

Tudorza  
(Aclidinium)  
Vs.  
Spiriva  
(Tiotropium)

Long-acting  
Anticholinergics

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## Introduction

More than 15 million Americans have Chronic Obstructive Pulmonary Disease (COPD) and it was the third leading cause of death in the United States in 2011.<sup>2,3</sup> According to the National Heart, Lung and Blood Institute, COPD kills more than 120,000 Americans each year with smoking accounting for as many as 9 out of 10 COPD-related deaths.<sup>4</sup> The number of people with COPD is increasing and it is estimated that 12 million have COPD that has not been diagnosed.<sup>4</sup> COPD is a progressive disease which includes emphysema, chronic bronchitis, and in some cases asthma.<sup>2</sup> It is characterized by chronic coughing (which may be daily and productive, but can also be intermittent and unproductive), breathlessness on exertion (initially intermittent and becoming persistent), sputum production (any pattern of sputum production may indicate COPD), and frequent exacerbations of bronchitis.<sup>5</sup> In the United States, the Centers for Disease Control and Prevention (CDC) reports that tobacco smoke is a key factor in the development and progression of COPD, but other factors such as air pollutants in the home and workplace (e.g. occupational dusts, home cooking and biomass fuels)<sup>5</sup>, genetic factors, and respiratory infections also contribute to disease progression.<sup>2</sup> According to the National Heart, Lung and Blood Institute, COPD most often occurs in people age 40 and over with a history of smoking (either current or former smokers), but as many as 1 out of 6 people with COPD have never smoked.<sup>4</sup> According to the CDC, groups that were more likely to report COPD included people aged 65–74 years, non-Hispanic whites, women, individuals who were unemployed, retired, or unable to work, individuals with less than a high school education, people with lower incomes, individuals who were divorced, widowed, or separated, current or former smokers, and those with a history of asthma.<sup>2</sup> In 2010, estimated direct costs of COPD care in the United States were \$29.5 billion (\$13.2 billion in hospital care, close to 20% in outpatient prescription drugs, 19% physician costs, 12.5% nursing home care and 4% home healthcare) and indirect costs were \$20.4 billion.<sup>6</sup>

Spirometry is considered the gold standard for accurate, reproducible, and objective measurement of lung function and it is the best way of making a definitive diagnosis of asthma and COPD.<sup>5</sup> It measures the volume of air that the patient can expel from the lungs after a maximal inspiration.<sup>5</sup> Values are compared with predicted normal values (for age, height, sex, and ethnicity) to determine the severity of airway obstruction (e.g. mild, moderate, or severe disease levels) and  $FEV_1/FVC < 70\%$  and a post-bronchodilator  $FEV_1 < 80\%$  predicted confirms the presence of airflow limitation that is not fully reversible.<sup>7</sup> Some other measures such as the Medical Research Council (MRC) dyspnea scale for measuring breathlessness, exacerbation frequency, body mass index, quality of life assessment, and exercise capacity can also be used for a better understanding of a patient's airflow status. According to the American Thoracic Society/European Respiratory Society (ATS/ERS) a change in  $FEV_1$  of  $\geq 20\%$  in short-term trials and  $\geq 15\%$  in long-term trials ( $\geq 1$  year) indicates a clinically meaningful change, and a minimum  $FEV_1$  difference of 100-140 mL from baseline is required for a COPD treatment to be considered effective.<sup>8-11</sup>

COPD is a chronic disease that is largely incurable, so the goal of management is to improve a patient's functional status and quality of life.<sup>12</sup> Initially, smoking cessation or avoidance of smoke and other air pollutants is fundamental.<sup>2</sup> According to the World Health Organization (WHO), smoking cessation is the single most effective and cost-effective way to reduce the risk of developing COPD and stop its progression.<sup>7</sup> The WHO states that brief tobacco dependence treatment is effective and recommends that every tobacco user should be offered at least this treatment at every visit to a health care provider.<sup>7</sup> COPD pharmacotherapy can alleviate symptoms such as wheezing and coughing, decrease the frequency and severity of exacerbations, and increase exercise tolerance (by acting on bronchial smooth muscle contraction, bronchial mucosal congestion and edema, airway inflammation, and increased airway secretions), but currently, no treatments (aside from lung transplantation) have been shown to significantly improve lung function or decrease mortality.<sup>2,12</sup> Also, reduction of therapy once symptom control has been achieved is not normally possible in COPD and further worsening of lung function usually requires the introduction of more treatments.<sup>7</sup> Currently, medications for COPD include beta-2 agonists (inhaled short and long-acting),

anticholinergics (inhaled short-acting and long-acting), corticosteroids (inhaled and systemic), methylxanthines and phosphodiesterase-4 inhibitors. Bronchodilators (including beta-2 agonists, anticholinergics, or theophylline) on an as-needed basis or on a regular basis provide symptomatic relief but do not alter disease progression or decrease mortality.<sup>7,12</sup> The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines note the long-term decline in lung function as a hallmark of the disease.<sup>1</sup> Up to Date states that in COPD, ipratropium is superior to the beta-agonists in short- and long-term studies of acute bronchodilation and in long-term improvement in dyspnea and quality of life, and it is preferred by many due to its minimal cardiac stimulatory effects compared to beta-agonists and its greater effectiveness (than beta-agonists and methylxanthines in most studies).<sup>13</sup> Chronic treatment with systemic glucocorticosteroids should be avoided because of an unfavorable benefit-to-risk ratio (associated with an increased risk of systemic side-effects), and inhaled glucocorticosteroids should only be prescribed for symptomatic patients with COPD with a documented spirometric response to glucocorticosteroids or for those with an FEV1 < 50% predicted and repeated exacerbations requiring treatment with antibiotics or oral glucocorticosteroids.<sup>7</sup> Oral theophylline is less effective than inhaled long-acting bronchodilators.<sup>14</sup> Patients with COPD often experience acute exacerbations of signs and symptoms which the WHO describes as another hallmark of COPD, and exacerbations and co-morbidities contribute to the overall severity of COPD in patients.<sup>7</sup> Effective treatment options for acute exacerbations include inhaled bronchodilators (particularly inhaled 2-agonists or anticholinergics), theophylline, and systemic, preferably oral, glucocorticosteroids and antibiotics for those with clinical signs of airway infection (e.g., increased volume and change of color of sputum, or fever).<sup>7</sup> Patients with COPD may also benefit from supplemental oxygen (if blood oxygen levels are low),<sup>2,7</sup> and flu or pneumonia vaccinations are recommended.<sup>2</sup> Treatment programs such as pulmonary rehabilitation teach COPD management strategies on an individualized basis (e.g. breathing strategies, energy-conserving techniques, and nutritional counseling) to increase quality of life.<sup>2</sup> It has been reported that COPD patients with poor nutritional status and low body weight are associated with impaired pulmonary status, reduced diaphragmatic mass, lower exercise capacity, and higher mortality rates.<sup>12</sup>

Until recently, Tiotropium (Spiriva – introduced in 2004) was the only inhaled long-acting muscarinic antagonist (LAMA) available in the US.<sup>15</sup> In July 2012, the second long-acting anticholinergic, aclidinium bromide (Tudorza) was approved, and it was launched in December 2012.<sup>16,17</sup> These drugs are inhaled as dry powders and they inhibit acetylcholine on the muscarinic M3 receptor in the airway smooth muscle, causing bronchodilation.<sup>18</sup> Spiriva® HandiHaler® uses individual daily capsule doses and is administered once daily, whereas Tudorza Pressair is administered using a multiple-dose dry powder inhaler (MDPI which delivers 60 doses) and it is administered as 400 micrograms twice daily.<sup>18</sup> The MDPI also known as the Pressair inhaler has some features to improve ease of use and adherence; a colored control window and audible "click" which confirm successful inhalation of the dose (it also has a slightly sweet taste), and a dose indicator to let patients know how many doses remain in the inhaler.<sup>14,18</sup> Tudorza is indicated for the long-term maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.<sup>16</sup> It is not indicated for the initial treatment of acute exacerbations (rescue therapy).

Glycopyrronium bromide (Seebri® Breezhaler®) is a long-acting muscarinic antagonist (LAMA) approved in the EU as a once-daily inhaled maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. It is also available in Canada, but not yet in the US.<sup>19,20</sup>

A summary of the current Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines will be included in this review.<sup>1</sup> This review will analyze the comparative effectiveness of aclidinium bromide for COPD and incorporate important safety information. Differences in specific patient subpopulations or indications where aclidinium bromide may be more or less effective or safer than other available treatment options will be discussed. Aclidinium bromide's potential place in therapy and potential inappropriate use (and potential clinical criteria if appropriate) will conclude this review.

## COPD therapies

Appendix 1 contains a summary comparison table of the available COPD medications in terms of classes, agents in classes, route of administration, mechanism of action, labeled indications, and notable adverse effects. Appendix 2 contains information on Tudorza (aclidinium) and Spiriva (tiotropium) in terms of uses and dosages, FDA information, and some pharmacokinetics. Tiotropium and aclidinium are longer-acting than ipratropium, but they do not have an acute bronchodilating effect.<sup>13</sup> Aclidinium is shorter acting than tiotropium.<sup>13</sup> According to Up to Date, in COPD, tiotropium provides superior long-term bronchodilation compared to ipratropium, and it reduces the frequency of exacerbations and hospitalizations, and improves dyspnea compared to long-acting beta-agonists.<sup>13</sup> Aclidinium's effectiveness is discussed in the clinical effectiveness section.

## Methodology

A Medline and Cochrane Library literature search ending in September 2013 for systematic reviews and randomized controlled trials (RCTs) for aclidinium, tiotropium, and COPD pharmacologic treatments was conducted. The Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Up To Date, the FDA website, ClinicalTrials.gov, The National Institute of Health (NIH) National Heart, Lung, and Blood Institute website, and the WHO website were searched for safety information, systematic reviews, clinical trials, and guidelines. As per the hierarchy of evidence, high quality systematic reviews and evidence based guidelines were identified first. Published phase 3 randomized controlled trials were included for aclidinium. After review of the sources, the following were examined: The GOLD guidelines<sup>1</sup>, two systematic review citations for aclidinium (of which one is a protocol<sup>14</sup> and one is a review<sup>21</sup> for which a provisional abstract was published by the Centre for Reviews and Dissemination<sup>22</sup>), and several studies on ClinicalTrials.gov with corresponding publications which included three phase 3 randomized placebo controlled clinical trials (Appendix 3: ATTAIN<sup>10</sup>, ACCORD COPD 1<sup>9</sup>, and ACCORD COPD 2<sup>23</sup>) and two crossover comparative trials<sup>24,25</sup> of aclidinium and tiotropium (appendix 4).

## Clinical Guidelines

The 2011 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines was updated in 2013.<sup>1</sup> The previous guidelines classified COPD severity by FEV1, whereas the updated guidelines included airflow obstruction, alveolar destruction and chronic inflammation in their definition.<sup>26</sup> The GOLD committee recommends assessing the patients' condition by:

- Using the Modified Medical Research Council (mMRC) questionnaire, the COPD Assessment Test (CAT), or the Clinical COPD Questionnaire (CCQ) to assess symptom burden and health status.
- Classifying patients as low or high risk for exacerbations based on their history and severity of exacerbations in the prior year.
- Assessing airflow limitation based on a patient's post-bronchodilator FEV1 (grade A, B, C, or D based on the results of this combined assessment).

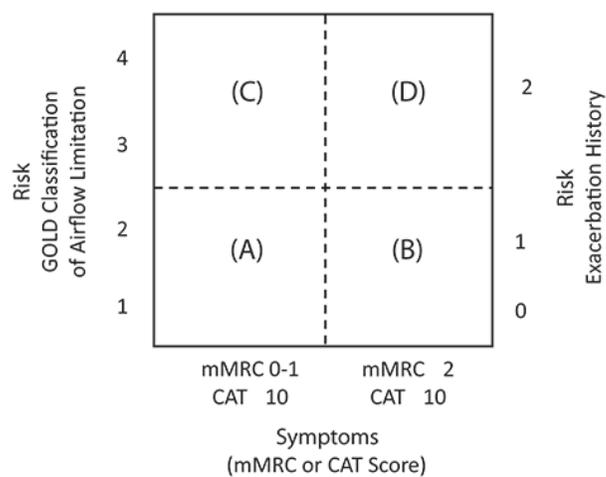
Current Global Initiative for Chronic Obstructive Lung Disease COPD (GOLD) guidelines discuss many treatment options for COPD. The preferred choice of treatment depends on the severity of symptoms and frequency of exacerbations. Classes of medication that are used include beta2-agonists, anticholinergics, methylxanthines, corticosteroids, and phosphodiesterase- 4 inhibitors.<sup>1</sup> The following table summarizes the recommended treatment based on severity of symptoms and frequency of exacerbations.

**Table 1. Pharmacological Management of COPD as per GOLD guidelines<sup>1</sup>**

Patient Group	First Line	Second Line	Other Possible Treatments
<b>A</b> (Few symptoms and low risk of exacerbations)	Short acting anticholinergic prn or Short-acting beta2- agonist prn	Long acting anticholinergic or long acting beta2-agonist or Short acting beta2agonist and short-acting anticholinergic	Theophylline
<b>B</b> (More significant symptoms and low risk of exacerbations)	Long acting anticholinergic or Long acting beta2-agonist	Long acting anticholinergic and long acting beta2-agonist	Short acting beta2 agonist and/or short acting anticholinergic  Theophylline
<b>C</b> (Few symptoms and high risk of exacerbations)	Inhaled corticosteroid with long acting beta2-agonist or Long-acting anticholinergic	Long acting anticholinergic and long acting beta2-agonist or Long acting anticholinergic and phosphodiesterase-4 inhibitor or Long acting beta 2 agonist and phosphodiesterase-4 inhibitor	Short acting beta2-agonist and/or short acting anticholinergic  Theophylline
<b>D</b> (Many symptoms and high risk of exacerbations)	Inhaled corticosteroid with long acting beta2-agonist and/or long acting anticholinergic	Inhaled corticosteroid with long acting beta2-agonist and long acting anticholinergic or Inhaled corticosteroid with long acting beta2-agonist and phosphodiesterase-4 inhibitor or Long acting anticholinergic and long-acting beta2-agonist or Long acting anticholinergic and phosphodiesterase-4 inhibitor	Carbocysteine  Short acting beta2-agonist and/or short acting anticholinergic  Theophylline

According to GOLD, none of the existing medications for COPD has been conclusively shown to modify the long-term decline in lung function.<sup>1</sup> The GOLD COPD guidelines<sup>1</sup> note that “pharmacologic therapy is used to reduce symptoms, frequency and severity of exacerbations, and improve health status and exercise tolerance.”<sup>1</sup> Bronchodilators are recommended as the standard of therapy in COPD.<sup>1</sup> Long-acting inhaled bronchodilators are preferred over short-acting formulations and should be used to reduce the occurrence of symptoms.<sup>1</sup> The choice of whether to initiate therapy with a long-acting beta<sub>2</sub>-agonist (LABA) or long-acting anticholinergic agent (long-acting muscarinic antagonist, LAMA) is left to the discretion of the physician and individual patient response. Oral theophylline has a modest bronchodilator effect and is less effective than inhaled long-acting bronchodilators.<sup>1,14</sup> According to GOLD, inhaled bronchodilators are preferred over oral bronchodilators (based on efficacy and side-effects) and theophylline is not recommended unless other long-term bronchodilators are not available or unaffordable.<sup>1</sup> In general the anticholinergics have little systemic absorption, reducing the rate at which side effects occur. The most common side effect is dry mouth. Tiotropium, a long-acting anticholinergic, has a duration of action that is greater than 24 hours. Tiotropium has been shown to be associated with improvements in lung function, symptoms, quality of life (QoL), and exacerbations but has not been shown to significantly reduce the rate of decline in FEV1.<sup>1</sup> In a systematic review, tiotropium has been shown to reduce COPD exacerbations and improve symptoms associated with the disease.<sup>27</sup> A long-term study demonstrated no effect on the rate of lung function decline when tiotropium was added to other standard therapies.<sup>28</sup> The guidelines recommend initiating either a long-acting anticholinergic or long-acting beta<sub>2</sub>-agonist in patients with a COPD severity B through D, as shown in the classification table below. The alternative choice is to initiate both classes of medications to achieve symptom relief. In GOLD patients C & D, the guidelines recommend either a long-acting beta<sub>2</sub>-agonist with inhaled corticosteroid or a long-acting anticholinergic alone. Acridinium was not mentioned or included in this guideline even though it had been approved at the time of publication. Tiotropium is the only recommended long-acting anticholinergic agent and it has been suggested that a possible reason for this could be the larger body of evidence on tiotropium.<sup>26</sup>

When assessing risk, choose the highest risk according to GOLD grade or exacerbation history



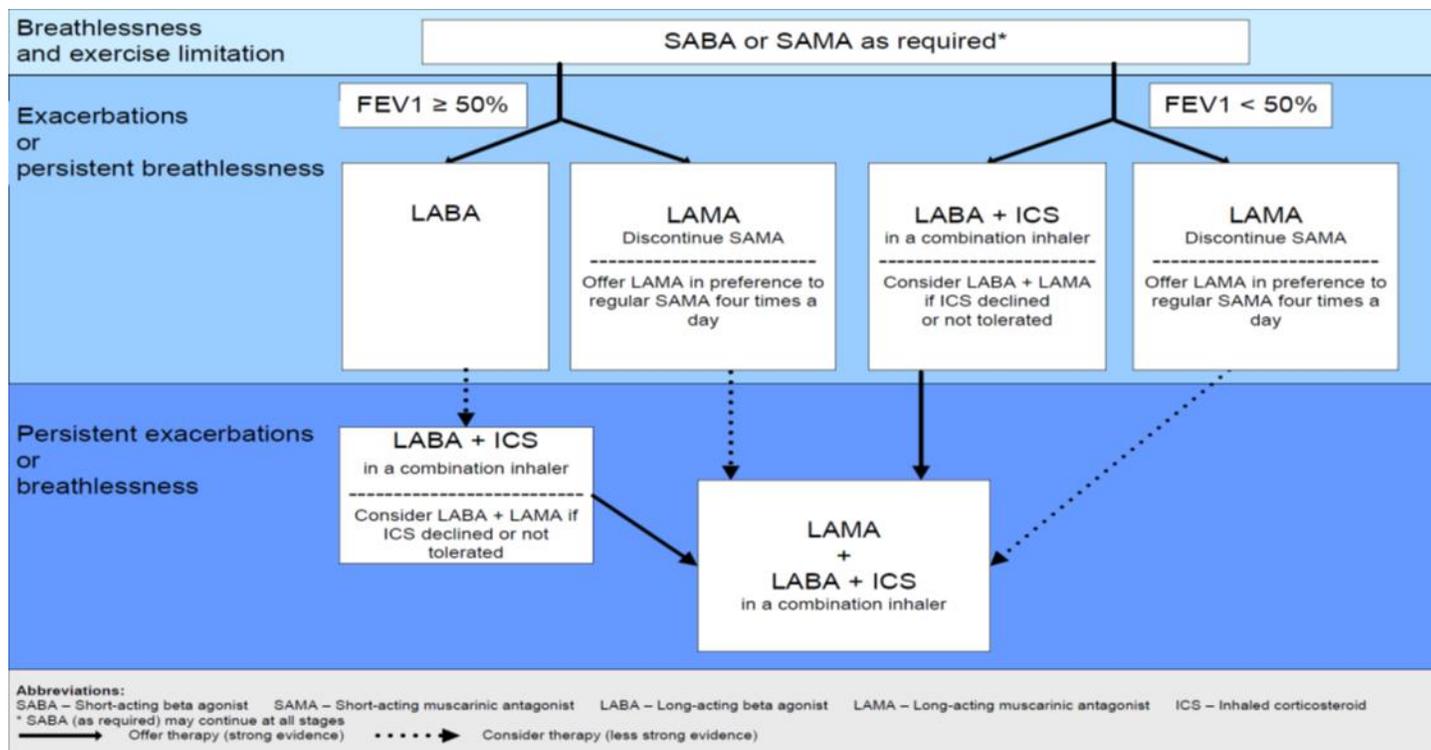
**Figure 1. GOLD guidelines: Combined assessment of COPD (from GOLD guidelines)<sup>1</sup>**

Patient Category	Characteristics	Spirometric Classification	Exacerbations Per Year	mMRC	CAT
A	Low Risk, Less Symptoms	GOLD 1-2	1	0-1	<10
B	Low Risk, More Symptoms	GOLD 1-2	1	2	10
C	High Risk, Less Symptoms	GOLD 3-4	2	0-1	<10
D	High Risk, More Symptoms	GOLD 3-4	2	2	10

The GOLD guidelines recommend that the combined use of short- or long-acting beta2-agonists and anticholinergics may be considered if symptoms are not improved by single agents.<sup>1</sup>

The National Institute for Clinical Excellence COPD guidelines (NICE clinical guideline 101)<sup>29</sup>, similarly to the GOLD guidelines, recommend initiating a LAMA, LABA, or LABA with an inhaled corticosteroid (ICS) in a combination inhaler (alone or in combination, with choice depending on several factors) in patients for control of symptoms in patients with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as needed. There is no preference given for which anticholinergic to use.

Figure 2. NICE guideline 101: Use of inhaled therapy (from NICE Guideline 101<sup>29</sup>)



## Clinical Efficacy

## Systematic Reviews

Summary information from the systematic review search results has been included in the next table (table 2).

**Table 2. Systematic Review(s) for Acclidinium**

Author	Year	Title	Objective(s)	Summary from abstract	Reason(s) provided for review/Authors' Conclusion
Ni H, et al. <sup>14</sup>	Published Online: 31 MAY 2013	Acclidinium bromide for stable chronic obstructive pulmonary disease	To assess the efficacy and safety of acclidinium bromide in stable COPD.	This is the protocol for a review and there is no abstract.	Although a long-lasting bronchodilator effect and favorable safety profile of acclidinium bromide has been shown in a number of clinical trials <sup>10</sup> , the summarized safety and efficacy profile of this agent compared to placebo, or currently established treatment options such as LABAs or LAMAs, is lacking.
Suppli Ulrik C <sup>21,22</sup>	2012	Acclidinium bromide: clinical benefit in patients with moderate to severe COPD (Provisional abstract - This is a systematic review that meets the criteria for inclusion on <i>Database of Abstracts of Reviews of Effects/DARE.</i> )	To provide an overview of the clinical studies evaluating the safety and efficacy of inhaled acclidinium bromide, a novel long-acting anticholinergic bronchodilator, for the treatment of COPD.	This review explored the efficacy and safety of acclidinium bromide in comparison with placebo and other long-acting bronchodilators for treatment of moderate to severe COPD. Ten trials (3,922 participants) were included. Acclidinium bromide appears to be a safe and well-tolerated long-acting anti-cholinergic bronchodilator with a relatively fast onset of action. Compared with other long-acting bronchodilators, including tiotropium bromide, acclidinium bromide leads to at least similar clinically important improvements in level of FEV <sub>1</sub> , health status, use of rescue medication, and day-time dyspnea scores in patients suffering from moderate to severe COPD. With twice-daily dosing, acclidinium bromide may have clinically important effect on night-time symptom scores in COPD patients, but further studies are needed in order to permit valid conclusions with regard to this point. The effect of acclidinium bromide on exercise tolerance, as assessed by exercise endurance time, and dynamic hyperinflation in patients with moderate to severe COPD seems to be at least comparable to other long-acting bronchodilators, incl. tiotropium bromide and indacaterol. Acclidinium bromide might reduce the rate of exacerbations in COPD patients, but conclusions must await further long-term controlled trials.	Acclidinium bromide has effects on relevant COPD outcome measures, including level of FEV <sub>1</sub> , similar to other long-acting bronchodilators, and therefore seems to have the potential for a significant role in the future management of moderate to severe COPD.

## Randomized Controlled Trials (RCTs) and Comparative studies (with tiotropium)

Appendix 3 contains a summary of the published randomized controlled phase 3 trials. The efficacy of acclidinium bromide in the maintenance treatment of COPD was investigated in three phase III published randomized, placebo-controlled studies including patients 40 years or older with moderate to severe COPD (FEV<sub>1</sub> <80%, ≥30%), and these studies lasted 12 and 24 weeks (ACCORD COPD I<sup>9</sup>, ACCORD COPD II<sup>23</sup>, and the ATTAIN study<sup>10</sup>). The primary endpoint in these studies was the change in baseline in morning trough FEV<sub>1</sub> and the minimum clinically important FEV<sub>1</sub> difference of 100-140 mL (required for a COPD treatment to be effective) was only seen consistently with the 400 mcg twice daily dose.<sup>8</sup> The trials did not have sufficient power to reliably determine patient-oriented outcomes such as exacerbations and also excluded patients with recent exacerbation-related hospital admissions.<sup>30</sup>

The RCTs identified were placebo-controlled and therefore information has been included on two comparative crossover studies that have been identified for acclidinium and tiotropium. In 2010, Vestbo et al<sup>24</sup> demonstrated similar clinical effects with tiotropium and acclidinium including onset to effect, increase in baseline FEV<sub>1</sub>, and the patients' perception of dyspnea. Another paper, by Fuhr et al<sup>25</sup> (randomized double-blind, double-dummy, crossover phase 2 trial), compared acclidinium to placebo and tiotropium. They found that both acclidinium and tiotropium significantly improved FEV<sub>1</sub> in patients with moderate to severe COPD compared to placebo. There was no difference between the two agents, except better response at night for patients taking acclidinium. This is likely due to the twice daily dosing of the product. Limitations of this study included a small population (n=27) and duration (15 days) per treatment arm. Additional summary information has been included in appendix 4.

Currently, there is no evidence demonstrating clinical superiority of acclidinium bromide over tiotropium. Long-term data to determine its long-term safety and effectiveness profile compared to tiotropium is also lacking.

## Safety and adverse effects

Muscarinic receptors 1,2, and 3 (M1, M2, M3) are present in the bronchial smooth muscle, but muscarinic receptors are also present as M1 receptors in the central nervous system (CNS); M2 receptors in the heart; M3 receptors in the gastrointestinal tract (GIT), iris and sphincter; M4 receptors in the neostriatum, and M5 receptors (functional role not clear).<sup>14</sup> Non-selective blockade of receptors can therefore cause systemic side-effects. Acclidinium bromide has an approximate six-fold kinetic selectivity for M3 receptors compared to M2 receptors and therefore causes more effective bronchodilator effects with fewer M2 receptor mediated cardiac side-effects.<sup>14</sup> Also, acclidinium is rapidly hydrolyzed in human plasma, unlike other currently available antimuscarinics such as tiotropium (table 4 appendix 2), and therefore has a reduced potential for systemic antimuscarinics side effects.<sup>14</sup> According to Micromedex and the Spiriva product label, tiotropium has similar affinity to muscarinic receptors M1 to M5, and in the airways it inhibits the M3-receptors at the smooth muscle leading to bronchodilation.<sup>31</sup> It was noted in the GOLD guidelines that tiotropium has an affinity for M3 and M1 receptors.<sup>1,32</sup>

Tudorza Pressair was studied in two 3-month and one 6-month placebo-controlled trials and the 400 mcg twice daily dose included 636 patients with COPD (94% Caucasian, mean FEV<sub>1</sub>=48%), 58% males, mean age=64 years).<sup>16</sup> Patients were excluded if they had unstable cardiac disease, narrow-angle glaucoma, symptomatic prostatic hypertrophy, or bladder outlet obstruction.<sup>16</sup>

In clinical trials, the most common side effects ( $\geq 3\%$  incidence and greater than placebo) reported by patients using aclidinium bromide inhalation powder included headache, inflammation of the nasal passage (nasopharyngitis), and cough.<sup>16</sup> The product label states that Tudorza Pressair may cause serious side effects, including paradoxical bronchospasm (as with any inhaled medicines), acute narrow-angle glaucoma, or new or worsened urinary retention (as with any anticholinergic).<sup>16,18</sup> Hypersensitivity reactions may occur and patients with a history of hypersensitivity to atropine (due to similar structural formula) or milk proteins should be closely monitored.<sup>16</sup> It appears to be generally well-tolerated with adverse effects in trials occurring at a rate similar to placebo. Systemic anticholinergic adverse effects should be uncommon.

There are no specific contraindications to either aclidinium or tiotropium other than hypersensitivity to the products.<sup>33-35</sup> Neither agent contains a black box warning from the FDA. Side effects for both medications are generally rare, due to limited absorption, with the most common being dry mouth, headache, and upper respiratory infection. Caution should be used when patients have concomitant conditions that may worsen with systemic anticholinergic effects. No adjustment in dosage is needed in renal impairment (no differences in aclidinium pharmacokinetics were noted), hepatic impairment (were not studied), or geriatric patients (no overall differences were noted). Only about 0.1% of aclidinium is excreted in the urine compared to 14% of tiotropium and tiotropium is therefore more likely to cause anticholinergic effects in patients with moderate to severe renal impairment.<sup>36</sup> COPD does not normally occur in children and Tudorza's safety and effectiveness have not been established in pediatric patients. There are no adequate and well-controlled studies in pregnant women, but teratogenic effects were observed in rats and rabbits, and it has been designated pregnancy category C (used only if potential benefit justifies the potential risk to the fetus).<sup>16</sup> Caution should be exercised in nursing women as excretion into human milk is probable (seen in female rats and decreased pup weights were observed).<sup>16</sup>

There are concerns regarding the cardiovascular safety of inhaled antimuscarinics bronchodilators.<sup>30</sup> It is important to note that prior to approval of Tudorza Pressair, the FDA was concerned that aclidinium may be linked to higher instances of cardiovascular deaths and they had to weigh whether safety questions concerning the medicine had been adequately assessed. In a QT study of healthy individuals, 200 and 800 mcg of aclidinium bromide inhaled once daily for 3 days had no significant QT prolonging effect.<sup>16,30</sup> In another study of 336 COPD patients (164 patients using 400 mcg aclidinium twice daily and 172 placebo), no clinically significant effects on cardiac rhythm was observed in the 3-month study period.<sup>16,30</sup> The FDA advisory panel voted 12-2 in favor of approval.<sup>17</sup> However, it has been stated by some that the data on aclidinium are insufficient to reliably detect small effects on major cardiovascular event (MACE) rates.<sup>30</sup>

The product label states that Tudorza Pressair's long-term safety was assessed in three long-term trials ranging from 40 to 52 weeks (two double blind and one open label). Of these only one was a dedicated long-term safety trial (the other two were extensions of the 3-month trials). The adverse events reported were similar to those in the short-term trials and no new safety findings were reported.<sup>16</sup>

## Place in therapy

Factors and limitations to consider when considering Tudorza Pressair's place in therapy:

- **Efficacy:** Short-term trials have shown that acclidinium is effective at improving lung function in patients with moderate to severe COPD using change in trough FEV<sub>1</sub> at 12 weeks or 24 weeks as the primary outcome. There is insufficient evidence for its effect on exacerbations and mortality. There is insufficient evidence comparing acclidinium with tiotropium (no head-to-head RCTs, only crossover design) and the limited evidence did not demonstrate clinical superiority of acclidinium bromide over tiotropium. The twice-daily dosing of acclidinium bromide may have a beneficial effect on night-time symptom scores in COPD patients, but a recent systematic review states that further studies are needed in order to permit valid conclusions with regard to this point.<sup>21</sup> Tiotropium's labeled indication includes the additional use "to reduce exacerbations".<sup>15</sup> The GOLD guidelines noted that tiotropium "reduces exacerbations, improves symptoms and health status"<sup>27</sup>, and improves the effectiveness of pulmonary rehabilitation."<sup>1,37</sup> According to GOLD, none of the existing medications for COPD has been conclusively shown to modify the long-term decline in lung function.<sup>1</sup>
- **Adverse effects:** Acclidinium appears to be generally well-tolerated with adverse effects in trials occurring at a rate similar to placebo. Systemic anticholinergic adverse effects should be uncommon (and potentially lower than other currently available inhaled antimuscarinics such as tiotropium). Tiotropium may cause anticholinergic adverse events in patients with moderate or severe renal impairment whereas there is a lesser risk with acclidinium in these patients.<sup>36</sup> With Spiriva, monitoring for anticholinergic side effects in patients with moderate to severe renal impairment (creatinine clearance of less than or equal to 50 mL/min) is recommended.<sup>31</sup> The GOLD guidelines noted that "extensive use of this class of inhaled agents in a wide range of doses and clinical settings has shown them to be very safe."<sup>1</sup>
- **Interactions with other drugs:** There is a potential for additive anticholinergic effects with concomitant anticholinergic medications, but this risk appears low with Tudorza and only slightly higher with Spiriva. The Tudorza and Spiriva product labels state that patients should avoid the use of concomitant anticholinergics and/or atropine. Anticholinergics are commonly used as sleep aids, antispasmodics (gastrointestinal and urinary), antihistamines, and ophthalmic cycloplegics and to treat Parkinson disease.<sup>31</sup>
- **Combined use of a short and long-acting anticholinergic inhalers:** The GOLD guidelines note that short-acting inhaled beta-agonists with or without short-acting anticholinergics are usually the preferred bronchodilators for treatment of an exacerbation.<sup>1</sup> In theory, competitive binding for the same muscarinic receptor sites could result in an antagonistic interaction between ipratropium and tiotropium.<sup>38</sup> Also, the concomitant use of ipratropium and tiotropium in COPD was recently reviewed and the authors concluded that "while ipratropium may provide spirometric improvements in lung function for patients receiving tiotropium maintenance therapy, the clinical significance of these improvements has not been documented and the risk of anticholinergic adverse effects is increased in combination therapy."<sup>39</sup> According to Pharmacist's Letter, many patients are getting Spiriva and ipratropium together and this is usually (but not always) a mistake.<sup>40</sup> Ipratropium could be used for about 8-10 days initially until Spiriva reaches its maximum effect.<sup>40</sup> It is important to question whether the combination is intended or duplicate therapy.<sup>40</sup> The Pharmacist Letter recommends adding albuterol to Spiriva for acute exacerbations because using two anticholinergic inhalers could increase the risk of side-effects such as dry mouth and urinary retention.<sup>40</sup> Similar recommendations could therefore apply to acclidinium.
- **Ease of use/administration:** Tudorza is dosed twice daily versus Spiriva once daily. The breath-actuated dry-powder multidose Tudorza Pressair inhaler has some features to improve ease of use and adherence; a colored control window (depress green button to release medication which will

turn the red control window green, indicating the device is ready for inhalation) and audible "click" which confirm successful inhalation of the dose (it also has a slightly sweet taste), and a dose indicator to let patients know how many doses remain in the inhaler.<sup>8,14,18</sup> It does not require priming or cleaning and is disposable.<sup>8</sup> The Spiriva HandiHaler on the other hand may be less desirable for patients with impaired dexterity. The capsules must be stored in the blister (not inhaler) and removed immediately before use.<sup>31</sup> The patient has to place a capsule into the center chamber of the HandiHaler device and has to press and release the green button on the side of the device to pierce the capsule before inhaling it through the mouthpiece.<sup>36</sup> Also, patients need to be warned not to swallow the capsule as it is for inhalation.

- Abuse potential: Anticholinergics are occasionally abused (mostly by adolescents) for their hallucinogenic effects.<sup>31</sup> This is more likely to be an issue with systemic anticholinergics.

The place of acclidinium bromide in the management of COPD cannot yet be determined due to limited published evidence on effectiveness and safety. The NICE 'Evidence summaries: new medicines' states that the publication of longer term studies comparing patient-orientated outcomes for acclidinium bromide with other active treatments for COPD would enable its place in therapy to be more clearly established.<sup>41</sup> In the meantime, it is suggested that local decision makers will need to consider the evidence for acclidinium bromide alongside that for the other treatments for COPD taking into account individual patient factors, costs, and safety profiles of each treatment.<sup>41</sup>

## Potential inappropriate use, safety concerns & potential clinical criteria

- Tudorza Pressair and Spiriva are indicated for COPD. A major differential diagnosis is asthma which usually has an onset early in life (often childhood) and symptoms vary widely from day to day, whereas COPD has an onset in mid-life with slowly progressive symptoms. Its safety and efficacy have not been established in children as COPD does not usually develop in this population.
  - ❖ Refer to utilization table (b) on page 16 and the age at first fill chart on page 17.
  - ❖ Consider a diagnosis code for COPD (i.e. in the past 2 years) and age criteria > 18 years.
  - ❖ Some plans include a diagnosis code for asthma in the past 2 years as denial criteria.
  - ❖ Some plans include<sup>42</sup>:
    - “Does the patient have a stage A diagnosis of COPD based on the GOLD Guidelines? Provide documentation of the following markers: A. Symptoms assessment scores of: mMRC score of 0-1 OR CAT less than 10; B. Less than or equal to 1 exacerbation per year.
    - Does the patient have a stage B diagnosis of COPD based on the GOLD Guidelines? Provide documentation of the following markers: A. Symptoms assessment scores of: mMRC greater than or equal to 2 OR CAT greater than or equal to 10; B. Less than or equal to 1 exacerbation per year.
    - Does the patient have a stage C diagnosis of COPD based on the GOLD Guidelines? Provide documentation of the following markers: A. Symptoms assessment scores of: mMRC score of 0-1 OR CAT less than 10; B. Greater than or equal to two exacerbations per year.
    - Does the patient have a stage D diagnosis of COPD based on the GOLD Guidelines? Provide documentation of the following markers: A. Symptoms assessment scores of: mMRC greater than or equal to 2 OR CAT greater than or equal to 10; B. Greater than or equal to 2 exacerbations per year.”<sup>42</sup>
  - ❖ Some plans include<sup>42</sup>: Has the patient failed therapy with either a short-acting anticholinergic or short-acting beta2-agonist?
  - ❖ Some plans require failure or intolerance to Spiriva, intolerability to anticholinergic side-effects of Spiriva, or dexterity limitations to manipulate the handihaler device.<sup>43,44</sup>
  - ❖ Other safety concerns - patients should be advised that:
    - Long-acting anticholinergic inhalers are NOT indicated for acute bronchospasm (rescue therapy).<sup>31</sup>
    - Spiriva capsules are for inhalation only and are not to be swallowed.<sup>31</sup>

- Tudorza<sup>45</sup> Pressair contains one month of therapy and should therefore not be filled more than once a month. Spiriva has a quantity limit of 1 in 30 days (UT Medicaid Drug Criteria and limits).
  - ❖ Consider quantity limit of 1 inhaler in 30 days for Tudorza.
  
- Tudorza should not be used with other anticholinergic medications or inhalers. Insufficient evidence exists for concurrent administration of inhaled anticholinergics and it would increase the risk of anticholinergic adverse effects.
  - ❖ Refer to utilization table (c) on page 16.
  - ❖ Consider no therapeutic duplication with overlapping days' supply between Spiriva and Tudorza.
  - ❖ Consider strategies to prevent mistakes with regards to concomitant use of short and long-acting anticholinergic inhalers.
  
- Monitoring for efficacy should begin with baseline pulmonary function tests (FEV1) and the patient should notice some relief as early as 30 minutes after the first administration. FEV1 should be measured yearly thereafter to determine disease progression (GOLD recommendation). Alternative options should be considered if symptoms do not improve or worsen or if side-effects become intolerable.<sup>8</sup>
  - ❖ Consider evidence of FEV1 annually.

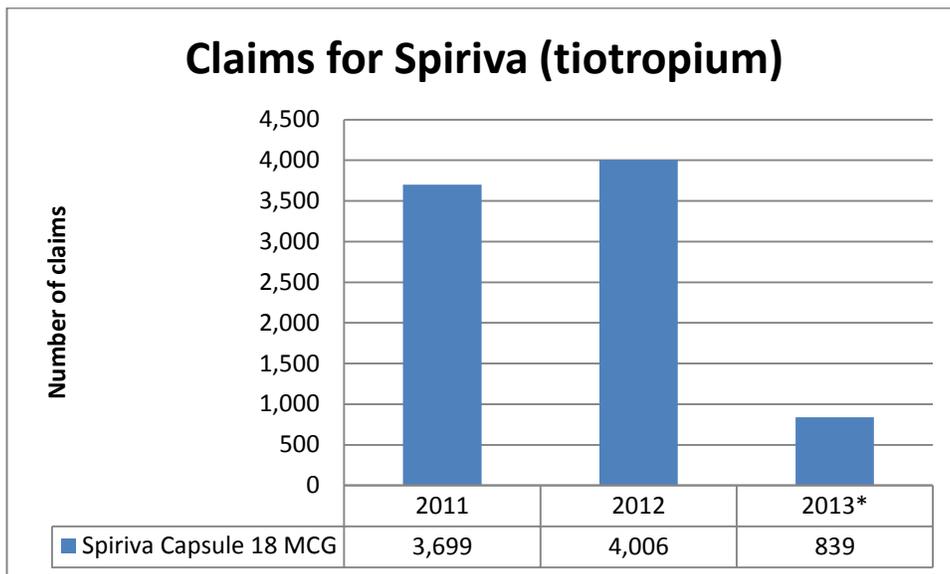
## Utah Medicaid Utilization Data

More detailed utilization data is included in appendix 5.

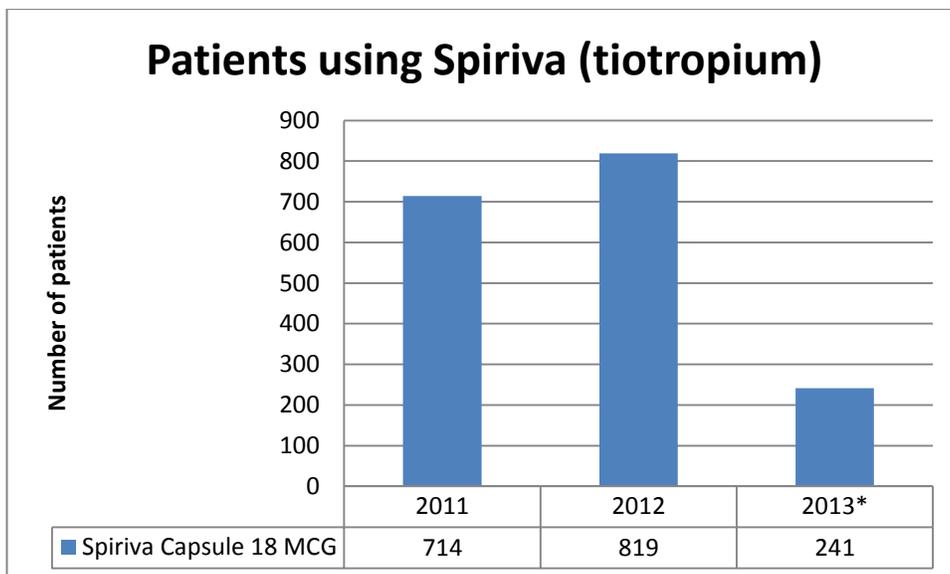
### Tudorza

Tudorza was launched in December 2012<sup>16,17</sup> so there was no utilization data for 2011, and 3 patients (3 claims) in 2012. It is important to note that our 2013 utilization data (January 1 - September 30) is for rural counties only as data for urban counties is unavailable due to significant delays in the processing of ACO claims information. In 2013 (January 1 - September 30; for rural counties), 9 patients have been filling prescriptions for Tudorza (13 claims).

### Spiriva



\*2013 data is only for rural counties



\*2013 data is only for rural counties

**(a) Diagnosis codes of patients using ipratropium**

DIAGNOSIS	ICD	2011		2012		2013*	
COPD	491-492.8 or 496	512	30%	598	33%	187	33%
Asthma without COPD	493 without 493.2	2	0%	1	0%	1	0%
Asthma and COPD	491-492.8 or 493 or 493.2 or 496	0	0%	1	0%	0	0%
<b>TOTAL PATIENTS USING IPRATROPIUM</b>		<b>1692</b>		<b>1837</b>		<b>564</b>	

\* 2013 DATA IS FOR RURAL COUNTIES ONLY, DATA FOR URBAN COUNTIES IS UNAVAILABLE DUE TO SIGNIFICANT DELAYS IN THE PROCESSING OF ACO CLAIMS INFORMATION

**(b) Diagnosis codes of patients using Spiriva (tiotropium) or Tudorza (aclidinium)**

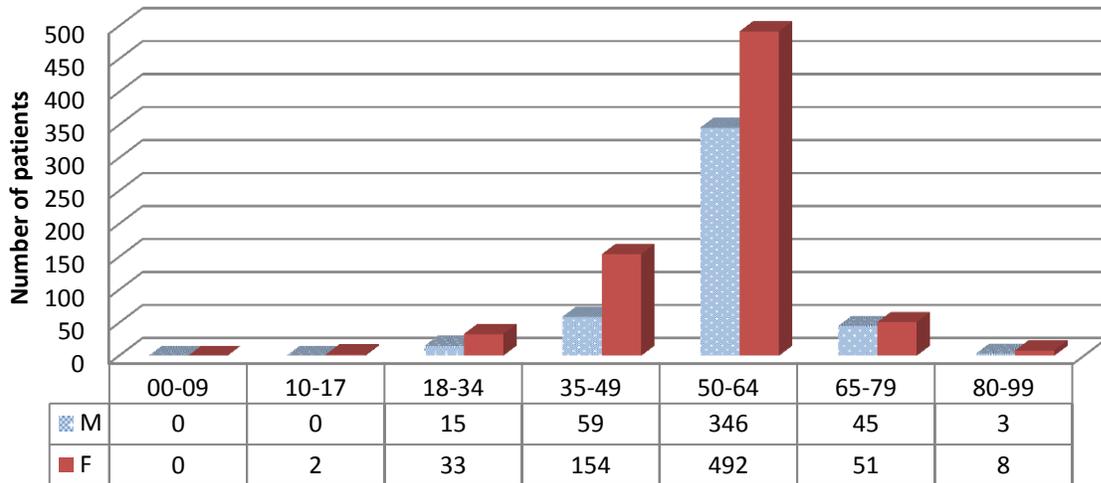
DIAGNOSIS	ICD	2011		2012		2013*	
COPD	491-492.8 or 496	518	73%	588	72%	189	76%
Asthma without COPD	493 without 493.2	2	0%	0	0%	0	0%
Asthma and COPD	491-492.8 or 493 or 493.2 or 496	0	0%	1	0%	0	0%
<b>TOTAL PATIENTS USING TIOTROPIUM OR ACLIDINIUM</b>		<b>714</b>		<b>822</b>		<b>250</b>	

\* 2013 DATA IS FOR RURAL COUNTIES ONLY, DATA FOR URBAN COUNTIES IS UNAVAILABLE DUE TO SIGNIFICANT DELAYS IN THE PROCESSING OF ACO CLAIMS INFORMATION

**(c) Concomitant use of anticholinergic inhalers**

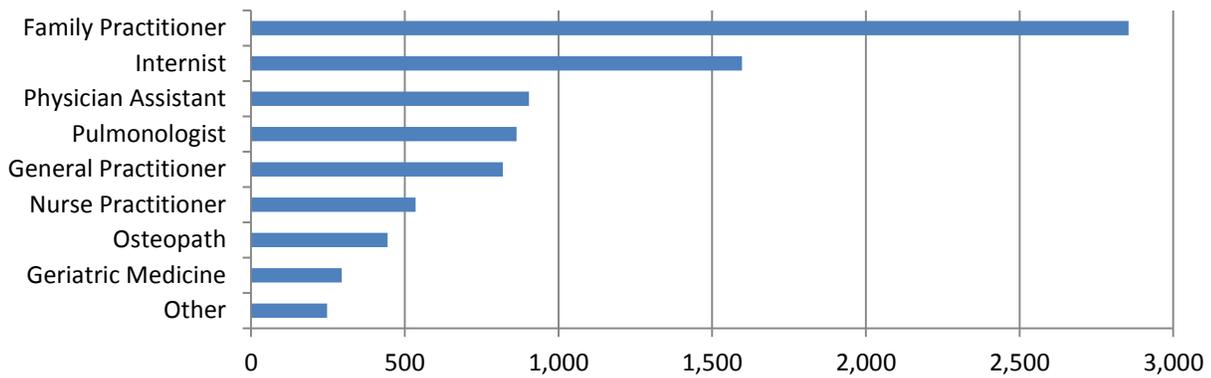
DRUG COMBINATION IN SAME MONTH (for more than one month)	PATIENTS	PERCENT
IPRATROPIUM AND TIOTROPIUM	263	21.88%
<b>TOTAL UNIQUE PATIENTS TAKING TIOTROPIUM</b>	<b>1,202</b>	
IPRATROPIUM AND ACLIDINIUM	1	8.33%
TIOTROPIUM AND ACLIDINIUM	2	16.67%
<b>TOTAL UNIQUE PATIENTS TAKING ACLIDINIUM</b>	<b>12</b>	

## Age at first tiotropium or acclidinium fill 2011-2013



At the time of their first fills, two female patients were 13 and 16, and one male patient was 18 years old.

## Prescriber types for tiotropium and acclidinium 2011-2013



## Conclusions

Tudorza has been shown to improve lung function (FEV1) and health status, reduce dyspnea, and reduce the requirement for rescue inhalers.<sup>21,22</sup> There is insufficient evidence regarding its effect on exacerbations and mortality. Its effects on lung function appear to be comparable to tiotropium, but it has not been directly compared with tiotropium in adequately designed trials. The GOLD guidelines noted that tiotropium “reduces exacerbations, improves symptoms and health status<sup>27</sup>, and improves the effectiveness of pulmonary rehabilitation”<sup>1,37</sup>, and aclidinium is not mentioned. According to GOLD, none of the existing medications for COPD have been conclusively shown to modify the long-term decline in lung function.<sup>1</sup> Long-acting beta2-agonists or long-acting antimuscarinics are the first-line maintenance therapy for moderate to severe, stable COPD.<sup>1,14</sup> There is limited published evidence for other outcomes of Tudorza such as effect on exacerbations and hospitalizations (the primary endpoint in trials has been change in trough FEV1). More data on patient oriented outcomes are needed to establish its place in therapy. Also, data comparing aclidinium bromide to tiotropium and in patients with mild or very severe disease is needed (participants in trials had moderate to severe COPD). The published trials have been short term and the long-term safety trials mentioned in the product label were ranging from 40 to 52 weeks so the real-world long term efficacy and safety of aclidinium bromide are not known.

At this stage, utilization data for Tudorza in the Utah Medicaid population is limited. Spiriva has a quantity limitation of 1 per month and the short-acting anticholinergic inhalers of 2 per month. A quantity limitation of 1 per month would be appropriate for Tudorza. Also, in the light of the utilization data showing that many patients are using more than one anticholinergic inhaler concomitantly, an overall class quantity limitation should be considered. Age criteria, COPD diagnosis code requirement, and a requirement of evidence of annual FEV1 measurements (to determine disease progression and the need for alternative options) could also be considered.

It is expected that aclidinium bromide will be used as an alternative to once daily tiotropium or a LABA.

## Appendix 1 – Medications commonly used in COPD

**Table 3. Comparison of medications used in COPD<sup>46-49</sup>**

Class	Agents in Class	Route of Administration	Mechanism of Action	Labeled Indications	Notable Side Effects
Anticholinergics (Short Acting)	Ipratropium Ipratropium/Albuterol	Inhalation	Antagonist of acetylcholine at cholinergic receptors, preventing the increase of cyclic GMP. This relaxes smooth muscle, causes bronchodilation, and reduces secretions.	COPD, nasal discharge	Xerostomia, constipation, sinusitis
Anticholinergics (Long Acting)	Aclidinium Tiotropium Glycopyrronium/Glycopyrrolate	Inhalation	Antagonist of acetylcholine at M3-receptors cholinergic receptors in smooth muscle causing bronchodilation.	COPD	Xerostomia, upper respiratory infection, constipation, sinusitis
Beta-Agonists (Short Acting)	Albuterol Albuterol/Ipratropium Levalbuterol Terbutaline	Inhalation  Oral tablets, Injection	Beta-adrenergic agonist selective for beta (2) receptors, causing smooth muscle relaxation and decreases release of hypersensitivity mediators from mast cells.	Asthma, Exercise-induced asthma, bronchospasm	Tachycardia, hypokalemia, pharyngitis, palpitations, tremor
Beta-Agonists (Long Acting)	Arformoterol Formoterol Formoterol/Budesonide Formoterol/Mometasone Indacaterol Salmeterol Salmeterol/Fluticasone Vilanterol/Fluticasone	Inhalation	Beta-adrenergic agonist selective for beta (2) receptors, causing smooth muscle relaxation and bronchodilation.	Asthma, Exercise-induced asthma, Nocturnal asthma, COPD	Musculoskeletal pain, headache, tremor, insomnia
Inhaled Corticosteroids	Beclomethasone Budesonide Budesonide/Formoterol Fluticasone Fluticasone/Salmeterol Fluticasone/Vilanterol	Inhalation	Inhibits inflammatory cells and the release of inflammatory mediators to exert potent anti-inflammatory effects.	Asthma, COPD	Headache, respiratory tract infections, pharyngitis,
Methylxanthines	Aminophylline Theophylline	Oral Tablets/Injection Oral Tablets	Bronchodilation through smooth muscle relaxation and suppression of airway stimuli. The exact MOA is not fully known, but is thought to be associated with	Acute exacerbations of Asthma, COPD	<u>Common:</u> Nausea, vomiting, Headache, insomnia, tremor, irritability,

			inhibition of two isoenzymes, phosphodiesterase 3 (PDE III) and 4 (PDE IV). Methylxanthines may also increase the force of contraction of the diaphragm through enhanced calcium uptake through adenosine-mediated channels.		restlessness. <u>Serious:</u> Atrial fibrillation, tachyarrhythmia, Stevens-Johnson syndrome, seizure, intracranial hemorrhage
<b>Systemic Corticosteroids</b>	Dexamethasone Methylprednisolone Prednisone	Oral Tablets/Injection Injection Oral Tablets	Corticosteroids exert potent anti-inflammatory effects in many organ systems by inhibiting inflammatory cells and the release of inflammatory mediators.	Allergic disorder, asthma, inflammatory disorders, exacerbation of multiple sclerosis, etc.	<u>short term use:</u> Hypertension, fluid retention, hypokalemia, weight gain, disturbance in mood, impaired glucose tolerance <u>Long term use:</u> Adrenal insufficiency, osteoporosis, hyperlipidemia, growth suppression
<b>Phosphodiesterase-4 Inhibitors</b>	Roflumilast	Oral Tablets	Inhibit phosphodiesterase 4 (PDE 4). Exact MOA is not known but is thought to be associated with increased levels of intracellular cyclic AMP in lung cells and reduced neutrophil and eosinophil cell counts in the lungs.	COPD	Weight loss, decrease in appetite, diarrhea, nausea, backache, headache, insomnia, suicidal thoughts

## Appendix 2 – COPD: Long-acting Anticholinergics

Table 4. Tudorza and Spiriva label and FDA approval information

Treatment	Generic	Indication	FDA Approval	Dosage Form(s)	Usual Dose	Maximal Recommended Dose
<b>Acclidinium</b> (Tudorza Pressair) <sup>16</sup>	No	For the long-term maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.	07/23/2012	Dry Aerosol powder: 400 mcg/Actuation	Bronchospasm in COPD: 400 mcg (one inhalation) inhaled twice daily	800 mcg/day
<b>Tiotropium</b> (Spiriva) <sup>15</sup>	No	For the long-term, once-daily, maintenance treatment of bronchospasm associated with COPD, and for reducing COPD exacerbations	01/30/2004	Capsule containing contents for inhalation: 18 mcg	Chronic Obstructive Pulmonary Disease: 18 mcg (1 capsule) via 2 inhalations daily	18 mcg/day
Treatment	Onset of action <sup>14</sup>		Duration of action <sup>14</sup>		Plasma half-life (shown in preclinical and clinical studies) <sup>14</sup>	
<b>Acclidinium</b> (Tudorza Pressair) <sup>16</sup>	30 minutes (similar to ipratropium) <sup>14</sup>		t1/2 = 29 hours (ipratropium's T1/2 = 8 hours)		Rapidly hydrolyze into two inactive metabolites in the plasma with plasma t1/2 = 2.4 minutes (ipratropium's plasma t1/2 = 96 minutes)	
<b>Tiotropium</b> (Spiriva) <sup>15</sup>	80 minutes		t1/2 = 64 hours		Plasma t1/2 > 6 hours	

## Appendix 3 – Published Acclidinium RCTs

From ClinicalTrials.gov and published trials

Trial	ATTAIN (Phase III) ClinicalTrials.gov Identifier NCT01001494	ACCORD COPD I (Phase III) ClinicalTrials.gov Identifier NCT00891462	ACCORD COPD II (Phase III) ClinicalTrials.gov Identifier NCT01045161
Publication	Jones et al. 2012 <sup>10</sup>	Kerwin et al. 2012 <sup>9</sup>	Rennard et al. 2013 <sup>23</sup>
Comparators	Acclidinium 200 mcg vs acclidinium 400 mcg vs placebo	Acclidinium 200 mcg vs acclidinium 400 mcg vs placebo	Acclidinium 200 mcg vs acclidinium 400 mcg vs placebo
Location	EU and South Africa	US, Canada, and Spain	US and Spain
Time Frame	October 2009 to November 2010	April 2009 to November 2009	December 2009 to June 2011
Objective	To assess the efficacy and safety of acclidinium 200 mg and 400 mg twice daily versus placebo over 24 weeks in patients with moderate to severe COPD.	To evaluate the efficacy and safety of 12-week twice daily acclidinium 200 mcg and 400 mcg in COPD patients.	To assess the efficacy and safety of 12 weeks of acclidinium twice-daily 200 and 400 mcg treatment in patients with moderate-to-severe COPD.
Study Design	RCT- placebo controlled, double blind, parallel group, multicenter study	RCT- placebo controlled, double blind, parallel group, multicenter study	RCT- placebo controlled, double blind, parallel group, multicenter study
Population	n = 828 randomized, with n = 819 included in final ITT and safety analyses. Patients randomized 1:1:1 to: Acclidinium 200 mcg twice daily n = 280 Acclidinium 400 mcg twice daily n = 272 Placebo twice daily n = 276  Male and female patients age ≥ 40, current or former smokers with history of ≥ 10 pack-yrs, diagnosis of COPD according to GOLD guidelines. Patients had to demonstrate good technique during lung function assessments. Inhaled salbutamol as needed was allowed, but discontinued 6 hours before and during study visits. A run-in period was utilized to assess disease severity. Baseline characteristics were fairly equal between all three groups.	n = 561 randomized, with n = 467 completing the study Patients randomized 1:1:1 to: Acclidinium 200 mcg bid n = 185 Acclidinium 400 mcg bid n = 190 Placebo twice daily n = 186  Male and female patients age ≥ 40, current or former smokers with history of ≥ 10 pack-yrs, diagnosis of moderate to severe COPD. Permitted the use of albuterol, inhaled corticosteroids, systemic steroids equivalent to 10 mg/day or less as long as treatment was stable for at least 4 weeks prior to screening. Albuterol was discontinued 6 hours before each visit, while theophylline and ICS were discontinued the morning of each visit. Baseline characteristics were fairly equal between all three groups.	n = 544 randomized, with n = 454 completing the study Patients randomized 1:1:1 to: Acclidinium 200 mcg bid n = 184 Acclidinium 400 mcg bid n = 178 Placebo bid n = 182  Same inclusion criteria as ACCORD COPD I. 400 mcg group had the greatest percentage of severe patients (p = 0.0027).
Results			
Primary Outcome	Change in trough FEV <sub>1</sub> at 24 weeks (least square mean) Acclidinium 200 mcg improved trough FEV <sub>1</sub> , compared to placebo, 99±22 mL and acclidinium	Change in trough FEV <sub>1</sub> at 12 weeks (least square mean) Acclidinium 200 mcg improved trough FEV <sub>1</sub> , compared to placebo, 86 mL and acclidinium 400	Change in trough FEV <sub>1</sub> at 12 weeks (least square mean) Acclidinium 200 mcg improved trough FEV <sub>1</sub> , compared to placebo, 51 mL and

	400 mcg improved it by 128±22 mL; p < 0.0001 for both.	mcg improved it by 124 mL; p < 0.0001 for both. These values were significantly higher than placebo at all study visits.	aclidinium 400 mcg improved it by 72 mL; p < 0.05 for both. Greater efficacy at 1, 4, and 8 weeks for both doses; p < 0.01.
Secondary Outcomes	Peak FEV <sub>1</sub> , health status (St. George's Respiratory Questionnaire, SGRQ), and dyspnea (Transitional Dyspnea Index, TDI)	Peak FEV <sub>1</sub> , SGRQ, TDI, rescue medication use, and exacerbations	Peak FEV <sub>1</sub> , SGRQ, TDI, rescue medication use, % over minimal clinically important difference (MCID)
	<p>Peak FEV<sub>1</sub> improved by baseline 185±23 mL with acclidinium 200 mcg and 209±24 mL with 400 mcg compared with placebo; p &lt; 0.0001 for both.</p> <p>SGRQ total score was -3.8±1.1 for acclidinium 200 mcg; p &lt; 0.001, and -4.6±1.1 for acclidinium 400 mcg compared with placebo; p &lt; 0.0001.</p> <p>Improvement in TDI score, compared to placebo, was 0.6±0.3 for acclidinium 200 mcg; p &lt; 0.05, and 1.0±0.3 for acclidinium 400 mcg; p &lt; 0.001. Clinically significant improvements in score (≥ 1 unit) was seen in 53.3% of those with acclidinium 200 mcg, 56.9 of those with acclidinium 400 mcg, and 45.5% of those with placebo; p &lt; 0.05 and p &lt; 0.01, respectively.</p>	<p>Peak FEV<sub>1</sub> improved by baseline 146 mL with acclidinium 200 mcg and 192 mL with 400 mcg compared with placebo; p &lt; 0.0001 for both.</p> <p>SGRQ total score at week 4 was -3.2 for acclidinium 200 mcg and -3.6 for acclidinium 400 mcg compared with placebo; p &lt; 0.0001 for both.</p> <p>Both doses produced significantly improved TDI focal scores compared with placebo at every visit, p &lt; 0.05, except acclidinium 200 mcg in week 8.</p> <p>Both doses produced a statistically, but not clinically, significant reduction in daily rescue medication use of 0.7 and 0.9 puffs/day fewer than placebo; p &lt; 0.001 and p &lt; 0.0001, respectively.</p> <p>The only significant finding in terms of COPD exacerbations was a significant reduction in any severity exacerbation with acclidinium 400 mcg versus placebo rate ratio of 0.52; p &lt; 0.009.</p>	<p>Peak FEV<sub>1</sub> improved by baseline 115 mL with acclidinium 200 mcg and 125 mL with 400 mcg compared with placebo; p &lt; 0.0001 for both.</p> <p>SGRQ improvement from baseline at week 12 was -6 for acclidinium 200 mcg and -5.4 for acclidinium 400 mcg compared with -4.3 for placebo; p &gt; 0.05.</p> <p>Both doses produced significantly improved TDI focal scores compared with placebo at week 12, p &lt; 0.05.</p> <p>No difference in rescue inhaler use, however the study was not powered to test this outcome.</p> <p>100 mL set as MCID in FEV<sub>1</sub> improvement. Acclidinium 400 mcg had 40% of subjects achieve MCID versus 25% of placebo, p &lt; 0.01.</p>
Safety	The percent of treatment-related side effects was equal between all three groups. Overall, anticholinergic side effects occurred in less than 1% of any treatment arm. The most common serious side effect was COPD exacerbation, occurring more frequently in the placebo arm (3.7% vs 1.4% and 0.7%). There were no deaths related to treatment.	Anticholinergic side effects were reported in <2% of any group. Serious side effects were similar between groups. COPD exacerbations were numerically fewer in acclidinium 400 mcg compared to 200 mcg and placebo.	Percent of patients with side effects was similar between acclidinium 400 mcg and placebo, and less with acclidinium 200 mcg. Most side effects were mild to moderate in nature. The most common serious side effect in any group was COPD exacerbation, however rates were similar between groups.
Limitations	Excluding patients with asthma or recent exacerbations reduces external validity. Follow up could be longer.	Excluding patients with asthma or recent exacerbations reduces external validity. Short duration of follow up. Nighttime symptoms were	Excluding patients with asthma or recent exacerbations reduces external validity.

		<p>reported using a non-validated instrument. Not powered or designed to assess exacerbations. Longer treatment duration would better describe safety profile.</p>	
<p>Author's Conclusion</p>	<p>Aclidinium twice daily may be an effective long-acting muscarinic antagonist therapy option for patients with stable moderate or severe COPD, with the risk-benefit profile favoring the 400 mcg dose.</p>	<p>Twice daily aclidinium 200 mcg and 400 mcg significantly improved lung function, health status, and reduced COPD symptoms. Thus, twice daily aclidinium may be an effective new treatment option for COPD patients.</p>	<p>The approved dose of twice daily aclidinium 400 mcg is an effective and well tolerated treatment option in COPD.</p>

## Appendix 4 – Evidence Table of Comparative Studies

Study	Study Design	Sample Size	Patient Population	Interventions	Outcomes	Adverse Effects
Vestbo et al. <sup>24</sup> 2012	22-center double-blind, double-dummy, crossover study	107	Adults ≥ 40 with stable COPD, post-salbutamol FEV <sub>1</sub> ≥ 30% and < 60% of predicted value, current or past history of smoking ≥ 10 pack-yr  Exclusions: Other respiratory conditions, recent exacerbation or hospitalization for COPD, clinically significant cardiovascular conditions, eosinophil count ≥ 600 cells/mm <sup>3</sup>	Three phase crossover: Acclidinium 200 mcg Tiotropium 18 mcg Placebo  Patients inhaled the medication and dummy medication once  Crossover occurred after a 5-7 day washout period	<u>% of Patients ≥ 10% above baseline FEV<sub>1</sub> at 30 min.</u> Acclidinium 49.5% Tiotropium 51.8% Placebo 13.8% p < 0.0001  Mean FEV <sub>1</sub> for acclidinium 127 mL higher than placebo p < 0.0001  Mean FEV <sub>1</sub> for tiotropium 110 mL higher than placebo p < 0.0001  <u>Perception of dyspnea</u> Acclidinium p < 0.0001 at 180 min Tiotropium p < 0.01 at 60 & 180 min	Similar side effects in all treatment arms  2 cases of anticholinergic effects after acclidinium: dizziness and dry mouth
Fuhr et al. <sup>25</sup> 2010	Phase IIa two-center, double-blind, double-dummy, placebo and active-controlled crossover study	27	Adults diagnosed with COPD according to GOLD guidelines, age ≥ 40, FEV <sub>1</sub> ≥ 30% and < 80% predicted post 400 mcg post-salbutamol, and current or ex-smokers with ≥ 10 pack-yr history  Exclusions: BMI ≥ 40, long-term oxygen therapy, past or current history of other respiratory conditions, recent MI, COPD exacerbation requiring hospitalization	Three phase crossover: Acclidinium 400 mcg twice daily Tiotropium 18 mcg daily Placebo  Patients inhaled 2 devices (medication and placebo) qam and acclidinium device (med or placebo) qpm  Crossover occurred every 15 days	<u>Change from Baseline FEV<sub>1</sub> Treatment Difference vs Placebo</u> Acclidinium 221 mL p < 0.0001 Tiotropium 244 mL p < 0.0001  <u>Relief Medication Use vs Placebo</u> Acclidinium -2.01 puffs/day p < 0.0001 Tiotropium -1.32 puffs/day p < 0.01  Acclidinium reduced breathlessness (p = 0.26), cough (p = 0.039), and nighttime symptoms (p = 0.049) vs placebo. Tiotropium p > 0.05	Acclidinium and placebo had similar number of patients with side effects (7 & 8), while tiotropium had only 3  The most common were COPD exacerbation and diarrhea  The only side effect reported in more than one patient on acclidinium was diarrhea

## Appendix 5 – Source Data

GENERIC	DESCRIPTION	2011				2012				2013*			
		CLAIMS	UNITS	DAYS	PTS	CLAIMS	UNITS	DAYS	PTS	CLAIMS	UNITS	DAYS	PTS
Acclidinium Bromide	Tudorza Aerosol Powder 400 MCG/AC	0	0	0	0	3	62	85	3	13	13	360	9
Ipratropium Bromide	Atrovent Aerosol Solution 17 MCG/ACT	618	7,416	15,285	182	615	7,398	15,514	158	203	2,436	4,945	73
Ipratropium Bromide	Atrovent Solution 0.06	0	0	0	0	2	30	35	2	0	0	0	0
Ipratropium Bromide	Ipratropium Solution 0.02	490	63,779	7,258	224	543	79,534	9,123	233	238	21,744	2,941	92
Ipratropium Bromide	Ipratropium Solution 0.03	55	1,650	1,488	40	70	2,221	1,816	48	18	540	456	10
Ipratropium Bromide	Ipratropium Solution 0.06	154	2,370	3,509	87	162	2,670	3,533	87	57	960	1,344	23
Ipratropium-Albuterol	Combivent Aerosol 0.00	2,194	31,781	54,798	563	2,242	32,711	56,695	547	70	1,100	1,810	58
Ipratropium-Albuterol	Combivent Aerosol Solution 0.00	0	0	0	0	26	104	594	10	10	40	236	8
Ipratropium-Albuterol	Duoneb Solution 0.00	30	5,442	602	11	15	1,830	240	3	1	90	7	1
Ipratropium-Albuterol	Ipratropium Solution 0.00	1,827	269,220	25,066	585	2,162	343,456	31,101	749	854	136,998	11,796	299
Tiotropium Bromide Monohydrate	Spiriva Capsule 18 MCG	3,699	111,905	110,110	714	4,006	120,212	120,027	819	839	25,170	25,170	241
		<b>9,067</b>	<b>493,563</b>	<b>218,116</b>	<b>2,406</b>	<b>9,846</b>	<b>590,228</b>	<b>238,763</b>	<b>2,659</b>	<b>2,303</b>	<b>189,091</b>	<b>49,065</b>	<b>814</b>

\* 2013 UTILIZATION DATA IS FOR RURAL COUNTIES ONLY, DATA FOR URBAN COUNTIES IS UNAVAILABLE DUE TO SIGNIFICANT DELAYS IN THE PROCESSING OF ACO CLAIMS INFORMATION

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