Wyeth®

IMPORTANT CORRECTION OF DRUG INFORMATION

To AST and ASTS Members

Dear Health Care Provider:

Recently you may have received a publication from Galen Press as a part of the Protocols Series. It had the title "Protocols Series – Guidelines from experts in transplantation: Sirolimus for liver transplantation: Primary and rescue immunosuppression." This publication was supported by an unrestricted educational grant from Wyeth.

This publication did not provide the following important information:

- **The safety and efficacy of Rapamune® (sirolimus) as immunosuppressive therapy has not been established in liver transplant patients, and therefore, such use is not recommended. The prescribing information has been updated to include the following black box WARNING.**

> Hepatic Artery Thrombosis:
> In two multicenter, randomized controlled studies in *de novo* liver transplant recipients, the use of sirolimus in combination with cyclosporine or tacrolimus was associated with an increase in hepatic artery thrombosis. Most cases occurred within 30 days post-transplantation and most led to graft loss or death. The safety and efficacy of Rapamune® (sirolimus) as immunosuppressive therapy have not been established in liver transplant patients, and therefore, such use is not recommended.

- Wyeth Research has suspended enrollment in a Phase II clinical study comparing sirolimus in combination with tacrolimus/corticosteroids to tacrolimus/corticosteroids alone in *de novo* liver transplant patients. This action was prompted by an imbalance in the observed rates of hepatic artery thrombosis with a rate of 5.5% (6/110) in the sirolimus-tacrolimus treatment group, all of which occurred within 16 days post-liver transplantation, versus 0.9% (1/112) in the tacrolimus-treated control arm.
- **As of April 10, 2002, based on additional information, we have learned that the use of sirolimus plus tacrolimus was associated with an excess rate of death and graft loss in a liver transplant study. Many of these patients had evidence of infection at or near the time of death. Additional revisions will be made to the product labeling, which will be available at www.Wyeth.com or 1-800-934-5556.**

- A previous clinical trial in *de novo* liver transplant patients in which RAPAMUNE was used in combination with cyclosporine and corticosteroids revealed an excess of hepatic artery thrombosis in patients on the combination regimen (10/112, 8.9%) as compared to the tacrolimus/corticosteroid control arm (2/52, 3.8%).

Prescribing Information

- RAPAMUNE is indicated for the prophylaxis of organ rejection in patients receiving renal transplants. It is recommended that RAPAMUNE be used in a regimen with cyclosporine and corticosteroids. Increased susceptibility to infection and the possible development of lymphoma and malignancy, especially of the skin, may result from immunosuppression. Only physicians experienced in the use of immunosuppressive therapy and the management of 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.

The following other changes have also been made to the Prescribing Information:

- In the *Food effects* subsection of CLINICAL PHARMACOLOGY, the kcal information has been corrected regarding the nutritional information for the high-fat breakfast used in this study and now reads:

  "In 22 healthy volunteers receiving Rapamune Oral Solution, a high-fat meal (861.8 kcal, 54.9% kcal from fat) altered the bioavailability characteristics of sirolimus."

- In the *Lipids* subsection of PRECAUTIONS, the statement regarding concomitant administration of RAPAMUNE and HMG-CoA reductase inhibitors and/or fibrates was revised to read:

  "In clinical trials, the concomitant administration of Rapamune and HMG-CoA reductase inhibitors and/or fibrates appeared to be well tolerated. During Rapamune therapy with cyclosporine, patients administered an HMG-CoA reductase inhibitor and/or fibrate should be monitored for the possible development of rhabdomyolysis and other adverse effects as described in the respective labeling for these agents."

- In the **Other clinical experience** subsection of ADVERSE REACTIONS, the following has been added:

  "Abnormal healing following transplant surgery has been reported, including fascial dehiscence and anastomotic disruption (e.g., wound, vascular, airway, ureteral, biliary)."

Serious adverse events or product problems should be reported to Wyeth Global Safety Surveillance and Epidemiology by FAX at (610) 989-5544 or by mail to GSSE, 201 King of Prussia Road, 6th Floor, Radnor, PA 19087.

A copy of the Prescribing Information for RAPAMUNE is enclosed for your reference.
Please contact Wyeth Medical Affairs at 1-800-934-5556 with any questions or concerns.

Sincerely,

Victoria Kusiak, M.D.
Vice President,
Global Medical Affairs
North American Medical Director
Wyeth Pharmaceuticals