



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

Therapeutic Class:

Long-acting Beta Agonist and Corticosteroid Combinations

Overview:

Beta₂-agonists are the most potent and rapidly acting bronchodilators available. The principal action of β_2 -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, β_2 -agonists prevent bronchoconstriction, regardless of the stimulus (allergen, exercise, or cold air). The long-acting β_2 -agonists have a duration of bronchodilation of at least 12 hours. The glucocorticoid component has potent anti-inflammatory activity.

Long-acting inhaled β_2 -agonists and corticosteroid combinations should not be used for acute exacerbations, but should instead be used for the long-term maintenance treatment of asthma. Studies have shown that the maintenance use of long-acting β_2 -agonists does not compromise the bronchodilator response to short-acting β_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. Available long-acting inhaled β_2 -agonists and corticosteroid combinations include Advair Diskus[®] and Advair[®] HFA (salmeterol/fluticasone), and Symbicort[®] (budesonide/formoterol). Both Advair Diskus[®] and Symbicort[®] are approved for use in the long-term maintenance treatment of asthma in adult patients as well as maintenance treatment of COPD.

Inhaled long-acting β_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 β_2 -agonist use. 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. 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 the product labeling for all long-acting beta agonists. Additionally, long-acting beta-agonists may increase the chance of severe asthma episodes and death when severe asthma episodes occur. As



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a result, a medication guide is now required for these agents. Therefore, when treating patients with asthma, physicians should only prescribe Advair[®] or Symbicort[®] for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies.

The FDA held an Advisory Committee meeting on December 10th and 11th of 2008 regarding the benefit/risk assessment of long acting beta-2 adrenergic agonists (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 be continued to be used.

Generic Name	Trade Name	Indications		Manufacturer
		Asthma	COPD	
Salmeterol and Fluticasone	Advair Diskus [®] , Advair [®] HFA	X	X (Advair Diskus)	GlaxoSmithKline
Formoterol and Budesonide	Symbicort [®]	X	X	AstraZeneca

Summary:

Salmeterol and formoterol are effective as adjunctive therapy to inhaled corticosteroids in the maintenance of asthma. Long-acting β_2 -agonists are not recommended as monotherapy because these agents do not affect the underlying inflammatory process of asthma. Both Advair Diskus[®] and Symbicort[®] are approved for use in the long-term maintenance treatment of asthma in adult patients as well as maintenance treatment 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). Selection of an agent for the preferred drug list should be based upon FDA-approved indications, efficacy, safety, and cost.