Wyeth

December 17, 2009

IMPORTANT DRUG INFORMATION

Dear Health Care Provider:

Wyeth is informing you of changes to the Rapamune prescribing recommendation for therapeutic drug monitoring of sirolimus [1], based on a change in the performance of an immunoassay.

Rapamune® (sirolimus) Oral Solution and Tablets are indicated for the prophylaxis of organ rejection in patients aged 13 years or older receiving renal transplants [1]. As described in the Indications section of the Prescribing Information, the recommended use of Rapamune in an immunosuppressive regimen for patients at low to moderate immunologic risk is different than that for those at high immunologic risk (defined as Black transplant recipients and/or repeat renal transplant recipients who lost a previous allograft for immunologic reason and/or patients with high-panel reactive antibodies [PRA; peak PRA level >80%]). Please read complete Prescribing Information for important treatment considerations including Indications, Contraindications, Warnings and Precautions, Adverse Reactions, and Dosage and Administration. Only physicians experienced in immunosuppressive therapy and management of renal transplant patients should prescribe Rapamune.

1.0 Background

For patients who are taking Rapamune, it is recommended that therapeutic drug monitoring be performed. The reference method for determination of sirolimus trough concentrations in the prescribing information for Rapamune is high performance liquid chromatography (HPLC).

Several immunoassays have also been developed and utilized that allow for rapid turnaround of such results. Generally, the immunoassays have been reported to have a positive bias relative to the reference assay HPLC with detection by tandem mass spectrometry (HPLC/MS/MS) due to detection antibody cross-reactivity with sirolimus metabolites [2, 3]. Values obtained with different assays cannot be used interchangeably, nor should conversion factors be applied between assays. Reference ranges may vary according to the specific immunoassay or HPLC test used, and should be established for each test used.

It has recently come to the attention of Wyeth that one of the more commonly used immunoassay platforms, IMx® [2], may yield results with a negative bias relative to HPLC/MS/MS in some cases [4]. This may vary from one laboratory to another and may also be affected by whether fresh or frozen blood samples are utilized. The newer ARCHITECT® assay [3] performs on average as expected (a positive bias relative to HPLC/MS/MS) based on a proficiency testing scheme. **Therefore, switching between platforms, whether between immunoassay platforms or between immunoassay and HPLC, can produce differing results that may be clinically significant**. As such, if different assays are used in monitoring a single patient without the knowledge of the Health Care Provider, the dose of Rapamune might be adjusted improperly with potential consequences, such as allograft rejection if drug exposure is too low or toxic side effects if exposure is too high.

Given this information, Wyeth has made several changes to the prescribing information for Rapamune.

2.0 Prescribing information regarding therapeutic drug monitoring

The prescribing information for Rapamune had included the following information with regards to therapeutic drug monitoring (with deleted text underlined):

> **"The above recommended 24-hour trough concentration ranges for sirolimus are based on chromatographic methods. On average, chromatographic methods (HPLC UV or LC/MS/MS) yield results that are approximately 20% lower than the immunoassay for whole blood concentration determinations. Currently in clinical practice, sirolimus**

whole blood concentrations are being measured by both chromatographic and immunoassay methodologies. Because the measured sirolimus whole blood concentrations depend on the type of assay used, the concentrations obtained by these different methodologies are not interchangeable [see *Warnings and Precautions (5.14), Clinical Pharmacology (12.3)*]. Adjustments to the targeted range should be made according to the assay utilized to determine sirolimus trough concentrations."

Based on the information presented above, the prescribing information has been updated to the following (with new text underlined):

"The above recommended 24-hour trough concentration ranges for sirolimus are based on chromatographic methods. Currently in clinical practice, sirolimus whole blood concentrations are being measured by both chromatographic and immunoassay methodologies. Because the measured sirolimus whole blood concentrations depend on the type of assay used, the concentrations obtained by these different methodologies are not interchangeable [see *Warnings and Precautions (5.14), Clinical Pharmacology (12.3)*]. Adjustments to the targeted range should be made according to the assay utilized to determine sirolimus trough concentrations. Since results are assay and laboratory dependent, and the results may change over time, adjustment to the targeted therapeutic range must be made with a detailed knowledge of the site-specific assay used. "

As therapeutic drug monitoring is recommended for patients taking Rapamune, Wyeth advises that all Health Care Providers involved in the management of patients taking Rapamune determine the following:

1) which assay is being used in their laboratory(ies);

2) if there is any change to the assay used;

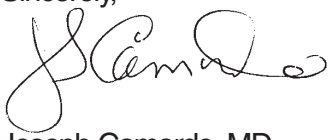
3) if there is a change to the laboratory's reference range and/or a subsequent change to the institution's or referring center's recommended range for sirolimus.

In doing so, your target levels can be appropriately adjusted in order to achieve optimal clinical results.

It is critical to keep in communication with your laboratory director(s).

Please share this information with your colleagues involved in the care of patients who may be taking Rapamune. Wyeth remains committed to supporting Rapamune and clinical research in renal transplantation. The updated Prescribing Information for Rapamune is enclosed for your reference and is also available at www.wyeth.com. Please contact Wyeth Medical Affairs at 1-800-934-5556 with any questions or concerns.

Sincerely,



Joseph Camardo, MD
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References

[1] Rapamune® - current US prescribing information, Wyeth Pharmaceuticals.
[2] IMx Sirolimus Assay Package Insert. Abbott Diagnostics Division. Abbott Park, IL. September, 2006.
[3] Architect System Sirolimus Assay Package Insert. Abbott Laboratories Diagnostics Division; Abbott Park, IL. January, 2009.
[4] Analytical Services International; London, UK.
http://www.bioanalytics.co.uk/pt/dates_and_results/sirol_dates2009.html. Accessed August 2009.