Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Phosphodiesterase-4 Inhibitors***
-August 2014-

Background:
The IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed the role of phosphodiesterase-4 (PDE-4) inhibitors in the treatment of chronic obstructive pulmonary disease at their August 2014 meeting. Based on the information presented, the committee did not add a PDE-4 inhibitor to the IHS National Core Formulary (NCF). This brief is intended to summarize this drug class to inform IHS clinicians of its role in therapy.

Discussion:
COPD is a respiratory disease involving airflow obstruction due to chronic bronchitis or emphysema. The incidence of COPD is increasing. Since 2008, it is now the 3rd leading cause of chronic morbidity and mortality in the US and the underlying cause of 1 of every 20 deaths[1]. Seventy-five percent of COPD cases are associated with tobacco use. Although rates of COPD are less for American Indian/Alaskan Natives (AI/AN) than for the general US population, it still impacts 4.6% of this group[2]. COPD is the 7th leading cause of death for AI/AN, with the highest mortality rates in the North Plains (RR=1.71), Alaska (RR=1.56) and the Pacific Coast (RR=1.29)[3].The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has established criteria for dividing patients into four stages of the disease[4]. They have further developed a rubric comparing either the disease stage or the exacerbation history to patient assessment of symptom impact to guide optimal drug therapy.

Phosphodiesterases are a group of isoenzymes found through various cells of the body. They convert cyclic-3'5'-AMP (active form) to 5'-AMP (the inactive form). PDE-4 is the isoenzyme found predominantly in most immune and proinflammatory cells. As well, it is found in all major cell types of the lung. The inhibition of PDE-4 increases cellular cyclic-AMP, promoting smooth muscle relaxation, inhibition of fibrosis/remodeling, and has an anti-inflammatory effect on CD8+ T cells, macrophages, and neutrophils. Roflumilast (Daliresp®) is the only PDE-4 inhibitor FDA-approved in the US. It is approved to reduce the risk of exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. It comes in a 500 mcg tablet and is dosed once daily. Roflumilast is not for the treatment of acute bronchospasm. Its use is contraindicated in patients with moderate to severe liver disease (Pugh-Child Class B or C). It carries warnings related to an increased incidence of psychiatric adverse effects (insomnia, anxiety, depression, and suicidality) and weight loss (20% with loss of 5-10% of body weight, 7% with loss of >10% of body weight) and a failure to regain weight after discontinuation. Roflumilast requires metabolism by CYP3A4 and CYP1A2 to its active form (roflumilast N-oxide). Concurrent use with strong P450 inducers may decrease its activity, while use with CYP3A4 and CYP1A2 inhibitors may increase roflumilast exposure and side effects. The other most common adverse effects are diarrhea (9.5%), nausea (4.7%), and headache (4.4%)[5].

Clinical Trials:
Two clinical trials were conducted to determine the efficacy of roflumilast. These were randomized, placebo-controlled trials with 1500+ patients >40 years with COPD, with approximately half receiving roflumilast. The treatment group had a 15-18% reduction in COPD exacerbations, with an absolute reduction of 0.2-0.3 episodes per patient-year. Also, the treatment group demonstrated an increase in FEV_1 from baseline of 39-58 mL[5].

Systematic Reviews:
In 2013, Cochrane conducted a review of 29 RCT involving the use of roflumilast or cilomilast. Fifteen (15) trials involved the use of roflumilast, involving 12,654 patients. The trials lasted 6-12 months, including patients with moderate to very severe COPD (GOLD grade II-IV), and with an average age of 64 years. The results showed significant improvement in FEV1 (Mean difference (MD) = 45.60 mL; 95% CI 39.45-51.75). It also noted small improvements in quality of life (MD=-1.04 on a St. George's Respiratory

Questionnaire) and COPD-related symptoms, but no improvement in exercise tolerance. The number needed to treat for an additional beneficial effect was 20 (95% CI 16-27). However, there were increased adverse effects, including headache, GI symptoms, weight loss, insomnia, and depressed mood[6].

In 2013, Pan et al. conducted a meta-analysis of RCTs involving the use of roflumilast. They included 4 high quality trials involving 4,767 patients with an FEV_1 <80% predicted. Although there was statistically significant improvement in the transition dyspnea index and minor reduction in symptom scores using a UCSD Shortness of Breath Questionnaire, these outcomes were judged to be below minimum clinically important differences leading the authors to conclude the sufficient evidence to support roflumilast of relieving dyspnea in COPD patients is lacking[7].

Guidelines:
Three clinical guidelines address the role of PDE-4 inhibitors in the management of COPD. The NICE Technology Appraisal Guidance (Jan 2012) recommends that roflumilast only be used in the context of further research as to its role as an add-on therapy to bronchodilators and other standard COPD therapies[8]. The Institute for Clinical Systems Improvement (ICIS) issues a 2013 guideline noting that a PDE-4 inhibitor could be considered as an add-on therapy for moderate COPD after bronchodilators and inhaled corticosteroids, noting "the exact place in treatment is not defined."[9] The GOLD guidelines were updated in 2014. They identified PDE-4 inhibitors as a treatment alternative used in conjunction with long-acting bronchodilators or long-acting anticholinergic agents for high risk patients identified in the Combined Assessment quartiles C and D[4].

Findings:
The IHS NPTC finds roflumilast to have marginal benefits in reducing exacerbations of COPD in patients with more severe disease not well controlled on bronchodilators. Adverse effects make this drug difficult for many patients to tolerate.

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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