



August 20, 2007

The warfarin drug labeling (Package Insert; PI) was revised on August 16, 2007 by the FDA to include genomic information. In the “Clinical Pharmacology” section of the labeling, evidence of reduced warfarin clearance in patients carrying mutations in the genes CYP2C9 and VKORC1 is discussed. In the “Precautions” section, it is stated that “...genetic variations in the CYP2C9 and VKORC1 enzymes may influence the response of the patient to warfarin.” In the “Dosage and Administration” section, it states that lower initial doses should be considered for patients with genetic variations in CYP2C9 and VKORC1.

A specific recommendation to perform genetic testing before prescribing warfarin is not included in the labeling, and the dosage recommendations have not been changed. In its press release, the FDA indicated that studies are ongoing to develop such specific recommendations. Thus, the FDA has included statements accompanying the press release that physicians are not required to perform genetic testing before initiating warfarin therapy, nor should they delay the initiation of warfarin therapy. Instead, the change in the labeling is intended to inform physicians that up to 30% of their patients (i.e. those who carry the CYP2C9 and/or VKORC1 genetic variations) may be at risk for an adverse response to warfarin.

This intention, combined with the new statements in the labeling, are understandably confusing to physicians. Many will wonder why the FDA chose to include in the labeling the statement “lower initial doses should be considered for patients with genetic variations in CYP2C9 and VKORC1,” then comment that physicians are not required to test nor should they delay initiation of warfarin therapy. How can physicians consider lower doses if they do not conduct a test to determine their patient’s genotype? Unfortunately, there is no clear answer. According to the FDA, physicians should continue to initiate warfarin therapy using the recommended low dose, then carefully monitor INR to achieve a stable therapeutic dose, keeping in mind that approximately 30% of patients may have complications.

The decision to stop short of recommending or requiring genetic testing very likely reflects the lack of clinical outcome data. There has been disagreement on the part of some physicians who argue that a warfarin labeling change is premature given the lack of such data. While it is very clear that those carrying CYP2C9 and VKORC1 variations have more bleeding complications, it is not yet clear that performing a genotyping test prior to warfarin therapy will decrease the number of bleeding events. Similarly, it is not clear what initial warfarin doses should be for patients with genetic variations. Current estimates have come from retrospective studies that have compared differences in stable warfarin dose among patients carrying genetic variations. Studies are currently underway that will reveal the clinical utility of CYP2C9 and VKORC1 genotyping, as well as suggest initial warfarin dose depending on genotype. It is likely that

further warfarin labeling changes, including test recommendations and adjustments in dose for patients with genetic variations, will be made as studies are completed.

Although not all laboratories currently offer the CYP2C9/VKORC1 test, there are many who do. It is likely that more labs will begin to offer the test as a result of the warfarin labeling change. We are currently working on including more information, including which labs offer the test, when it will be available, and what the cost will be, on the AMA's Molecular Medicine website. We will also have a warfarin brochure available this fall that was developed in collaboration with the Critical Path Institute. The brochure summarizes the genetic basis for determining warfarin dosing, and also presents a brief background on pharmacogenomics. The brochure is intended for physicians and other health care providers who may not have experience with pharmacogenomics, but who are confronted with the increasing availability of genetic tests to aid in drug dosing. Additionally, an AMA/FDA-developed CME on pharmacogenomics and personalized medicine is available online at <http://ama.learn.com>. The CME is designed for physicians who have had little exposure to pharmacogenomics in clinical practice or who want to better understand the current levels of pharmacogenomic information in prescription drug labeling.

The genetic basis of warfarin dosing is a subject in transition, and it is likely that there will be further labeling changes as the results of research on clinical outcomes become available. Insurance coverage for the genetic test may be dependent on such outcome data, although Medicare already has indicated it will cover the test. In the meantime, it may be reasonable to interpret the labeling change as an effort by the FDA to inform physicians that there is a genetic basis to warfarin dosing, and that there are patients who are at an increased risk for adverse events because of genetic variations. There are CYP2C9 and VKORC1 genotyping tests available, and these tests may eventually become more routine in the initiation of warfarin therapy.