

The FDA and Safe Use of Long-Acting Beta-Agonists in the Treatment of Asthma

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For over a decade, the Food and Drug Administration (FDA) and the medical community have discussed how to safely use long-acting beta-agonists (LABAs) — drugs designed to provide bronchodilation for 12 hours or longer through stimulation of the β_2 -adrenergic receptor.¹ Even before U.S. approval of the first LABA, there was concern about a paradoxical increase in serious asthma exacerbations in some patients treated with these drugs. The Serevent nationwide surveillance (SNS) study suggested an increased risk of asthma-related death in patients treated with salmeterol as compared with albuterol, a short-acting beta-agonist (SABA). Shortly after approving salmeterol in 1994, the FDA began to receive reports of serious asthma exacerbations and deaths in patients treated with the drug. To further evaluate these reports, the manufacturer conducted the Salmeterol Multi-center Asthma Research Trial (SMART), in which, over the course of 28 weeks, there were eight more asthma-related deaths per 10,000 patients among patients treated with salmeterol than among those given placebo (95% confidence interval, 3 to 13).¹ Smaller studies of formoterol showed an excess of serious asthma exacerbations, some necessitating intubation.¹ Although the absolute risk observed is small, it is not inconsequential, given the number of patients with asthma currently receiving these drugs. There is particular

concern about the risk among children. Public discussions at FDA advisory committee meetings in 2005, 2007, and 2008 (summarized at www.fda.gov), as well as discussions in the *Journal*,²⁻⁴ reflect the varied interpretations of these data and their implications for the safe use of LABAs.

The FDA has now conducted a comprehensive review of the benefits and risks of using LABAs to treat asthma. The agency has concluded that the benefits of LABAs continue to outweigh the risks when the drugs are used appropriately and that the agents should remain available for the treatment of asthma. However, because of their serious risks, the FDA recommends that LABAs be reserved for patients whose asthma cannot be adequately managed with asthma-controller medication such as an inhaled corticosteroid. Furthermore, until additional data are available from large, randomized, controlled trials evaluating the safety of LABAs when administered with an inhaled corticosteroid, the FDA believes that long-term

use of LABAs should be limited to patients who require prolonged use of these drugs.

On February 18, 2010, exercising new authority under the FDA Amendments Act (FDAAA) of 2007, the FDA implemented these updated recommendations by requiring professional drug-label changes on all U.S.-manufactured LABAs (see table).

There are several reasons for these label changes. First, although it is already common practice that a LABA not be used without concurrent use of an asthma-controller medication, the new contraindication emphasizes the seriousness of the risk associated with LABA monotherapy. Second, the FDA believes that the risks of LABAs can be minimized if the agents are used judiciously and that patients who do not require long-term LABA therapy should not be exposed to the risk. Data suggest that many patients are administered the combination products containing an inhaled corticosteroid and a LABA without first undergoing stepwise increases in treatment with an

Specific Label Changes for Long-Acting Beta-Agonists (LABAs).

1. Contraindicate the use of LABAs for asthma in patients of all ages without concomitant use of an asthma-controller medication such as an inhaled corticosteroid.
2. Stop use of the LABA, if possible, once asthma control is achieved and maintain the use of an asthma-controller medication, such as an inhaled corticosteroid.
3. Recommend against LABA use in patients whose asthma is adequately controlled with a low- or medium-dose inhaled corticosteroid.
4. Recommend that a fixed-dose combination product containing a LABA and an inhaled corticosteroid be used to ensure compliance with concomitant therapy in pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid.

inhaled corticosteroid alone. Third, long-term use of LABAs in patients with asthma should be limited to those whose asthma cannot be controlled with asthma-controller medications. Finally, the FDA recommends the use of combination products containing an inhaled corticosteroid and a LABA in children and adolescents because of the difficulty of ensuring compliance with both medications when they are administered separately in these groups.

The FDA's recommendation that LABA use be discontinued if possible after asthma control has been achieved may cause consternation among prescribers, since asthma treatment guidelines and current practice focus on stepping down the dose of inhaled corticosteroids in patients who require combination corticosteroid and LABA therapy.⁵ The guidelines recommending long-term use of LABAs were partly influenced by studies showing a benefit from adding a LABA to an inhaled corticosteroid for the long-term treatment of persistent asthma. These studies have several limitations, however. For instance, the benefits shown were largely a measure of the beta-agonist effect, such as improved airflow and reduced rescue use of SABAs. There are no studies showing that LABAs (alone or in conjunction with inhaled corticosteroids) increase survival or positively affect severe asthma exacerbations (those necessitating intubation or hospital-based care). Given the clear benefits of inhaled corticosteroids in patients with asthma and the fact that they have not been associated with serious ad-

verse outcomes, the FDA believes it is prudent to emphasize their use and limit the long-term use of LABAs.

An important unanswered question about LABA use is whether concomitant use of an inhaled corticosteroid mitigates the risk of asthma-related death. The SNS study and SMART did not systematically test the effect of concomitant use and cannot answer this question. At the 2008 advisory committee meeting, findings from meta-analyses of controlled clinical trials of LABAs used to treat asthma were presented by the FDA and the LABA manufacturers. Some of the analyses suggested a decreased risk of serious asthma-related adverse events in association with combination therapy as compared with a LABA alone, but other analyses did not. Given the seriousness of the risks associated with LABA use and the uncertainty about the role of inhaled corticosteroids in mitigating this risk, the FDA believes that long-term use of LABAs should be limited to patients who truly need them.

The risk of serious asthma exacerbations and asthma-related death is not unique to LABAs. It has been known for over 50 years that SABAs can worsen asthma and cause asthma-related death. Although the mechanisms by which beta-agonist bronchodilators cause asthma-related death remain uncertain, it is hypothesized that they may increase sensitivity to bronchoconstrictive stimuli or mask the symptoms of worsening asthma. To minimize this risk, current asthma-treatment guidelines recommend that albuterol and

other SABAs be used only as needed for short-term symptom relief and that asthma-controller medications be used to minimize SABA use.⁵ Other than the duration of bronchodilatation, the basic pharmacologic activity and clinical effect of LABAs and SABAs are the same. The FDA therefore believes it is inconsistent to recommend long-term use of LABAs, particularly since LABAs have also been shown to increase the risk of asthma-related death.

The FDA intends to take several actions to ensure that prescribers and patients are aware of the new recommendations for the safe use of LABAs. Under its Safe Use Initiative, the agency will work with public and private health care groups to widely disseminate information about the new labeling. The FDA will also work with these partners to assess whether prescribing patterns change, leading to the prescribing of LABAs only with concomitant use of a controller drug, compliance with the recommendation of dual LABA and inhaled-corticosteroid therapy, and overall decreased use of LABAs.

Further studies are needed to definitively determine whether the addition of LABAs to inhaled corticosteroids increases the risk of serious asthma outcomes. Using new authorities under FDAAA, the FDA will require manufacturers of LABAs to conduct large clinical trials that evaluate this risk by comparing inhaled corticosteroids plus LABAs with inhaled corticosteroids alone. The agency will seek input into the design of these studies at an open advisory committee meeting in March 2010. Until such data are available, the FDA believes that

the existing evidence supports the approaches outlined here.

Disclosure forms provided by the authors are found with the full text of this article at NEJM.org.

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