Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: *Long Acting Muscarinic Antagonists*

-May 2019-

Background:

In May 2019, the IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed long-acting muscarinic antagonists (LAMAs). Specifically, the NPTC evaluated and compared the currently available LAMAs, clinical data supporting the role of LAMA therapy in asthma treatment, and the role of combination LAMA/long-acting beta2 agonists (LABA) or combination LAMA/LABA/Inhaled Corticosteroids (ICS) in COPD management. **Ultimately, the NPTC voted to ADD umeclidinium/vilanterol as a LAMA/LABA combination to the National Core Formulary.**

Discussion:

Anti-muscarinic agents have long been used for the treatment of respiratory diseases, dating back to the use of atropine-containing herbs in ancient times[1]. The mechanism of action of anti-muscarinic agents in the human airway is via blockade of the muscarinic receptor that regulate airway tone, smooth muscle contraction and mucus secretion[2]. Tiotropium was the first selective, long-acting anti-muscarinic agent developed specifically for chronic maintenance therapy in COPD. Tiotropium was added to the IHS National Core Formulary in 2011[3]. In the intervening years, several new LAMAs have been developed and marketed individually and as double or triple combination therapy with other respiratory medications such as the LABAs and ICS[4]. Additionally, tiotropium has been investigated and recently gained approval as a potential adjunct therapy for asthma treatment in adults and children[5].

Comparison of LAMAs

A 2015 systematic review and network meta-analysis of 24 RCTs including 21,311 patients compared the efficacy of the currently available LAMAs. All LAMAs resulted in clinically relevant improvements in trough FEV1 at 12 and 24 weeks. There were minimal clinically important differences in quality of life measures for umeclidinium, aclidinium & glycopyrronium vs placebo at 24 weeks. Aclidinium and umeclidinium had similar efficacy for lung function and patient-reported outcomes, compared with other LAMAs. There was no evidence that a twice-daily regimen (i.e., aclidinium) was more efficacious than once-daily regimens. Umeclidinium showed modest numerical improvements in 12-week lung function, compared with other LAMAs but these were not statistically significant. Glycopyrronium had superior efficacy to tiotropium in terms of 24-week FEV1 and questionnaire score. However, patients in the tiotropium trials tended to include patients with severe COPD compared to the glycopyrronium trials which predominantly included patients with moderately severe COPD. Overall, data suggested that aclidinium, glycopyrronium, tiotropium, and umeclidinium are efficacious relative to placebo, and newer LAMAs were at least non-inferior to tiotropium[6].

LAMA vs LABA vs LAMA/LABA

A 2015 Cochrane review comparing LABA + tiotropium versus tiotropium alone or LABA alone reviewed 10 trials including 10,894 participants with moderate or severe COPD. Compared to tiotropium alone, treatment with tiotropium + LABA resulted in a slightly greater improvement in the mean health-related quality of life (MD -1.34, 95% CI -1.87 to -0.80). However, there were no significant differences in the other primary outcomes (hospital admissions and mortality). Pre-bronchodilator FEV1 showed a modest but statistically significant improvement with tiotropium + LABA compared to tiotropium alone[7].

A 2017 review of 18 studies of 20,185 patients with stable moderate-to-severe COPD compared LAMA/LABA versus LAMA monotherapy or LABA/ICS and found that the LAMA/LABA combination product offered superior efficacy and comparable safety compared to LAMA alone or LABA/ICS[8].

A 2017 meta-analysis of 16 RCTs compared LAMA versus LABA monotherapies in patients with stable COPD. This trial found that patients receiving LAMA therapy had lower risk of acute exacerbations (OR: 0.84, 95% CI: 0.74–0.90; P=0.004, I^2 = 61%) and increased trough FEV1, but not meeting statistical significance (WMD: 0.02, 95% CI: −0.01 to 0.02, P=0.06, I^2=99%). There was no difference in quality of life measures or serious adverse events[9].

LAMA vs LAMA/LABA vs ICS/LABA
A 2017 Cochrane Database review compared LAMA/LABA versus LABA/ICS for stable COPD. This review included 11 studies comprising 9,839 participants with stable disease. In this analysis, the LAMA/LABA group had fewer exacerbations, a larger improvement of FEV1, lower risk of pneumonia, and more frequent improvement in QoL as measured by the Saint George Respiratory Questionnaire[10].

A 2018 systematic review and meta-analysis of 74 RCTs of 74,832 patients compared the efficacy of inhaled medications (ICS/LABA, LAMA, LAMA/LABA and SAMA) for COPD. In this study, LAMA/LABA showed the greatest improvement in lung function at weeks 12 and 24, while SAMA showed the least improvement. There were no significant differences among LAMAs and LAMA/LABAs within their respective classes. LAMAs, LAMA/LABAs and ICS/LABAs led to a greater improvement in trough FEV1 compared with placebo and SAMA monotherapy. All LAMA/LABAs except aclidinium/formoterol were significantly better than LAMA monotherapy in improving lung function. Limited evidence suggested LAMA/LABAs led to greater improvements than ICS/LABAs[11].

Triple Therapy
A 2019 meta-analysis of 13 RCTs of 15,519 patients with COPD compared ICS/LABA vs triple therapy with ICS/LAMA/LABA. In this study, adding a LAMA to an ICS/LABA combination resulted in relevant clinical benefit with significant improvement in FEV1 (p=0.01) and a decrease in acute COPD exacerbations (p=0.05). The number needed to treat (NNT) to prevent one COPD exacerbation in 12 months was 22.5. The NNT to improve FEV1 by at least 100mL was 3.38 (2.84-4.24). The authors concluded that therapy can be improved without an increase of cardiovascular SAEs when a LAMA is added to ICS/LABA combination therapy in patients with COPD[12].

A 2018 RCT of 10,355 patients with COPD compared once-daily, single-inhaler, triple therapy vs dual therapy. In this study, patients on triple therapy experienced 0.91 asthma exacerbations/year, compared to 1.07 in patients on ICS/LABA and 1.21 in patients on LAMA/LABA (RR 0.85; 95% C: 0.80 to 0.90, p<0.001) and 1.21 per year among those assigned to umeclidinium–vilanterol (RR 0.75; 95% CI, 0.70 to 0.81, p<0.001). The conclusion of this study was that triple therapy resulted in a lower rate of moderate or severe COPD exacerbations and lower rate of hospitalizations than dual therapy in this population[13].

Efficacy and safety of LAMAs for the treatment of asthma
A 2015 Cochrane review examined the effect of adding a LAMA to ICS vs ICS alone for adults with asthma. The study included 2563 adult participants with poorly controlled asthma and found the rate of exacerbations requiring oral corticosteroids (OCS) was significantly lower in patients prescribed a LAMA add-on (27 fewer per 1000 participants, 95% CI: 6 to 42 fewer) than in those receiving the same dose of ICS alone. Addition of LAMA therapy did not show clear benefit for quality of life compared with ICS alone. However, addition of a LAMA led to significant improvement in lung function compared with the same dose of ICS alone, with FEV1 increased by 0.14 L[14].

A 2016 Cochrane review of a LAMA added to ICS/LABA (vs ICS/LABA only) for adults with asthma, included 8 studies of 2049 patients. This review showed moderate quality evidence that LAMAs had small benefits over LABA on some measures of lung function and high quality evidence that LABAs modestly improved quality of life. However, the overall differences were all very small. Given the much larger evidence base for LABA vs placebo, current evidence does not support substitution of LABA by a LAMA as add-on therapy[15].

The NPTC also reviewed the two RCTs that were the basis for the approval of tiotropium in pediatric patients. A 12-week study in patients with severe asthma using an ICS plus one or more controller medication showed no significant difference between tiotropium 2.5 mcg and placebo with a mean difference of 0.04 L (95% CI, -0.03 to 0.10) at 12 weeks. A 48-week study in patients with moderate asthma and on at least an ICS for maintenance therapy showed a mean difference of 0.17 L (95% CI, 0.11 to 0.23) between tiotropium 2.5 mcg and placebo, which did meet clinical significance[16].

Findings:
Overall, the available evidence supports the safety and efficacy of LAMAs in the treatment of COPD. There is also evidence that LAMAs may prove as effective add-on treatment for difficult-to-control asthma, although the evidence is too weak to support routine use for most asthmatic patients at this time. There is no convincing evidence that one LAMA agent or LAMA/LABA agent is superior over other in-class products. Published evidence also shows clear benefit of the LAMA/LABA combination as first line treatment in patients with COPD, or as a step-up therapy before transitioning patients to triple therapy.

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:

1. Chu C, Drazen J. Asthma: One hundred years of treatment and onward. *Am J Respir Crit Care Med.* 2005; 171:1202-08.
2. Sentana K. Long-acting Asthma and COPD Drugs. Drug Effectiveness Review Project Summary Report – Drug Use Research and Management. 2016.
3. Indian Health Service National Pharmacy and Therapeutics Committee. Inhaled Anticholinergics. 2011.
4. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD, 2019 Report.
5. Morris MJ, Pearson DJ, Mosenifar Z, et al. Asthma guidelines. *Medscape.* Jan 2019.
6. Ismaila AS, Huisman EL, Punekar YS, et al. Comparative efficacy of long-acting muscarinic antagonist monotherapies in COPD: a systematic review and network meta-analysis. *Int J Chron Obstruct Pulmon Dis.* 2015; 10:2495–2517.
7. Farne HA, Cates CJ. Long-acting beta2-agonist in addition to tiotropium versus either tiotropium or long-acting beta2-agonist alone for COPD. *Cochrane Database Syst Rev.* 2015, Issue 10. Art. No.: CD008989.
8. Rodrigo GJ, Price D, Anzueto A, et al. LABA/LAMA combinations versus LAMA Monotherapy or LABA/ICS in COPD: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis.* 2017; 12:907-922.
9. Chen WC, Huang CH, Sheu CC, et al. Long-acting beta2-agonists versus long-acting muscarinic antagonists in patients with stable COPD: A systematic review and meta-analysis of randomized controlled trials. *Respirol* 2017; 22:1313–19.
10. Horita N et al. Long-acting muscarinic antagonist plus long-acting beta-agonist versus long-acting beta-agonist plus inhaled corticosteroid for stable COPD. *Cochrane Database Syst Rev.* 2017, Issue 2. Art. No.: CD012066
11. Aziz MI, Tan LE, Wu DB, et al. Comparative efficacy of inhaled medications (ICS/LABA, LAMA, LAMA/LABA and SAMA) for COPD: a systematic review and network meta-analysis. *Int J Chron Obstruct Pulmon Dis.* 2018; 13:3203–3231.
12. Calzetta L, Cazzola M, Matera MG, et al. Adding a LAMA to ICS/LABA Therapy. A Meta-analysis of Triple Combination Therapy in COPD. *CHEST* 2019: 155(4) 758-770.
13. Lipson DA, Barnhart F, Brealey N, et al. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. *NEJM.* 2018; 378:1671-1680.
14. Anderson DE, Kew KM, Boyter AC. Long-acting muscarinic antagonists added to inhaled corticosteroids (ICS) versus the same dose of ICS alone for adults with asthma. *Cochrane Database Syst Rev.* 2015, Issue 8. Art. No.: CD011397
15. Kew KM, Dahri K. Long-acting muscarinic antagonists added to combination long-acting beta2-agonists and inhaled corticosteroids (LABA/ICS) versus LABA/ICS for adults with asthma. *Cochrane Database Syst Rev.* 2016; (1):CD011721.
16. Goldstein S, Vogelberg C, Graham L, et al. Tiotropium provides greater improvements in FEV than an LTRA as add-on to ICS in children and adolescents with asthma: a systematic review. Presented at: the Annual Meeting of the American Academy of Allergy, Asthma & Immunology; February 22-25, 2019; San Francisco, CA. Abstract 279.