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IMPORTANT SAFETY INFORMATION

Direct Healthcare Professional Communication on immunoassay performance changes and their associated impact on the therapeutic drug monitoring of RAPAMUNE® (sirolimus).

Dear Health Care Professional **please note the following important information**:

Summary

- Adjustments to the targeted therapeutic dose range of sirolimus must only be made with a detailed knowledge of the specific assay used to measure the drug concentration in the patient.
- Currently, sirolimus whole-blood concentrations are measured using either the reference assay high performance liquid chromatography (HPLC), or an immunoassay
- Switching between different immunoassays, or between an immunoassay and HPLC, in a single patient can lead to clinically significant differences in results, and, therefore, incorrect dose adjustments. This, in turn, may have potential adverse consequences, such as allograft rejection if drug exposure is too low or toxic side effects if exposure is too high
- Prescribers are therefore encouraged to regularly contact their laboratory and ascertain whether the assay used recently has been changed, and whether there have been any changes to the laboratory's reference range.

This information has been approved for distribution by the European Medicines Agency (EMA) and the Irish Medicines Board.

Further information on the safety concern

Sirolimus (Rapamune) is indicated for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk, who are receiving a renal transplant. As you are aware, therapeutic drug monitoring is recommended for patients treated with sirolimus.
The reference method for determination of sirolimus trough concentrations is high performance liquid chromatography (HPLC).[1] In addition, several immunoassays have also been developed to measure concentrations of this drug.

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) [2,3].
However, one of the more commonly used immunoassay platforms, IMx, yields 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 used. The newer ARCHITECT assay performs as expected, with a positive bias relative to HPLC/MS/MS.

Therefore, switching between different immunoassays or between an immunoassay and HPLC can produce different results that may be clinically significant. These differences may lead to improper dose adjustments of sirolimus with potential adverse consequences, such as allograft rejection if drug exposure is too low or toxic side effects if exposure is too high.

On the basis of these findings, section 4.2 (Posology and method of administration) of the Summary of Product Characteristics has been revised (see Annex).

Further information on recommendations to healthcare professionals

In order to be able to appropriately adjust the target level and achieve optimal clinical results, physicians are reminded to determine:

the assay being used in their laboratory(ies)
if there is any change to the assay used
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.

Physicians are also reminded to keep in communication with their laboratory director(s).

Communication information

This letter is being distributed to the following individuals in Ireland:

- Consultant Nephrologists
- Renal Transplant Surgeons
- Cardiothoracic & Cardiopulmonary Surgeons

- Hepatic Transplant Surgeons
- Hospital Pharmacy Directors
- Hospital Laboratory Directors

If you wish to report a suspected adverse reaction or medication error contact Wyeth at 01 4493500 or do so via the IMB website www.imb.ie.

For more information please contact the Wyeth Medical Information department on 01 4493500.

Sincerely,

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Dr Declan O'Callaghan,
Medical Director.

Annexes

Revised product information text (SPC):

Bolded wording indicates added text:
A ~~strikethrough~~ in text indicates a deletion:

"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.
~~When using a proprietary immunoassay system, always refer to the manufacturer's information to correlate values to a reference chromatographic assay~~. All sirolimus concentrations reported in this Summary of Product Characteristics were either measured using chromatographic methods or have been converted to chromatographic method equivalents Adjustments to the targeted range should be made according to the assay being utilized to determine the sirolimus trough concentration.
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. Physicians should therefore remain continuously informed by responsible representatives for their local laboratory on the performance of the locally used method for concentration determination of sirolimus"

Please refer to www.medicines.ie for the revised Summary of Product Characteristics (SPC).

References:

[1] Rapamune® - current 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.