

# Wyoming Drug Utilization Review

## Chronic Obstructive Pulmonary Disease IV: Long Acting Muscarinic Antagonists

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Chronic obstructive pulmonary disease (COPD) is a common and potentially life-threatening disease characterized by abnormalities of the airway and alveoli (1). The 2019 GOLD guidelines recommend bronchodilators as first line therapy for all patients with COPD. The bronchodilators include short acting beta agonists (SABA), long acting beta agonists (LABA), short acting muscarinic antagonists (SAMA), and long acting muscarinic antagonists (LAMA). They are used in combination with each other, alone, or with inhaled corticosteroids (ICS) depending on patient specific factors and severity of symptoms (1).

The 2019 GOLD guidelines suggest therapy based on symptoms and past exacerbations, placing patients into one of four groups including A, B, C, and D (1). Patients in group A should receive either a short or long acting bronchodilator based on symptom relief. Patients in group B should receive a long acting bronchodilator based on patient's perception of symptom relief. Patients in group C should receive LAMA monotherapy as first line because LAMAs have been shown to be superior to LABAs in preventing exacerbations. One change in the 2019 GOLD guidelines is that group D patients can receive monotherapy with a LAMA as first line. This change is based on prevention of exacerbations not being consistently shown with LABA/LAMA combinations over LAMA monotherapy. A LABA/LAMA combination should still be considered first line in group D patients who are highly symptomatic. A LABA/ICS should be considered first line in group D patients if blood eosinophil count is  $\geq 300$  cells/ $\mu$ L or in patients with a history of asthma (1).

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Naturally occurring muscarinic antagonists have been used as bronchodilators for centuries (2). In the 1800s, the leaves and roots of jimson weed, a plant with antimuscarinic properties, were administered in cigarettes to treat respiratory diseases. Systemic side effects were prevalent with early muscarinic antagonists, which led to development of synthetic derivatives containing quaternary ammonium groups. These agents have a more limited bioavailability and are unable to cross the blood brain barrier, leading to less systemic side effects (2).

All five muscarinic receptor subtypes are present in the lungs (2). LAMAs bind to and antagonize all of them, but their selectivity comes from a longer dissociation half-life from the M<sub>3</sub> receptors (2). The two most prevalent muscarinic receptors relating to COPD therapy are the M<sub>2</sub> and M<sub>3</sub> subtypes (1,2). Under normal physiologic conditions, the M<sub>3</sub> receptors induce bronchoconstriction and increase mucus production (2). When the M<sub>3</sub> receptors are blocked, their effects on bronchoconstriction and mucus production are antagonized (2). Under normal physiologic conditions, the M<sub>2</sub> receptors inhibit release of acetylcholine (2). Blocking the inhibitory M<sub>2</sub> receptors results in increased acetylcholine release which can lead to vagally induced bronchoconstriction (1,2). The undesired effects of M<sub>2</sub> antagonism are overcome by their short dissociation half-life when compared to the longer dissociation half-life of LAMAs from the M<sub>3</sub> receptors (1,2).

The currently available LAMAs in the United States are tiotropium, glycopyrrolate, aclidinium, and umeclidinum (3). They are available in a number of different inhalers which include single agents, combination with LABAs, and one containing a LABA and an ICS (4). The comparative efficacy of available LAMAs appears to be similar based on current studies, therefore choice in therapy may be guided by other factors (5,6). When a current therapy is considered insufficient, inhaler technique and adherence should always be assessed (1), but when a patient has a problem with a certain inhaler, a low threshold for switching to an alternative should be in place (6).

LAMAs are considered very safe based on extended experience in clinical use at a range of doses (1,3). The most widely reported adverse effect is dry mouth (1). The rate of anticholinergic side effects across the agents are low and generally similar (1,6); some serious side effects can include intestinal obstruction, urinary retention, glaucoma, arrhythmias, and pneumonia (7).

Contraindications to the LAMAs include hypersensitivity to the particular drug product, as well as any components of their formulation (3). A severe hypersensitivity to milk proteins is also a contraindication for aclidinium and umeclidinum (3). All of the LAMA agents have the possibility to cause paradoxical bronchospasm and hypersensitivity reactions. In the event of either of these, therapy should be stopped immediately, and alternative therapies should be considered (3,8).

Renal adjustment is not required for any of the LAMAs (3,9,10). Systemic exposure may be increased and caution should be used in patients with a creatinine clearance (CrCl) <30 mL/min with glycopyrrolate, and a CrCl <60 mL/min with tiotropium (9,10). While significant systemic absorption is rare among the inhaled LAMAs, caution should be taken when administering them to patients with preexisting conditions that might be exacerbated (3,8). The conditions include: closed/narrow-angle glaucoma, urinary tract obstruction, myasthenia gravis, geriatric population, and cardiovascular disease (3,8).

There are numerous inhaler options available, and selection of an appropriate one may be difficult. The most important factor in selecting an inhaler device lies in the patient's ability and preference, but access, cost, and prescriber preference should also be taken into consideration (1,6). Some of the major considerations for patient-specific inhaler choice include ease of use, multi-dose vs single dose, frequency of dosing, and dose recording (6). The chart below details LAMA inhaler attributes.

The LAMAs are considered very safe in the treatment of COPD. They are first line in the treatment of moderate to severe COPD and are often used in combination with LABAs. The most important factor for inhaler choice is in the patient's ability and preference which may be guided by prescriber preference, cost, and access.

## Practical attributes of LAMA inhalers available in the United States: (4,6,11)

Inhaler Type	Dosage Form and Frequency	Possible Advantages	Possible Disadvantages
Pressair® (Tudorza® Pressair®-acclidinium)	Dry powder inhaler; multidose. Twice daily.	No priming required, no shaking required, indicator shows how many doses are left. Colored indicator shows full delivery	Requires ability to perform a rapid, deep inhalation.
Neohaler® (Utibron® Neohaler®-glycopyrrolate/ indacaterol)	Dy powder inhaler; single dose. Twice daily.	Capsules are transparent; may be helpful in determining if full dose was administered. No priming required, no shaking required.	Requires ability to perform a rapid, deep inhalation. Capsules come in a blister pack; may be difficult for some patients to remove the capsule and insert it into the inhaler. Capsules should not be swallowed.
Bevespi Aerosphere®-glycopyrrolate/formoterol	Pressurized metered dose inhaler; multidose. Twice daily.	Indicator shows how many doses are left. No assembly required.	Requires hand/ breath coordination. Priming required, shaking required.
HandiHaler® (Spiriva® HandiHaler®-tiotropium)	Dry powder inhaler; single dose.	No priming required, no shaking required.	Requires ability to perform a rapid, deep inhalation. Capsles come in a blister pack; may be difficult for some patients to remove the capsule and insert it into the inhaler. Capsules should not be swallowed. No confirmation of dose.
Respimat® (Stiolto® Respimat®-tiotropium/olodaterol; Spiriva® Respimat®-tiotropium)	Soft mist spray inhaler; multidose.	Delivery is not dependent on ability to perform a rapid, deep inhalation. No shaking required. Indicator for doses remaining.	Assembly may be difficult for some patients. Priming is required.
Ellipta® (Incruse® Ellipta®-umeclidinium; Anoro® Ellipta®-umeclidinium/vilanterol; Trelegy® Ellipta®-umeclidinium/vilanterol/fluticasone)	Dry powder inhaler; multidose.	No assembly required, no priming required. No shaking required, indicator for doses remaining.	Requires ability to perform a rapid, deep inhalation. May not be possible to taste or feel the medication. Doses may be wasted if opened/closed accidentally.

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## P&T Committee Meeting Update

The P&T Committee met for its quarterly business meeting on August 15, 2019.

Highlights of this meeting include:

- Diacomit, Ruzurgi, Vyndaqel and Vyndamax will be limited to product label.
- Evenity use will be limited to a 12 month period per label. In addition, concurrent use of other osteoporosis agents will not be approved.
- Zolgensma will require prior authorization with review by the Department of Health. It will be limited to indication.
- Sunosi will be limited to indication. In addition, approval will require evidence of compliance with and effectiveness of obstructive sleep apnea treatment.
- Enbrace HR will be non-preferred. Prescribers requesting this medication will be referred to the wide variety of other prenatal vitamin products that are preferred.
- Mayzent and Skyrizi will be referred to the Department of Health for cost analysis and PDL placement. Mavenclad will be non-preferred for treatment of multiple sclerosis due to safety concerns.

The proposed prior authorization criteria will be posted for public comment at [www.uwyo.edu/DUR](http://www.uwyo.edu/DUR). Comments may be sent by email to [alewis13@uwyo.edu](mailto:alewis13@uwyo.edu) or by mail to: Wyoming Drug Utilization Review Board, Dept. 3375, 1000 E. University Avenue, Laramie, WY 82071. Comments should be received prior to September 30, 2019.

The next P&T Committee meeting will be held November 14, 2019 in Cheyenne. An agenda will be posted approximately two weeks prior to the meeting.

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