

Louisiana Drug Utilization Review Education

Long-Acting Beta-Agonist (LABA) Use in Asthma Is Focus of FDA's Concern

Larry J. Humble, PharmD, PhD

The University of Louisiana at Monroe College of Pharmacy

Office of Outcomes Research and Evaluation

FDA Drug Safety Communication: New Safe Use Requirements for Inhaled LABAs¹

- In February 2010, the FDA announced that based on its analyses of clinical trials the use of LABAs was associated with an increased risk for asthma exacerbations leading to hospitalization in pediatric and adult patients as well as death in some patients. (See table at conclusion of article for a description of available LABAs.)
- Even though the FDA had considered limiting the indications for LABAs, a risk-benefit review demonstrated that the benefits of LABAs continued to outweigh the risks when the drugs were used appropriately. The FDA concluded that the agents should remain available for use in the treatment of asthma.
- To ensure that the risk-benefit ratio remains acceptable, the FDA required manufacturers of LABA products to revise the prescribing information for all LABAs and to develop a risk evaluation and mitigation strategy (REMS).
 - The specific drug-label revisions included four recommendations which the FDA asserted were necessary for the safe use of these products. These recommendations only apply to the use of LABAs in the treatment of asthma. (See Recommendations to Ensure Safe LABA Use.)

Recommendations to Ensure Safe LABA Use

1. **The use of LABAs is contraindicated without the use of an asthma controller medication such as an inhaled corticosteroid. Single-ingredient LABAs should only be used in combination with an asthma controller medication; they should not be used alone.**
2. **LABAs should only be used long-term in patients whose asthma cannot be adequately controlled on asthma controller medications.**
3. **LABAs should be used for the shortest duration of time required to achieve control of asthma symptoms and discontinued, if possible, once asthma control is achieved. Patients should then be maintained on an asthma controller medication.**
4. **Pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid should use a combination product containing both an inhaled corticosteroid and a LABA, to ensure compliance with both medications.**

Louisiana Drug Utilization Review Education

- As a part of the REMS requirement, manufacturers of LABAs developed new Medication Guides and implemented plans to educate healthcare providers regarding the appropriate use of LABAs.
 - Medication Guides must be issued when LABAs are dispensed (new prescription or refill). Medication Guides approved by the FDA are available for download at <http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm>
- More information regarding LABAs, including the complete FDA safety communication, is available at <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm199565.htm>

One Big Question Left Unanswered

- The FDA based the LABA recommendations on the Serevent Nationwide Surveillance (SNS) Study, the Salmeterol Multicenter Asthma Research Trial (SMART), and a FDA-conducted meta-analysis of 110 studies which evaluated LABA use in asthma treatment. Each of these studies showed a higher risk of death in patients diagnosed with asthma who used a LABA compared to patients diagnosed with asthma who did not use a LABA.¹
- These studies did not, however, answer one important question:

Does the concurrent use of a LABA with an inhaled corticosteroid mitigate the LABA risk? ^{1,2}

- To answer this question, the FDA is requiring manufacturers of LABAs to initiate post-marketing safety trials to determine whether the addition of a LABA to an inhaled corticosteroid regimen increases the risk for negative outcomes.^{1,2}
- In March 2010, manufacturers of LABAs and FDA officials discussed research requirements and methodological strategies to provide a definitive answer to this question.³

Louisiana Drug Utilization Review Education

Asthma Experts Question FDA's LABA Recommendations

- According to a leading asthma expert, **"Everyone is in total agreement with the FDA's recommendation that LABAs should not be used as the sole therapy for anyone with persistent asthma."**^{4,5}
- Three experts, who were members of the panel that developed the NAEPP 2007 Expert Panel Report (EPR-3), are concerned about the FDA recommendation to discontinue LABAs, if possible, once asthma control is achieved.^{4,5} (See recommendation number 3.)
 - These experts argue that this recommendation runs counter to the EPR-3 and that no new data are available subsequent to the release of the EPR-3 to support the recommendation.
 - They further contend that while existing data support step-up therapy to gain asthma control no data are currently available to support discontinuation of LABAs as the first rung in step-down therapy. (As a point of information, the EPR-3 recommends titrating down the dose of inhaled corticosteroid once control is reached and maintained for three months in patients who require concurrent LABA and steroid therapy.^{2,6})
 - The danger, according to these experts, is that stepping down too soon once asthma control is achieved could possibly lead to a return to loss of control. One of these experts contended that prescribers should continue to monitor patients on LABAs because those who had an exacerbation in the past year are at risk for an exacerbation in the coming year.
- Two FDA officials who helped craft the new LABA recommendations understand that the new recommendations may cause "consternation among prescribers."² However, these FDA officials make the following points:
 - There are no studies showing that LABAs (alone or concurrently with inhaled corticosteroids) increase survival or reduce severe asthma exacerbations.
 - Inhaled corticosteroids provide clear benefits and have not been linked to serious adverse effects; therefore, the FDA believes that the use of inhaled corticosteroids should be promoted and the use of LABAs for long-term management of asthma should be limited.
- Professional organizations and experts are in agreement with the FDA that new studies are required to "truly ascertain any potential adverse consequences of LABAs."^{4,5,7}

Louisiana Drug Utilization Review Education

Some Prescribing Considerations for LABA Use in Asthma Treatment^{1,6}

- Consider carefully the need to add a LABA to asthma therapy.
 - LABAs should not be started in patients with acutely deteriorating asthma.
 - LABAs are not considered first-line therapy in the treatment of asthma. LABAs are not for use in patients whose asthma can be controlled with inhaled corticosteroids and occasional use of short-acting beta agonist inhalers, such as albuterol.
- Ensure patients have a prescription for a controller medication, preferably an inhaled corticosteroid, once a decision is made to prescribe a LABA.
 - **LABAs should never be used alone in the treatment of asthma.**
- Encourage compliance with the LABA and, especially, the controller medication. When possible, prescribe a combination product.
- Inform patients of the benefits and risks of LABAs. Encourage patients/caregivers to read the Medication Guide and to ask questions, if needed.
- Educate patients/caregivers on how to identify and handle signs of worsening asthma.
 - Indicators of worsening asthma may include: decrease in FEV₁ or peak expiratory flow, increase in frequency/severity of asthma symptoms, increase in rescue inhaler use, and nighttime or early morning awakenings due to asthma.
- Remind patients/caregivers that LABAs do not replace fast-acting inhalers, such as albuterol.

Louisiana Drug Utilization Review Education

Conclusion

- The risks of LABAs in the management of asthma are known. However, the FDA determined the benefits of LABAs in improving asthma symptoms outweigh the risks when used appropriately with an asthma controller medication in patients who need the addition of LABAs to achieve control.
- To ensure the risk-benefit ratio is acceptable, the FDA required manufacturers to revise prescribing information and to develop strategies to mitigate risks.
- There is complete agreement that LABAs should NEVER be used as monotherapy to treat asthma. Controller medications, preferably inhaled corticosteroids, should be prescribed concurrently.
- The decision to prescribe a LABA for asthma should be carefully considered. Such factors as appropriate patient selection, open communication with patients/caregivers concerning the benefits and risks of LABA therapy, suitable self-management education, and scheduled follow-ups are necessary to ensure safe use.

FDA-Approved Medications Containing a LABA¹

Brand Name	LABA Active Ingredient	Corticosteroid Active Ingredient	FDA Approved Indications
Foradil Aerolizer	formoterol	None	Asthma, COPD, EIB
Foradil Certihaler*	formoterol	None	Asthma
Serevent Diskus	salmeterol	None	Asthma, COPD, EIB
Advair Diskus	salmeterol	fluticasone	Asthma, COPD
Advair HFA	salmeterol	fluticasone	Asthma
Symbicort	formoterol	budesonide	Asthma, COPD
Brovana	arformoterol	None	COPD
Perforomist	formoterol	None	COPD

*approved, but not currently marketed in the U.S.

COPD = chronic obstructive pulmonary disease; EIB = exercise-induced bronchospasm

Louisiana Drug Utilization Review Education

References

1. Food and Drug Administration. FDA Drug Safety Communication: New Safety Requirements for Long-Acting Inhaled Asthma Medications Called Long-Acting Beta-Agonists (LABAs). Posted February 18, 2010; Available at <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm> (Accessed May 2, 2010)
2. Chowdhury BA and Pan GD. The FDA and Safe Use of Long-Acting Beta-Agonists in the Treatment of Asthma. *N Engl J Med* 2010; 362(13):1169-71.
3. Slides for the March 10-11, 2010, Joint Meeting of the Pulmonary-Allergy Drugs Advisory Committee and Drug Safety and Risk Management Committee. Available at <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/ucm206720.htm#main> (Accessed May 2, 2010)
4. Brauser D. New FDA Recommendations for Discontinuation of Long-Acting Beta-Agonists Run Counter to Asthma Management Guidelines. *Medscape Medical News*. Posted March 2, 2010; <http://www.medscape.com/viewarticle/717782> (Accessed May 2, 2010)
5. American Academy of Allergy, Asthma, and Immunology 2010 Annual Meeting. Video of late-breaking press conference on LABA use after the recent FDA decision: What Do You Do Now? (Parts I-IV). Posted March 1, 2010. Available at http://www.aaaai.org/members/annual_meeting/am2010/press/video.asp (Accessed May 2, 2010)
6. National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Bethesda, MD: National Heart, Lung, and Blood Institute, August 2007. (NIH publication no. 07-4051.) Available at <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm> (Accessed May 2, 2010)
7. American Academy of Allergy, Asthma, and Immunology Statement to the FDA's Pulmonary-Allergy Drugs and Safety and Risk Management Advisory Panels: Special Hearing on Safety Studies of LABAs. Presented by R. Lemanske on March 10, 2010. Statement available at http://www.aaaai.org/patients/resources/statement_on_labas.pdf (Accessed May 2, 2010)