Pharmacy Policy Bulletin

Title: Long Acting Beta Agonist (LABA) combination policy
Policy #: Rx.01.146

Application of pharmacy policy is determined by benefits and contracts. Benefits may vary based on product line, group, or contract. Some medications may be subject to precertification, age, quantity, or formulary restrictions (ie limits on non-preferred drugs). Individual member benefits must be verified.

This pharmacy policy document describes the status of pharmaceutical information and/or technology at the time the document was developed. Since that time, new information relating to drug efficacy, interactions, contraindications, dosage, administration routes, safety, or FDA approval may have changed. This Pharmacy Policy will be regularly updated as scientific and medical literature becomes available. This information may include new FDA-approved indications, withdrawals, or other FDA alerts. This type of information is relevant not only when considering whether this policy should be updated, but also when applying it to current requests for coverage.

Members are advised to use participating pharmacies in order to receive the highest level of benefits.

**Intent:**
The intent of this policy is to communicate the medical necessity criteria for fluticasone propionate/salmeterol xinafoate (Advair®), umeclidinium/ vilanterol (Anoro Ellipta®), fluticasone furoate/ vilanterol trifenate (Breo Ellipta®), tiotropium/ olodaterol (Stiolto Respimat®), glycopyrrolate/ formoterol (Bevespi Aerosphere), and indacaterol/ glycopyrrolate (Utibron™ Neohaler) as provided under the member's pharmacy benefit.

**Description:**
Fluticasone propionate/salmeterol xinafoate (Advair®), fluticasone furoate/vilanterol trifenate (Breo Ellipta®), umeclidinium/vilanterol (Anoro Ellipta®), tiotropium/olodaterol (Stiolto Respimat®), glycopyrrolate/ formoterol (Bevespi Aerosphere), and indacaterol/glycopyrrolate (Utibron™ Neohaler) are indicated for the treatment of chronic obstructive pulmonary disease (COPD). Fluticasone propionate/salmeterol xinafoate (Advair®) is also indicated for the treatment of asthma.

Salmeterol, indacaterol, olodaterol, formoterol, and vilanterol are long-acting beta-2 adrenergic agonist that is selective for beta-2 adrenoceptors (LABA). The pharmacologic effects of beta-2 adrenoceptor agonist drugs are at least in part attributable to stimulation of intracellular adeny cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate to cyclic-3′,5′-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Fluticasone is a corticosteroid with anti-inflammatory activity, immunosuppressive properties, and antiproliferative actions.
Glycopyrrolate, tiotropium, and umeclidinium are long-acting muscarinic antagonists, often referred to as anticholinergics. They have similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, they exhibit pharmacological effects through inhibition of M3 receptor at the smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations.

**Policy:**

Fluticasone propionate/salmeterol xinafoate (Advair®) or fluticasone furoate/vilanterol trifenate (Breo Ellipta®) is approved when ONE of the following is met:

1. Diagnosis of COPD and an inadequate response or inability to tolerate Symbicort®
2. Diagnosis of asthma and an inadequate response or inability to tolerate either Symbicort® or Dulera®

Note: Advair Diskus does not require PA under 12 years of age

Umeclidinium/vilanterol (Anoro Ellipta®), glycopyrrolate/formoterol (Bevespi Aerosphere), tiotropium/oldaterol (Stiolto Respimat®), or indacaterol/glycopyrrolate (Utibron™ Neohaler) is approved when BOTH of the following are met:

1. Diagnosis of Chronic Obstructive Pulmonary Disease (COPD) including chronic bronchitis and/or emphysema
2. An inadequate response or inability to tolerate Combivent Respimat®

**Black Box Warning:**

Advair®, Anoro Ellipta®, Breo Ellipta®, Stiolto Respimat®, Utibron™ Neohaler, Bevespi Aerosphere:

LABAs increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of salmeterol with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol (13 deaths out of 13,176 subjects treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 subjects on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, physicians should only prescribe LABA containing products for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use LABA-steroid combinations for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

The safety and efficacy of Stiolto Respimat, Anoro Ellipta, Bevespi Aerosphere, and Utibron Neohaler in patients with asthma have not been established. These drugs are not indicated for the treatment of asthma.

**Guidelines:**
Refer to the specific manufacturer's prescribing information for administration and dosage details and any applicable Black Box warnings.

**BENEFIT APPLICATION**

Subject to the terms and conditions of the applicable benefit contract, the applicable drug(s) identified in this policy is (are) covered under the pharmacy benefits of the Company's products when the medical necessity criteria listed in this pharmacy policy are met. Any services that are experimental/investigational or cosmetic are benefit contract exclusions for all products of the Company.

**References:**


**Applicable Drugs:**

Inclusion of a drug in this table does not imply coverage. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
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</thead>
<tbody>
<tr>
<td>Advair</td>
<td>fluticasone propionate/salmeterol xinafoate</td>
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<tr>
<td>Brand Name</td>
<td>Active Ingredients</td>
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<tr>
<td>----------------------------</td>
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<tr>
<td>Anoro Ellipta</td>
<td>umeclidinium/vilanterol</td>
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<tr>
<td>Breo Ellipta</td>
<td>fluticasone furoate/vilanterol trifenate</td>
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<tr>
<td>Stiolto Respimat</td>
<td>tiotropium/oldaterol</td>
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<tr>
<td>Utibron Neohaler</td>
<td>indacaterol/glycopyrrolate</td>
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<tr>
<td>Bevespi Aerosphere</td>
<td>glycopyrrolate/formoterol</td>
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**Cross References:**

**Policy Version Number:** 8.00

**P&T Approval Date:** October 13, 2016

**Policy Effective Date:** December 01, 2016

**Next Required Review Date:** October 13, 2017

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