FDA's New Plavix Black-Box Warning Could Trigger Surge in CYP2C19 Testing

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Clinical labs that perform gene-based drug-metabolism assays, and that have robust cardiovascular departments, could soon start seeing more orders for CYP2C19 testing in patients treated with a commonly used blood thinner.

In a statement last Friday, FDA said it has added a black-box warning to the label of the drug, Plavix, that says mutations in the CYP2C19 gene render certain patients unable to respond to the drug, which places them at increased risk for heart attack and stroke.

The call for genetic testing, seen here in Plavix's black-box warning, could keep clinical labs busy when one considers the depth of Plavix's penetration in the market: The drug generated $8.6 billion in global sales in 2008 and was the world's second-best selling therapeutic behind Pfizer's untouchable cholesterol drug Lipitor.

To be sure, the black-box warning comes 10 months after FDA added a general warning to the drug's label, but "felt it was important to highlight this risk in a boxed warning … after reviewing more data."

It also comes around one month after FDA asked updated the label of another popular blood thinner, warfarin, to include pharmacogenomically guided dosing ranges. The agency initially updated the drug's label in 2007 to reflect the influence of the CYP2C9 and VKORC1 genes in metabolizing the drug.

FDA' Plavix gambit also highlights the agency's growing commitment to using genetic information, such as gene testing and drug-diagnostic combinations, to better tailor therapeutic dosing.

Trouble is, FDA has typically been slow off the mark: Researchers have known for many years that mutations in the CYP2C9, VKORC1, and other genes affect how the body metabolizes scores of drugs. New studies appear nearly daily.

Plavix, made by Bristol-Myers Squibb and known generically as clopidogrel, is designed to make platelets less likely to form blood clots, which has been shown to reduce the risk of heart attack, unstable angina, stroke, and cardiovascular death in patients with cardiovascular disease.

However, the drug "does not have its anti-platelet effects until it is metabolized into its active form" by the CYP2C19 liver enzyme. Therefore, "people who have reduced functioning of their CYP2C19 liver enzyme cannot effectively convert Plavix to its active form." Plavix may be less effective in those so-called "poor metabolizers," and who may therefore "remain at risk for heart attack, stroke, and cardiovascular death." FDA estimates that between 2 percent and 14 percent of the US population are poor metabolizers.

"We want to highlight this warning to make sure health care professionals use the best information possible to treat their patients," FDA said in its statement.

To that end, the agency said it "recommends that health care professionals consider alternative dosing of Plavix for these patients, or consider using other anti-platelet medications." Also, genetic tests "are available to assess CYP2C19 genotype to determine if a patient is a poor metabolizer."

However, such tests can cost around $500, and "experts say it's unlikely such testing will become standard for patients taking Plavix," according to a report by the Associated Press.

"I think based on this people will do more genetic testing, but I think it's premature to say that everyone who gets Plavix needs to be tested," Louis Teichholz, head of cardiology at Hackensack University Medical Center, was quoted as saying in the AP article

Indeed, Teichholz said the black-box warning "could push more doctors to prescribe Effient," a rival blood thinner launched by Eli Lilly last summer.

Meantime, the Wall Street Journal on Friday interviewed a cardiologist who said he expects "mass confusion" among doctors "about how to handle the FDA's recommendations, noting the lack of rapid tests that could be used in an emergency setting."

The article also said "at least one company, Quest Diagnostics," recently started offering a CYP2C19 test." The reference lab has said some private insurance companies do pay for it.

FDA officials said CYP2C19 tests typically cost less than $500. Roche Holdings, for instance markets a gene chip-based homebrew assay that tests for CYP2C19.

A spokeswoman for New York-based Bristol-Myers Squibb said the company would add the new labeling to bottles of Plavix over the next two months, the AP reports.