaction between azithromycin and sirolimus with the review division for the whole sirolimus use population.

## **2. PRODUCTS, INDICATIONS, PEDIATRIC FILING HISTORY and PEDIATRIC LABELING**

### **Products:**

NDA 21-083	Oral solution, 1 mg/ml	Approved 9/15/1999
NDA 21-110	Oral tablets 1 mg	Approved 8/25/2000
	Oral tablets 2 mg	Approved 8/22/2002
	Oral tablets 5 mg	Approved 2/23/2004

### **Indications:**

Rapamune® is indicated for the prophylaxis of organ rejection in patients aged 13 years or older receiving renal transplants. It recommended that Rapamune® be used initially in a regimen with cyclosporine and corticosteroids. In patients at low to moderate

immunologic risk cyclosporine should be withdrawn 2 to 4 months after transplantation and Rapamune® dose should be increased to reach recommended blood concentrations.

The safety and efficacy of cyclosporine withdrawal in high-risk patients have not been adequately studied and it is therefore not recommended.

The safety and efficacy of Rapamune® has not been established in pediatric patients less than 13 years old, or in pediatric (<18 years) renal transplant recipients considered at high immunologic risk.

**Pediatric Filing History:**

The original Pediatric Written Request (WR) was issued on September 15, 1999 and reissued unchanged on July 3, 2002. The WR was amended twice, on May 17, and May 24, 2004, to include categorization of patients by race and ethnicity and to allow obtaining pharmacokinetic profiles from patients. The sponsor’s response to the WR included two studies, Protocol 0468E1-217-US and Protocol 0468H1-315-US:

- An Open-Label, Comparative Study of the Effect of Sirolimus versus Standard Treatment o Clinical Outcomes and Histologic Progression of Allograft Nephropathy in High Risk Pediatric Renal Transplant Patients.
- A Double-Blind Randomized Trial of Steroid Withdrawal in Sirolimus and Cyclosporine-Treated Primary Transplant Recipients.

These studies fulfilled the requirements of the Written Request.

**Pediatric labeling:**

Pediatric use is addressed in the following sections of the labeling: **CLINICAL STUDIES/Pediatrics; INDICATIONS and USAGE; PRECAUTIONS/Pediatric Use;** and **ADVERSE REACTIONS/Pediatrics.**

These sections are reproduced in Appendix One.

**3. AERS SEARCH RESULTS**

AERS was searched on January 13, 2006, to retrieve reports received by the Agency up to the cut-off date of December 18, 2005, that listed sirolimus as a suspect drug, in adult and pediatric populations. The search included all sources, foreign and domestic. In the tables below, the *US counts are in parenthesis.*

**A. Adverse events through December 18, 2005:**

**Counts of reports:**

Table 1. Raw counts of total sirolimus reports in AERS through cut-off date of December 18, 2005 (US counts in parentheses)			
	All reports (US)	Serious <sup>2</sup> (US)	Death (US)
All ages <sup>3</sup>	3172 (1415)	2981 (1231)	375 (160)
Adults (≥ 17 yrs.)	2554 (1011)	2471 (931)	322 (133)
Pediatrics (0-16 yrs.)	88 (57)	82 (51)	6 (5)

<sup>1</sup> May include duplicates

**Table 1: Raw counts<sup>1</sup> of total sirolimus reports in AERS through cut-off date of December 18, 2005 (US counts in parentheses)**

<sup>2</sup> Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.

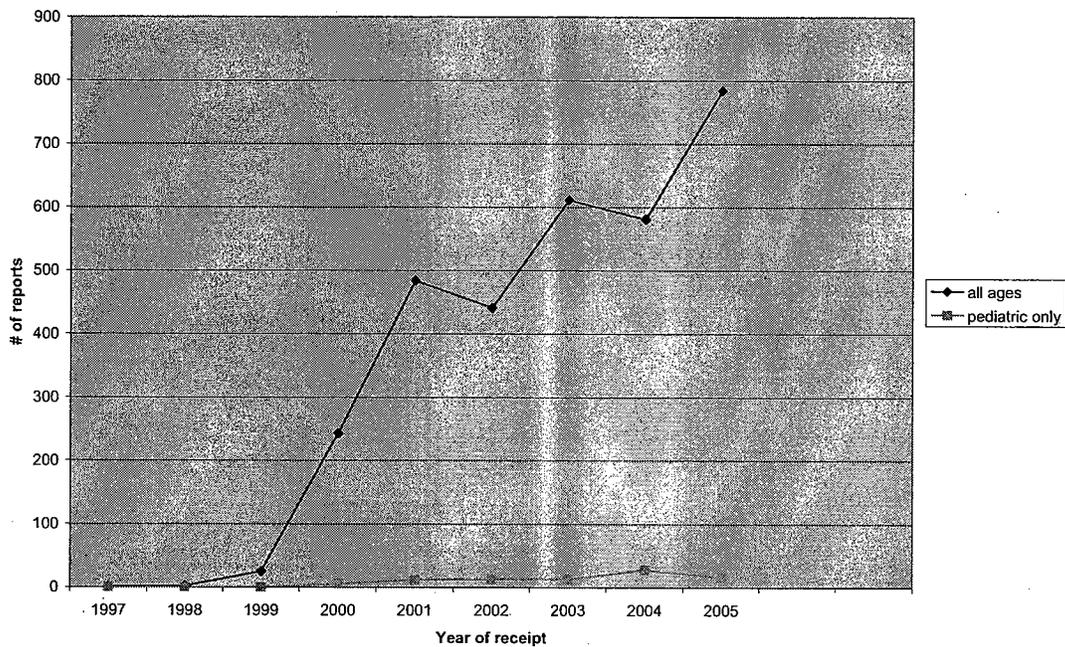
<sup>3</sup> Includes reports where age was not provided

**Reporting trend for pediatric reports through December 18, 2005:**

Table 2: Reporting trend in AERS reports through December 18, 2005 <sup>1</sup>		
Number of cases, all ages <sup>2</sup>	Year	Number of pediatric cases (0-16 years) <sup>3</sup>
1	1997	-
2	1998	-
25	1999	-
243	2000	6
484	2001	12
441	2002	13
611	2003	13
581	2004	28
784	2005	16

<sup>1</sup> Raw counts, may include duplicates  
<sup>2</sup> May include reports where age was not specified  
<sup>3</sup> Only includes reports where age was listed in the pediatric age grouping of 0-16 years

**Frequency of reporting by year of receipt**



**B. Adverse event from pediatric exclusivity approval date, November 17, 2004, through November 18, 2005 (pediatric exclusivity period):**

**Counts of reports:**

Table 4: Raw counts <sup>1</sup> of total sirolimus reports from pediatric exclusivity approval date through cut-off date of February 28, 2005 (US counts in parenthesis)			
	All reports (US)	Serious <sup>2</sup> (US)	Death (US)
All ages <sup>3</sup>	862 (342)	845 (325)	86 (36)
Adults (≥17 yrs.)	713 (273)	706 (266)	66 (26)
Pediatrics (0-16 yrs.)	19 (10)	19 (10)	0

May include duplicates  
<sup>2</sup> Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.  
<sup>3</sup> Includes reports where age was not specified

**4. Postmarketing Hands-on Review of All Pediatric Adverse Event Reports From All Sources Received During the Pediatric Exclusivity Period (November 17, 2004 through December 18, 2005)**

**Demographic characteristics:**

Our search of the AERS database yielded 19 pediatric cases submitted to the Agency during the pediatric exclusivity period. There were no duplicate reports. The demographic characteristics for these unique 19 cases are listed in Table 6 below.

Table 6: Characteristics of pediatric cases reported during the pediatric exclusivity period (November 17, 2004 through December 18, 2005) n=19	
Gender [n=18]	Male: 7 Female: 11
Age [n=19]	1-3 years: 6 4-7 years: 3 8-11 years: 2 12-16 years: 8 Mean 8.6 years; Median 8 years; Range 14 months to 16 years
Origin [n=19]	10 US, 9 Foreign
Event date (n=19)	2003 4 2004 13 2005 2
Daily dose [n=18]	Average 3.4 mg, Median , Range 1-8 mg
Duration of therapy [n=6]*	Average 7.5 months, Median 4 months, Range: 20 days to 28 months
Indications [n=19]	Prophylaxis against transplant rejection: 19 (15 renal; 2 heart; 2 liver)
Outcomes [n=19]	Death: 0 Disability 2 Hospitalization: 17

\* Two reports indicated that therapy continued after more than a year on the drug, but the actual duration was unclear and thus were not included in the calculations.

### **Fatalities in the pediatric population during the exclusivity period (n=0)**

There were no fatalities in pediatric patients during the exclusivity period.

### **Non-fatal outcome reports in pediatric population during the exclusivity period (n=19)**

Seventeen of 19 cases indicated that patients were hospitalized. Admissions were associated with the reported symptoms or events (ex. pericardial effusion, neurotoxicity, etc.), altered laboratory values (ex. increased creatinine, increased drug levels, etc.) and procedures (ex. renal biopsy, pericardiocentesis). In the two cases where it was reported that patients experienced a disability, such disability was not described. Where stated (17/19) the majority of the patients (n=13) recovered from the adverse events.

### **Summary of the 19 non-fatal pediatric cases during the pediatric exclusivity period by adverse events**

#### **Transplant complications/Rejection (n=8)**

<b>Table 7— Characteristics of the AERS transplant complication cases [transplant rejection/graft dysfunction.] (received during the pediatric exclusivity period)*</b>	
Gender (n=8)	4 M, 4 F
Age (n=8)	Average 11.7 years, Median 13 years Range 34 months-16 years
Origin (n=8)	4 US, 4 foreign
Daily dose (n=8)	Average 6 mg, Median 6 mg, Range 1-8 mg
Duration of therapy (n=4)	Average 4.6 months, Median 5 months, Range 20 days – 9 months
Indication (n=8)	6 RTP 1 HTP 1 LTP
Outcome (n=8)	8 H
Sequelae (n=8)	6 recovered, 2 events continue
Type of events (n=3)	1 Heart transplant rejection (with drug levels ↓) 1 Liver transplant rejection (with fungal and viral infection, rash, oral blisters, headache, LPD, and drug level ↑) 6 Renal transplant rejection (with vomiting, abdominal pain, biopsy kidney abnormal, Citrobacter infection, complications of transplanted kidney, creatine ↑, culture urine positive, diarrhea, dysuria, glucose ↑, graft dysfunction, headache, immunosuppressant drug level ↑, lipase ↑, potassium ↑, pneumonia, pyelonephritis, renal artery occlusion, renal impairment, renal vein occlusion, renal tubular necrosis)

\* The following abbreviations appear in Tables I through 11:

HTP = Heart Transplant Prophylaxis

LPD=Lymphoproliferative disorder

LTP = Liver Transplant Prophylaxis

RTP = Renal Transplant Prophylaxis

All of the eight patients who experienced organ-rejection required new or prolonged hospitalization, mainly due to symptoms or abnormal laboratory values which manifested on average five months after initiation of sirolimus therapy. All of those experiencing kidney transplant rejection recovered; however the decreased sirolimus level in the heart transplant rejection case continued, and the aspergillosis and LPD in the liver transplant

rejection case were not completely resolved at the time of reporting. All of the patients receiving a kidney transplant were study participants, two of which indicated that the study involved steroid withdrawal. All eight patients were on multiple concomitant medications at the time of reporting (range 3-11), however only one indicated concomitant cyclosporine therapy.

Most of the reported adverse events in this group are addressed in the labeling for this product. The potential for organ rejection following kidney transplant is addressed in the **CLINICAL STUDIES** section of the labeling. The **WARNINGS** section contains a box indicating that the use of sirolimus in combination with tacrolimus was associated with excess mortality and graft loss. Even though aspergillosis and citrobacter infections are not specifically mentioned, the **WARNINGS** section of the labeling states that increased susceptibility to infection may result from immunosuppression. Fluctuations in sirolimus levels are addressed in the **Drug Interactions** section, indicating that increases in sirolimus concentrations can be expected in patients also treated with voriconazole. Mouth ulceration is listed in the **ADVERSE REACTIONS** section.

The events not specifically listed in the labeling can be attributed to underlying renal deterioration, associated with labeled events, infections, poor compliance, procedural complications or other reasons not specifically associated with sirolimus use. For instance, the reported increased lipase was associated by the investigator with acute and chronic graft dysfunction. Abnormal kidney biopsy, complication of kidney transplant and renal impairment are alluded to under the **CLINICAL STUDIES** and **ADVERSE REACTIONS** sections of the labeling. Culture urine positive was associated with an infection and decreased sirolimus levels with poor compliance. Renal artery and renal vein occlusion appear to be most likely related to a procedural complication and not related to sirolimus use. Heart transplant rejection in humans is not addressed and no data supporting efficacy was listed.

Thus, at this time it appears that these cases do not indicate emerging signals in the pediatric population.

### Gastrointestinal events (n=3)

Table 8 – Characteristics of the pediatric gastrointestinal event cases (received during the pediatric exclusivity period) [n=3]*	
Gender (n=3)	3 F
Age (n=3)	Average 7 years, Median 4 years, Range 14 months to 16 years
Origin (n=3)	2 US, 1 foreign
Daily dose (n=3)	Average 2.9 mg, Median 4 mg, Range 1-3.6 mg
Duration of therapy (n=3)	Average 12 months, Median 5 months Range 3-28 months
Indication (n=3)	3 RTP
Sequelae (n=3)	3 recovered
Outcome (n=3)	3 H
Types of events (n=7)	Gastritis, esophagitis, bloody stool, paralytic ileus, fever, pneumonia, LPD

\* Abbreviations used in the table: LPD= Lymphoproliferative disease

In these three patients all of the reported adverse events are listed or alluded to in the labeling (see **ADVERSE REACTIONS** section). For instance, paralytic ileus and haematochezia are not specifically mentioned, but the related events of ileus, rectal disorder and hemorrhage are mentioned. The medical monitor in the study case where rectal bleeding was reported indicated that the “bloody stools” may be secondary to gastric complications of the post-transplant lymphoproliferative disease in this 4-year old patient.

An additional search in AERS indicated that there are few reports of haematochezia (n=10, raw counts) in adult patients, representing 0.3% of all the AERS reports regardless of age. Future individual review of these adult cases is necessary to determine if this event is also a manifestation of lymphoproliferative disease or if there is an association between the use of sirolimus and the development of haematochezia.

### Drug interactions/drug level fluctuations (n=3)

Table 9 – Characteristics of the pediatric drug interactions cases (received during the pediatric exclusivity period) (n=3)	
Gender (n=3)	2 F, 1 M
Age (n=3)	Average 8.6 year , Median 6 years, Range 5-15 years
Origin (n=3)	1 US, 2 Foreign
Daily dose (n=3))	Average 4 mg, Median 3 mg, Range 3-6 mg
Duration of therapy (n=)	
Indication (n=3)	2 RTP 1 HTP
Sequelae	2 unknown 1 recovered
Outcome (n=3)	2 H, 1 DS
Type of events	2 Drug interactions 1 Drug level increase

The AERS data show that in two cases the reported increases in sirolimus levels occurred in close association with the use of azithromycin suggesting a drug interaction.

The sirolimus label states the following regarding CYP3A4 drug interactions:

#### Other drug interactions

Co-administration of sirolimus with strong inhibitors of CYP3A4 and/or P-gp (such as ketoconazole, voriconazole, itraconazole, erythromycin, telithromycin, or clarithromycin) or strong inducers of CYP3A4 and/or P-gp (such as rifampin or rifabutin) is not recommended (see **WARNINGS**). Sirolimus is extensively metabolized by the CYP3A4 isoenzyme in the intestinal wall and liver and undergoes counter-transport from enterocytes of the small intestine into the gut lumen by the P-gp drug efflux pump. Sirolimus is potentially recycled between enterocytes and the gut lumen to allow continued metabolism by CYP3A4.

Thus, it is not unexpected to find an increase in sirolimus levels with concomitant use of azithromycin as this is an azalide which is a subclass of macrolide antibiotics. However, the drug interaction with azithromycin is not specifically stated while erythromycin, telithromycin, or clarithromycin are specifically stated in the label. Since azithromycin is the drug in this class that is now most prescribed, it will be important to see if there are more reports of this specific drug-interaction in AERS as a whole.

One of these two cases (6-year old) also reported unspecified neurotoxicity and bone marrow toxicity. Some examples of these types of reactions are listed in the sirolimus label (ex. insomnia, tremor, thrombocytopenia, anemia, etc.). However, these events in this patient are more likely attributable to the tacrolimus overdose resulting from a dispensing error where 5 mg capsules of tacrolimus were dispensed instead of the prescribed 0.5 mg capsules. In the third case, where the 15-year old experienced nausea and vomiting at the time of increased sirolimus levels, the patient had a history of erratic sirolimus levels.

Note that the reported adverse events in this group of patients are reported in the **ADVERSE REACTIONS** section of the sirolimus labeling or closely associated with tacrolimus overdose. A drug interaction between sirolimus and cytochrome 3A4 inhibitors such as the macrolide antibiotics is listed in the labeling.

### Cardiac events (n=2)

Gender (n=2)	1 M, 1 F
Age (n=2)	2 years, 3 years
Origin (n=2)	2 US
Daily dose (n=2)	1 mg; 1.5 mg
Duration of therapy (n=2)	> 8 months in both, and continues at time of reporting
Indication (n=2)	RTP
Sequelae	2 recovered
Outcome (n=2)	2 H
Type of cardiac events (n=2):	2 Pericardial effusion

Both cases are similar in that pericardial effusion, an unlabeled event, occurred after 7-9 months of therapy in patients where the event may have been associated with a viral infection. However, in both the diagnosis of viral infection (upper respiratory tract infection in the 2-year old and adenovirus in the stool of the 3-year old) occurred after patients had experienced an initial bout of pericardial effusion. Both patients recovered. A reduction in the sirolimus dose in the 3-year old was considered by the reporters to be helpful in the patient's recovery.

Pericardial effusion is not a labeled event. In the published case<sup>1</sup> (3-year old patient) the authors contacted the sponsor (Wyeth) who indicated that “their clinical trial data on file mentioned pericardial effusion as a complicating factor in 2% of sirolimus vs. 0% of the placebo treated patients.” However, the authors also state that a possible viral etiology can't be discounted in the 3-year old. In the 2-year old patient in this group, the reporters do not attribute the event to the use of sirolimus. Thus, at this time it is difficult to determine if the event in these two patients was due to the use of sirolimus, a viral infection, a combination of both, or some other unknown factor.

### Other events (n=3)

<sup>1</sup> Truong U, Moon-Grady AJ, Butani L Cardiac tamponade in a pediatric renal transplant recipient on sirolimus therapy *Pediatr Transplantation* 2005;9: 541-544

**Infections (n=1)**

Case # 5725206

2-year old female, US, H

Study patient received kidney transplant in \_\_\_\_\_, and was subsequently treated with daclizumab, tacrolimus, sirolimus, prednisone and prednisolone. A month later she experienced a UTI, with dehydration \_\_\_\_\_. Four months later / \_\_\_\_\_ she had another infection, diagnosed as pneumonia, port-a-cath infection with enterococcus and staph and CMV infection. Three months later / \_\_\_\_\_, she was diagnosed with upper respiratory tract infection presumed to be of viral origin. Approximately two weeks after the last infection \_\_\_\_\_, she experienced severe diarrhea and dehydration, elevated creatinine, electrolyte imbalance, sunken eyes, dry pharynx, rash and decreased urinary output. In \_\_\_\_\_ our months after the last infection and a year after the transplant, she was noted to have hematuria. She was hospitalized on each of the dates mentioned. The investigator considered that the infections, dehydration, diarrhea and hematuria to be possibly/probably related to the study therapy. Patient recovered from all events, except for hematuria which was persisting at the time of reporting.

Note that increased susceptibility to infections, diarrhea, dehydration and hematuria are listed in the labeling for sirolimus (**WARNINGS** and **ADVERSE REACTIONS** sections)

**Panniculitis (n=1)**

Case # 5788853

14-year male, UK, H

Patient experienced panniculitis of lower limb approximately two months after starting therapy with sirolimus for RTP. The patient was hospitalized for the event. Therapy continued for another seven months. Patient recovered from the event after drug withdrawal. Dose was reported as 5 mg, although frequency was unknown.

The reporter did not provide an assessment of the role of sirolimus in this event, an explanation for the prolonged continuation of therapy after onset of event, or any other factors that may have contributed to the event. The positive dechallenge suggest a possible association between sirolimus use and the occurrence of panniculitis. However, because this is the only report in AERS of such event with the use of sirolimus regardless of age group and because of the scant information provided we will continue to monitor AERS reports to determine the role of sirolimus if any in the occurrence of this event.

**Intracranial bleeding (n=1)**

Case # 5694484

2-year patient, gender not stated, UK, DS, LT

Patient with a history of liver transplant and concurrent short-bowel syndrome was treated with 2 mg of sirolimus during 28 days. The day after stopping therapy, the patient experienced intracranial hemorrhage confirmed by brain scan. Two additional brain scans done at 1- and 2- weeks after the event indicated "new bleeding." Patient is recovering from the event. Interval between transplant and cerebral hemorrhage was not provided.

Hemorrhage is listed in the labeling in the **ADVERSE REACTIONS** section, although the specific site of the bleeding is not defined. Additional helpful information (such as previous medical history, contributory factors, possible trauma, etc) is missing in this case, which together with the reported “new bleeding” episodes post discontinuation of sirolimus make it difficult to determine if sirolimus played a role in this patient’s cerebral bleed. We will continue to monitor this event in AERS.

## **5. Summary**

Individual review of the 19 unique cases retrieved from AERS on January 13, 2006, indicated that all had a serious outcome although there were no fatalities. The AERS database shows that sirolimus is used in patients as young as 14 months of age, with the majority of the patients in this case series being under 12 years of age. Sirolimus is indicated for patients 13 years and older, so the majority of patients in this case series are outside the indicated age range. In both US and foreign patients sirolimus was used almost exclusively to treat RTP. Few cases clearly indicated the duration of therapy; where stated, the majority of patients received between 1 and 8 months of therapy.

Seventeen of the 19 cases indicated that patients were hospitalized. Admissions were associated with the reported symptoms or events (ex. pericardial effusion, neurotoxicity, etc.), altered laboratory values (ex. increased creatinine, increased drug levels, etc.) and procedures (ex. renal biopsy, pericardiocentesis). In the two cases where it was reported that patients experienced a disability, such disability was not described. Where stated (17/19) the majority of the patients (n=13) recovered from the adverse events.

The most frequently reported adverse events are labeled events. Of the unlabeled events reported in this population during the exclusivity period, two reports of pericardial effusion and one case of cerebral bleeding were of particular interest due to the young age of the children and the seriousness of the events. However, given the confounding of the pericardial effusion cases with viral infections and the cerebral bleeding episodes occurring after sirolimus was discontinued, it is premature to determine if sirolimus use played a clear role in these adverse events.

We will continue to monitor adverse events in the pediatric population and communicate any emerging signal to the review division. We will also discuss the need for the further evaluation of the specific drug interaction between azithromycin and sirolimus with the review division for the whole sirolimus use population.

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## APPENDIX ONE

### 1. Sirolimus label – Relevant sections

#### WARNING:

Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. ...

#### CLINICAL PHARMACOLOGY

##### Metabolism

Sirolimus is a substrate for both cytochrome P450 IIIA4 (CYP3A4) and P-glycoprotein (P-gp). Sirolimus is extensively metabolized by the CYP3A4 isozyme in the intestinal wall and liver and undergoes counter-transport from enterocytes of the small intestine into the gut lumen by the P-gp drug efflux pump.

Sirolimus is potentially recycled between enterocytes and the gut lumen to allow continued metabolism by CYP3A4. Therefore, absorption and subsequent elimination of systemically absorbed sirolimus may be influenced by drugs that affect these proteins. Inhibitors of CYP3A4 and P-gp increase sirolimus concentrations. Inducers of CYP3A4 and P-gp decrease sirolimus concentrations. (See **WARNINGS and PRECAUTIONS, Drug Interactions and**

##### Other drug interactions).

**Pediatric:** Sirolimus pharmacokinetic data were collected in concentration-controlled trials of pediatric renal transplant patients who were also receiving cyclosporine and corticosteroids. The target ranges for trough concentrations were either 10-20 ng/mL for the 21 children receiving tablets, or 5-15 ng/mL for the one child receiving oral solution. The children aged 6-11 years (n = 8) received mean SD doses of 1.75±0.71 mg/day (0.064±0.018 mg/kg, 1.65±0.43 mg/m<sup>2</sup>). The children aged 12-18 years (n = 14) received mean SD doses of 2.79±1.25 mg/day (0.053 ±0.0150 mg/kg, 1.86 ±0.61 mg/m<sup>2</sup>). At the time of sirolimus blood sampling for pharmacokinetic evaluation, the majority (80%) of these pediatric patients received the sirolimus dose at 16 hours after the once daily cyclosporine dose.

#### CLINICAL STUDIES

**Rapamune Oral Solution:** The safety and efficacy of Rapamune Oral Solution for the prevention of organ rejection following renal transplantation were assessed in two randomized, double-blind, multicenter, controlled trials. These studies compared two dose levels of Rapamune Oral Solution (2 mg and 5 mg, once daily) with azathioprine (Study 1) or placebo (Study 2) when administered in combination with cyclosporine and corticosteroids. Study 1 was conducted in the United States at 38 sites. Seven hundred nineteen (719) patients were enrolled in this trial and randomized following transplantation; 284 were randomized to receive Rapamune Oral Solution 2 mg/day, 274 were randomized to receive Rapamune Oral Solution 5 mg/day, and 161 to receive azathioprine 2-3 mg/kg/day. Study 2 was conducted in Australia, Canada, Europe, and the United States, at a total of 34 sites. Five hundred seventy-six (576) patients were enrolled in this trial and randomized before transplantation; 227 were randomized to receive Rapamune Oral Solution 2 mg/day, 219 were randomized to receive Rapamune Oral Solution 5 mg/day, and 130 to receive placebo. In both studies, the use of antilymphocyte antibody induction therapy was prohibited. In both studies, the primary efficacy endpoint was the rate of efficacy failure in the first 6 months after transplantation. Efficacy failure was defined as the first occurrence of an acute rejection episode (confirmed by biopsy), graft loss, or death. The tables below summarize the results of the primary efficacy analyses from these trials.

Rapamune Oral Solution, at doses of 2 mg/day and 5 mg/day, significantly reduced the incidence of efficacy failure (statistically significant at the  $\alpha$ 0.025 level; nominal significance level adjusted for multiple [2] dose comparisons) at 6 months following transplantation compared with both azathioprine and placebo.

#### INCIDENCE (%) OF EFFICACY FAILURE AT 6 AND 24 MONTHS FOR STUDY 1a,b

Parameter	Rapamune Oral Solution 2 mg/day (n = 284)	Rapamune Oral solution 5 mg/day (n=274)	Azathioprine 2-3 mg/kg/dy (n=161)
<b>Efficacy failure at 6 months</b>	18.7	16.8	32.3
<i>Components of efficacy failure</i>			

Biopsy-proven acute rejection	16.5	11.3	29.2
Graft loss	1.1	2.9	2.5
Death	0.7	1.8	0
Lost to follow-up	0.4	0.7	0.6
<b>Efficacy failure at 24 months</b>	<b>32.8</b>	<b>25.9</b>	<b>36.0</b>
<i>Components of efficacy failure</i>			
Biopsy-proven acute rejection	23.6	17.5	32.3
Graft loss	3.9	4.7	3.1
Death	4.2	3.3	0
Lost to follow-up	1.1	0.4	0.6

a: Patients received cyclosporine and corticosteroids.

b: Includes patients who prematurely discontinued treatment.

c: Primary endpoint.

**Pediatrics:** Rapamune<sup>®</sup> was evaluated in a 36-month, open-label, randomized, controlled clinical trial at 14 North American centers in pediatric (aged 3 to  $\leq$  18 years) renal transplant recipients considered to be at high immunologic risk for developing chronic allograft nephropathy, defined as a history of one or more acute allograft rejection episodes and/or the presence of chronic allograft nephropathy on a renal biopsy. Seventy-eight (78) subjects were randomized in a 2:1 ratio to Rapamune<sup>®</sup> (sirolimus target concentrations of 5 to 15 ng/mL, by chromatographic assay, n = 53) in combination with a calcineurin inhibitor and corticosteroids or to continue calcineurin-inhibitor-based immunosuppressive therapy (n = 25). The primary endpoint of the study was efficacy failure as defined by the first occurrence of biopsy confirmed acute rejection, graft loss, or death, and the trial was designed to show superiority of Rapamune added to a calcineurin-inhibitor-based immunosuppressive regimen compared to a calcineurin-inhibitor-based regimen. The cumulative incidence of efficacy failure up to 36 months was 45.3% in the Rapamune<sup>®</sup> group compared to 44.0% in the control group, and did not demonstrate superiority. There was one death in each group. The use of Rapamune in combination with calcineurin inhibitors and corticosteroids was associated with an increased risk of deterioration of renal function, serum lipid abnormalities (including but not limited to increased serum triglycerides and cholesterol), and urinary tract infections. This study does not support the addition of Rapamune<sup>®</sup> to calcineurin-inhibitor-based immunosuppressive therapy in this subpopulation of pediatric renal transplant patients.

#### INDICATIONS AND USAGE

Rapamune (sirolimus) is indicated for the prophylaxis of organ rejection in patients aged 13 years or older receiving renal transplants. It is recommended that Rapamune be used initially in a regimen with cyclosporine and corticosteroids. In patients at low to moderate immunologic risk cyclosporine should be withdrawn 2 to 4 months after transplantation and Rapamune dose should be increased to reach recommended blood concentrations (See **DOSAGE AND ADMINISTRATION**).

The safety and efficacy of cyclosporine withdrawal in high-risk patients have not been adequately studied and it is therefore not recommended. This includes patients with Banff grade III acute rejection or vascular rejection prior to cyclosporine withdrawal, those who are dialysis-dependent, or with serum creatinine  $\geq$  4.5 mg/dL, black patients, re-transplants, multi-organ transplants, patients with high panel of reactive antibodies (See **CLINICAL STUDIES**).

The safety and efficacy of Rapamune<sup>®</sup> have not been established in pediatric patients less than 13 years old, or in pediatric ( $\leq$  18 years) renal transplant recipients considered at high immunologic risk (see **PRECAUTIONS, Pediatric use, and CLINICAL STUDIES, Pediatrics**).

#### CONTRAINDICATIONS

Rapamune is contraindicated in patients with a hypersensitivity to sirolimus or its derivatives or any component of the drug product.

#### WARNINGS

Increased susceptibility to infection and the possible development of lymphoma and other malignancies, particularly of the skin, may result from immunosuppression (see **ADVERSE REACTIONS**). Oversuppression of the immune system can also increase susceptibility to infection including opportunistic infections, fatal infections, and sepsis. Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should use Rapamune. Patients

receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, and hypersensitivity vasculitis, have been associated with the administration of sirolimus (see **ADVERSE REACTIONS**).

As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Increased serum cholesterol and triglycerides, that may require treatment, occurred more frequently in patients treated with Rapamune compared with azathioprine or placebo controls (see **PRECAUTIONS**).

In Studies 1 and 2, from month 6 through months 24 and 36, respectively, mean serum creatinine was increased and mean glomerular filtration rate was decreased in patients treated with Rapamune and cyclosporine compared with those treated with cyclosporine and placebo or azathioprine controls. The rate of decline in renal function was greater in patients receiving Rapamune and cyclosporine compared with control therapies (see **CLINICAL STUDIES**).

Renal function should be closely monitored during the administration of Rapamune in combination with cyclosporine since long-term administration can be associated with deterioration of renal function. Appropriate adjustment of the immunosuppression regimen, including discontinuation of Rapamune and/or cyclosporine, should be considered in patients with elevated or increasing serum creatinine levels. Caution should be exercised when using other drugs which are known to impair renal function. In patients at low to moderate immunologic risk continuation of combination therapy with cyclosporine beyond 4 months following transplantation should only be considered when the benefits outweigh the risks of this combination for the individual patients (see **PRECAUTIONS**).

In clinical trials, Rapamune has been administered concurrently with corticosteroids and with the following formulations of cyclosporine:

Sandimmune Injection (cyclosporine injection)

Sandimmune Oral Solution (cyclosporine oral solution)

Sandimmune Soft Gelatin Capsules (cyclosporine capsules)

Neoral Soft Gelatin Capsules (cyclosporine capsules [MODIFIED])

Neoral Oral Solution (cyclosporine oral solution [MODIFIED])

The efficacy and safety of the use of Rapamune in combination with other immunosuppressive agents has not been determined.

**Liver Transplantation – Excess Mortality, Graft Loss, and Hepatic Artery Thrombosis (HAT):** The use of sirolimus in combination with tacrolimus was associated with excess mortality and graft loss in a study in de novo liver transplant recipients. Many of these patients had evidence of infection at or near the time of death. In this and another study in de novo liver transplant recipients, the use of sirolimus in combination with cyclosporine or tacrolimus was associated with an increase in HAT; most cases of HAT occurred within 30 days post-transplantation and most led to graft loss or death.

**Lung Transplantation – Bronchial Anastomotic Dehiscence:** Cases of bronchial anastomotic dehiscence, most fatal, have been reported in de novo lung transplant patients when sirolimus has been used as part of an immunosuppressive regimen. The safety and efficacy of Rapamune (sirolimus) as immunosuppressive therapy have not been established in liver or lung transplant patients, and therefore, such use is not recommended.

Co-administration of sirolimus with strong inhibitors of CYP3A4 and/or P-gp (such as ketoconazole, voriconazole, itraconazole, erythromycin, telithromycin, or clarithromycin) or strong inducers of CYP3A4 and/or P-gp (such as rifampin or rifabutin) is not recommended (see **CLINICAL PHARMACOLOGY, Metabolism, and PRECAUTIONS, Drug Interactions and Other drug interactions**).

## **PRECAUTIONS**

### ***Renal Function***

Patients treated with cyclosporine and Rapamune were noted to have higher serum creatinine levels and lower glomerular filtration rates compared with patients treated with cyclosporine and placebo or azathioprine controls (Studies 1 and 2). The rate of decline in renal function in these studies was greater in patients receiving Rapamune and cyclosporine compared with control therapies. In patients at low to moderate immunologic risk (See **CLINICAL STUDIES**) continuation of combination therapy with

cyclosporine beyond 4 months following transplantation should only be considered when the benefits outweigh the risks of this combination for the individual patients. (see **WARNINGS**). Renal function should be monitored during the administration of Rapamune<sup>®</sup> in combination with cyclosporine. Appropriate adjustment of the immunosuppression regimen, including discontinuation of Rapamune and/or cyclosporine, should be considered in patients with elevated or increasing serum creatinine levels. Caution should be exercised when using agents (e.g., aminoglycosides, and amphotericin B) that are known to have a deleterious effect on renal function.

**Antimicrobial Prophylaxis**

Cytomegalovirus (CMV) prophylaxis is recommended for 3 months after transplantation, particularly for patients at increased risk for CMV disease.

**Laboratory Tests**

Whole blood sirolimus concentrations should be monitored in patients receiving concentration-controlled Rapamune. Monitoring is also necessary in patients likely to have altered drug metabolism, in patients 13 years who weigh less than 40 kg, in patients with hepatic impairment, and during concurrent administration of potent CYP3A4 inducers and inhibitors (see **PRECAUTIONS: Drug Interactions**).

**Drug Interactions**

Sirolimus is known to be a substrate for both cytochrome CYP3A4 and P-gp. The pharmacokinetic interaction between sirolimus and concomitantly administered drugs is discussed below. Drug interaction studies have not been conducted with drugs other than those described below.

**Cyclosporine capsules MODIFIED:**

**Diltiazem:**

**Erythromycin:** Erythromycin is a substrate and inhibitor of CYP3A4 and P-gp; co-administration of sirolimus oral solution or tablets and erythromycin is not recommended (see **WARNINGS**). The simultaneous oral administration of 2 mg daily of sirolimus oral solution and 800 mg q 8h of erythromycin as erythromycin ethylsuccinate tablets at steady state to 24 healthy volunteers significantly affected the bioavailability of sirolimus and erythromycin. Sirolimus C<sub>max</sub> and AUC were increased 4.4- and 4.2-fold respectively and t<sub>max</sub> was increased by 0.4 hr. Erythromycin C<sub>max</sub> and AUC were increased 1.6- and 1.7-fold, respectively, and t<sub>max</sub> was increased by 0.3 hr.

**Ketoconazole:**

**Rifampin:**

**Verapamil:**

**Drugs which may be coadministered without dose adjustment**

Clinically significant pharmacokinetic drug-drug interactions were not observed in studies of drugs listed below. A synopsis of the type of study performed for each drug is provided. Sirolimus and these drugs may be coadministered without dose adjustments.

**Acyclovir:**

**Atorvastatin:**

**Digoxin:**

**Glyburide:**

**Nifedipine:**

**Norgestrel/ethinyl estradiol (Lo/Ovral<sup>®</sup>):**

**Prednisolone:**

**Sulfamethoxazole/trimethoprim (Bactrim<sup>®</sup>):**

**Other drug interactions**

Co-administration of sirolimus with strong inhibitors of CYP3A4 and/or P-gp (such as ketoconazole, voriconazole, itraconazole, erythromycin, telithromycin, or clarithromycin) or strong inducers of CYP3A4 and/or P-gp (such as rifampin or rifabutin) is not recommended (see **WARNINGS**). Sirolimus is extensively metabolized by the CYP3A4 isoenzyme in the intestinal wall and liver and undergoes counter-transport from enterocytes of the small intestine into the gut lumen by the P-gp drug efflux pump. Sirolimus is potentially recycled between enterocytes and the gut lumen to allow continued metabolism by CYP3A4. Therefore, absorption and the subsequent elimination of systemically absorbed sirolimus may be influenced by drugs that affect these proteins. Strong inhibitors of CYP3A4 and P-gp significantly decrease the metabolism of sirolimus and increase sirolimus concentrations, while strong inducers of CYP3A4 and P-gp significantly increase the

metabolism of sirolimus and decrease sirolimus concentrations. In patients in whom strong inhibitors or inducers of CYP3A4 are indicated, alternative therapeutic agents with less potential for inhibition or induction of CYP3A4 should be considered. Sirolimus is a substrate for the multidrug efflux pump, P-gp in the small intestine. Therefore, absorption of sirolimus may be influenced by drugs that affect P-gp. Aside from those mentioned above, other drugs that increase sirolimus blood concentrations include (but are not limited to):

Calcium channel blockers: nicardipine.

Antifungal agents: clotrimazole, fluconazole.

Antibiotics: troleandomycin.

Gastrointestinal prokinetic agents: cisapride, metoclopramide.

Other drugs: bromocriptine, cimetidine, danazol, HIV-protease inhibitors (e.g., ritonavir, indinavir).

Aside from those mentioned above, other drugs that decrease sirolimus concentrations include (but are not limited to):

Anticonvulsants: carbamazepine, phenobarbital, phenytoin.

Antibiotics: rifampine.

Care should be exercised when drugs or other substances that are metabolized by CYP3A4 are administered concomitantly with Rapamune. Grapefruit juice reduces CYP3A4-mediated metabolism of Rapamune and must not be used for dilution (see **DOSAGE AND ADMINISTRATION**).

#### *Herbal Preparations*

St. John's Wort (*hypericum perforatum*) induces CYP3A4 and P-gp. Since sirolimus is a substrate for both cytochrome CYP3A4 and P-gp, there is the potential that the use of St. John's Wort in patients receiving Rapamune could result in reduced sirolimus concentrations.

#### *Vaccination*

Immunosuppressants may affect response to vaccination. Therefore, during treatment with Rapamune, vaccination may be less effective. The use of live vaccines should be avoided; live vaccines may include, but are not limited to measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid.

#### **Pediatric use**

The safety and efficacy of Rapamune in pediatric patients below the age of 13 years have not been established. The safety and efficacy of Rapamune Oral Solution and Rapamune Tablets have been established in children aged 13 or older judged to be at low to moderate immunologic risk. Use of Rapamune Oral Solution and Rapamune Tablets in this subpopulation of children aged 13 or older is supported by evidence from adequate and well-controlled trials of Rapamune Oral Solution in adults with additional pharmacokinetic data in pediatric renal transplantation recipients (see **CLINICAL PHARMACOLOGY, Special Populations, Pediatric**). Safety and efficacy information from a controlled clinical trial in pediatric and adolescent (13-18 years of age) renal transplant recipients judged to be at high immunologic risk, defined as a history of one or more acute rejection episodes and/or the presence of chronic allograft nephropathy, do not support the chronic use of Rapamune Oral Solution or Tablets in combination with calcineurin inhibitors and corticosteroids, due to the increased risk of lipid abnormalities and deterioration of renal function associated with these immunosuppressive regimens, without increased benefit with respect to acute rejection, graft survival, or patient survival (see **CLINICAL STUDIES, Pediatrics**).

#### **ADVERSE REACTIONS**

**Rapamune Oral Solution:** The incidence of adverse reactions was determined in two randomized, double-blind, multicenter controlled trials in which 499 renal transplant patients received Rapamune Oral Solution 2 mg/day, 477 received Rapamune Oral Solution 5 mg/day, 160 received azathioprine, and 124 received placebo. All patients were treated with cyclosporine and corticosteroids. Data ( $\geq 12$  months post-transplant) presented in the table below show the adverse reactions that occurred in any treatment group with an incidence of  $\geq 20\%$ . Specific adverse reactions associated with the administration of Rapamune (sirolimus) Oral Solution occurred at a significantly higher frequency than in the respective control group. For both Rapamune Oral Solution 2 mg/day and 5 mg/day these include hypercholesterolemia, hyperlipemia, hypertension, and rash; for Rapamune Oral Solution 2 mg/day acne; and for Rapamune Oral Solution 5 mg/day anemia, arthralgia, diarrhea, hypokalemia, and thrombocytopenia. The elevations of triglycerides and cholesterol and decreases in platelets and hemoglobin occurred in a dose-related manner in patients receiving Rapamune.

Patients maintained on Rapamune Oral Solution 5 mg/day, when compared with patients on Rapamune Oral Solution 2 mg/day, demonstrated an increased incidence of the following adverse events: anemia, leukopenia, thrombocytopenia, hypokalemia, hyperlipemia, fever, and diarrhea.

In general, adverse events related to the administration of Rapamune were dependent on dose/concentration.

With longer term follow-up, the adverse event profile remained similar. Some new events became significantly different among the treatment groups. For events which occurred at a frequency of  $\geq 20\%$  by 24 months for Study 1 and 36 months for Study 2, only the incidence of edema became significantly higher in both Rapamune groups as compared with the control group. The incidence of headache became significantly more common in the Rapamune 5mg/day group as compared with control therapy.

At 24 months for Study 1, the following treatment-emergent infections were significantly different among the treatment groups: bronchitis, Herpes simplex, pneumonia, pyelonephritis, and upper respiratory infections. In each instance, the incidence was highest in the Rapamune 5 mg/day group, lower in the Rapamune 2 mg/day group and lowest in the azathioprine group. Except for upper respiratory infections in the Rapamune 5 mg/day cohort, the remainder of events occurred with a frequency of  $\leq 20\%$ . At 36 months in Study 2 only the incidence of treatment-emergent Herpes simplex was significantly different among the treatment groups, being higher in the Rapamune 5 mg/day group than either of the other groups.

Among the adverse events that were reported at a rate of  $\geq 3\%$  and  $\leq 20\%$  at 12 months, the following were more prominent in patients maintained on Rapamune 5 mg/day, when compared with patients on Rapamune 2 mg/day: epistaxis, lymphocele, insomnia, thrombotic thrombocytopenic purpura (hemolytic-uremic syndrome), skin ulcer, increased LDH, hypotension, facial edema.

The following adverse events were reported with  $\geq 3\%$  and  $\leq 20\%$  incidence in patients in any Rapamune treatment group in the two controlled clinical trials for the prevention of acute rejection, BODY AS A WHOLE: abdomen enlarged, abscess, fever cellulitis, chills, face edema, flu syndrome, generalized edema, hernia, *Herpes zoster* infection, lymphocele, malaise, pelvic pain, peritonitis, sepsis; CARDIOVASCULAR SYSTEM: atrial fibrillation, congestive heart failure, hemorrhage, hypervolemia, hypotension, palpitation, peripheral vascular disorder, postural hypotension, syncope, tachycardia, thrombophlebitis, thrombosis, vasodilatation, venous thromboembolism; DIGESTIVE SYSTEM: anorexia, dysphagia, eructation, esophagitis, flatulence, gastritis, gastroenteritis, gingivitis, gum hyperplasia, ileus, liver function tests abnormal, mouth ulceration, oral moniliasis, stomatitis; ENDOCRINE SYSTEM: Cushing's syndrome, diabetes mellitus, glycosuria; HEMIC AND LYMPHATIC SYSTEM: ecchymosis, leukocytosis, lymphadenopathy, polycythemia, thrombotic thrombocytopenic purpura (hemolytic-uremic syndrome); METABOLIC AND NUTRITIONAL: acidosis, alkaline phosphatase increased, BUN increased, creatine phosphokinase increased, dehydration, healing abnormal, hypercalcemia, hyperglycemia, hyperphosphatemia, hypocalcemia, hypoglycemia, hypomagnesemia, hyponatremia, lactic dehydrogenase increased, AST/SGOT increased, ALT/SGPT increased, weight loss; MUSCULOSKELETAL SYSTEM: arthrosis, bone necrosis, leg cramps, myalgia, osteoporosis, tetany; NERVOUS SYSTEM: anxiety, confusion, depression, dizziness, emotional lability, hypertonia, hypesthesia, hypotonia, insomnia, neuropathy, paresthesia, somnolence; RESPIRATORY SYSTEM: asthma, atelectasis, bronchitis, cough increased, epistaxis, hypoxia, lung edema, pleural effusion, pneumonia, rhinitis, sinusitis; SKIN

AND APPENDAGES: fungal dermatitis, hirsutism, pruritus, skin hypertrophy, skin ulcer, sweating; SPECIAL SENSES: abnormal vision, cataract, conjunctivitis, deafness, ear pain, otitis media, tinnitus; UROGENITAL SYSTEM: albuminuria, bladder pain, dysuria, hematuria, hydronephrosis, impotence, kidney pain, kidney tubular necrosis, nocturia, oliguria, pyelonephritis, pyuria, scrotal edema, testis disorder, toxic nephropathy, urinary frequency, urinary incontinence, urinary retention.

Less frequently occurring adverse events included: mycobacterial infections, Epstein-Barr virus infections, and pancreatitis.

Among the events which were reported at an incidence of  $\geq 3\%$  and  $\leq 20\%$  by 24 months for Study 1 and 36 months for Study 2, tachycardia and Cushing's syndrome were reported significantly more commonly in both Rapamune groups as compared with the control therapy.

Events that were reported more commonly in the Rapamune 5 mg/day group than either the Rapamune 2 mg/day group and/or control group were: abnormal healing, bone necrosis, chills, congestive heart failure, dysuria, hernia, hirsutism, urinary frequency, and lymphadenopathy.

**Rapamune Tablets:** The safety profile of the tablet did not differ from that of the oral solution formulation. The incidence of adverse reactions up to 12 months was determined in a randomized, multicenter controlled trial (Study 3) in which 229 renal transplant patients received Rapamune Oral Solution 2 mg once daily and 228 patients received Rapamune Tablets 2 mg once daily. All patients were treated with cyclosporine and corticosteroids. The adverse reactions that occurred in either treatment group with an incidence of  $\geq 20\%$  in Study 3 are similar to those reported for Studies 1 and 2. There was no notable difference in the incidence of these adverse events between treatment groups (oral solution versus tablets) in Study 3, with the exception of acne, which occurred more frequently in the oral solution group, and tremor which occurred more frequently in the tablet group, particularly in Black patients. The adverse events that occurred in patients with an incidence of  $\geq 3\%$  and  $\leq 20\%$  in either treatment group in Study 3 were similar to those reported in Studies 1 and 2. There was no notable difference in the incidence of these adverse events between treatment groups (oral solution versus tablets) in Study 3, with the exception of hypertonia, which occurred more frequently in the oral solution group and diabetes mellitus which occurred more frequently in the tablet group. Hispanic patients in the tablet group experienced hyperglycemia more frequently than Hispanic patients in the oral solution group. In Study 3 alone, menorrhagia, metrorrhagia, and polyuria occurred with an incidence of 3% and  $\leq 20\%$ . The clinically important opportunistic or common transplant-related infections were identical in all three studies and the incidences of these infections were similar in Study 3 compared with Studies 1 and 2. The incidence rates of these infections were not significantly different between the oral solution and tablet treatment groups in Study 3.

In Study 3 (at 12 months), there were two cases of lymphoma/lymphoproliferative disorder in the oral solution treatment group (0.8%) and two reported cases of lymphoma/lymphoproliferative disorder in the tablet treatment group (0.8%). These differences were not statistically significant and were similar to the incidences observed in Studies 1 and 2.

**Rapamune following cyclosporine withdrawal:** The incidence of adverse reactions was determined through 36 months in a randomized, multicenter controlled trial (Study 4) in which 215 renal transplant patients received Rapamune as a maintenance regimen following cyclosporine withdrawal and 215 patients received Rapamune with cyclosporine therapy. All patients were treated with corticosteroids. The safety profile prior to randomization (start of cyclosporine withdrawal) was similar to that of the 2-mg Rapamune groups in Studies 1, 2, and 3. Following randomization (at 3 months) patients who had cyclosporine eliminated from their therapy experienced significantly higher incidences of abnormal liver function tests (including increased AST/SGOT and increased ALT/SGPT), hypokalemia, thrombocytopenia, abnormal healing, ileus, and rectal disorder. Conversely, the incidence of hypertension, cyclosporine

toxicity, increased creatinine, abnormal kidney function, toxic nephropathy, edema, hyperkalemia, hyperuricemia, and gum hyperplasia was significantly higher in patients who remained on cyclosporine than those who had cyclosporine withdrawn from therapy. Mean systolic and diastolic blood pressure improved significantly following cyclosporine withdrawal.

In Study 4, at 36 months, the incidence of Herpes zoster infection was significantly lower in patients receiving Rapamune following cyclosporine withdrawal compared with patients who continued to receive Rapamune and cyclosporine.

The incidence of malignancies in Study 4 is presented in the table below. In Study 4, the incidence of lymphoma/lymphoproliferative disease was similar in all treatment groups. The overall incidence of malignancy was higher in patients receiving Rapamune plus cyclosporine compared with patients who had cyclosporine withdrawn.

**Pediatrics:** Safety was assessed in the controlled clinical trial in pediatric ( $\leq 18$  years of age) renal transplant patients considered high immunologic risk, defined as a history of one or more acute allograft rejection episodes and/or the presence of chronic allograft nephropathy on a renal biopsy (see **CLINICAL STUDIES**). The use of Rapamune in combination with calcineurin inhibitors and corticosteroids was associated with an increased risk of deterioration of renal function, serum lipid abnormalities (including but not limited to increased serum triglycerides and cholesterol), and urinary tract infections.

**Other clinical experience:** Cases of interstitial lung disease (including pneumonitis, and infrequently bronchiolitis obliterans organizing pneumonia [BOOP] and pulmonary fibrosis), some fatal, with no identified infectious etiology have occurred in patients receiving immunosuppressive regimens including Rapamune. In some cases, the interstitial lung disease has resolved upon discontinuation or dose reduction of Rapamune. The risk may be increased as the sirolimus trough concentration increases (see

**PRECAUTIONS, General, *Interstitial Lung Disease***). There have been reports of neutropenia and rare reports of pancytopenia. Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, and hypersensitivity vasculitis, have been associated with the administration of sirolimus (see **WARNINGS**). Hepatotoxicity has been reported, including fatal hepatic necrosis with elevated sirolimus trough concentrations. There have been rare reports of lymphedema. Abnormal healing following transplant surgery has been reported, including fascial dehiscence and anastomotic disruption (e.g., wound, vascular, airway, ureteral, biliary). The concomitant use of sirolimus with a calcineurin inhibitor may increase the risk of calcineurin inhibitor-induced HUS/TTP/TMA.

The safety and efficacy of conversion from calcineurin inhibitors to sirolimus in maintenance renal transplant population has not been established. In an ongoing study evaluating the safety and efficacy of conversion from calcineurin inhibitors to sirolimus (target concentrations of 12 - 20 ng/mL) in maintenance renal transplant patients; enrollment was stopped in the subset of patients (n=90) with a baseline glomerular filtration rate of less than 40 mL/min. There was a higher rate of serious adverse events including pneumonia, acute rejection, graft loss and death in this sirolimus treatment arm.

**OVERDOSAGE**

Reports of overdose with Rapamune have been received; however, experience has been limited. In general, the adverse effects of overdose are consistent with those listed in the **ADVERSE REACTIONS** section (see **ADVERSE REACTIONS**).

## 2. Summary of Pediatric cases received in the 12-months subsequent to pediatric exclusivity approval

Table 11 – Summary of ADBS pediatric cases received during the 1-year following approval of pediatric exclusivity						
Case #	Age	Sex	Country	Daily Dose Duration of therapy	Adverse Events	Concomitant drugs
Receipt date	Out	Country	Indication	Transplant complication/rejection/graft dysfunction (n=6)	Adverse Events	Concomitant drugs
Report type	Country	Indication	Indication	Transplant complication/rejection/graft dysfunction (n=6)	Adverse Events	Concomitant drugs
5693879	14	F	US	NS Intermittently for 9 months LTP	Liver transplant rejection EBV LPD Aspergillosis Drug level ↑ Headache Oral mucosa blistering Rash	Tacrolimus Voriconazole Amibosome
5933003	12	F	US	1 mg continues HTP	Heart transplant rejection Drug level ↓	Magnesium Enalapril Pravastatin Bumetanide Prednisone Atenolol Potassium Aspirin Neurontin Ranitidine Tacrolimus
5852917	16	F	US	6 mg continues RTP	Kidney transplant rejection Creatinine ↑	Tacrolimus Prednisone Pantoprazole Baetrim Polysaccharide-iron complex Multivitamins Ganciclovir Erythropoietin
5810768	16	M	GER	6 mg x 5 mth then both ↑ ↓ RTP	Kidney transplant rejection Creatinine ↑	Mycophenolate mofetil Methylprednisolone Ramipril Epoetin beta Calcitriol
5906416	14	M	H	8 mg continues RTP	Kidney transplant rejection Chronic allograft	Prednisone Minoxidil Tacrolimus

Comments/Summary of case

About 6 weeks after liver transplant patient experienced central rejection. Tacrolimus and sirolimus were started to "wipe out her immune system." Both drugs were restarted at higher doses. She developed LPD, was treated with Rituximab and had sirolimus and tacrolimus stopped again. The patient began rejection sirolimus was restarted. Aspergillosis was diagnosed, and she was hospitalized and treated with voriconazole drug level was "5-15" on admission. Approximately 3 weeks later sirolimus level was 47, and it was stopped was sent home on Amibosome and tacrolimus. At home she experienced rash on her legs, headache and blisters mouth. After 30 days of therapy aspergillosis and LPD had not resolved.

Patient's concurrent illnesses included hypertension, blood cholesterol increased, heart rate abnormal, convulsion of heart transplant and overweight. A month after starting therapy with sirolimus the drug level decreased, patient indicated no deviations in her regimen. Patient was hospitalized for 'persistent transplant rejection' hospital stay, drug level returned to normal. However, when she went home the drug level decreased again and her mother deny non-compliance. The report indicates that at unspecified time liver and renal disease.

Study patient with a history of chronic renal failure, glomerulonephritis and nephrectomy was admitted six starting sirolimus therapy for protocol biopsy. Patient had intermittent elevations of creatinine a week prior Blood creatinine levels fluctuated from 1.1 to 2.8 mg/dL. Sirolimus levels fluctuated from 13.1 on admission month later. At hospitalization, biopsy showed acute cellular rejection. Patient was treated with IV Solum recovered.

A 16-year old with concurrent hypertension and a history of toxic nephropathy while on cyclosporine therapy increased creatinine. He was hospitalized. A biopsy showed acute kidney transplant rejection. He was treated with high doses of corticosteroids and subsequently the sirolimus dose was modified (increased to 8 mg for 7 months) and eventually decreased to Patient continues on sirolimus therapy at time of reporting.

Patient with concurrent hypertension, anemia, iron deficiency, ventricular hypertrophy and aortic valve incision a history of hyperkalemia and impaired glucose tolerance, experienced acute graft dysfunction 9 months after sirolimus therapy. At that time he was hospitalized for elevated creatinine (226, normal range 44-88). He:

Table 11 – Summary of AERS pediatric cases received during the 1-year following approval of pediatric exclusivity							
Case #	Receipt date	Report type	Age Sex Out Country	Daily Dose Duration of therapy Indication	Adverse Events	Concomitant drugs	Comments/Summary of case
4181024	2005	Study	11 F H, LT CAN	3 mg 9 months RTP	nephropathy Acute graft dysfunction Lipase ↑ CK ↑ Creatinine ↑ Glucose ↑ Potassium ↑	Losartan Sodium chloride Fosinopril Septtra Sodium bicarbonate Calcitriol Darbepoetin alfa Iron	elevated lipase and blood creatine phosphokinase (CK). The patient had long-standing difficulties with acute intake. The elevated enzyme levels were associated with reduced renal function. No clinical evidence of p rhabdomyolysis or cardiac ischemia. Events resolved partially. Investigator suggested that the acute graft related to insufficient fluid and sodium intake, an that the lipase and CK increases were related to the acute graft dysfunction.
4035135	2005	15-day study	8 M H US	3 mg 20 days RTP	Kidney transplant rejection Chronic allograft nephropathy Fever Chills dysuria Vomiting Pain	Tacrolimus Alfalcidol Ferroin sulfate Epoetin Amlodipine Ranitidine	Patient with a history of renal dysplasia and urinary tract infections experienced rejection and pyelonephriti starting sirolimus therapy. She developed fever, chills, dysuria, vomiting and pain over the transplant site. positive for <i>Citrobacter freundii</i> and creatinine level was 4.1 mg/dL. She was admitted for IV antibiotic the biopsy revealed mild acute rejection. She was treated with pulse steroid therapy. She was discontinued frc The patient was readmitted two weeks later for a second course of steroid due to increase in creatinine leve After discontinuation of tacrolimus and starting cyclosporine therapy, creatinine levels improved. Transpla considered resolved.
5909173	2005	Study	2 M H GER	1.8 mg 45 days RTP	Kidney transplant failure Pneumonia	Magnesium gluconate Prednisone Ranitidine Bactrim Tacrolimus Labetalol Amlodipine Cefazolin Promethazine	Patient with Eagle Barrett Syndrome experienced increased creatinine level and abdominal pain while host kidney ultrasound showed no flow to the transplanted kidney, and it was confirmed that the patient had kid obstruction and early changes of tissue necrosis. Surgeons found that the renal artery and vein had twisted there was no flow to the transplanted kidney. A new ureter was created. Sirolimus was discontinued as the concerned about wound healing. A week later the patient underwent a transplant nephrectomy due to a nor transplanted kidney, which was completely thrombosed and ischemic. The patient was considered recover
5909173	2005	Study	2 M H GER	1.8 mg 45 days RTP	Kidney transplant failure Pneumonia	Cyclosporine Methylprednisolone Captopril Atenolol Amlodipine Colecalciferol Ferrous sulfate	Patient with concurrent hypertension was hospitalized due to pneumonia and acute kidney transplant renal patient needed dialysis and additional treatment not described in the report. The patient recovered. The in considered the pneumonia and renal failure possibly related to the study product. For the 7 months prior to patient had been on a sliding dose of sirolimus which was started at 5 mg and decreased to 1.8, 1 and 0.8 m of the events the dose was 1.8 mg daily.
<b>Gastrointestinal (n=3)</b>							
5853026	2005	Study	16 F H MX	4 mg 5 months RTP	Gastritis Esophagitis	Clonidine Hydralazine Propranolol Losartan Nitroprusside Ceftazidime Ganciclovir Nystatin	Patient with history of hypertension experienced approximately 5 months after starting therapy with sirolin kidney transplant, experienced vomiting, abdominal pain and hypertension. On admission, endoscopy show esophagitis. Patient recovered after therapy with omeprazole and sucralfate.

Table 11 – Summary of AERS pediatric cases received during the 1-year following approval of pediatric exclusivity					Comments/Summary of case
Case # Receipt date Report type	Age Sex Onset Country	Daily Dose Duration of therapy Indication	Adverse Events	Concomitant drugs	
579801 2005 15-day	1.2 yrs F H US	3.6 mg 3 months RTP	Fever Pneumonia Paralytic ileus	Atorvastatin Captopril Cephalothin Ranitidine Prazosin Salicylic acid Clonazepam Fluoxetine  Tacrolimus Ganciclovir Methylprednisolone	Three to five days after starting sirolimus patient experienced fever, pneumonia and paralytic ileus. She was on antibiotics, metoclopramide and glycerin suppository. Patient recovered.
4196410 2004 Study/15- Day	4 F H US	1 mg 28 months RTP	Bloody stools LPD	Lansoprazole Pramipexole Tacrolimus Amlodipine Prednisone Mupirocin Erythromycin Baclofen Valganciclovir Sucralfate Senna fruit Metoclopramide Hydralazine Diphenhydramine Ondansetron Paracetamol Levosulbutamol Lactulose glycerol	Patient was hospitalized due to rectal bleeding, after approximately 2 years of sirolimus therapy. A biopsy of the rectum was performed. The investigator considered that rectal bleeding was a gastrointestinal complication of the LPD. Sirolimus dose was decreased to 0.5 mg daily.
<b>Drug interaction/drug level alteration (n=3)</b>					
5936612 2005 periodic	15 F H US	6 mg > 1 year, continues HTP	Nausea Vomiting "Erratic sirolimus levels"	Mycophenolate mofetil Tacrolimus	A pharmacist reported that after a year of therapy the patient sirolimus trough level was 24. She experienced vomiting, and was admitted for work-up. It was also reported that the patient had previous erratic sirolimus further information was provided.
5703501 2005 15-day	6 M H CAN	3 mg >7 months, ongoing RTP	Medication error resulting in drug overdose Drug interaction	Tacrolimus Azithromycin Prednisone Septra	Accidental overdose resulting in tacrolimus intoxication [Accidental overdose] Medication error resulting in accidental overdose [Medication error] Prograf/Zithromax/Sirolimus drug intake in increased levels [Drug interaction] Tacrolimus intoxication resulting in neurological symptoms, erratic delusions, discomfort, bone marrow to:

Table II - Summary of AERS pediatric cases received during the 1-year following approval of pediatric exclusivity				
Case #	Age Sex Out Country	Daily Dose Duration of therapy Indication	Adverse Events	Concomitant drugs
5753591	5	3 mg	Erratic delusion Discomfort Bone marrow toxicity Anemia Decline in renal function	ASA
<p>decline in renal function[Drug level increased]  Physician reported that on 02-NOV-2004 the patient's mother needed a refill on the patient's Prograf (tacrolimus) prescription (the prescription had run out and there were no capsules left when she received the refill). At that time the patient was very stable and follow-up visits were required once per month. There were no issues. A few days later the patient became very unwell. He went to see his pediatrician who diagnosed pneumonia. She phoned the reporter and insisted on treatment with a macrolide. This imposes a problem as both tacrolimus and sirolimus have to be taken with macrolides, and there already was evidence for a drug interaction between both drugs. In this situation the best possible is Zithromax (azithromycin), and trough levels have to be monitored carefully. The reporter/physician thought that the patient was to be seen at his clinic the following workday. The physician reduced the sirolimus dose to 0.7 mg BID. The patient's condition deteriorated slightly over the weekend, but the fever subsided. An x-ray was repeated and found no evidence for pneumonia, just bronchitis and sinusitis. Blood was drawn; however, tacrolimus and sirolimus levels were not received that same day. The liver enzymes, complete blood count and creatinine were unchanged and the patient's fever had disappeared, therefore the patient was sent home. At that time the tacrolimus levels were in vain until 5:30 at night. The reporter assumed the lab would call if the levels were high. The patient showed no evidence of neurological symptoms at all on 8-NOV-04. The patient's mother phoned the following morning about the patient's neurological symptoms and indicated he did not sleep at night. It was decided the patient should go to the emergency room for assessment. The patient clearly had a delusion and was in a state of erratic delusion. He was not oriented, hot but afebrile, not hyperventilating, and in disorientation. CT was normal. Tacrolimus levels on 10-NOV-04 revealed &gt;30. No one was contacted about that result, consequently, the patient's morning dose was not held. The dilution of the sample revealed a value of 25.0 ng/mL, considered toxic. The next value was 33.5 ng/mL, drawn in the emergency room at 11:00. The patient's sirolimus level was adequate at 5.1 ng/mL. Subsequently, the patient was admitted with the diagnosis of tacrolimus intoxication on 11-NOV-04 with a half-life of 12.2 hours. His mean residence time was actually 17.2 hours. It was decided to restart him on tacrolimus 1 mg every 24 hours. Zithromax was held from 08-NOV-2004. An unreported severe drug interaction was suspected because of the intake of 3 macrolides. Unfortunately, the patient's trough level was 29 ng/mL on 15-NOV-2004. Dosing interval was increased to 36 hours which resulted in a trough level of 5.4 on the 15-NOV-2004. Dosing interval was increased to 36 hours which resulted in a trough level of 5.4 on the 15-NOV-2004. It appeared as though the patient was back to his old levels and the parents were satisfied with the required readmission. His trough level was 24.7 ng/mL. Dosing errors then had to be considered. Incidentally, the pharmacy discovered their dosing error independently and phoned the parents just as it was suggested to restart him on tacrolimus 1.0 mg BID that evening. Unfortunately, the patient deteriorated rapidly after two days and required readmission. The pharmacy had dispensed 5 mg capsules instead of 0.5 mg capsules. The pharmacy had labeled the patient incorrectly. Since the family had no capsules at home for comparison, they did not realize the differences. The patient's half life was 11.5 hours, only marginally shorter than when he still had an effect from the Zithromax residence time amounted to 16.2 hours. It was concluded that there was only a small drug interaction between tacrolimus and sirolimus. However, the patient's sirolimus levels fell with a weaning effect of the Zithromax and they were on his old sirolimus dose. The patient is currently recovering slowly and has major anemia as a result of the frequent blood work and marrow toxicity secondary to the toxic tacrolimus levels. The patient's bone marrow has not recovered and Darbepoetin alpha and iron were started. The patient also experienced a temporary decline of renal function criteria are associated with events bronchitis, sinusitis, and decline in renal function.</p>				
5753591	5	3 mg	Drug interaction	Tacrolimus



Table 11 - Summary of AERS pediatric cases received during the 1-year following approval of pediatric exclusivity								
Case #	Receipt date	Report type	Age	Sex	Country	Indication		
			Daily Dose	Adverse Events		Concomitant drugs		
			Duration of therapy			Comments/Summary of case		
5694484	2004	NS	2	NS	UK	Diarrhea Elevated creatinine, Electrolyte imbalance, Sunken eyes, Dry pharynx Rash Decreased urinary output Ascites Haematuria Leukopenia Liver function test abnormal Lobar pneumonia Lymphocele Sleep disorder Wound dehiscence Fluid overload	<p>Prilosec Aspirin Lomotil Fer-in-sol Pepcid Reglan Lactobacillus Florinef Epogen Iron Ganciclovir Famotidine Septira Ferrous sulfate Lasix Mag plus Albuterol Floven Epogen Norvasc Bactrim Niferex Sodium bicarbonate Sodium chloride Valyte Focogercort Magnesium sulfate Codeine Gentamicin Tacrolimus Prednisolone Loperamide</p>	<p>diarrhea and dehydration, elevated creatinine, electrolyte imbalance, sunken eyes, dry pharynx, rash and de output. In four months after the last infection and a year after the transplant, she was noted to h She was hospitalized on each of the dates mentioned. The investigator considered that the infections, dehy and hematuria to be possibly/probably related to the study therapy. Patient recovered from all events, exce which was persisting at the time of reporting.</p>
5694484	2004	NS	2	NS	UK	Intracranial bleeding	<p>Patient with a history of liver transplant and concurrent short-bowel syndrome was treated with 2 mg of sir 28 days. The day after stopping therapy, the patient experienced intracranial hemorrhage confirmed by bra additional brain scans done at 1- and 2- weeks after the event indicated "new bleeding." Patient is recover event. Interval between transplant and cerebral hemorrhage was not provided</p>	

Abbreviations used in the table:

Country abbreviations: FR= France, IN=India, JP=Japan, MX=Mexico; NLD= Netherlands; UK= United Kingdom; US=United States  
Disease abbreviations: EBV=Epstein-Barr Virus, HTP=Heart Transplant Prophylaxis, LTP=Liver Transplant Prophylaxis, RTP= Renal Transplant Prophylaxis, LPD = Lymphoproliferative Disorder

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/s/

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