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

Therapeutic Class:

Long- and Short-Acting Beta₂-Agonists

Overview:

Beta₂-agonists are the most potent and rapidly acting bronchodilators available. The principal action of β₂-agonists is to relax airway smooth muscle by stimulating beta₂-receptors, which increases cyclic adenosine monophosphate (AMP) and produces functional antagonism to bronchoconstriction. In addition to their bronchodilatory effects, β₂-agonists also prevent bronchoconstriction, regardless of the stimulus (allergen, exercise, or cold air). Beta₂-agonists are often subgrouped by their durations of action. The short-acting β₂-agonists have a duration of bronchodilation of 3-8 hours. The long-acting β₂-agonists have a duration of bronchodilation of at least 12 hours.

Short-acting inhaled β₂-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 β₂-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 β₂-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[®] HFA, Ventolin[®] HFA, and Proair[®] 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. CFC albuterol inhalers will be completely withdrawn from the market by December 31, 2008.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[®]) 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[®]) and as a MDI (Xopenex[®] 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[®] products may benefit patients who are hypersensitive to the β₁ stimulation associated with racemic albuterol. Metaproterenol use has declined because of the availability of more selective and longer acting β₂-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[®]) was discontinued from the US market in 1999.



Pirbuterol is unique in that it is available as a breath-actuated inhaler (Maxair™ Autohaler™), 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®) was used very rarely, and the manufacturer has discontinued its production. Other products that have been discontinued include Volmax®, Prometa®, and Maxair® Inhalation Aerosol.

Long-acting inhaled β₂-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 β₂-agonists does not compromise the bronchodilator response to short-acting β₂-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 β₂-agonists have an important role in treating chronic asthma as adjunct therapy to inhaled corticosteroids. Available long-acting inhaled β₂-agonists and corticosteroid combinations include Advair Diskus® and Advair® HFA (salmeterol/fluticasone), and Symbicort® (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 β₂-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. Perforomist® was recently approved for the treatment of bronchoconstriction in patients with COPD including chronic bronchitis and emphysema. Brovana™, 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.



The FDA held an Advisory Committee meeting in December 2008 regarding the benefit/risk assessment of LABAs for the treatment of asthma in adults and children. This was a joint meeting of the Pulmonary-Allergy Drugs Advisory Committee, the Drug Safety and Risk Management Advisory Committee, and the Pediatric Advisory Committee. After an extensive review of the available data, the Committees concluded that the benefits of Advair and Symbicort outweigh the risks in adult and adolescent asthma patients, and should continue to be used. However, the panel voted that Serevent and Foradil should be banned from use in the treatment of asthma.

Generic Name	Trade Name	Indications				Manufacturer
		AB	Asthma	COPD	EIB	
Short-acting						
Albuterol	Ventolin [®] Proventil, Vospire ER [®] Proair HFA [®] AccuNeb [®]	X	X		X	Schering, GlaxoSmithKline, Dey, various
Levalbuterol	Xopenex [®] Xopenex [®] HFA	X	X		X	Sepracor, various
Metaproterenol	Alupent [®]	X	X	X		Boehringer Ingelheim, various
Pirbuterol	Maxair [®]	X	X	X	X	3M
Terbutaline	Brethine [®]	X	X	X		AAI Pharma Inc.
Long-acting						
Arformoterol	Brovana™			X		Sepracor
Formoterol	Foradil [®] Aerolizer Perforomist [®]		X	X	X	Schering, Dey
Salmeterol	Serevent [®]		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 β_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 and COPD. Long-acting β_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. Furthermore, both drugs have 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 (i.e., formoterol and salmeterol). In addition, the FDA Advisory Committee meeting in December 2008 regarding the benefit/risk assessment of LABAs for the treatment of asthma in adults and children recommended that Serevent and Foradil be banned from use in the treatment of asthma.