



Questions and Answers on New Labeling for Warfarin (marketed as Coumadin®)

What is warfarin and the recently approved change in the label for the drug?

Warfarin is a drug prescribed to help prevent blood clots. Following oral ingestion, it acts by blocking the action of certain proteins that cause blood to clot. Since warfarin acts to keep blood from clotting, one of the side effects of the drug is an increased risk for bleeding. This risk increases importantly if patients receive too much warfarin. Patients frequently differ in the dose of warfarin necessary to prevent blood clots and also differ in the risk for bleeding.

The recently approved change in the warfarin label provides information on how people with certain genetic differences may respond to warfarin. Specifically, people with variations in two genes may need lower warfarin doses than people without these genetic variations. The two genes are called CYP2C9 and VKORC1. The CYP2C9 gene is involved in the breakdown (metabolism) of warfarin and the VKORC1 gene helps regulate the ability of warfarin to prevent blood from clotting.

How will this new warfarin label information benefit patients?

This information will benefit patients because it will describe why patients with a variation in the CYP2C9 and/or VKORC1 genes may need a lower warfarin dose than patients with the usual forms of these genes. For patients with these genetic variations, the new label information may help physicians prescribe the correct warfarin dose and also encourage them to give increased attention to how these patients respond to warfarin. Identification of patients with these genetic variations is thought to improve the safe use of warfarin since choosing the correct warfarin dose is important to prevent blood clots and avoid bleeding.

How might healthcare professionals use this information in their practice?

Healthcare professionals might incorporate the genetic information on CYP2C9 and VKORC1, along with various clinical considerations and patient characteristics (e.g., age, body weight) to better estimate the initial warfarin doses for patients. Warfarin is often administered daily and the response to the drug is mainly measured by a laboratory test result called the INR. The INR measures, in part, the blood's ability to clot and the INR should be performed regularly in all patients receiving warfarin. Genetic information does not replace regular INR testing.

Response to warfarin and the risk for bleeding may be influenced by many factors, such as the presence of serious underlying heart disease or the simultaneous use of other drugs which can interact with warfarin. These clinical considerations impact the healthcare professional's decision to prescribe warfarin as well as the selection of the initial warfarin dosages. The recently revised warfarin product label adds CYP2C9 and VKORC1 genetic variations to the list of these clinical considerations for warfarin use. The label's specific warfarin dose recommendations have not changed.

Will healthcare professionals be required to test patients for these genetic variations prior to prescribing warfarin?

No, healthcare professionals are not required to conduct CYP2C9 and VKORC1 testing before initiating warfarin therapy, nor should genetic testing delay the start of warfarin therapy.

Are tests available to detect variations in the CYP2C9 and/or VKORC1 genes?

Yes, laboratory developed tests are available to determine if a patient has certain CYP2C9 and/or VKORC1 gene variants that may influence the response to warfarin. The availability and reliability of these tests may vary from lab to lab and healthcare professionals should check with their local or reference clinical laboratory to obtain more information about the specific tests.

What did clinical studies show to support the addition of genetic information to the warfarin label?

Clinical studies have suggested that patients with CYP2C9*2 and CYP2C9*3 genetic variations are at an increased risk for bleeding with warfarin therapy. In these studies, patients with these variants generally required lower doses of warfarin to achieve a desired INR control and decrease the risk of bleeding.

In general, more limited information is available for VKORC1 genetic variations than for CYP2C9. Among the more notable studies was the importance of VKORC1 detected in a study of 201 Caucasian patients who needed a wide variation in warfarin doses to maintain an acceptable INR test. Of the factors that were examined to determine why the dose varied so much, the presence of a VKORC1 genetic variation was thought to be responsible for 30% of the warfarin dose variation. The presence of either a VKORC1 or a CYP2C9 variation was thought to be responsible for 40% of the warfarin dose variation. Other non-genetic factors, such as age and weight, were responsible for 10% to 15% of warfarin dose variation.

Published studies have estimated the prevalence of CYP2C9 and VKORC1 gene variants in a number of ethnic groups. These studies have estimated the frequency of CYP2C9 gene variants, or genotypes, that may influence warfarin doses at approximately 10% to 20% in Caucasians and African-Americans. For the same populations the frequency of important genotypes of VKORC1 is 14% to 37%. The frequency of the important VKORC1 genotype in the Asian population has been reported to be as high as 89%.

The usual genetic form of CYP2C9 with normal enzyme activity is called CYP2C9*1. Studies indicate that the CYP2C9*2 and CYP2C9*3 genetic variations are important because patients with these variations metabolize warfarin slower than patients with CYP2C9*1. In a study among Caucasians, approximately 11% of the patients carried the CYP2C9*2 and 7% carried the CYP2C9*3 variation. Limited clinical data suggest CYP2C9 genetic variations in non-Caucasians occur less frequently.

Clinical studies have shown that patients with CYP2C9 and VKORC1 genetic variations require lower warfarin initial and maintenance dose to stay within the target INR. Future clinical studies are expected to identify which initial warfarin doses are most appropriate for people with different CYP2C9 and VKORC1 gene variants. Many of these studies are described at the internet address of: www.clinicaltrials.gov (using the "warfarin" search term).

If a patient has one of these genetic variations, does it mean the patient is more likely to bleed if given warfarin?

The available clinical data suggests that the patient is at an increased risk for bleeding. Not all patients with one or more gene variants in either CYP2C9 or VKORC1 will bleed, nor will all patients without gene variants avoid a bleeding episode. Careful INR monitoring is essential to maintain INR control in all patients irrespective of their genetic and non-genetic factors.

Can a patient's response to warfarin be affected by factors other than genetic variations in CYP2C9 or VKORC1?

Yes, a patient's response to warfarin may be affected by many factors, such as age, body surface area (weight and height), hypertension, serious heart disease, concomitant drugs that interact with warfarin, renal status, past history of bleeding if any, and food that could interfere with warfarin absorption or anticoagulation response.

What is personalized medicine?

Personalized medicine is a term that has been applied to clinical practice when a doctor uses information about a patient's genotype or gene expression along with other information such as the physical exam, medical history, age, race, gender, co-administered drugs to select a medicine or a dose of a medical product that is thought to be best suited for that patient. The promise of personalized medicine is to improve the safety and effectiveness of drug therapy in an individual patient.

What is FDA doing to advance personalized medicine?

Personalized medicine is a component of the personalized health care initiative of the U.S. Department of Health and Human Services (HHS). The FDA is involved with many activities related to personalized medicine. They include 1) relabeling previously approved drugs with new genetic information when appropriate, 2) including genetic information in the labels of newly approved drugs when genetic tests can differentiate patients in advance with regard to predicting benefit, risk or doses, and 3) encouraging the pharmaceutical industry to include the study of genetics in new drug development. These activities are described at the internet address of: http://www.fda.gov/fdac/features/2005/605_genomics.html

How does the coumadin labeling change fit into this strategy?

The label change highlights the opportunity for healthcare providers to use genetic tests to improve their initial estimate of a reasonable warfarin dose for a specific patient; this process may optimize the use of warfarin and lower the risk for bleeding.

Has FDA asked other companies to include information in the labeling about genetic variations?

Yes. Specifically, genetic variation information has been approved in the product labeling for the following drugs: 6-mercaptopurine, azathioprine, irinotecan, and atomoxetine.

Can we expect more labeling changes like this in the future? What about other initiatives?

Yes, as new pharmacogenetic data provides evidence that genetic variations importantly affect a drug's benefit, risk or dosing, the FDA expects the drug label to be revised to include the new information. In the area of new drug development, the FDA is encouraging industry to include the collection of genetic data in clinical trials with the intent that this information would help identify patients most likely to benefit from the new drug as well as to help identify any patients at high risk for adverse reactions to the drug.