Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

New Drug Evaluation: Aclidinium bromide

Month/Year of Review: January 2013
Generic Name: Aclidinium bromide
PDL Class: Pulmonary- anticholinergic inhalers

End date of literature search: November 2012
Brand Name (Manufacturer): Tudorza Pressair® (Forest Pharmaceuticals)
Dossier Received: Pending

FDA Approved Indication: Aclidinium bromide is an anticholinergic indicated for the long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including bronchitis and emphysema.

Research Questions:

- Is aclidinium safe and effective in the maintenance treatment of bronchospasm associated with COPD?
- How does the efficacy and safety of aclidinium compare to currently available treatment options?
- Are there subpopulations where aclidinium is more efficacious or safer than other available agents?

Conclusions:

- There is moderate quality evidence that twice daily aclidinium is effective at improving lung function in patients with moderate to severe COPD, as measured by the trough FEV_1 after 12 and 24 weeks of treatment, compared to placebo. Trials have been short-term, and the long-term efficacy and safety of aclidinium bromide are not known.
- Published trials use the surrogate marker of change in FEV_1 to evaluate the efficacy of aclidinium, while mortality remains most desired clinical outcome. There remains insufficient evidence to determine its effects on mortality and other patient-orientated outcomes, including exacerbations.
- There are no head-to-head, phase 3 trials comparing aclidinium to tiotropium, which has more long-term data available and is dosed once daily.
- Aclidinium has an acceptable safety profile, which is similar to that of placebo. Serious adverse event rates were low, however the cardiovascular risks of aclidinium are not well defined and need to be studied in larger clinical trials.

Recommendations:

- Due to no evidence demonstrating clinical superiority of this agent over tiotropium and a lack of long-term efficacy and safety data, recommend making aclidinium non-preferred on the PDL.

Background:

Chronic Obstructive Pulmonary Disease (COPD) is the fourth leading cause of death worldwide with over 60% of the cases worldwide going undiagnosed.[1] [2] COPD is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lungs.[3] The lung parenchyma becomes damaged, causing loss of elastic recoil, which leads to emphysema, and allows for the infiltration of inflammatory cells. The most common risk factor of COPD is tobacco smoking.[1] Other risk factors include indoor air pollution and occupational dusts and chemicals, outdoor air pollution, and factors that affect lung growth during gestation and childhood. There is a genetic component to COPD linked to a deficiency in the protease inhibitor alpha 1-Antitrypsin (A1AT), which protects tissues from enzymes of inflammatory cells.[3] COPD has a higher prevalence among men and prevalence increases with age.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines provide recommendations for the diagnosis, management, and prevention of COPD. Patients are classified as mild, moderate, severe, or very severe based on the forced expiratory volume over one second (FEV_1) divided by the forced vital capacity (FVC). The diagnosis of COPD is done using spirometry and is defined as a $FEV_1/FVC < 0.70$ based on a post-bronchodilator FEV_1.[3]

Therapies for COPD include both non-pharmacologic and pharmacologic options. Smoking cessation remains one of the most important interventions. Other non-pharmacologic options are modification of occupational exposure, reducing or avoiding indoor air pollution, and participating in physical activity. Pharmacologic therapies can be an effective method to reduce the frequency and severity of COPD exacerbations. Optimal therapy must factor in the severity of disease, comorbidities, frequency and severity of exacerbations, cost, and general health status.[3] Classes of medications used to treat COPD are beta2-agonists, anticholinergics, inhaled corticosteroids, methylxanthines, systemic steroids, phosphodiesterase-4 inhibitors, vaccines, alpha-1 antitrypsin augmentation therapy, antibiotics, mucolytic agents, antitussives, and vasodilators. Those with severe COPD have the option of lung volume reduction surgery, which has shown a mortality benefit, and improvement of quality of life.

Patients with COPD have an elevated cholinergic tone which can be partially reversed with anticholinergic agents. Based on the GOLD guidelines, long-acting anticholinergics are the first or second line treatment for patients with mild or moderate COPD and are a part of the first line treatment for patients classified with severe or very severe disease.[3] Ipratropium and tiotropium are two anticholinergic agents that are used to treat COPD; tiotropium is the only long-acting anticholinergic previously available.[3] Guidelines from the National Institute for Health and Clinical Excellence (NICE) National Clinical Guideline Centre also recommend either long-acting beta2 agonist (LABA) or long acting anticholinergic in people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as required.

Aclidinium is a new long-acting anticholinergic drug that is administered twice daily. After inhalation, aclidinium selectively inhibits the muscarinic M3 receptor, which in turn causes bronchodilation. Because of its selectivity, patients using aclidinium could potentially be at lower risk for anticholinergic side effects that are a result of nonselective inhibition of muscarinic receptors.[4] Typical anticholingeric side effects include dry mouth, constipation, and urinary retention. Cardiovascular side effects are also a concern, as anticholinergic agents are associated with an increased risk for stroke, cardiovascular death, and myocardial infarction.

Aclidinium is delivered using the dry powder inhaler, Genuair, which contains 60 doses and contains a dose indicator to alert the user of how many doses remain.[4] After pressing and releasing a green button, 13mg of powder containing 400μg of aclidinium bromide and lactose carrier, is released into a chamber in

Author: Brandy Fouts, Pharm.D.

the inhaler. The control window changes from red to green and the patient should then breathe in quickly and deeply through a mouthpiece. A successful inhalation is confirmed by an audible "click".

Clinical Efficacy:

Summary

Two phase 2, double-blind, double-dummy, cross-over trials with active comparators were completed. In the phase 2a trial, patients received aclidinium 400μg, tiotropium 8μg or placebo for 15 days, with a washout between treatment periods. For the primary endpoint of mean change in FEV_1AUC (area under the curve where the numbers represent the time period for which data were collected divided by the number of hours over which the data are averaged), aclidinium and tiotropium were significantly better than placebo; treatment differences vs. placebo were 221mL and 244mL, respectively ($p<0.0001$ for both). In the phase 2b trial, patients were randomized to receive twice daily doses of aclidinium 100μg, 200μg, 400μg, formoterol 12μg or matched placebo for 7 days. For the primary endpoint of mean change from baseline in FEV_1 normalized AUC, aclidinium 400μg and formoterol were significantly better than placebo; treatment differences were 208mL and 210mL, respectively ($p<0.0001$ for both). Because of the short durations and small sample sizes (n=30 and 79), these studies will not be further evaluated.

The ACCLAIM/COPD I and ACCLAIM/COPD II studies were phase 3 studies completed that evaluated the efficacy of aclidinium. These studies used a lower dose of aclidinium than what was ultimately approved (200μg once daily was studied, 400μg twice daily was ultimately approved). In these studies, patients treated with aclidinium experienced a statistically significant improvement in lung function, although the clinical significance of the improvement in forced expiratory volume (FEV_1) was called into question by the FDA. These clinical studies with the 200 μg once daily dose will not be evaluated further because this dose is lower than the 400μg twice daily dose recommended, as well as the lack of clinically meaningful efficacy demonstrated. Two additional phase 3 studies were conducted, the ATTAIN and ACCORD COPD I studies, which evaluated the efficacy and safety of twice-daily aclidinium 200μg and 400μg versus placebo. Both studies found that treatment of moderate-to-severe COPD patients with twice-daily aclidinium of either dose was associated with significant improvements in bronchodilation, health status, and COPD symptoms. The treatment effect for the 400μg dose ranged from 61mL to 124mL across the studies at week 12.[5] A minimum clinically important difference for FEV1 has not been defined in COPD, although improvement of around 100 to 140ml has been suggested as a benchmark. Tiotropium has been shown to increase FEV1 by around 140ml compared to placebo. ACCORD COPD II is a third phase III trial evaluating efficacy and safety, however it has not been published yet and therefore cannot be appraised for quality and validity.

The ATTAIN Study

The ATTAIN study is a phase 3 study that evaluates the efficacy and safety of aclidinium bromide in 828 patients from Europe and South Africa with moderate to severe COPD. In the double-blind, placebo-controlled, multicenter, 24 week trial, patients were randomized 1:1:1 to receive aclidinium 200μg twice daily, 400μg twice daily, or placebo. All doses were administered using the multi-dose Genuair dry powder inhaler. The primary endpoint of the study was change in trough FEV_1 at week 24. Efficacy analyses were performed on the intent-to-treat (ITT) population and missing data were imputed using last observation carried forward (LOCF). Results demonstrated that the aclidinium groups showed significant improvements from baseline for FEV_1 for both the aclidinium 200μg and 400μg groups versus placebo (99 and 128 mL; both $p<0.0001$). Both treatment groups showed an improvement in peak FEV_1 from baseline (185 mL for 200μg and 209 mL for 400μg; both $p<0.001$).[7]

Author: Brandy Fouts, Pharm.D.

Quality of life and dyspnea were measured as secondary outcomes, using the St. George's Respiratory Questionnaire (SGRQ) and the Transitional Dyspnea Index (TDI) focal score. The SGRQ is a self-administered health related quality of life measure. A clinically relevant improvement in the SGRQ is defined as ≥4 points on totals score. The aclidinium clinical development program proposed a 1-unit increase as the threshold for meaningful clinical difference in TDI, however there is no regulatory precedent for this and it has not been accepted as a validated measure of dyspnea. Significant improvements were seen in the aclidinium 200μg and 400μg groups over placebo for the baseline-adjusted mean SGRQ total score (-3.8 and -4.6 units; p<0.001 for both) and TDI focal score (0.6 and 1.0 nits; p<0.05 and p<0.001) at week 24.[7] More patients had a clinically significant improvement in SGRQ total score at week 24 with aclidinium 200μg and 400μg compared to placebo (56% vs. 57.3% vs. 41%; OR 1.83 and 1.87, p<0.001 for both).

There were fewer COPD exacerbations in the treatment groups compared to placebo (15.9% 200μg, 14.1% 400μg, 20.5% placebo; p value not provided). The rate ratio was statistically significant for exacerbations of any severity for both 200μg (RR 0.72, 95% CI 0.52-0.99; p<0.05) and 400μg (RR 0.67, 95% CI 0.48-0.94; p<0.05) compared to placebo, however the difference in frequency of moderate or severe exacerbations did not reach statistical significance. Potential anticholinergic adverse events occurred with an incidence of <1% in any treatment group except for urinary tract infections, which showed a higher incidence in the higher dose treatment group (0.7% 200μg, 2.2% 400μg, 0.7% placebo).[7]

The results of the ATTAIN study show that aclidinium improves lung function in patients with moderate to severe COPD. This study showed improvements of both studied aclidinium doses over placebo for the primary endpoint change in trough FEV_1 as well as the secondary endpoints peak FEV_1, heath status (SGRQ) and dyspnea (TDI). The safety profile of aclidinium was similar to placebo. The 400μg dose performed numerically better throughout the study, but the study was not designed to find differences between doses.

ACCORD COPD I Study

The ACCORD COPD I study is a phase 3 study that evaluated the efficacy and safety of twice-daily aclidinium in 561 patients with moderate to severe COPD. In the double-blind, placebo-controlled, multicenter, 12 week trial, patients were randomized 1:1:1 to receive aclidinium 200μg twice daily, aclidinium 400μg twice daily, or placebo. The Genuair multi-dose inhaler was used to administer all doses. The primary endpoint of the study was change from baseline to week 12 in morning predose (trough) FEV_1, the average of 2 predose FEV_1 values. ACCORD COPD I found an improvement in mean trough FEV_1 compared to placebo by 86 (95% CI 45,127) mL in the aclidinium 200μg group and 124 (83,164) mL in the aclidinium 400μg group ($p \leq 0.0001$ for both). Similar improvements were seen for improvement in peak FEV_1 from baseline [146 (101,190) mL for the 200μg and 192 (148, 236) mL for the 400μg group; $p \leq 0.0001$ for both).[8]

Heath status and COPD symptoms were measured using the SGRQ and TDI respectively. Significant improvements were seen in the SGRQ for patients in the treatment groups compared to placebo at 12 weeks [-2.7 (aclidinium 200μg, p=0.013) and -2.5 (aclidinium 400μg, p=0.019)]. For TDI focal scores the difference from placebo was significant in the 200μg group of (0.9, p=005) and 400μg group (1.0, p<0.005).[8] A trend towards a reduction in the rate of moderate-to-severe COPD exacerbations per patient/year were observed with both doses compared with placebo, however these changes were not significant (p=0.130 and p=0.091, respectively).

The ACCORD COPD I study showed that aclidinium improves lung function in patients with moderate to severe COPD. Improvements were seen in peak and trough FEV_1 as well as the SGRQ and TDI scores compared to placebo. Improvements were evident the first day of treatment and were maintained during the 12-

Author: Brandy Fouts, Pharm.D.

week study. The safety profile of both doses of active drug were similar to placebo. The aclidinium 400μg group performed numerically better throughout the study.

Clinical Safety:

Adverse events were mild and similar to placebo across the phase 3 studies. There were a total of four deaths reported in the ATTAIN and ACCORD COPD I studies, three in the patients treated with aclidinium and one in patients using placebo. The causes of death were one from metastatic lung cancer in the ACCORD COPD I study.[8] In the ATTAIN study one subject died from myocardial infarction (200μg), one from acute cardiac failure (400μg), and one from a road traffic accident (placebo).[7] None of the deaths were attributed to the study drug.

Treatment groups of both doses were well tolerated during the studies. In the ACCORD COPD I study, the percentage of patients having a treatment-emergent adverse event was 44.7% in the aclidinium 400μg group, 50.5% in the aclidinium 200μg group, and 52.5% in the placebo group. Fewer COPD exacerbations were reported in the aclidinium 400μg group compared to the 200μg and placebo groups. Incidences of anticholinergic-related adverse effects were <2% in all groups. The incidence of serious adverse effects was 2.2% for placebo, 4.3% aclidinium 200μg, and 3.2% 400μg.[7]

Serious adverse events and discontinuation due to adverse events in the aclidinium studies are not concerning. The overall incidence rate was greater in the placebo group (105 events/1000 patient years) compared to 76 events/1000 patient years) in the aclidinium 400μg group. There was a wide range of events reported and most occurred in one or two patients.[5]

To assess the impact on cardiovascular health, the FDA conducted an analysis of major adverse cardiac events (MACE). The MACE score is defined as the total number of cardiovascular deaths, nonfatal myocardial infarctions, and nonfatal strokes. The results do not indicate an increased overall MACE score for aclidinium, although the assessment is limited by a relatively small sample size and a low event rate. Some of the differences seen in the studies were due to only one event, which is not enough to make a definitive conclusion. The FDA is requiring Forest Laboratories to conduct a post-marketing study of a larger sample size to address this issue.[5]

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Mortality
2) Rate of exacerbations
3) Health related quality of life
4) Dyspnea

Primary Study Endpoint:

1) Change from baseline in trough FEV_1 at weeks 12, 24, or 28 weeks
2) Peak FEV_1 at week 12

Author: Brandy Fouts, Pharm.D.

Ref./Study Design[a]	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
RCT, DB, PC, MC ATTAIN Trial 24 weeks	1. Aclidinium 200µg twice daily (200µg) 2. Aclidinium 400µg twice daily (400µg) 3. Placebo twice daily (pbo) All were administered using the Genuair inhaler Concomitant meds permitted: • inhaled corticosteroids • oral sustained-release theophyllines • systemic corticosteroids at doses equivalent to 10mg per day of prednisone or 20mg every other day • oxygen therapy (<15 h per day) • salbumatol prn (had to be discontinued 6 hours prior to and during a study visit)	Demographics (200µg, 400µg,pbo): • Age: 62.3, 62.9, 62.0 yrs • Male: 65, 68, 69% • Current Smoker: 50.5, 55.0, 52.8% • Post-bronchodilator FEV_1: 57.6, 56.2, 56.6 % predicted Inclusion Criteria: • ≥ 40 years old • Diagnosis of COPD per GOLD criteria • Post-bronchodilator FEV_1/FVC < 70% • FEV_1 <80% • ≥ 10 pack years • Good technique during lung function assessments Exclusion Criteria: • Asthma • Unstable cardiac conditions, including myocardial infarction, within the previous 6 months • Respiratory tract infection or COPD exacerbation 6 wks prior • Contraindication to anticholinergic drugs	Randomized: 200µg – 277 400µg - 269 Pbo - 273	Improvement from baseline of trough FEV_1 at 24 weeks (mean +/- SE) mL: 200µg: 99 ±22 400µg: 128 ±22 p-value: <0.0001 for both Mean peak FEV_1 from baseline with treatment versus placebo at 24 weeks: 200µg vs pbo: 185 ±23 mL 400µg vs pbo: 209 ±24 mL p-value: <0.0001 for both Improvement over placebo in baseline-adjusted mean SGRQ total score (units): 200µg vs Pbo: -3.8 400µg vs Pbo: -4.6 p-value: <0.001 for both Improvement over placebo in baseline-adjusted mean +SE TDI focal score at wee 24 (units): 200µg: 0.6 ±0.3 mL p<0.05 400µg vs Pbo: 1.0 ±0.3 mL p-value: <0.001	NA NA NA NA	Total AEs: 200µg: 54.5% 400µg: 53.5% Pbo: 57.1% p-value: Not reported SAEs: 200µg: 4.3% 400µg: 5.6% Pbo: 5.5% p-value: Not reported Deaths: 200µg: 0.4% 400µg: 0.4% Pbo: 0.4% p-value: Not reported	NA NA NA	**Quality Rating: Fair** **Internal Validity: RoB** Selection: Patients were screened during a 2 week run-in period to assess disease stability and then randomized 1:1:1 afterwards, baseline characteristics simila in all groups. Unclear on randomization technique or on adequate concealment of allocation. Performance: All three groups received doses via multiple-dose dry powder inhaler Detection: Study described as double-blind but no details given; BDI and TDI tests were administered by independent reviewers. Attrition: 14.9% placebo, 8.6% 200µg, 6.3% 400µg **External Validity:** Recruitment: Not reported. Study was conducted in 9 European countries and South Africa. Patient Characteristics: Subjects were about 62 years old with at least 65% being males in each group. Patients had to have at least 10 pack-yrs of smoking and a diagnosis of COPD and had to have good technique during lung function assessment. Patients were allowed to be on theophyllines, systemic corticosteroids and oxygen therapy (<15 h per day). Setting: Patients had to be stable for ≥4 weeks before screening Outcomes: Limited evidence for patient-orientated outcomes, data in patients with less severe disease, and data comparing aclidinium to tiotropium or long acting beta2 agonists.

Author: Brandy Fouts, Pharm.D.

RCT, DB, PC, MC ACCORD COPD I Trial 12 weeks	1. 200µg twice daily aclidinium (200µg) 2. 400µg twice daily aclidinium (400µg) 3. Placebo (Pbo) All were administered using the Genuair inhaler	Demographics (200µg, 400µg,Pbo): • Age: 63.1, 64.9, 65.1 yrs • Male: 55, 53, 52% • Current Smoker: 45.7, 42.1, 46.8% • Post-bronchodilator FEV_1: 52.8, 54.1, 54.6 % predicted Inclusion Criteria: • ≥ 40 years old • Post-bronchodilator FEV_1/FVC ≤ 70% • FEV_1 ≥30% but <80% of predicted • ≥ 10 pack years Exclusion Criteria: • Other significant respiratory conditions (including asthma) • Significant cardiovascular conditions, including myocardial infarction within the previous 6 months • Respiratory tract infection or COPD exacerbation ≤6 wks prior (≤3 months if it resulted in hospitalization) • QTc >470 msec • Medical conditions wherein anticholinergic drugs are contraindicated	Randomized: 200µg – 185 400µg - 190 Pbo -186 ITT: 200µg – 152 400µg - 166 Pbo -149 Attrition: 200µg – 17.8% 400µg – 12.6% Pbo -19.9%	Improvement from baseline of trough mean FEV_1 over placebo at 12 weeks (95% CI) mL: 200µg: 86 (45,127) 400µg: 124 (83,164) p-value: <0.0001 for both Change from baseline in peak FEV_1 over placebo at 12 weeks: 200µg: 146 (101,190) mL 400µg: 192 (148,236) p-value: <0.0001 for both Improvements over placebo in baseline-adjusted mean SGRQ total score (units) at 12 weeks: 200µg vs Pbo: -3.2 400µg vs Pbo: -3.6 p-value: <0.001 for both Improvement over placebo in baseline-adjusted mean +SE TDI focal score at week 12 (units): 200µg: 0.9 400µg vs Pbo: 1.0 p-value: <0.005 for both	NA NA NA NA	Treatment-emergent adverse effects: 200µg: 50.5% 400µg: 44.7% Pbo: 52.2% p-value: Not reported SAEs: 200µg: 4.3% 400µg: 3.2% Pbo: 2.2% p-value: Not reported Deaths: 200µg: 0 400µg: 1 patient (patient died 23 days after first drug intake and he had metastatic lung cancer – death found to be unlikely due to drug0 Pbo: 0 p-value: Not reported		**Quality Rating: Fair** **Internal Validity: RoB** Selection: Patients were randomized but not described how and no information on allocation concealment; baseline characteristics were similar in all groups Performance: All three groups received doses via multiple-dose dry powder inhaler Detection: Details on the blinding were not given Attrition: 19.9% Pbo, 17.8% 200 µg, 12.6% 400 µg **External Validity:** Recruitment: Patients were evaluated for eligibility at screening and at baseline before randomization Patient Characteristics: Baseline characteristics were similar across all groups Setting: There was a two week run in period, and the study was conducted in an outpatient setting Outcomes: Patients were instructed to take their medications between 8-10am and 8-10pm. Efficacy and safety of patients were evaluated at study visits at week 1,4,8, and 12. Limited evidence fo patient-orientated outcomes, data in patients with less severe disease, and data comparing aclidinium to tiotropium or long acting beta2 agonists.

References:

1. Decramer M, Janssens W, Miravitlles M. Chronic obstructive pulmonary disease. *The Lancet*. 2012;379(9823):1341–1351.

2. Hvidsten SC, Storesund L, Wentzel-Larsen T, Gulsvik A, Lehmann S. Prevalence and predictors of undiagnosed chronic obstructive pulmonary disease in a Norwegian adult general population. *Clin Respir J*. 2010;4(1):13–21.

3. GOLD_Report_2011_Feb21.pdf.

4. Aclidinium prescribing info.pdf.

5. FDA Summary Review.pdf. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202450Orig1s000SumR.pdf. Accessed November 21, 2012.

6. Jones PW, Rennard SI, Agusti A, et al. Efficacy and safety of once-daily aclidinium in chronic obstructive pulmonary disease. *Respiratory research*. 2011;12(1):55.

7. Jones PW, Singh D, Bateman ED, et al. Efficacy and safety of twice-daily aclidinium bromide in COPD patients: The ATTAIN study. *European Respiratory Journal*. 2012. Available at: http://erj.ersjournals.com/content/early/2012/03/22/09031936.00225511.short. Accessed November 21, 2012.

8. Kerwin EM, D'Urzo AD, Gelb AF, Lakkis H, Gil EG, Caracta CF. Efficacy and safety of a 12-week treatment with twice-daily aclidinium bromide in COPD patients (ACCORD COPD I). *COPD: Journal of Chronic Obstructive Pulmonary Disease*. 2012;9(2):90–101.

9. Cazzola M, MacNee W, Martinez FJ, et al. Outcomes for COPD pharmacological trials: from lung function to biomarkers. *European Respiratory Journal*. 2008;31(2):416–469.

Author: Brandy Fouts, Pharm.D.

Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Parameter	Result
Bioavailability	~6% (following inhalation)
Distribution	Vd of 300L following intravenous administration of 400μg
Elimination	Clearance 170 L/h, 1% excreted unchanged in the urine; after administration to healthy volunteers 54-65% of radioactivity was excreted in urine and 20-33% excreted in feces
Half-Life	5-8 hours
Metabolism	Hydrolysis both chemically and enzymatically by esterases. Not expected to alter disposition of medications, which use the CYP450 enzymes for metabolism.

DOSE & AVAILABILITY

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
400mcg	Inhalation	Twice daily	400μg	No adjustments	No adjustments	Not approved	Refer to adult dosing	

Author: Brandy Fouts, Pharm.D.

DRUG SAFETY

Serious (REMS, Black Box Warnings, Contraindications): There are no REMS programs, black box warnings, or contraindications identified for aclidinium bromide.

Warnings and Precautions:

- *Not for acute use:* Aclidinium is intended for use as a maintenance treatment for COPD and is not indicated for the initial treatment of acute episodes of bronchospasm (i.e., rescue therapy).
- *Paradoxical bronchospasm:* Inhaled medicines, like aclidinium, may cause paradoxical bronchospasm. If this occurs, treatment should be stopped.
- *Worsening of narrow-angle glaucoma:* Aclidinium should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.
- *Worsening of urinary retention:* Aclidinium should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of prostatic hyperplasia or bladder-neck obstruction (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately should any of the signs or symptoms develop.
- *Immediate hypersensitivity reactions:* Immediate hypersensitivity reactions may occur after administration of aclidinium. If such a reaction occurs, therapy should be stopped and alternative treatments should be considered. Given the similar structural formulary of atropine to aclidinium, patients with a history of hypersensitivity reactions to atropine should be closely monitored for similar hypersensitivity reactions to aclidinium. In addition, aclidinium should be used with caution in patients with severe hypersensitivity to milk proteins.

Look-alike / Sound-alike (LA/SA) Error Risk Potential:

Aclidinium may be confused with clidinium

Tudorza™ may be confused with Jolessa™, Lodosyn®, Taclonex®, Tekturna HCT®, Tekturna®, Tikosyn®, Tobrex®, Toradol®, Truvada®, Tubersol®, Zaditor®

Pressair™ may be confused with Provera®, Precose®, Primacor®

Author: Brandy Fouts, Pharm.D.