SIROLIMUS (RAPAMUNE) AND INCREASED MORTALITY IN STABLE LIVER TRANSPLANT PATIENTS

This New Drug FAX Sheet issue provides updated information from the FDA regarding an increase in mortality among stable liver transplant patients. The verbatim communication from the FDA is provided below. If you need further information, please contact the Samford University Drug Information Service at (205) 726-2659.

The FDA is notifying healthcare professionals of clinical trial data that suggest increased mortality in stable liver transplant patients after conversion from a calcineurin inhibitor (CNI)-based immunosuppressive regimen to sirolimus (Rapamune). The trial was conducted by sirolimus manufacturer, Wyeth.

Sirolimus is indicated for the prophylaxis of organ rejection in patients aged 13 years or older receiving kidney transplants. The safety and efficacy of this drug in liver or lung transplant patients have not been established by the FDA.

The FDA is determining whether a labeling change for sirolimus is needed. In the interim, physicians should continue to use the drug’s professional labeling as a guide to therapy [see below for further recommendations]. The Agency will continue to examine the data on mortality and other adverse events in this study, and will make further recommendations, as appropriate.

Background Information

On March 25, 2009, Wyeth submitted to FDA results of a clinical trial, titled A Randomized, Open-Label, Comparative Evaluation Of Conversion From Calcineurin Inhibitor Treatment to Sirolimus Treatment Versus Continuation Of Calcineurin Inhibitor Treatment In Liver Allograft Recipients Undergoing Maintenance Therapy. The trial compared stable liver transplant patients who were converted from a CNI to sirolimus to patients who remained on CNI-based therapy. The trial data suggested that there may be increased mortality in patients converted from calcineurin inhibitor (CNI) therapy to sirolimus.

The trial also provided additional safety and efficacy information on sirolimus:

- The overall treatment failure rates at one year, defined as the occurrence of acute rejection or premature discontinuation for any reason, for the Intent-to-Treat population were significantly higher for the cohort of stable liver transplant patients converted to sirolimus compared to the cohort that continued on CNIs.
- Drug discontinuation due to an adverse event was also more frequent in the sirolimus cohort compared to those patients continued on CNI.
- Peripheral edema, stomatitis, rash, and mouth ulceration were the most frequent adverse events resulting in discontinuation in the trial.
- Mean fasting lipid concentrations increased significantly after the sirolimus conversion, and remained elevated throughout the one year follow-up evaluation period.
At this time, FDA has not made any changes to the professional label for sirolimus.

Recommendations and Information for Healthcare Professionals:

- Sirolimus is indicated for the prophylaxis of organ rejection in patients aged 13 years or older receiving kidney transplants.
- The safety and the efficacy of sirolimus as an immunosuppressant have not been established in liver or lung transplant patients. This information is in the Boxed Warning of the sirolimus label.
- The current Boxed Warning of sirolimus indicates that the use of sirolimus in combination with tacrolimus was associated with excess mortality and graft loss in a study in de novo liver transplant patients. Many of these patients had evidence of infection at or near the time of death.
- Therapeutic drug monitoring is recommended for all patients receiving sirolimus.
- Therapeutic drug monitoring should not be the sole basis for adjusting sirolimus therapy. Careful attention should be paid to clinical signs and symptoms, tissue biopsy findings, and laboratory parameters.
- Patients unable to take the tablets should be prescribed the sirolimus oral solution and instructed in its use.
- Patients should be counseled that sirolimus is to be taken by mouth, once a day, consistently and with or without food.
- Sirolimus tablets should not be crushed, chewed or split.

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