



**Health Canada Endorsed Important Safety Information on  
Rapamune® (sirolimus)**

2009-11-26

Dear Healthcare Professional:

**SUBJECT: Sirolimus Therapeutic Drug Monitoring Assay Comparison**

Wyeth (a Pfizer company)\* in collaboration with Health Canada, would like to bring your attention to the fact that different laboratory assays used to measure Rapamune trough concentrations generate results that are not interchangeable.

- Health Care Providers should be aware that the methods used to measure Rapamune whole blood concentration have a direct impact on the values obtained.
- Health Care Providers should be aware of the type of assay being used in the laboratory, and should stay informed of any changes to the assay methods or reference range for Rapamune.
- Improper adjustment to the dose of Rapamune based on the use of differing assay methods can lead to allograft rejection (if the patient is underdosed) or toxicity (if the patient is overdosed).

Therapeutic drug monitoring is recommended for patients taking Rapamune. The reference method for determining sirolimus trough concentrations in the Rapamune Product Monograph is high performance liquid chromatography (HPLC) [1].

In clinical practice, sirolimus whole blood concentrations are being measured using both chromatographic and immunoassay methodologies. The concentration values obtained by these different assays are not interchangeable. Adjustments to the targeted range should be made according to the assay being used to determine the sirolimus trough concentration [1].

Several immunoassays have been developed that allow for rapid turnaround of results. Most immunoassays, including the newer ARCHITECT assay, have a positive bias of approximately 15 – 20% relative to the reference HPLC assay with detection by tandem mass spectrometry (HPLC/MS/MS) due to antibody cross-reactivity with sirolimus metabolites [2, 3]. However, it has recently come to the attention of Wyeth that one of the more commonly used immunoassay platforms, IMx, generally yields results with a negative bias of approximately 10% relative to HPLC/MS/MS [4].

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\* Wyeth is now a part of Pfizer Inc. The merger of local Wyeth and Pfizer entities may be pending in various jurisdictions and is subject to completion of various local legal and regulatory obligations.



Assay results may vary from one laboratory to another and may also be affected by whether fresh or frozen blood samples are used. Similarly, switching between platforms, whether between immunoassay platforms or between immunoassay and HPLC, can produce differing results that may be clinically significant. Health Care Providers should be aware of this information and keep in communication with their Laboratory Directors to appropriately adjust the dose in order to achieve optimal clinical results.

Managing marketed health product-related adverse reactions depends on health care professionals and consumers reporting them. Reporting rates determined on the basis of spontaneously reported post-marketing adverse reactions are generally presumed to underestimate the risks associated with health product treatments. Any case of serious or unexpected adverse reactions in patients receiving Rapamune should be reported to Wyeth Canada or Health Canada at the following addresses:

Wyeth, a Pfizer Company  
Medical Information & Pharmacovigilance  
50 Minthorn Boulevard  
Markham, Ontario L3T 7Y2  
Tel: 1-800-461-8844  
Fax: 905-470-4385

**Any suspected adverse reaction can also be reported to:**

Canada Vigilance Program  
Marketed Health Products Directorate  
HEALTH CANADA  
Address Locator: 0701C  
Ottawa, Ontario, K1A 0K9  
Tel: 613-957-0337 or Fax: 613-957-0335  
To report an Adverse Reaction, consumers and health professionals may call toll free:  
Tel: 866-234-2345  
Fax: 866-678-6789  
[CanadaVigilance@hc-sc.gc.ca](mailto:CanadaVigilance@hc-sc.gc.ca)

The [AR Reporting Form](#) and the [AR Guidelines](#) can be found on the Health Canada web site or in *The Canadian Compendium of Pharmaceuticals and Specialties*.

[http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/ar-ei\\_form\\_e.html](http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/ar-ei_form_e.html)  
[http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/\\_fs-if/2009-ar-ei-guide-patient/index-eng.php](http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_fs-if/2009-ar-ei-guide-patient/index-eng.php)

**For other inquiries related to this communication, please contact Health Canada at:**

Marketed Health Products Directorate (MHPD)  
E-mail: [MHPD\\_DPSC@hc-sc.gc.ca](mailto:MHPD_DPSC@hc-sc.gc.ca)  
Tel: 613-954-6522  
Fax: 613-952-7738



Please share this information with your colleagues involved in the care of renal transplant patients. The Rapamune Product Monograph can be accessed at [www.wyeth.ca](http://www.wyeth.ca) or on the [Health Canada website](#). Please contact Wyeth Canada Medical Information at 1-800-461-8844 with any questions or concerns.

Sincerely,

A handwritten signature in black ink, appearing to read "Neil Maresky".

Dr. Neil Maresky, M.B., B.Ch.  
Vice-President  
Scientific Affairs

**References:**

- [1] Rapamune<sup>®</sup> - Product Monograph dated Oct. 9, 2009, Wyeth Canada.
- [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.