FDA pulls one generic form of wellbutrin off the market

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Research found extended-release Budeprion at 300 mg dose was not equivalent to brand-name version of antidepressant.

(HealthDay)—People taking the antidepressant Wellbutrin now have one less option for a generic version of the drug.

In October, the U.S. Food and Drug Administration recommended that generic Wellbutrin, or bupropion, made by Impax Laboratories and distributed by Teva Pharmaceuticals, be taken off the market, and Impax and Teva have agreed to stop shipping the drug.

The decision is based on an FDA study that found that the extended release (XL) form of bupropion—Budeprion XL—at the 300 milligram (mg) dose was not bioequivalent to brand-name Wellbutrin XL at the same dose, suggesting that it may not be as safe and effective.

The study was published Dec. 5 in the *New England Journal of Medicine*.

Four other manufacturers make bupropion XL in 300 mg tablets, and patients can still get their prescription filled with these products.

"The other four generic versions of 300 mg extended-release bupropion tablets are not affected by FDA's recent announcement," said FDA spokesperson Sandy Walsh.

Although the agency stated that lack of bioequivalence might only apply to the Impax/Teva product because of its unique formulation, the agency is requesting that the other four manufacturers submit bioequivalence data to the agency by March 2013.

"This kind of result puts a cloud over all of the generic XL [forms of bupropion]," said Dr. David Hellerstein, a professor of psychiatry at Columbia University Medical Center, in New York City.

Companies including Impax/Teva also make a bupropion XL in 150-mg tablets, which are also not affected by the FDA decision.

But even before the FDA decision, Hellerstein avoided any kind of generic bupropion XL. "Patient would complain that generic XL is not the same as brand-name XL—it wears off sooner, it has more side effects," he said. "I tell patients not to go to XL unless you're committed to taking brand name."

For patients who want a less expensive generic, he recommends sustained release (SR) because there does not seem to be a clinical difference between the brand name and generic versions in that form. SR has to be taken twice a day, while XL is taken once a day.

"If it were me and I could afford it and/or my insurance company allowed me to take it, I would err on the side of caution and take the brand name until the generics were proven at the higher doses to be

bioequivalent," said Dr. Sheldon Preskorn, a professor of psychiatry at University of Kansas School of Medicine-Wichita.

The FDA decided to study the bioequivalence of bupropion XL 300 mg made by Impax/Teva to the brand-name counterpart because of adverse events that had been reported to the agency since the generic was approved in 2006.

"The adverse event reports we got included loss of antidepressant effect and, in some instances, worsening of depression symptoms, following a switch from the brand name to a generic product," Walsh said.

Some patients also reported that adverse effects associated with bupropion, including headache, fatigue and anxiety, got worse after switching to Impax/Teva's generic version, Walsh added.

About half of these patients said their depressive symptoms and adverse events improved after switching back to Wellbutrin XL 300 mg, according to the FDA.

"Relapsing of major depression is not inconsequential," Preskorn said. "Major depression causes problems with social functioning, work performance and some level of a suicide risk."

For the bioequivalence study, the FDA measured the level of Wellbutrin and bupropion XL 300 mg in the blood of 24 healthy adult volunteers over the course of the day after taking the medications.

The FDA requires the level of generic drug absorbed in the blood to be, on average, within 80 and 125 percent of the level of the brand-name version. However the range of absorption of bupropion XL was only between 77 and 96 percent of the level of Wellbutrin.

The difference in blood concentration between Wellbutrin and bupropion in this study could explain the clinical difference in safety and effectiveness, Preskorn said. "If the concentration is substantially lower or higher, then your concern would be reduced efficacy or greater likelihood of off-target effects," he said.

Although it is unclear why only the generic XL in 300-mg tablets and not in 150-mg tablets, or only the Impax/Teva version of the 300-mg tablets, would lack bioequivalence, it could be because higher doses of the drug have trouble dissolving in the gastrointestinal tract, Preskorn said.

The FDA approved the generic versions of Wellbutrin XL based on the studies demonstrating bioequivalence at the lower, 150-mg dose.

Typically the FDA recommends that makers of generic drugs test the blood concentration of the drug at the highest dose and then extrapolate bioequivalence data for the lower doses based on these findings.

However, in the case of bupropion, the FDA granted a waiver to companies to test the lower dose because of concern that the higher dose could cause seizures in the volunteers, Walsh wrote.

Either way, extrapolating information about safety and efficacy from one dose is usually appropriate, said Dr. Sidney Wolfe, director of the health research group at Public Citizen, a nonprofit consumer advocacy organization based in Washington, D.C.

"For most drugs, there is such a wide difference between the amount that works and the amount that causes trouble that checking out every single dose is not necessary," he said.

However bupropion might be an exception. Ever since it entered the market in 1985, it was known there was a fine line between

antidepressant effect and seizure risk, Wolfe said. The FDA knows which drugs have this type of narrow therapeutic window, and for them it might have been better to check out all the doses, he added.

More information: To learn more about depression and treatments, visit the U.S. National Institute of Mental Health.

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