



Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists

Professor Frank Ierino
President, TSANZ
145 Macquarie St
Sydney NSW 2000

Saturday, 30 January 2010

Dear Prof Ierino,

Re: Wyeth letter (17/12/2009) to TSANZ regarding sirolimus assay methods

We refer to the recent advisory letter from Wyeth warning about the discrepancies between immunoassays and chromatographic methods (such as Mass Spectrometry) for measuring sirolimus. Wyeth is to be commended for addressing such important laboratory assay method issues. Whilst we agree with the broad message of the letter, we are concerned that some of the message presented is simplistic and potentially clinically misleading. We offer the following comments to be considered when interpreting test results where the immunoassay is used.

- Sirolimus metabolites are well known to cross-react with the antibody in the immunoassay
- Individual graft recipients will be expected to have a wide spectrum of metabolite concentrations in blood samples for genetic reasons, ie., some patients will produce high metabolite concentrations, others low
- These metabolite concentrations will be further modified significantly by concomitant medications, etc, that utilize the same (CYP3A4/5) metabolic pathways
- One cannot therefore adopt a 'constant' correction factor to normalize immunoassay results to equate to chromatographic methods, as implied in the letter. To do so will result in grossly underestimating the (active) parent sirolimus concentration in some patients, and overestimate it in others
- The magnitude of the errors are clinically significant

We would emphasize that this issue is not unique to sirolimus, but applies equally to immunoassays for other immunosuppressants (CsA, TRL, ERL, MPA). In Australia and New Zealand, we have an increasing number of laboratories offering Mass Spectrometry testing for immunosuppressant drugs, including sirolimus. We encourage users to know which assay technique was used when interpreting results, and to exercise caution when immunoassay data are provided given the greater uncertainty in the result. We congratulate Wyeth for considering analytical issues that impact on the clinical use of sirolimus. We hope that our comments are a clinically useful contribution.

Sincerely,

Raymond G Morris PhD
President, Australasian Society of Clinical
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Disclosure: RGM directs a clinical laboratory that uses HPLC-MS/MS analysis for the 4 immunosuppressant drugs, CsA, TRL, SRL, ERL), for the reasons presented above.

Laboratories offering HPLC-MS/MS methods are available in each State and in NZ.

**ASCEPT is the professional and independent society in Australia and New Zealand
with expertise in the use and toxicity of medicines and chemicals**

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