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## FDA Panel: Ban 2 Popular Asthma Drugs

Bridget M. Kuehn

**A** PANEL OF ADVISORS TO THE US Food and Drug Administration (FDA) recommended that the agency ban the marketing of 2 popular asthma drugs that have been associated with an increased risk of rare but serious adverse events and, in some cases, death.

The panel was charged with assessing the risks and benefits of certain asthma treatments, specifically the long-acting  $\beta$ -agonist (LABA) drugs formoterol and salmeterol and combination products containing both a LABA and an inhaled corticosteroid (formoterol plus budesonide and salmeterol plus fluticasone). Previously, the FDA's Office of Drug Safety and the agency's pulmonary and allergy drug products division had made contradictory recommendations concerning LABAs.

The panel, which consisted of members from 3 committees that advise the FDA on drug safety, pediatric issues, and pulmonary and allergy drugs, recommended that the agency ban the marketing of products containing a LABA only (formoterol or salmeterol) as asthma treatments in all age groups. However, they also recommended the continued sale of combination products (formoterol plus budesonide for adults and adolescents or salmeterol plus fluticasone for all ages) for treating this disorder, noting that these drugs appeared to be less risky.

The agency typically follows the recommendations offered by its advisory committees.

"What we have come to learn is that LABAs, when used alone, are associated with more deaths [among asthma patients]," said Marsha D. Rappley, MD, dean of the College of Human Medicine

at Michigan State University in East Lansing. Rappley serves as chair of the FDA's pediatric advisory committee.

As part of its deliberations, the committee reviewed a new FDA meta-analysis of data from 110 clinical trials of LABA products used to treat asthma;



Ted Grudzinski/AMA

**Asthma treatments containing long-acting  $\beta$ -agonists alone are associated with an increased risk of rare but serious adverse events.**

these trials included more than 60 000 patients taking formoterol, salmeterol, formoterol plus budesonide, salmeterol plus fluticasone, or a non-LABA therapy (<http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4398b1-01-FDA.pdf>). Overall, the LABAs were associated with a greater risk of asthma-related death, asthma-related intubation, or asthma-related hospitalization. However, this trend was only significant for salmeterol, which is not surprising because of the majority of the patients included in the analysis (more than 43 000) were involved in trials of salmeterol. Use of salmeterol plus fluticasone was not associated with an increased risk of adverse events.

Of the 20 asthma-related deaths documented in the trials, 16 were among patients taking LABAs, while only 4 were using non-LABA therapies. All 16 deaths were among patients taking salmeterol.

Rappley noted that overall data collected on this class of drugs since the 1990s have consistently shown a small increased risk of rare but serious asthma-related events associated with LABAs, particularly LABA-only products.

It is not clear why taking LABA drugs alone may cause asthma-related events. Some scientists have hypothesized that because LABA drugs, which widen airways, provide patients an immediate sense of relief, patients with separate LABA and corticosteroid inhalers may fail to use the corticosteroid, leading to uncontrolled inflammation.

"Our recommendation is that the combined agent is clearly the wiser choice," Rappley said.

Although prior to the panel's meeting several medical organizations expressed objections to the idea of a complete ban on LABA products for use in asthma patients, the split decision seems to have won support from some. Thomas B. Casale, MD, executive vice president of the American Academy of Allergy, Asthma, and Immunology and chief of allergy and immunology at Creighton University in Omaha, Neb, said the academy supports the committee's recommendations, which are consistent with the National Institutes of Health's (NIH's) guidelines on the treatment of asthma. In addition, he warned that patients who hear about the ban should not abruptly change their treatment regimen, but should instead discuss any possible changes with their physician.

Rappley also emphasized the importance of following the NIH's guidelines. The guidelines recommend asthma



patients first receive a low-dose inhaled corticosteroid; then, if their asthma remains uncontrolled, they should they receive additional medications.

"The committee reviewed data that indicated asthma medications are being

prescribed in ways that don't follow the guidelines and that place adults and children with asthma at risk," she said.

Accordingly, the panel recommended that the agency, medical organizations, and the manufacturers of LABA products

work to educate physicians about the importance of following the guidelines. They also said that large trials designed specifically to assess the risks and benefits of combination LABA-inhaled corticosteroid products are needed. □

## Clinicians Advised to Step Up HIV Tests

Rebecca Voelker

**E**XPERTS IN HIV/AIDS CARE HAVE called upon physicians and other health professionals in the United States to follow federal recommendations issued more than 2 years ago that call for routine HIV testing of all patients aged 13 to 64 years.

Since the US Centers for Disease Control and Prevention (CDC) released the recommendations in 2006, some headway has been made in increasing the number of patients tested routinely. Even so, experts meeting at a national summit in Alexandria, Va, in late November said routine HIV testing has not been widely implemented.

"We still are not anywhere near [routine HIV testing] being the national norm," said Veronica Miller, PhD, executive director of the Forum for Collaborative HIV Research, an independent, public-private partnership based at the George Washington University School of Public Health and Health Services in Washington, DC.

"Testing for HIV should be as routine as the flu shot," said Miller.

### STOP THE CYCLE

Support for routine testing is based on several factors. Rapid screening using a saliva test that is highly sensitive and specific for HIV-1 and HIV-2 has been available for more than 6 years (CDC advises that rapid HIV tests require confirmatory testing). With treatment advances that have occurred over the past decade, physicians and patients can approach HIV infection as a chronic, rather than fatal, illness.

"The test is fast, cheap, and easy. It's almost perfect in terms of getting positive or negative results, and it detects a lethal disease that can now be treated," said John Bartlett, MD, professor of medicine at Johns Hopkins University School of Medicine, Baltimore, Md.



Experts are calling on US physicians and other health professionals to follow federal recommendations that advise routine HIV testing for all patients 13 to 64 years.

Routine testing could help tens of thousands receive lifesaving treatment while preventing new infections. Of the 1.1 million individuals in the United States estimated to have HIV infection, about 20% are unaware of their status, often because their behaviors are not particularly high risk, said Ken Mayer, MD, director of the Brown University AIDS Program in Providence, RI. "Those individuals are much more likely to transmit HIV to their partners, so you have an ongoing cycle of new transmissions occurring," he noted.

### MISSED OPPORTUNITIES

New data presented during the summit showed that missed opportunities for HIV testing are widespread. One study, which Mayer co-wrote with researchers from Health Benchmarks Inc, a Woodland Hills, Calif, health services research company, and Gilead Sciences, Inc, a Foster City, Calif, biopharmaceutical company, reviewed 2006 claims data from 8 health plans covering nearly 8 million enrollees throughout the country. Only 4.9% of the plan members who had an illness suggestive of AIDS, such as recurrent pneumonia or tuberculosis, received an HIV test.

Richard Rothman, MD, PhD, associate professor of emergency medicine at Johns Hopkins, noted that many missed opportunities for HIV testing occur at hospital emergency departments (EDs). He said many of the patients who account for the more than 120 million ED visits annually are uninsured and have no regular source of health care where testing otherwise may take place. In an analysis of ED visits nationwide between 1993 and 2005, Rothman and his colleagues found that HIV tests were performed in 3.2 per 1000, or 0.32%, of ED visits. Of those tested, 6% were HIV-positive.

Experts at the summit said lack of reimbursement by many private and public insurers is a substantial barrier standing in the way of increased routine HIV testing. Kevin Fenton, MD, PhD, of the CDC, said Aetna Health Plans and Blue Cross Blue Shield plans have been among the most progressive commercial insurers in paying for HIV tests. But he noted that Medicare and Medicaid do not routinely reimburse for HIV tests and "need to come on board." □