

# OREGON DUR BOARD NEWSLETTER<sup>©</sup>

## AN EVIDENCE BASED DRUG THERAPY RESOURCE

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## The Role of Advair for Treatment of Asthma and COPD

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Drug utilization trend data from the Office of Medical Assistance Programs (OMAP) has shown more than a 30% increase in expenditures for asthma related medications during the year 2001. The new combination product of inhaled salmeterol and fluticasone (Advair), available since March 2001, was identified as a major cost center responsible for this rapid growth in asthma spending. This article will review the clinical evidence that supports the use of Advair for the treatment of asthma and chronic obstructive pulmonary disease (COPD) and present the results of an Advair drug utilization review (DUR).

### ASTHMA

Asthma is a common airway disease associated with substantial morbidity, mortality, and resource utilization.<sup>1</sup> It has been estimated that more than 17 million people in the United States have asthma.<sup>2</sup> As of October 2001, the prevalence of asthma in Oregon was approximately 8%, or more than 282,000 people.<sup>3</sup>

As with other chronic conditions, pharmacotherapy plays an important role in reducing disease burden, improving survival, and enhancing quality of life for patients with asthma. Inhaled corticosteroids (ICS) are considered the most effective therapy for controlling asthma-related morbidity and mortality.<sup>5</sup> The long-acting inhaled  $\beta$ 2-agonists (LABA), salmeterol and formoterol, are used primarily as adjuncts to ICS. While the primary action of LABA is to produce sustained bronchodilation, *in vivo* and *in vitro* evidence suggest a synergistic effect when added to ICS. LABA are thought to prime inactive corticosteroid receptors, thus enabling them to be activated at a much lower steroid concentration.<sup>6</sup>

Many large, multicenter, double-blinded, randomized controlled trials (RCTs) have shown that in patients with mild to moderate persistent asthma, adding a LABA to low-to-medium doses of ICS results in significantly better improvement in pulmonary function than further increases in ICS dose alone.<sup>7-16</sup> While consistently compelling, most of these trials looked at changes in forced expiratory volume in one second (FEV<sub>1</sub>) or morning/evening peak expiratory flow rate (PEF) as a primary outcome.

Table 1 - NAEPP Asthma Guidelines

Severity	Recommended Maintenance Medication(s)*
Step 4: Severe Persistent <i>Continual daytime symptoms Frequent nighttime symptoms FEV<sub>1</sub> ≤ 60%</i>	<ul style="list-style-type: none"><li>• High-dose ICS AND LABA</li></ul>
Step 3: Moderate Persistent <i>Symptoms: daily or &gt;1night/week FEV<sub>1</sub> 60%-80%</i>	<ul style="list-style-type: none"><li>• Low dose ICS AND LABA OR</li><li>• Medium dose ICS</li></ul>
Step 2: Mild Persistent <i>Symptoms: &gt;2days/week but &lt;1x/day or &gt;2nights/month FEV<sub>1</sub> ≥ 80%</i>	<ul style="list-style-type: none"><li>• Low dose ICS</li></ul>
Step 1: Mild Intermittent <i>Symptoms: ≤2 days/week or ≤2nights/month FEV<sub>1</sub> ≥ 80%</i>	No daily controller medication needed

\*ICS = Inhaled corticosteroids, LABA = Long-acting inhaled  $\beta$ 2-agonist

More relevant clinical outcomes, such as exacerbation rate and rescue inhaler use, have shown variable results. In the majority of trials, low-dose ICS plus LABA produced significantly greater reductions in rescue inhaler use than doubling the ICS dose alone.<sup>7-17</sup> In a pooled analysis of two similar, but distinct RCTs with 24 weeks of follow-up, Matz et al demonstrated that patients receiving salmeterol plus low-dose inhaled fluticasone experienced a 36% reduction in risk of an exacerbation event compared to patients receiving a doubling of fluticasone dose alone (8.8% vs. 13.8%, p=0.017).<sup>17</sup> Pauwels et al, however, showed conflicting results.<sup>9</sup> In this RCT, 852 patients with mild persistent asthma previously treated with low-moderate doses of ICS were randomized to one of four treatment arms: budesonide (BD) 100 mcg bid or BD 400 mcg bid ± formoterol (FOR) 12 mcg bid and followed for one

year. The rate of exacerbation per patient per year was 0.46 in high-dose BD monotherapy group compared to 0.67 in low-dose BD plus FOR group (p<0.001). O'Byrne et al evaluated the efficacy of initiating low-dose BD or low dose BD plus FOR in patients with mild-intermittent asthma not previously managed with an ICS.<sup>7</sup> The initiation of combination therapy in these patients resulted in no additional benefit over low-dose BD alone for most outcome measures including exacerbation rate.

The recent update to the National Asthma Education and Prevention Program (NAEPP) clinical practice guidelines reflects some of the efficacy data reported from these clinical trials. Table 1 summarizes the NAEPP recommendations.<sup>1</sup>

### Chronic Obstructive Pulmonary Disease

Approximately 16 million Americans have COPD, and like asthma, the prevalence is increasing. Unlike asthma, COPD is largely preventable, as cigarette smoking is the major risk factor.<sup>18</sup>

Despite the lack of strong evidence, both ICS and LABA are widely prescribed for the treatment of COPD.<sup>19</sup> Unlike asthma, where chronic airway inflammation is a hallmark of disease, COPD has a markedly different histopathologic presentation and widely variable airway inflammation. As such, the benefits conferred by ICS are much less established for patients with COPD. Clinical trials of ICS have suggested that these agents do not modify the long-term progressive decline of lung function in patients with COPD.<sup>20-23</sup> However, it is recognized that some patients, particularly those with reversible airway disease (>15% improvement in FEV<sub>1</sub> following  $\beta$ 2-agonists inhalation), will exhibit a substantial short-term spirometric and symptomatic response from ICS.<sup>20-24</sup>

Ipratropium bromide (IPBR), an inhaled anticholinergic agent, is the bronchodilator of choice for patients with COPD. However, the short and long-acting inhaled  $\beta$ 2-agonists can also be effective for patients in this population.<sup>18</sup> In controlled studies, salmeterol has demonstrated superiority over placebo for improving FEV<sub>1</sub>, improving daytime and nighttime dyspnea, and decreasing the need for rescue inhalers.<sup>25</sup> In a 12-week comparative trial with IPBR, salmeterol was significantly better at improving FEV<sub>1</sub> and forced vital capacity.<sup>26</sup> When patients with non-reversible disease were examined separately, the benefits of salmeterol over IPBR on airflow mechanics disappeared. Salmeterol failed to demonstrate any consistent advantage over IPBR in dyspnea score, walking distance, patient self-assessment, or supplemental albuterol use.

Advair is not currently approved for the treatment of COPD; however, clinical data has been submitted and reviewed by the FDA Pulmonary Advisory Panel as part of the new drug application for this indication.<sup>27</sup> Two unpublished, 24-week studies evaluated the efficacy and safety of Advair for the treatment of COPD.<sup>27</sup> Both studies randomized patients to one of four arms in a double-blind fashion: placebo, fluticasone alone, salmeterol alone or Advair. Studies were limited to only those patients with confirmed chronic bronchitis. A large proportion (54%-55%) of studied subjects exhibited airway reversibility. The primary outcomes, pre-dose and 2 hours post-dose FEV<sub>1</sub>, showed significantly better improvements for patients randomized to Advair compared to placebo. However, Advair was not consistently superior to either fluticasone or salmeterol alone in either trial. No difference was seen among treatment arms for secondary endpoints including quality of life, frequency of exacerbation, and withdrawals due to lack of effectiveness. One trial showed a significant difference in the dyspnea metric Transition Dyspnea Index that favored Advair over salmeterol alone and placebo, but not fluticasone alone. The favorable effect in dyspnea was only seen in patients treated with Advair 500/50 and not in Advair 250/50.<sup>27</sup>

In their review, the FDA Advisory Panel raised several issues regarding the efficacy and safety of Advair for long-term treatment of patients with COPD.<sup>27</sup> First, the failure of Advair to demonstrate efficacy with most secondary endpoints has questioned the relevance of FEV<sub>1</sub> as a useful measure of effectiveness in patients with COPD. Second, the external validity of these data is suspect because of the

higher than normal prevalence of patients with reversible airway disease enrolled in these two studies. Finally, the studies were not designed, nor were they of sufficient duration, to evaluate endpoints of corticosteroid toxicity such as bone mineral density or ocular effects. A recent clinical trial has found that the sustained use of inhaled triamcinolone in patients with COPD was responsible for significant reductions in lumber spine and femur bone density.<sup>22</sup>

## ADVAIR DUR

A DUR was undertaken in an effort to characterize the drug use patterns for Oregon Health Plan (OHP) open-card members having a prescription filled for Advair using prescription and medical claims data. A patient was eligible for inclusion in this analysis if they had a claim for Advair between March 1, 2001 and April 1, 2002 and were continuously eligible, without managed care enrollment, for the 90 days prior to their first fill (sentinel fill) of Advair. Drug claims were classified into drug classes (Table 2). Medical claim ICD-9-CM codes were also examined to determine the nature of the patient's respiratory disease (COPD vs. asthma).

A total of 1148 patients met the inclusion criteria. The mean age of this group was 53 years old (3.99 years, SD=23). Approximately 70% of patients in this analysis were female. A total 165 patients (14%) had a medical claim for a COPD-related condition alone. An asthma-related condition alone was found in 247 patients (21%). There were 179 patients (16%) who were coded as having both conditions. The remaining 557 patients (49%) had no coded respiratory diagnosis during the study period. Table 2 shows the results of the prescription claims analysis. The combination totals convey the number of patients on the drug classes previously described. The category designations are not mutually exclusive and therefore do not sum to 100%.

**Table 2 - Prescription Claim Analysis**

Drug Class	No. of Pts	% of Total (1148)
Inhaled Corticosteroid (ICS)	351	30.6%
+ LABA	167	14.5%
+ LM	107	9.3%
Long-Acting Beta2-Agonist (LABA)	233	20.3%
Leukotriene modifiers (LM)	200	17.4%
Ipratropium Bromide (IPBR)	376	32.8%

Close to half (495) of all patients were found to be on no controller medication (i.e., ICS, LABA, LM or IPBR) prior to their sentinel Advair fill. Out of these 495 patients, 71.5% also had no short-acting  $\beta_2$ -agonists (SABA) filled during the 90 days prior to their sentinel fill. Of remaining 28.5% who had a claim for a SABA and no controller, the majority (66%) had only 1 fill during the previous 3 months.

This DUR suggests that a large proportion of patients who were started on Advair may have COPD as evidenced by the numerous medical claims for a COPD-related condition, the advanced age of the cohort, and the substantial number of patients also receiving IPBR therapy. One of the most striking findings was that almost half of all new starts of Advair were receiving no inhaled controller agent (e.g. ICS, LABA, etc.) prior to their sentinel Advair fill. It could be argued that these patients were initiated on combination therapy for aggressive control of previously uncontrolled moderate or severe persistent asthma. However, in this analysis a large majority (72%) of patients who were on no controller also had no fills for a SABA. Thus, if SABA use is a reasonable surrogate for disease severity, these findings do not strongly support this hypothesis.

A small proportion of patients (14%) were identified as taking both an ICS and a LABA. For these patients a combined drug product, such as Advair, could potentially enhance compliance and reduce overall drug acquisition costs. Table 3 shows the recommended conversions for the various available ICS to Advair and their respective costs.

## CONCLUSION

Clinical trials data and current NAEPP guidelines support the use of adding a LABA to an ICS in patients with mild to moderate persistent asthma who remain symptomatic on ICS. Advair can be considered as a drug option as it includes both a LABA and an ICS. Lack of strong clinical efficacy and long-term safety data should discourage use of Advair in COPD patients.

**Table 3 - Cost Comparison for Advair Conversion**

Inhaled Corticosteroid (mcg)	Cost of ICS (\$)*	Advair BID	Advair Cost (\$)*
Beclomethasone	$\leq 420$	76 -110	100/50
	462-840	114 -164	250/50
Budesonide (Pulmicort Turbuhaler®)	$\leq 400$	94	100/50
	800-1200	140	250/50
Flunisolide (AeroBid®)	1600	140	500/50
	$\leq 1000$	71	100/50
Fluticasone aerosol (Flovent®)	1250-2000	213	250/50
	$\leq 176$	53	100/50
Fluticasone powder (Flovent Rotadisk®)	440	74	250/50
	660-880	115	500/50
Triamcinolone (Azmacort®)	$\leq 200$	80	100/50
	500	112	250/50
	1000	155	500/50
	$\leq 1000$	69	100/50
	1100-1600	137	250/50
			135

\*Prices (30-days of therapy) based on AWP, 2002 Drug Topics Sept. 2002 update

\*Salmeterol MDI AWP \$74

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