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VETERANS HEALTH ADMINISTRATION (VHA) PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP), CENTER FOR MEDICATION SAFETY (VA MEDSAFE), VA TRANSPLANT BOARD, & VA DIAGNOSTIC SERVICES

SIROLIMUS: NON-INTERCHANGEABILITY OF DRUG MONITORING ASSAYS

I. ISSUE

The methods for assessing sirolimus whole blood concentrations are not interchangeable, and adjusting the sirolimus dose without knowledge of differing methods may result in serious consequences such as allograft rejection if drug exposure is too low or toxic side effects if exposure is too high.[1]

II. BACKGROUND

Sirolimus (Rapamune®) is indicated for the prophylaxis of organ rejection in patients 13 years or older receiving renal transplants.[2] The target 24-hr trough concentration in transplant patients at low- to moderate-immunologic risk following cyclosporine withdrawal should be within 16 to 24 ng/mL for the first year post-transplantation, and 12 to 20 ng/mL thereafter.[2] This recommendation is based on the high performance liquid chromatography (HPLC) method. For more rapid turnaround of results, immunoassays have been developed and utilized that, in general, have been reported to have a positive bias relative to the reference HPLC by approximately 20%.[3] However, the manufacturer has recently received reports that commonly used immunoassays may also yield results with a negative bias relative to the HPLC method. Therefore, switching between methods, whether between immunoassays or between immunoassay and HPLC, can produce differing results that may be clinically significant. Of serious concern is that if different methods are used in a single patient without the knowledge of the healthcare provider, the sirolimus dose may be adjusted improperly and potentially result in allograft rejection or toxicity. This is particularly problematic when patients are co-managed by their VA physician and local transplant centers.

III. PROVIDER RECOMMENDATIONS

Healthcare providers managing patients on sirolimus therapy should:

1. Plan to consistently use sirolimus levels from a single laboratory.
2. Communicate with laboratory personnel to determine which assay is being used for monitoring.
3. Review each lab report throughout the course of treatment to determine if there has been a change in the lab assay and adjust the dose in accordance with information in the manufacturer's product labeling.
4. Discuss with laboratory personnel the potential problems with assays and/or changes in assays for other transplant medications (e.g., tacrolimus and mycophenolic acid).

IV. REFERENCES

1. MedWatch: The FDA Safety Information and Adverse Event Reporting Program http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm197059.htm (Posted 1-11-2010)
2. Rapamune® Prescribing Information. Revised 11/09. (http://www.wyeth.com/content/showlabeling.asp?id=139 (Accessed 1-15-10)
3. Wyeth Dear Healthcare Professional Letter (December 17, 2009) http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM197064.pdf

ACTIONS:

- ***Facility COS and Chief Nurse Executives:*** *Forward this document to all appropriate providers who prescribe/use/handle/assay this agent (e.g., Transplant, nephrology, and laboratory, including contract providers, etc.). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.*
- ***ACOS for R&D:*** *Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).*