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# Wyeth

17<sup>th</sup> December 2009

Professor Frank Ierino  
President  
Transplant Society of Australia & New Zealand  
145 Macquarie St  
Sydney NSW 2000

Dear Professor Ierino

**Re: Important Information – Sirolimus Therapeutic Drug Monitoring**

I am writing to you to request your assistance in bringing some important information to the attention of the members of the TSANZ.

The following are the key points of this communication:

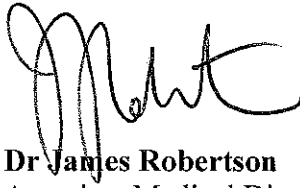
- The reference method for determination of sirolimus trough concentrations in the prescribing information for Rapamune<sup>®</sup> (sirolimus) is high performance liquid chromatography (HPLC)
- Several immunoassays have been developed and these are reported to have a positive bias of approximately 15 – 20% relative to the reference assay HPLC with detection by tandem mass spectrometry (HPLC/MS/MS) due to detection antibody cross-reactivity with sirolimus metabolites
- It has recently come to the attention of Wyeth that one of the more commonly used immunoassay platforms, IMx, is now generally yielding results with a negative bias of approximately 10% relative to HPLC/MS/MS
- IMx is soon to be replaced by a new platform (Architect) and this produces results as expected ie a positive bias relative to HPLC/MS/MS

**Therefore, switching between platforms, whether between immunoassay platforms or between immunoassay and HPLC, can produce differing results that may be clinically significant. It is therefore essential that prescribers of sirolimus are familiar with the assay method used by their particular laboratory, and that they are made aware of any change to the assay method should one occur.**

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Wyeth has communicated this information to the TGA and Medsafe, and changes to the Product Information/Data Sheet are being implemented. In addition, Wyeth is sending the enclosed communication to as many of those Health Care Practitioners potentially impacted by this change as our internal database allows. However given the potential limitations of this database and to ensure that communication is as comprehensive as possible, we would appreciate your assistance in bringing this important information to the attention of your members.

Yours sincerely

A handwritten signature in black ink, appearing to read 'J. Robertson', written in a cursive style.

**Dr James Robertson**  
Associate Medical Director  
Wyeth Australia/NZ

# Wyeth

[Insert Date]

[Insert Address]

Dear Health Care Provider:

**RE: Therapeutic Drug Monitoring For Rapamune<sup>®</sup> (Sirolimus)**

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

## 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 Product Information for Rapamune is high performance liquid chromatography (HPLC).

Several immunoassays have also been developed and utilised that allow for rapid turnaround of such results. The immunoassays have been reported to have a positive bias of approximately 15 – 20% 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].

It has recently come to the attention of Wyeth that one of the more commonly used immunoassay platforms, IMx, is now generally yielding results with a negative bias of approximately 10% relative to HPLC/MS/MS [4]. This may vary from one laboratory to another and may also be affected by whether fresh or frozen blood samples are utilised. The newer ARCHITECT assay performs as expected (a positive bias relative to HPLC/MS/MS). **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.

## **2.0 Changes to prescribing information regarding therapeutic drug monitoring**

Based on the information presented above, Wyeth is currently amending Rapamune's Product information to reflect the changes described below, as approved by the TGA. These changes to the "Assay Methodology" text of the Dosage and Administration section of the current Product Information are as follows: (additional text is underlined and deleted text marked with strike-through):

**The recommended 24-hour trough concentration ranges for sirolimus are based on chromatographic methods. Several assay methodologies have been used to measure the whole blood concentrations of sirolimus. Currently in clinical practice, sirolimus whole blood concentrations are being measured by both chromatographic and immunoassay methodologies. The concentration values obtained by these different methodologies are not interchangeable. Adjustments to the targeted range should be made according to the assay being utilised 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. ~~A discussion of the different assay methods is contained in *Clinical Therapeutics*, Volume 22, Supplement B, April 2000. Since assay results are also laboratory dependent, 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 centre's recommended range for sirolimus.

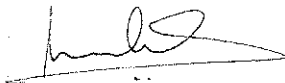
In doing so, your target levels can be appropriately adjusted in order to achieve optimal clinical results.

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.

Please contact Wyeth Medical Communications on 1800 500 498 or via email (medinfo@wyeth.com) with any questions or concerns.

Sincerely,



Dr Michael Lee

Medical Director

## References

- [1] Rapamune® - Product Information – Australia 6<sup>th</sup> October 2009
- [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](http://www.bioanalytics.co.uk/pt/dates_and_results/sirol_dates2009.html). Accessed August 2009.