



## Therapeutic Class Review<sup>SM</sup>

### Respiratory – budesonide and formoterol (Symbicort<sup>®</sup>)

December 2007

**New Product for Review:**

budesonide/formoterol (Symbicort<sup>®</sup>)

[AstraZeneca]

**Dossier Provided by Manufacturer:**

**Dossier Evaluation: (2)**

- 1 - Dossier missing significant clinical trial(s).
- 2 - Mfg. provided all relevant trials; Missing pharmacoeconomic model.
- 3 - Mfg. provided all relevant trials and information.

**Executive Summary**

- Symbicort combines two well established asthma therapies into a single metered dose inhaler:
  - budesonide (Pulmicort) as the inhaled corticosteroid (ICS); and
  - formoterol (Foradil) as the long-acting beta agonist (LABA).
  
- Budesonide/formoterol (Symbicort) was approved by the FDA on July 21, 2006, and was launched at the end of May 2007.<sup>[2]</sup> This combination:
  - Has been available outside the U.S. for many years, but in a different device (dry powder inhaler vs. metered dose inhaler).
  - Provides competition with salmeterol/fluticasone (Advair<sup>®</sup>), another ICS/LABA combination.
  - Symbicort is not FDA indicated for the relief of acute bronchospasm. This marketing message may cause confusion and result in potential to harm patients when used as a rescue medication.
  - Outside the United States the combination is recognized as offering protection from severe exacerbations. Global Initiative for Asthma (GINA) guidelines state that it may be used for both rescue and maintenance.<sup>[12]</sup>
  
- National and international guidelines recognize the following as rational primary options to achieve control of asthma symptoms:
  - ICS products as the preferred long-term maintenance therapy for adults and children with mild, moderate and severe persistent asthma.<sup>[6]</sup>
  - Titrated doses if ICS is administered alone; or
  - The addition of a LABA to an ICS.

- Budesonide/formoterol (Symbicort) should be used for patients not adequately controlled on low-to-medium dose ICS products or whose disease severity clearly warrants initiation of treatment with two maintenance therapies (ICS plus LABA).
- Updated 2007 National Heart, Lung and Blood Institute (NHLBI) guidelines recognize benefits of the addition of long-acting beta<sub>2</sub>-agonists to ICS therapy for patients whose asthma is not well controlled with ICS alone. These benefits should be weighed against the increased risk for severe exacerbations, although uncommon, associated with the daily use of LABAs.<sup>[32]</sup>
- Practical considerations regarding combined (single inhaler) asthma therapy include:
  - Potential for over-utilization/inappropriate first-line use when ICS alone may be effective.
  - Convenience of one inhaler for simplified treatment.
  - Theoretical increase of adherence of using one versus two inhalers for combination therapy.
  - Market-driven desire of patients/families and practitioners for single inhaler treatment option.
  - Off-label use of budesonide/formoterol (Symbicort) in chronic obstructive pulmonary disease (COPD).
- Several ICS and LABA options are available as preferred/formulary which:
  - Supports clinical practice guidelines; and
  - Offers the best flexibility in dosing of step therapy to manage variability in asthma control.
- Both budesonide/formoterol (Symbicort) and salmeterol/fluticasone (Advair) are viable options because of:
  - Longstanding data supporting the efficacy of the ICS/LABA components.
  - Well understood safety and efficacy profiles.
  - Evidence and clinical practice supporting the use of the ICS/LABA combination in appropriate patients.

## Evidence

- The efficacy of adding a LABA to ICS for greater improvement in lung function (FEV<sub>1</sub>) and reducing the rate of exacerbations over ICS treatment alone is well recognized.
  - Budesonide/formoterol (Symbicort) produces greater improvement in lung function (FEV<sub>1</sub>) compared to the same doses of either of budesonide or formoterol administered alone or placebo.<sup>[2]</sup>
- Evidence supporting improved clinical outcomes or the theoretical benefit of enhanced compliance with administration of combination therapy as one inhaler or separately as two individual inhalers has not been demonstrated.
- There were four studies appraised for budesonide/formoterol (Symbicort). These trials are not useful in making healthcare decisions about budesonide/formoterol (Symbicort) due to:
  - Short duration of studies.
  - Lack of clinically relevant endpoints measured (e.g., reduced exacerbations).
  - Open label trial design, lending to potential bias and subjectivity in reporting changes in FEV<sub>1</sub> (primary endpoint used to report efficacy).
  - Underpowered superiority trial that did not reach statistical significance.

**Decision**

Budesonide/formoterol (Symbicort) and salmeterol/fluticasone (Advair) are non-preferred/non-formulary because:

- There is no evidence of improved clinical outcomes with administration of an ICS plus LABA in a single inhaler versus two separate inhalers.
- The potential for improved compliance using one inhaler has not been demonstrated.
- All of the individual components for both products are available as formulary/preferred options.
- For many patients, treatment with ICS alone is the preferred option. Adding a LABA when an ICS alone is appropriate may put patients at increased risk of harms.

## Products

Drug Products	FDA approval <sup>a</sup>	Patent Expiration(s) <sup>c</sup>	FDA approved indications	Usual Dose/Route	Potential Off-label Uses <sup>d</sup>
budesonide/ formoterol (Symbicort®) <sup>1</sup>	9/2006	12/2012	<ul style="list-style-type: none"> <li>• Asthma</li> <li>• 12 years and older</li> </ul>	1-2 puffs BID Metered dose inhaler	COPD, asthma in pediatrics less than 12
fluticasone/salmeterol (Advair® Diskus®) <sup>16</sup>	8/2000	8/2008	<ul style="list-style-type: none"> <li>• Asthma</li> <li>• 4 years and older</li> </ul>	1 puff BID Dry powder inhaler	Extrinsic asthma prophylaxis
fluticasone/salmeterol (Advair® HFA) <sup>15</sup>	6/2006	8/2008	<ul style="list-style-type: none"> <li>• COPD associated with chronic bronchitis</li> </ul>	2 puffs BID Metered dose inhaler	Extrinsic asthma prophylaxis
budesonide (Pulmicort®) <sup>19</sup>	6/1997	1/2018 (3/2007-1/2018)	<ul style="list-style-type: none"> <li>• Asthma</li> <li>• 6 years and older</li> </ul>	2-3 puffs BID Dry powder inhaler	COPD
fluticasone propionate (Flovent® HFA) <sup>20</sup>	11/1997	9/2014	<ul style="list-style-type: none"> <li>• Asthma</li> <li>• 4 years and older</li> </ul>	220mcg BID-TID Metered dose inhaler	COPD, chronic bronchitis
salmeterol xinafoate (Serevent® Diskus®) <sup>18</sup>	2/1994	3/2011	<ul style="list-style-type: none"> <li>• Asthma</li> <li>• 4 years and older</li> <li>• Exercise-induced bronchospasm</li> <li>• COPD</li> </ul>	1 puff BID Dry powder inhaler	Cystic fibrosis; high altitude pulmonary edema
formoterol fumarate (Foradil® Aerolizer®) <sup>17</sup>	2/2001	12/2016	<ul style="list-style-type: none"> <li>• Asthma</li> <li>• 5 years and older</li> <li>• Exercise-induced bronchospasm</li> <li>• COPD</li> </ul>	1 puff BID Dry powder inhaler	Cystic fibrosis; high altitude pulmonary edema
beclomethasone dipropionate HFA (QVAR®) <sup>24</sup>	9/2000	11/2009	<ul style="list-style-type: none"> <li>• Asthma</li> <li>• 5 years and older</li> </ul>	2-3 puffs BID Metered dose inhaler	COPD
flunisolide (AeroBid®) <sup>28</sup>	8/1984	6/2007	<ul style="list-style-type: none"> <li>• Asthma</li> <li>• 6 years and older</li> </ul>	2-4 puffs BID Metered dose inhaler	COPD
mometasone furoate (Asmanex® Twisthaler™) <sup>29</sup>	3/2005	6/2012	<ul style="list-style-type: none"> <li>• Asthma</li> <li>• 12 years and older</li> </ul>	1 puffs QD - BID Dry powder inhaler	COPD
triamcinolone acetonide (Azmacort®) <sup>30</sup>	4/1982	-	<ul style="list-style-type: none"> <li>• Asthma</li> <li>• 12 years of age and older</li> </ul>	3-5 puffs QID Metered dose inhaler	COPD

<sup>a</sup> Date applies to approval date for the original brand name medication where there are now generics available.

<sup>c</sup> Based on patents listed in Orange Book as of 05/31/07.

<sup>d</sup> As listed in © 1974 - 2007 Thomson MICROMEDEX database or as referenced.

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