



**Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: Long-Acting Beta Agonists
-May 2019-**



Background:

In May 2019, the IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed the long-acting beta agonists (LABAs) alone and in combination with inhaled corticosteroids (ICS) for the management of asthma and COPD. When the NPTC last reviewed this class of medications in October 2012, mometasone/ formoterol (Dulera®) was added to the National Core Formulary (NCF) and it has remained the sole combination LABA/ICS product. Following comprehensive clinical review at the Spring 2019 meeting as well as subsequent evaluation of procurement and new pricing data made available shortly thereafter, **the NPTC voted to REMOVE mometasone/formoterol and ADD fluticasone/salmeterol to the NCF.**

Discussion:

Long-Acting Beta Agonists (LABAs) are FDA-approved for asthma and COPD. However, the FDA has issued Black Box Warnings for all LABA medications stating that, as monotherapy, LABAs increase the risk of asthma-related deaths and are therefore contraindicated (as monotherapy) in the treatment of asthma¹. The FDA found no significant increase in risk of serious asthma outcomes when LABAs are used in combination with ICS and removed the black box warning for combination LABA/ICS medications.

The current treatment standards for COPD are identified in the 2019 guidelines from the [Global Initiative for Chronic Obstructive Pulmonary Disease \(GOLD\)](#)². These guidelines address the role of LABA therapy in treating patients categorized in Group B and Group C. For those patients in Group B (0-1 moderate exacerbations; mMRC ≥ 2 CAT ≥ 10), the choice of either a LABA or long-acting muscarinic agonists (LAMA) can be selected. For Group C (>2 moderate exacerbations leading to hospitalization; mMRC 01-CAT < 10), LAMA therapy is recommended over LABA therapy as evidence has demonstrated superiority in reducing exacerbations and hospitalizations with LAMA therapy. The combination of LABA/LAMA in the guidelines may be preferred to LABA/ICS because ICSs increase the risk of pneumonia. The remainder of this Formulary Brief will focus on the use of LABAs in patients with COPD, as monotherapy in asthma is contraindicated¹.

The Toward a Revolution in COPD Health (TORCH) Trial was a randomized, controlled, double-blind trial comparing salmeterol/fluticasone (LABA/ICS) twice daily to salmeterol alone (LABA), fluticasone (ICS) alone or placebo³. The primary outcome was death from any cause, and secondary endpoints included frequency of exacerbations, health status and spirometric values. The results demonstrated that the LABA/ICS combination did not significantly increase all-cause mortality (HR 0.83, 95% CI: 0.68-1.00). Additionally, monotherapy with salmeterol or fluticasone did not differ from LABA/ICS. The combination LABA/ICS was superior to placebo in decreasing annual rates of exacerbations from placebo (HR 0.75, 95% CI: 0.69-0.81) and higher rates of pneumonia were statistically significant with ICS and LABA/ICS (19.6% and 18.3%, compared to placebo 12.3%, $p < 0.001$). Salmeterol significantly decreased exacerbation rates, improved lung function and improved health-related quality of life compared to placebo, but not in comparison to fluticasone alone or combination LABA/ICS.

The POET-COPD trial compared tiotropium to salmeterol in the prevention of exacerbations of COPD⁴. The primary outcome was time to first COPD exacerbation. Tiotropium was superior to salmeterol in time to first exacerbation (187 days vs. 145 days- HR 0.83, 95% CI: 0.77 to 0.9; $p < 0.001$). Tiotropium was superior to salmeterol in reducing annual number of moderate to severe exacerbations and severe exacerbations (HR 0.89, 95% CI: 0.83 to 0.96; $p = 0.002$) and (HR 0.73, 95% CI: 0.66 to 0.82; $p < 0.001$) respectively. There were no significant differences in adverse drug events leading to discontinuation with either therapy. This study supports the current GOLD guideline recommendations to consider the favorability of LAMA monotherapy over LABA monotherapy.

Several Cochrane systematic reviews for LABAs used in COPD were performed between 2011 and 2018. A 2011 review evaluated 7 randomized controlled trials (N=5,997 participants) comparing ICS/LABA to LABA and ICS monotherapy. The analysis demonstrated no significant changes in the rate of exacerbations per patient between ICS and LABA (OR 1.22, 95% CI: 0.89 to 1.67) however patients receiving ICS monotherapy were shown to have higher rates of pneumonia (OR 1.38, 95% CI: 1.10 to 1.73) and mortality (OR 1.17, 95% CI: 0.97 to 1.42) when compared to LABAs⁵. This review supports current guidelines advocating LABAs as first line therapy for COPD, with regular ICS therapy as an adjunct in patients experiencing frequent exacerbations.

A 2012 Cochrane review (7 RCTs, N=12,223 participants) compared tiotropium monotherapy to LABA monotherapy⁶. The results demonstrated that tiotropium was superior to LABA at reducing exacerbations (OR 0.87, 95%CI: 0.77 to 0.99), however results were similar in all secondary outcomes including symptom improvement, changes in lung function, FEV₁, quality of life, overall all-cause hospitalizations and mortality. Overall, tiotropium was more effective than LABAs in preventing COPD exacerbations.

In a recent Cochrane Review published in 2018 (99 studies, N=101,311 participants), LABA monotherapy was compared to ICS/LABA, LABA/LAMA and LAMA monotherapy⁷. The results demonstrated that the LABA/LAMA combination had the greatest reduction in COPD exacerbations, followed by LAMA monotherapy. Other measures, including quality of life and symptom improvement scores, trended towards favorability in those receiving combination therapy (vs. monotherapy).

Findings:

Treatment of asthma with LABA monotherapy is contraindicated due to increased risk of asthma-related mortality. The role of combination ICS/LABA therapy in patients with asthma continues to be supported by respiratory guidelines for long-term control and prevention of symptoms in moderate to persistent asthma⁸. Current guidelines for the management of COPD do support the use of LABA monotherapy in certain patient populations (Groups B and C) although recent studies suggest that patient outcomes are improved when LABAs are used in combination with a LAMA.

The NPTC review of the ICS/LABA inhalers, fluticasone/salmeterol and mometasone/formoterol, failed to identify a superior product in terms of patient efficacy and/or safety outcomes. Comparatively, generic fluticasone/salmeterol is approved for an expanded age range (>4 years old), has the added FDA indication for COPD maintenance therapy, and provides a considerable cost avoidance opportunity for the agency.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the [NPTC website](#).

References:

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