

## 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 3 albuterol aerosol products that are free of chlorofluorocarbon propellants. All 3 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. CFC albuterol inhalers will be completely withdrawn from the market by December 31, 2008. Beginning in early 2006, there have been temporary outages of CFC and HFA albuterol inhaler products from some manufacturers. Albuterol inhalation solution (AccuNeb<sup>®</sup>) is also available. All available albuterol products are racemic, ie, 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 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 be of benefit in patients who are hypersensitive to the β<sub>1</sub> stimulation associated with racemic albuterol. Metaproterenol use has declined because of the availability of more selective and longer acting β<sub>2</sub>-agonists. Only terbutaline tablets are available generically, and they 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. 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 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. Additionally, long-acting beta-agonists may increase the chance of severe asthma episodes and death when severe asthma episodes occur; a medication guide is now required for these agents. The manufacturing of the inhaled formulation of salmeterol has been phased out; however, Serevent Diskus remains available. 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.

Generic Name	Trade Name	Indications				Manufacturer
		AB	Asthma	COPD	EIB	
<i>Short-acting</i>						
Albuterol	Ventolin <sup>®</sup> , Proventil <sup>®</sup> , Vospire ER <sup>®</sup> , Proair HFA <sup>®</sup> , AccuNeb <sup>®</sup> Inh Solution	X	X		X	Schering, GlaxoSmithKline, Dey, various
Levalbuterol	Xopenex <sup>®</sup> , Xopenex <sup>®</sup> HFA	X	X		X	Sepracor
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> Aerolizer, 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 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 maintenance of asthma. 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's labeling. Long-acting beta-agonists may increase the chance of severe asthma episodes and death when severe asthma episodes occur. A medication guide is now required for the long-acting beta agonists (ie, formoterol and salmeterol).