



Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: Atypical Respiratory Medications
-May 2019-



Background:

In May 2019, the IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed atypical respiratory medications which included biologic therapies for uncontrolled/severe asthma and phosphodiesterase inhibitors for COPD. Currently, none of these medications are available on the National Core Formulary. Following clinical and pharmacoeconomic analyses, **no modifications were made to the National Core Formulary.**

Discussion:

Asthma is a lung disease associated with chronic inflammation and airway narrowing due to an imbalance and shift towards generating more T-helper 2 (Th2) cytokines.¹ For those who do not achieve symptom control with high dose inhaled corticosteroids (ICS) and a long-acting beta-agonist (LABA), biologics can be considered. These biologics target specific interleukins produced by the Th2 cytokines to disrupt the signaling cascade which includes: omalizumab (binds to IgE), reslizumab and mepolizumab (bind to IL-5), benralizumab (blocks IL-5 receptor), dupilumab (blocks IL-4 receptor).²

Chronic Obstructive Pulmonary Disease (COPD) is a progressive lung disease due to long term damage from irritants, primarily tobacco smoke.³ Phosphodiesterase (PDE) inhibitors can be utilized as alternative agents for severe, uncontrolled COPD. Theophylline is a non-selective PDE inhibitor; however, the utility of this agent is limited by its narrow therapeutic window and increased risk of significant adverse events. Roflumilast selectively inhibits phosphodiesterase-4 which is expressed in airway smooth muscle. Overall, PDE inhibition results in airway smooth muscle relaxation.⁴

=Guidelines=

Biologics are reserved as adjunctive therapy for patients with uncontrolled difficult-to-treat/severe asthma despite optimized standard therapy. The April 2019 update to the [Global Initiative for Asthma \(GINA\) Difficult-to-Treat & Severe Asthma: Diagnosis and Management guidelines](#) recommends omalizumab for allergic asthma and an IL-5 binder/receptor antagonist for eosinophilic asthma.⁵ The GINA guidelines also recommend an adequate trial of at least four months' duration before switching to an alternate agent. The [2017 NICE Asthma guidelines](#) were consistent with the GINA guidelines but presented additional specific criteria of minimum blood eosinophil counts and number of exacerbations requiring oral corticosteroids before initiation of a biologic agent.⁶ Dupilumab was not discussed in the guidelines.

The [2019 Global Strategy for the Diagnosis, Management, and Prevention of COPD \(GOLD\) guidelines](#) discussed utilizing roflumilast if initial preferred therapy was inadequate in controlling symptoms in Group D COPD patients with a post-bronchodilator forced expiratory volume in one second (FEV₁) <50% predicted and chronic bronchitis.⁷ The new update also discussed obtaining blood eosinophil levels in patients with persistent symptoms and to consider roflumilast if eosinophil levels are <100 cells/ μ L. Theophylline was **not** recommended unless other long-term bronchodilators were unavailable or unaffordable. If considered, only the slow-release formulations have been studied in treatment for COPD. The [2018 NICE COPD guidelines](#) also discussed that theophylline should only be used after a trial of short acting beta-agonists and LABAs or for those unable to use inhaled therapy.⁸ Roflumilast can be used as an add-on to bronchodilator therapy and is recommended in adults with severe COPD with chronic bronchitis if post bronchodilator FEV₁ is <50% of predicted and ≥ 2 exacerbations in the past year despite being on triple inhaled therapy with a long-acting muscarinic antagonist (LAMA), LABA, and ICS. The guidelines further mentioned that roflumilast should be started by a pulmonary specialist.

=Clinical Studies=

A 2012 Cochrane review evaluated 25 randomized controlled trials (RCTs) comparing omalizumab to placebo in adults and children with moderate to severe asthma regarding asthma exacerbation events, quality of life, and adverse events.⁹ Significant reductions in exacerbations (OR 0.55, 95% CI: 0.46 to 0.65) were seen overall with omalizumab. Significant improvements were seen in quality of life (AQLQ) from baseline with omalizumab (mean difference 0.31, 95% CI: 0.23 to 0.39); however, the difference did not meet the AQLQ minimal clinically important difference (MCID) of ≥ 0.5 .¹⁰ Significantly fewer serious adverse reactions were seen with omalizumab (OR 0.72, 95% CI: 0.57 to 0.91); however, patients on omalizumab were significantly more likely to have skin reactions at the injection site (OR 1.72, 95% CI: 1.33 to 2.24).⁹

A 2017 Cochrane review evaluated 13 RCTs comparing IL-5 antagonists (mepolizumab SubQ and IV formulations, reslizumab, benralizumab) to placebo.¹¹ Overall, IL-5 antagonists reduced exacerbations rates by 50%. Significantly reduced rates of ED/hospitalizations were seen with mepolizumab SubQ (RR 0.36, 95% CI: 0.20 to 0.66) and benralizumab (RR 0.68, 95% CI: 0.47 to 0.98). Modest improvements were seen with all three interventions but did not exceed MCID for AQLQ of ≥ 0.5 . No significant differences in adverse events were found with mepolizumab and reslizumab compared to placebo; however, significantly more patients discontinued benralizumab due to adverse effects (RR 2.15, 95% CI: 1.02 to 4.57). The authors concluded that further investigation is warranted with benralizumab due to the slightly different mechanism of action as a receptor antagonist.¹¹ Conversely, no significant differences were found in patients discontinuing benralizumab due to adverse effects (2.2% vs. 1.0%, RR 1.84, 95% CI: 0.92 to 3.68) according to the 2018 asthma biologics update from the Oregon State University Drug Effectiveness Review Project Summary Report.¹²

A 2018 network meta-analysis reviewed 26 RCTs comparing the IL-5 antagonists and dupilumab along with lebrikizumab and tralokinumab in adults and children with eosinophilic asthma.¹³ Most biologics except for tralokinumab were found to be superior to placebo on lung function (FEV₁), symptoms (ACQ), and quality of life (AQLQ); however, none of the biologics met the MCID for ACQ and AQLQ. Only dupilumab and reslizumab were statistically significant for reducing asthma exacerbation rates (rate ratio 0.37, 95% CI: 0.17 to 0.80 and 0.64, 95% CI: 0.53 to 0.78 respectively).¹³

A 2012 Cochrane review evaluated 20 RCTs comparing oral theophylline vs. placebo in adults with COPD.¹⁴ The authors noted modest improvements on FEV₁ and forced vital capacity with theophylline. Although the risk of nausea was significantly greater in the theophylline group (RR 7.67, 95% CI: 1.47 to 39.94), very few dropouts occurred throughout the studies.¹⁴ A 2017 Cochrane review evaluated 34 RCTs comparing PDE-4 inhibitors, oral roflumilast (250 and 500 mcg daily) and cilomilast 15 mg twice daily, in adults with COPD.¹⁵ These agents were superior to placebo in significantly improving prebronchodilator FEV₁ and quality of life (SGRQ scores MD -1.06, 95% CI: -1.68 to -0.43, $p=0.0009$), but both outcomes did not meet MCID. Significant reductions in number of patients experiencing ≥ 1 COPD exacerbation were also seen in the active treatment group (OR 0.78, 95% CI: 0.73 to 0.83). Although there were no significant increases in mortality, significantly higher rates of adverse effects were seen with the PDE-4 inhibitors (OR 1.29, 95% CI: 1.22 to 1.37).¹⁵

An observational, prospective study evaluated 55 adults with COPD, chronic bronchitis, and frequent exacerbations (≥ 2 exacerbations in the previous year) despite being on at least 1 year with LABA/ICS + LAMA.¹⁶ Roflumilast significantly reduced the rate of COPD exacerbations compared to the previous year (2.75 ± 0.29 vs. 3.57 ± 0.26 ; $p=0.022$). Significantly greater number of patients experienced adverse effects (69.1%), and 27 patients (49%) discontinued therapy due to side effects. The most common side effects were GI disorders (e.g., diarrhea, abdominal pain, nausea, hyporexia, and weight loss).¹⁶

Findings:

Biologic treatments for asthma are considered as adjunct therapy to standard of care for asthma if uncontrolled/severe. PDE inhibitors can be used in severe, refractory COPD. Roflumilast is considered as a last-line therapy for severe COPD (Group D) with chronic bronchitis; however, the use of theophylline is limited due to narrow therapeutic window and significant adverse effects. Improvements in clinical outcomes (e.g., exacerbation rates, lung function) with no significant increases in adverse events or mortality were seen with asthma biologics. Similar clinical outcomes were seen with roflumilast with minimal benefits on quality of life and significantly higher GI and psychiatric adverse effects.

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](#).

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