



## **Indiana Medicaid Therapeutics Committee** **Therapeutic Class Review Summary**

### **Therapeutic Class:**

Long- and Short-Acting Beta<sub>2</sub>-Agonists

### **Overview:**

Beta<sub>2</sub>-agonists are the most potent and rapidly acting bronchodilators available. The principal action of β<sub>2</sub>-agonists is to relax airway smooth muscle by stimulating beta<sub>2</sub>-receptors, which increases cyclic adenosine monophosphate (AMP) and produces functional antagonism to bronchoconstriction. In addition to their bronchodilatory effects, β<sub>2</sub>-agonists also prevent bronchoconstriction, regardless of the stimulus (allergen, exercise, or cold air). Beta<sub>2</sub>-agonists are often subgrouped by their durations of action. The short-acting β<sub>2</sub>-agonists have a duration of bronchodilation of 3-8 hours. The long-acting β<sub>2</sub>-agonists have a duration of bronchodilation of at least 12 hours.

Short-acting inhaled β<sub>2</sub>-agonists cause a prompt increase in airflow and are the therapy of choice for relief of acute asthma symptoms and exacerbations. However, regular use of short-acting β<sub>2</sub>-agonists can enhance airway responsiveness and result in increased morbidity from asthma; therefore, these medications are not recommended for maintenance treatment of asthma.

Three short-acting β<sub>2</sub>-agonists are available generically: albuterol, metaproterenol, and terbutaline. Albuterol is available in the widest variety of dosage forms of all the agents in the class. Proventil<sup>®</sup> HFA, Ventolin<sup>®</sup> HFA, and Proair<sup>®</sup> HFA are albuterol aerosol products that are free of chlorofluorocarbon propellants. All three products are reference-listed drugs and are not therapeutically equivalent. The clinical and/or environmental significance of products being free of chlorofluorocarbon propellants is as of yet undetermined; however, CFC albuterol inhalers were completely withdrawn from the market as of December 31, 2008. Additionally, there have been temporary outages of CFC and HFA albuterol inhaler products from some manufacturers since early 2006. Albuterol inhalation solution (AccuNeb<sup>®</sup>) is also available. All commercially marketed albuterol products are racemic, i.e., an equal mixture of (R)-albuterol and (S)-albuterol. Only the (R)-isomer, levalbuterol, is therapeutically active. Lower doses of levalbuterol have demonstrated equal efficacy when compared to higher doses of racemic albuterol. Levalbuterol is available as a nebulizer solution (Xopenex<sup>®</sup>) and as a MDI (Xopenex<sup>®</sup> HFA). Substituting levalbuterol for



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racemic albuterol in the emergency department management of children with acute asthma has been shown to significantly reduce the number of hospitalizations. Both Xopenex<sup>®</sup> products may benefit patients who are hypersensitive to the  $\beta_1$  stimulation associated with racemic albuterol. Metaproterenol use has declined because of the availability of more selective and longer acting  $\beta_2$ -agonists. Terbutaline tablets are available generically, and are more commonly used off-label as a treatment for premature labor. The terbutaline inhaler (Brethaire<sup>®</sup>) was discontinued from the US market in 1999.

Pirbuterol is unique in that it is available as a breath-actuated inhaler (Maxair<sup>™</sup> Autohaler<sup>™</sup>), which may be useful in patients having difficulty using a standard aerosol inhaler due to coordination problems. Of the remaining brand products, bitolterol inhaler (Tornalate<sup>®</sup>) was used very rarely, and the manufacturer has discontinued its production. Other products that have been discontinued include Volmax<sup>®</sup>, Prometa<sup>®</sup>, and Maxair<sup>®</sup> Inhalation Aerosol.

Long-acting inhaled  $\beta_2$ -agonists should not be used for acute exacerbations. Rather, they are used as an adjunct to anti-inflammatory therapy for providing long-term control of symptoms, especially nocturnal symptoms, and to prevent exercise-induced bronchospasm (EIB). Studies have shown that the maintenance use of long-acting  $\beta_2$ -agonists does not compromise the bronchodilator response to short-acting  $\beta_2$ -agonists during acute episodes of asthma. In general, inhaled long-acting beta agonists are preferred over oral sustained-release agents because they are longer acting and have fewer side effects.

Inhaled long-acting  $\beta_2$ -agonists have an important role in treating chronic asthma as adjunct therapy to inhaled corticosteroids. Available long-acting inhaled  $\beta_2$ -agonists and corticosteroid combinations include Advair Diskus<sup>®</sup> and Advair<sup>®</sup> HFA (salmeterol/fluticasone), and Symbicort<sup>®</sup> (formoterol/ budesonide). In randomized, controlled trials, the addition of salmeterol or formoterol to inhaled corticosteroid therapy resulted in statistically significant improvements in pulmonary function and asthma symptoms, and statistically significant reductions in supplemental short-acting  $\beta_2$ -agonist use. Salmeterol and formoterol were also shown to be effective in improving airflow obstruction in patients with COPD. In addition, maintenance treatment with either salmeterol or formoterol did not affect bronchodilator responses to albuterol in patients with asthma or partially reversible COPD. Data from a large, placebo-controlled U.S. study that compared the safety of salmeterol or placebo added to usual asthma therapy showed a small but significant increase in asthma-related deaths in patients receiving salmeterol versus those on placebo. Subgroup analysis suggests the



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risk may be greater in African-American patients compared to Caucasians. As a result of this study, a black-box warning has been added to salmeterol and formoterol labeling.

Due to safety concerns, the FDA announced in February of 2010 that it is requiring changes to how LABAs are used in the treatment of asthma. These changes are based on the analyses of studies showing an increased risk of severe exacerbation of asthma symptoms, leading to hospitalizations in pediatric and adult patients as well as death in some patients using LABAs for the treatment of asthma. The new recommendations only apply to the use of LABAs in the treatment of asthma. To ensure the safe use of these products, the following recommendations should be followed:

- 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.
- LABAs should only be used long-term in patients whose asthma cannot be adequately controlled on asthma controller medications.
- 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.
- 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.

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FDA is also requiring a risk management program called a Risk Evaluation and Mitigation Strategy (REMS) for LABAs which will include a revised Medication Guide written specifically for patients, and a plan to educate healthcare professionals about appropriate use. In addition, FDA is requiring the manufacturers to conduct additional clinical trials to further evaluate the safety of LABAs when used in combination with inhaled corticosteroids. FDA has determined that the benefits of LABAs in improving asthma symptoms outweigh the potential risks when used appropriately with an asthma controller medication in patients who need the addition of LABAs.

Available long-acting inhaled  $\beta_2$ -agonists and corticosteroid combinations include Advair Diskus<sup>®</sup> and Advair<sup>®</sup> HFA (salmeterol/fluticasone), and Symbicort<sup>®</sup> (formoterol/ budesonide). Both Advair Diskus<sup>®</sup> and Symbicort<sup>®</sup> are approved for use in the long-term maintenance treatment of asthma in adult patients, as well



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as maintenance treatment of COPD. An inhalation solution formulation of formoterol, Perforomist<sup>®</sup>, was recently approved for the treatment of bronchoconstriction in patients with COPD including chronic bronchitis and emphysema. (Brovana<sup>™</sup>), an enantiomer of formoterol, is a selective, long-acting beta-2 adrenergic receptor agonist indicated for the long-term, twice-daily maintenance treatment of bronchoconstriction in patients with COPD.

In April 2010, the The U.S. Food and Drug Administration announced, in accordance with longstanding U.S. obligations under the Montreal Protocol on Substances that Deplete the Ozone Layer, several metered-dose inhalers (MDI) used to treat asthma and chronic obstructive pulmonary disease (COPD) will be gradually removed from the U.S. marketplace. These inhalers contain ozone-depleting chlorofluorocarbons (CFCs), which are propellants that move medication out of the inhaler and into the lungs of patients. The beta agonist containing inhalers that will be phased out are Alupent Inhalation Aerosol and Maxair Autohaler. Alternative medications that do not contain CFCs are available.

Generic Name	Trade Name	Indications				Manufacturer
		AB	Asthma	COPD	EIB	
<b>Short-acting</b>						
Albuterol	Ventolin <sup>®</sup> Proventil, Vospire ER <sup>®</sup> Proair HFA <sup>®</sup> AccuNeb <sup>®</sup>	X	X		X	Schering, GlaxoSmithKline, Dey, various
Levalbuterol	Xopenex <sup>®</sup> Xopenex <sup>®</sup> HFA	X	X		X	Sepracor, various
Metaproterenol	Alupent <sup>®</sup>	X	X	X		Boehringer Ingelheim, various
Pirbuterol	Maxair <sup>®</sup>	X	X	X	X	3M
Terbutaline	Brethine <sup>®</sup>	X	X	X		AAI Pharma Inc.
<b>Long-acting</b>						
Arformoterol	Brovana <sup>™</sup>			X		Sepracor
Formoterol	Foradil <sup>®</sup> AEROLIZE <sup>®</sup> Perforomist <sup>®</sup>		X	X	X	Schering, Dey
Salmeterol	Serevent <sup>®</sup>		X	X	X	GlaxoSmithKline

### Summary:

The use of metaproterenol and terbutaline has declined significantly since their initial release to the US market. Albuterol and pirbuterol account for the majority



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of prescriptions, while the use of levalbuterol is mainly reserved for patients who are hypersensitive to the  $\beta_1$  stimulation associated with racemic albuterol. Albuterol, pirbuterol and levalbuterol are generally considered equivalent in efficacy at recommended doses. Pirbuterol offers a breath-actuated inhaler dosage form, which may be useful in patients having difficulty coordinating the use of a standard inhaler.

Salmeterol and formoterol are effective as adjunctive therapy to inhaled corticosteroids in the long-term maintenance treatment of asthma in adult patients as well as maintenance treatment of COPD. Available combination products containing a long-acting  $\beta_2$ -agonist plus a corticosteroid are Advair Diskus<sup>®</sup> (salmeterol/fluticasone) and Symbicort<sup>®</sup> (formoterol/ budesonide). Long-acting  $\beta_2$ -agonists are not recommended as monotherapy because these agents do not affect the underlying inflammatory process of asthma. They are also not recommended as initial therapy, and should be reserved for those patients refractory to other therapies. Both drugs have also been approved for adjunctive use with ipratropium in the maintenance of COPD. Data from a large, placebo-controlled US study that compared the safety of salmeterol or placebo added to usual asthma therapy showed a small but significant increase in asthma-related deaths in patients receiving salmeterol versus those on placebo. As a result of this study, a black-box warning has been added to salmeterol and formoterol labeling. Long-acting beta-agonists may increase the chance of severe asthma episodes and death when severe asthma episodes occur. Due to safety concerns, the FDA announced in February of 2010 that it is requiring changes to how LABAs are used in the treatment of asthma. These changes are based on the analyses of studies showing an increased risk of severe exacerbation of asthma symptoms, leading to hospitalizations in pediatric and adult patients as well as death in some patients using LABAs for the treatment of asthma. The new recommendations only apply to the use of LABAs in the treatment of asthma, to ensure the safe use of these products.