Aclidinium Bromide (Tudorza Pressair)
National PBM Drug Monograph

VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VACO PBM-SHG drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary

- Aclidinium is an inhaled long-acting anticholinergic approved for long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

- Aclidinium is administered via a breath-actuated multi-dose dry powder inhaler metering 400mcg of aclidinium per actuation. The dose is 400mcg twice daily.

- There are 3 Phase 3 trials (two 12-week and one 24-week) conducted in patients with moderate-severe COPD comparing aclidinium 200mcg and 400mcg twice daily (BID) to placebo.
  - There was significantly greater improvement in the primary endpoint, trough FEV1, with aclidinium compared to placebo (mean ranging from 72-128mL for 400mcg BID).
  - Average rescue inhaler use was reduced by 1.2-1.6 puffs/day with 400mcg BID; however, this was statistically significant vs. placebo in 2 out of the 3 phase 3 trials.
  - The improvement in the transitional dyspnea index focal score and the percentage of patients having a clinically meaningful improvement was significantly greater with aclidinium 400mcg BID than placebo. Approximately half the patients had an improvement of ≥ 1 unit in the total dyspnea score.
  - Results for improvement in quality of life score (SGRQ) were inconsistent; 2 out of 3 trials showed significant improvement over placebo.
  - The combined rate of mild/moderate/severe exacerbations was significantly lower with aclidinium 400mcg than placebo in 2 out of the 3 trials. It appears that the rate was driven by fewer mild exacerbations because the difference was not significant when considering only moderate-severe exacerbations.

- At this time the only comparisons with tiotropium or a long-acting beta-agonist are in short-term (7-15 days) phase 2 trials. Pulmonary function studies showed aclidinium to be comparable to tiotropium or formoterol.

- There are 2 extension trials from the 12-week parent trials (1 trial additional 40 weeks; 1 trial additional 52weeks) and one 52-week dedicated safety trial. Only safety results are available at this time.

- In the BID program, 1471 patients with COPD were exposed to the approved dose of 400mcg BID (mean duration 211 days). Among these, 733 were exposed for ≥ 182 days and 329 for approximately ≥ 1 year. For the unapproved 200mcg dose, 1173 patients were exposed (mean duration 170 days). Total patient years of exposure were 848.3 and 545.2 for the 400mcg and 200mcg doses respectively.

- In the short-term trials, adverse events ≥2% occurring more often with aclidinium were headache, nasopharyngitis, and cough. Other AEs ≥ 2% that were reported in the long-term trials with the 400mcg BID dose were: upper respiratory tract infection (4.7%), sinusitis (3.9%), urinary tract infection (2.9%), nausea (2.5%), arthralgia (2.2%), and peripheral edema (2.1%).

- The incidence of Major Adverse Cardiovascular Events (MACE) was low in the short-term trials (0.3% aclidinium 400BID; 0.6% placebo). The incidence was higher (2.1% aclidinium 400BID) in the long-term trials; however, there was no placebo group for comparison. The FDA reviewers did point out that the incidence rate for CV death was lower than what is reported for the general COPD population. This might be explained by the small sample size, short study duration, and the controlled nature of clinical trials.

- Disadvantages of aclidinium include need for twice daily dosing (vs. once daily with tiotropium), limited efficacy and safety data, and substantially higher cost. Advantages of aclidinium may include ease of handling device and lower inspiratory flow needed to inhale the dose of medication.

Introduction
Aclidinium is approved in July 2012 and joins tiotropium as the second long-acting inhaled anticholinergic. The frequency of administration differs between the 2 long-acting agents; aclidinium is dosed twice daily and tiotropium once daily.

Pharmacokinetics
Pharmacokinetic studies were conducted in healthy volunteers. See **Table 1.**

Table 1: Pharmacokinetics of Aclidinium

Absorption	Absolute bioavailability was 6%*
Peak plasma levels	10 minutes after inhalation*
Distribution	300L‡
Metabolism	Hydrolysis (chemical and enzymatic by esterases). Metabolites do not have pharmacologic activity
Total Clearance	170L/h (36% inter-individual variability)‡
Elimination	54-65% urine; 20-33% feces‡

*after 400mcg inhaled twice daily
‡after IV dose

FDA Approved Indication(s)
Long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

Not indicated for initial treatment of acute episodes of bronchospasm (i.e., rescue therapy)

Potential Off-Label Uses
This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

- Treatment of asthma (there are no data to support use)

Current VA Formulary Alternatives
Long-acting anticholinergic class: Tiotropium

Dosing/Administration
One oral inhalation of 400mcg twice daily

Dosage Form/Strengths and Handling
Aclidinium is administered via a breath-actuated multi-dose dry powder inhaler metering 400mcg of aclidinium per actuation. Each inhaler is preloaded with 60 doses of the drug. The inhaler has a dose indicator that shows the number of remaining doses.

Store aclidinium in a dry place at 77°F; excursions between 59-86°F are permitted. Aclidinium is supplied in a sealed aluminum pouch. The inhaler should be discarded 45 days after opening the pouch, when the indicator shows "0", or the device locks out, whichever comes first.

Device
Patients using dry powder inhalers must be able to generate adequate inspiratory force to overcome the intrinsic resistance of the inhaler An open-label, randomized, cross-over study evaluated the peak inspiratory flow (PIF) needed to inhale placebo powder via the Genuair (Pressair in the US) and Handihaler devices in patients with

moderate (n=24) or severe (n=24) COPD. Pressair and Handihaler are the devices used to deliver aclidinium and tiotropium respectively.

The average PIF of 3 attempts generated through the Pressair and Handihaler devices were 92.0±15.4L/min and 46.1±9.6L/min respectively. This shows that Pressair has a lower flow resistance than the Handihaler; therefore, a lower inspiratory effort needs to be generated to inhale the drug.

Efficacy

Initial dose finding studies evaluated aclidinium 25-400mcg once daily. It was found that the 200mcg once daily dose was similar to 400mcg once daily; therefore, the 200mcg dose was selected for Phase 3 trials. The phase 3 trials (studies 30 and 31) did not confirm 200mcg once daily as the optimal dose. The FDA suggested studying a higher dose and more frequent administration. For the purpose of this review, only the aclidinium BID studies will be reviewed for efficacy.

Pulmonary function

The primary endpoint for the phase 2 and phase 3 trials was FEV1 $AUC_{0\text{-}12h}$ and change from baseline in trough FEV1 respectively. Mean age of patients was approximately 63 years, 60% were male, and 50% were current smokers. Approximately 60% of the patients in these trials were classified as having moderate COPD and 40% as severe.

Both the phase 2 dose-finding and phase 3 trials showed a dose-dependent improvement in pulmonary function compared to placebo; however, the effect change was greater with the 400mcg dose. The phase 2 trials also included an active comparator; formoterol (Singh et al.) and tiotropium (Fuhr et al.). In these separate trials, aclidinium 400mcg twice daily was comparable to formoterol 12mcg twice daily or tiotropium 18mcg once daily with the exception that FEV1 $AUC_{12\text{-}24}$ was significantly greater with aclidinium than tiotropium. Results for other pulmonary function endpoints can be found in the **Appendix**.

Table 2: Improvement in Pulmonary Function and Rescue Inhaler Use

Study	Design	Duration	n	Treatment	FEV1 endpoints (mL)			Rescue SABA Use (puffs/d)‡
					Δ FEV1 $AUC_{0\text{-}12h}$ (diff vs. PBO)	Δ trough FEV1 (diff vs. PBO)	Δ peak FEV1 (diff vs. PBO)	
Singh 2012 Study 29	Phase 2 Dose-finding (R, DB, DD, CO)	7-days/ arm	79	ACL 100 BID	154[116, 192]*	106 [64,149]*	189[146, 232]*	-0.27
				ACL 200 BID	176[137, 215]*	114 [71, 157]*	201[158, 245]*	-0.39*
				ACL 400 BID	208[170, 247]*	154 [112, 197]*	242[199, 285]*	-0.48*
				FOR 12 BID	210[172, 249]*	148 [105, 190]*	246[203, 289]*	-0.67*
				Placebo BID	-	-	-	-
Fuhr 2012 Study 23	Phase 2 (R, DB, DD, CO)	15-days/ arm	30	ACL 400 BID	221[136, 306]*	186*	277*	-1.48*
				TIO 18 QD	244[159, 330]*	150*	251*	-0.79*
				Placebo	-	-	-	0.53
Kerwin 2012 Study 33	Phase 3 Pivotal (R, DB)	12-weeks	561	ACL 200 BID (n=185)	-	86±21*	146*	-1.4±0.1*
				ACL400 BID (n=190)	-	124±21*	192*	-1.6±0.1*
				Placebo BID (n=186)	-	-	-	-0.7±0.1
Jones 2012 Study 34	Phase 3 Pivotal (R, DB)	24-weeks	828	ACL 200 BID (n=280)	-	99±22*	185*	-0.8±0.2
				ACL 400 BID (n=272)	-	128±22*	209*	-1.2±0.2*
				Placebo BID (n=276)	-	-	-	-0.2±0.2
Study 38A	Phase 3 Supportive (R, DB)	12-weeks	544	ACL 200 BID (n=183)	-	51±22*	-	-1.3±0.2
				ACL 400 BID (n=177)	-	72±22*	-	-1.4±0.2
				Placebo BID (n=182)	-	-	-	-1.1±0.2

Abbreviations: ACL=aclidinium; BID=twice daily; CO=cross-over; DB=double-blind; DD=double-dummy; FOR=formoterol; PBO=placebo; QD=once daily; R=randomized, SABA=short-acting beta-agonist; TIO=tiotropium

*Significant versus placebo

‡For Singh et al. rescue SABA use shown as difference from placebo

Rescue Inhaler Use

Change in as needed albuterol use was significantly greater with aclidinium 400mcg than placebo. However, the difference was not significant in study 38A. In the phase 2 trial by Fuhr et al, there was no significant difference in change in albuterol use between aclidinium and tiotropium; significance between aclidinium and formoterol was not calculated in the study by Singh et al. (**Table 2**).

Dyspnea

The transitional dyspnea index (TDI) was used to assess relief of dyspnea. An improvement in score of ≥ 1 unit is considered to be clinically meaningful. The improvement in the TDI focal score and the percentage of patients having a clinically meaningful improvement was significantly greater with aclidinium 400mcg than placebo. **(Table 3)**

Health-related quality of life

Health-related quality of life was measured using the St George's Respiratory Questionnaire (SGRQ). The SGRQ is widely used in clinical trials to measure symptoms, activities, and impact of COPD on daily life as reported by patients. An improvement in score of ≥4 units is considered to be clinically meaningful. The results were inconsistent among the 3 trials. Two trials showed a statistically significant greater improvement with aclidinium than placebo for change in total score. Only 1 trial showed that the 400mcg dose resulted in a significant difference in the percentage of patients who had a clinically meaningful improvement (**Table 3**).

Table 3: Improvement in Dyspnea and Health-Related Quality of Life

Study	Duration	N	Treatment Arms	SGRQ		TDI	
				Total score	≥ 4 unit Improvement (%)	Total Score	≥ 1 unit Improvement (%)
Kerwin 2012 Study 33	12-weeks	561	ACL 200 BID (n=185)	-4.8*	49.4*	1.4*	50*
			ACL400 BID (n=190)	-4.6*	44.4	1.5*	48*
			Placebo BID (n=186)	-2.0	35.9	0.5	32
Jones 2012 Study 34	24-weeks	828	ACL 200 BID (n=280)	-5.5*	56.0*	1.2	53.3*
			ACL 400 BID (n=272)	-6.5*	57.3*	1.7*	56.9*
			Placebo BID (n=276)	-2.4	41.0	0.9	45.5
Study 38A	12-weeks	544	ACL 200 BID (n=183)	-6.0	47.2	1.0*	-
			ACL 400 BID (n=177)	-5.4	44.8	1.3*	-
			Placebo BID (n=182)	-4.3	38.8	0.3	-

ACL=aclidinium; SGRQ=St. George's Respiratory Questionnaire; TDI=transitional dyspnea index
*Significant vs. placebo

COPD Exacerbations

COPD exacerbations were defined as an increase in COPD symptoms (e.g., dyspnea, cough, sputum volume, sputum purulence) for at least 2 consecutive days. Exacerbations were classified as mild (self-managed with increased SABA and or ICS use), moderate (treated with antibiotics and/or systemic steroids; not requiring hospitalization) or severe (requiring hospitalization or ER visit).

The combined rate of mild/moderate/severe exacerbations was significantly lower with aclidinium 400mcg than placebo in 2 out of the 3 trials. It appears that the rate was driven by fewer mild exacerbations because the difference was not significant when considering only moderate-severe exacerbations. More studies of longer duration (≥ 24 weeks) are needed to examine the impact aclidinium has on exacerbation rates (**Table 4**).

Table 4: COPD Exacerbations

Study	Duration	N	Treatment Arms	COPD Exacerbations Events/pt-yr [95% CI]	
				Mild/Moderate/Severe	Moderate/Severe
Kerwin 2012 Study 33	12-weeks	561	ACL 200 BID (n=185)	0.548 [0.32, 0.94]	0.422 [0.25, 0.71]
			ACL400 BID (n=190)	0.411 [0.23, 0.74]*	0.417 [0.24, 0.71]
			Placebo BID (n=186)	0.785 [0.46, 1.33]	0.629 [0.38, 1.03]
Jones 2012 Study 34	24-weeks	828	ACL 200 BID (n=280)	0.429 [0.33, 0.55]*	0.352 [0.27, 0.45]
			ACL 400 BID (n=272)	0.404 [0.31, 0.52]*	0.342 [0.25, 0.44]
			Placebo BID (n=276)	0.600[0.48, 0.75]	0.474 [0.38, 0.60]
Study 38A	12-weeks	544	ACL 200 BID (n=183)	0.359 [0.25, 0.52]	0.285 [0.19, 0.42]*
			ACL 400 BID (n=177)	0.478 [0.35, 0.66]	0.412 [0.29, 0.58]
			Placebo BID (n=182)	0.499 [0.36, 0.69]	0.501 [0.37, 0.68]

ACL=aclindinium
*Significant vs. placebo

Long-term Trials

There are 2 extension trials (from the 3-month parent trials) and 1 dedicated safety trial (**Table 5**). As with the shorter-term trials, the long-term safety trials evaluated trough FEV1 as the primary efficacy endpoint and peak FEV1 as a secondary endpoint. Other measures of efficacy evaluated included: peak and trough FVC, rescue SABA use, and quality of life. Trial 38-B also specified COPD exacerbations as an additional efficacy assessment.
In study 36, patients who were initially randomized to aclidinium 200 and 400mcg in the parent trial remained on that dose; those who had placebo were randomized 1:1 to 200mcg and 400mcg. In study 38A, those initially randomized to 200mcg or placebo, were switched to 400mcg and those initially receiving 400mcg remained on that dose. Pooled together, there were a total of 891 patients who received 400mcg BID and 448 that received the 200mcg BID. Efficacy results were not available at this time; however, initial safety results were and are discussed in the adverse events section.

Table 5: Long-term Trials

Study	Design	Duration	Treatment Arms
Study 35	R, DB	52-weeks	ACL 200BID ACL400 BID
Study 36 (Extension trial of study 33)	R, DB	Additional 52-weeks (64 weeks total)	ACL 200BID ACL400 BID
Study 38B (Extension study of study 38A)	Open-label	Additional 40 weeks (52 weeks total)	ACL400BID

ACL=aclidinium; DB=double-blind; R=randomized

Adverse Events (Safety Data)

In the BID program, 1471 patients with COPD were exposed to the approved dose of 400mcg BID (mean duration 211 days). Among these, 733 were exposed for ≥ 182 days and 329 for approximately ≥ 1 year. For the unapproved 200mcg dose, 1173 patients were exposed (mean duration 170 days). Total patient years of exposure were 848.3 and 545.2 for the 400mcg and 200mcg doses respectively.

In a pooled-analysis of the 3 phase 3 trials, 13.6%, 11.4%, and 17.2% of patients randomized to aclidinium 200, 400, and placebo respectively did not complete the trial. Adverse event was the reason for discontinuation in 2.9%, 3.0% and 2.6% of patients respectively. In the long-term safety trials, 39% (ACL200) and 31.8% (ACL400) did not complete the trial; adverse events were the reason for discontinuation in 8.2% and 6.6% respectively.

Commonly occurring adverse events (AEs) ≥ 2% that were common to both the short-term and long-terms trials are shown in **Table 6**. Other AEs ≥ 2% that were reported in the long-term trials with the 400mcg BID dose were: upper respiratory tract infection (4.7%), sinusitis (3.9%), urinary tract infection (2.9%), nausea (2.5%), arthralgia (2.2%), and peripheral edema (2.1%). The frequency of anticholinergic-associated AEs with 400mcg BID was < 1.0% (exceptions: in the long-term studies, constipation dry mouth was 1.5% and 1.2% respectively).

In the short-term trials, pneumonia occurred in 0.6%, 0.3%, and 0.8% of patients in the aclidinium 200, 400, and placebo groups. In the long-term trials, the rates were 3.1% and 2.4% for 200 and 400 respectively.

Table 6: Adverse Events Occurring ≥ 2% Patients in any Treatment Group

	Short-Term Trials			Long-Term Trials	
	ACL200 BID (%) (n=644)	ACL400 BID (%) (n=636)	Placebo (%) (n=640)	ACL200 BID (%) (n=448)	ACL400 BID (%) (n=891)
≥1 TEAE	49.8	50.2	53.7	67.0	66.6
Non-fatal SAE	2.2	2.4	3.1	5.8	6.4
COPD	12.0	11.8	15.6	21.2	19.3
Headache	6.7	6.6	5.0	3.3	3.1
Nasopharyngitis	6.2	5.5	3.9	5.4	5.2
Cough	2.6	3.0	2.2	4.2	2.9
Diarrhea	1.9	2.7	1.4	1.6	2.1
Hypertension	1.2	1.6	2.5	2.7	2.2
Back Pain	2.8	1.3	1.9	2.0	2.7
Bronchitis	0.8	1.1	2.0	2.5	2.6

ACL=aclidinium; TEAE=treatment emergent adverse event
Data obtained from FDA review

Non-fatal Serious Adverse Events (SAEs)
In the short-term phase 3 trials, non-fatal SAEs occurred more often in the placebo group (**Table 6**). COPD exacerbation was more common in the placebo group (2.7%) compared to the aclidinium groups (1.4% 200mcg; 1.6% 400mcg). Congestive heart failure (0.0% 200mcg; 0.3% 400mcg) and angina pectoris (0.3% 200mcg; 0.2% 400mcg) were reported with aclidinium compared to none with placebo; however, the overall number of events was small.

In the long-term trials, the most commonly reported events were COPD exacerbation (2.2% 200mcg; 3.0% 400mcg), pneumonia (1.3% 200mcg; 0.7% 400mcg), acute MI (0.4% 200mcg; 0.6% 400mcg), and coronary artery disease (0.4% 200mcg, 0.6% 400mcg). Because of the lack of a placebo arm, one cannot conclude how these rates would have compared.

Deaths
Deaths that occurred while on treatment for the short-term and long-term trials are shown in **Table 7**.
In the short-term trials, there were also 2 deaths reported, one each in the 200 and 400mcg groups, after treatment was discontinued. Reasons were completed suicide (200mcg) and sepsis (400mcg). Likewise, in the long-term trials, there were 2 deaths reported after treatment was discontinued; malignant lung neoplasm (200mcg) and pneumonia (400mcg). The rate of death was greater in the 400mcg group compared to 200mcg or placebo. Several of the deaths can be categorized as being cardiovascular in nature.

Table 7: On-Treatment Deaths

	200mcg BID	400mcg BID	Placebo	Cause of Death
Short-term trials (trials 33, 34, 38A)	1 (0.2%) 5.0 per 1000 PY	3 (0.5%) 15.1per 1000 PY	2 (0.3%) 10.5 per 1000PY	200mcg: myocardial infarction 400mcg: metastatic lung cancer, acute cardiac failure, cardio-respiratory arrest Placebo: traffic accident, not stated
Long-term trials (trials 35, 36, 38B)	2 (0.4%) 5.9 per 1000PY	5 (0.6%) 7.8 per 1000 PY	N/A	200mcg: biliary sepsis, accidental multiple-drug overdose 400mcg: subarachnoid hemorrhage, esophagitis, cardiac arrest (2 pts), cardio-respiratory arrest

PY=patient-year
Data obtained from FDA review

Major Adverse Cardiovascular Events (MACE)
The MACE score was the total number of CV deaths, nonfatal, MIs, and nonfatal strokes that occurred within 30 days of the last dose of trial medication. Values for the total score and individual events are shown in **Table 8**.

The MACE score was lower with aclidinium than placebo in the short-term trials and lower in the short-term trials compared to the long-term trials. All the CV deaths occurred in the aclidinium groups; however, the FDA reviewers did point out that the incidence rate for CV death was lower than what is reported for the general COPD population. This might be explained by the small sample size, short study duration, and the controlled nature of clinical trials.

Table 8: Major Adverse Cardiovascular Events

	Short-Term Trials			Long-Term Trials	
	ACL200 BID	ACL400 BID	Placebo	ACL200 BID	ACL400 BID
n	644	636	640	448	891
MACE score	2 (0.3)	2 (0.3)	4 (0.6)	8 (1.8)	19 (2.1)
CV death	1 (0.2)	1 (0.2)	0	0	4 (0.4)
Non-fatal MI	0	0	1 (0.2)	5 (1.1)	8 (0.9)
Non-fatal stroke	1 (0.2)	1 (0.2)	3 (0.5)	3 (0.7)	8 (0.9)

ACL=aclindinium; CV=cardiovascular; MACE= Major Adverse Cardiovascular Events; MI=myocardial infarction
Data obtained from FDA review

Cardiovascular and cerebrovascular events were also analyzed using Standard MedDRA Queries (SMQs). In the short-term trials, the incidence compared favorably with placebo except for a higher rate of bradyarrhythmias and cardiac failure with the 400mcg dose. In general, the rate was higher in the long-term trials compared to the short-term ones. The FDA reviewers concluded that the overall numbers of events was low making it difficult to draw conclusions.

Table 9: Cardiovascular and Cerebrovascular SMQ Results

	Short-Term Trials			Long-Term Trials	
	ACL200 BID	ACL400 BID	Placebo	ACL200 BID	ACL400 BID
n	644	636	640	448	891
Ischemic Heart Disease	7 (1.1)	3 (0.5)	6 (0.9)	11 (2.5)	22 (2.5)
SVT	4 (0.6)	1 (0.2)	4 (0.6)	4 (0.9)	6 (0.7)
Bradyarrhythmia	6 (0.9)	10 (1.6)	5 (0.8)	18 (4.0)	12 (1.3)
Cardiac failure	1 (0.2)	5 (0.8)	2 (0.3)	2 (0.4)	8 (0.9)
CNS hemorrhage and cerebrovascular conditions	1 (0.2)	1 (0.2)	3 (0.5)	3 (0.7)	9 (1.0)

ACL=aclindinium; CNS=central nervous system; SVT=supraventricular tachyarrhythmia
Data obtained from FDA review

Contraindications

None

Warnings and Precautions

Consult product package insert for further information and instructions

- May cause paradoxical bronchospasm
- Use with caution in patients with narrow-angle glaucoma
- Worsening of urinary retention
- Immediate hypersensitivity reactions
- The formulation contains lactose monohydrate; use with caution in patients with severe hypersensitivity to mild proteins

Look-Alike/Sound-Alike (LASA) Error Risk Potential

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion.

Table 10: LASA Error Risk Potential

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Aclidinium bromide	Not assessed	None	None	Alclometasone Aliskiren
Tudorza	Not assessed	None	None	Tekturna Truvada

Drug Interactions

The potential for aclidinium and CYP450-related drug interactions is limited based on in vitro studies. As a result, no formal drug interaction studies were conducted.

There were no increases in adverse drug interactions when aclidinium was co-administered with other drugs used to treat COPD (i.e., short-acting beta-agonists, methylxanthines, and oral/inhaled corticosteroids).
Because of the potential for an additive effect when used concomitantly with other anticholinergic medications, co-administration of aclidinium with other anticholinergic-containing drugs should be avoided.

Comparative Cost

Refer to VA pricing sources for updated information.

Conclusions

Aclidinium has only been compared to placebo in the phase 3 trials. In the 3- and 6-months trials, pulmonary function improved and the rate of mild COPD exacerbations was reduced in patients treated with aclidinium 400mcg BID. Data from the longer-term trials are needed.

Comparisons to other long-acting bronchodilator drugs used to treat COPD such as tiotropium LABAs were assessed in phase 2 trials lasting 7-15 days. Pulmonary function studies showed aclidinium to be comparable to tiotropium or formoterol. Longer-term comparative data are needed.

Disadvantages of aclidinium include need for twice daily dosing (vs. once daily with tiotropium), limited efficacy and safety data, and substantially higher cost. Advantages of aclidinium may include ease of handling device and lower inspiratory flow needed to inhale the dose of medication.

References

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FDA Center for Drug Evaluation and Research. Medical Review for Aclidinium
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202450Orig1s000MedR.pdf

Appendix: Phase 3 Clinical Trials (BID dosing)

Study	Inclusion/Exclusion Criteria	Dosing	Demographics/Baseline Information	Results
Kerwin 2012 Study 33 Phase 3 (pivotal) R, DB, PC 12-weeks N=561 ITT analysis (took ≥ 1 dose and baseline and at least 1 post baseline FEV1 assessment)	**Inclusions** GOLD stage II/III moderate to severe COPD Postbronchodilator FEV1/ FVC ratio <70% at Visit 1 Postbronchodilator FEV1 ≥30% to <80% of the predicted value ≥40 years of age Current or former smokers with a smoking history ≥10 pack-years **Exclusions** Other significant respiratory conditions including asthma, respiratory tract infection or COPD exacerbation ≤ 6 weeks prescreening (≤3 months if resulting in hospitalization), chronic use of O2 ≥ 15h/day, participation in pulmonary rehab within prior 6 months, clinically significant CV conditions (including MI) during the previous 6 months, newly diagnosed arrhythmia during prior 12 months, unstable angina, unstable arrhythmia, Bazett-corrected QTc > 470msec, contraindication/ hypersensitivity to anticholinergic drugs (e.g., h/o acute urinary retention, symptomatic BPH, bladder neck obstruction, narrow-angle glaucoma), NYHA class III/IV HF requiring hosp in prior 12 months	Aclidinium 200 BID (n=185) Aclidinium 400 BID (n=190) Placebo BID (n=186) Allowable respiratory treatment: SABA, ICS, theophylline, stable dose oral prednisone ≤10mg/day or ≤20mg every other day	**Values for ACL200, 400, and PBO respectively** **Males (%):** 54.9; 52.6; 51.6 **Mean age (yrs):** 63.1; 64.9; 65.1 **Severe COPD (%):** 43.5; 35.8; 39.2 **Mean smoking history (pack-yrs):** 53.0; 57.2; 52.7 **Current smokers (%):** 45.7; 42.1; 46.8 **Pre-bronchodil FEV1 (L):** 1.35; 1.35; 1.38 **Pre-bronchodil FEV1 % pred:** 46.1; 47.5; 48.1 **Post-bronchodil FEV1 % pred:** 52.8; 54.1; 54.6 **Post-bronchodil FEV1/FVC:** 50.9; 51.5; 52.7 **Bronchodilator reversibility (%):** 16.7; 15.5; 17.1 **SGRQ total score:** 45.9; 48.3; 45.1 **BDI focal score:** 6.4; 6.2; 6.5 **COPD meds used before screening:** **SABA(%):** 64.1; 66.8; 61.3 **Long-acting anticholinergic (%):** 32.6; 27.9; 30.1 **Short-acting anticholinergic (%):** 3.8; 8.4; 2.7 **LABA (%):** 4.9; 3.2; 6.5 **ICS (%):** 6.5; 8.4; 10.2 **Combination LABA+ICS (%):** 39.7; 38.4; 34.4 **SABA+short-acting anticholinergic (%):** 0; 1.1; 0 **Xanthines (%):** 0.5; 2.6; 1.1 **Oxygen (%):** 5.4; 5.8; 6.5	

	A200 BID	A400 BID	PBO
Completed study (%)	82.2	87.4	80.1
d/c due to LOE (%)	2.7	0.5	5.4
Trough FEV1 (mL)	61±15*	99±14*	-25±15
Peak FEV1 (mL) diff from PBO	146*	192*	N/A
Trough FVC (mL)	162±23*	217±22*	-3.0±23
Peak FVC (mL)	456±26*	472±26*	194±26
Trough IC (mL)	48±23*	67±22*	-71±22
SGRQ total score	-4.7*	-4.5*	-2.0
SGRQ total score ≥4 point improvement (% pts.)	49.4*	44.4	35.9
TDI focal score	1.4*	1.5*	0.5
TDI focal score ≥ 1 unit improvement (% pts)	50*	48*	32
Nighttime symptom scores	Significantly greater improvement with A200 and A400 vs. PBO: Frequency of symptoms, severity and impact on activity, severity and impact on early AM sxs., 24h sputum production Significantly greater improvement with A400 vs.PBO: Severity and impact on sleep, nighttime sputum production		
Rescue SABA (puffs/d)‡	-1.4±0.1*	-1.6±0.1*	-0.7±0.1
COPD exacerbation Mild/mod/sev (E-pt/yr)	0.548	0.411*	0.785
COPD exacerbation Mod/sev (E-pt/yr)	0.422	0.417	0.629

Values for SGRQ total score and TDI focal score estimated from graph
*Significant vs. PBO

Appendix continued

Study	Inclusion/Exclusion Criteria	Dosing	Demographics/Baseline Information	Results
Jones 2012 Study 34 Phase 3 (pivotal) R, DB, PC 24-weeks N=828 ITT analysis (took ≥ 1 dose and baseline and at least 1 post baseline FEV1 assessment)	See Kerwin et al. 2012	Aclidinium 200 BID (n=280) Aclidinium 400 BID (n=272) Placebo BID (n=276) Allowable respiratory treatment: SABA, ICS, sustained-release theophylline, stable dose oral prednisone ≤10mg/day or ≤20mg every other day, O2 therapy < 15hours/day	**Values for ACL200, 400, and PBO respectively** **Males (%):** 65.3; 67.7; 69.2 **Mean age (yrs):** 62.3; 62.9; 62.0 **Severe COPD (%):** 30.4; 31.3; 34.1 **Mean smoking history (pack-yrs):** 40.0; 41.7; 38.9 **Current smokers (%):** 50.5; 55.0; 52.8 **Pre-bronchodil FEV1 (L):** 1.49; 1.48; 1.48 **Pre-bronchodil FEV1 % pred:** 52.0; 51.2; 51.5 **Post-bronchodil FEV1 % pred:** 57.6; 56.2; 56.6 **SGRQ total score:** 46.3; 47.6; 45.1 **BDI focal score:** 7.0; 6.7; 6.7 **SABA use (puffs/day):** 3.3; 3.5; 3.8 **COPD meds used before screening:** **SABA(%):** 48.7; 52.4; 50.2 **Long-acting anticholinergic (%):** 31.0; 28.6; 21.2 **Short-acting anticholinergic (%):** 16.2; 15.2; 16.5 **LABA (%):** 27.8; 30.1; 33.0 **ICS (%):** 35.0; 37.2; 42.1 **Combination LABA+ICS (%):** 13.4; 14.1; 15.4 **SABA+short-acting anticholinergic (%):** 11.6; 11.2; 10.7 **Xanthines (%):** 22.4; 18.6; 21.6 **Other (%):** 4.3; 4.8; 4.0	**A200 BID / A400 BID / PBO** Completed study (%): 90.4 / 92.6 / 84.1 d/c due to LOE (%): 0.7 / 0 / 2.9 Trough FEV1 (mL): 26±16* / 55±16* / -73±16 Peak FEV1 (mL) diff from PBO: 185±23* / 209±24* / N/A Trough FVC (mL): 62±24* / 131±27* / -86±26 Peak FVC (mL) Trough IC (mL): -10±20* / 41±22* / -72±22 SGRQ total score: -5.5* / -6.5* / -2.4 SGRQ total score ≥4 point improvement (% pts.): 56.0* / 57.3* / 41.0 TDI focal score: 1.2 / 1.7* / 0.9 TDI focal score ≥ 1 unit improvement (% pts): 53.3* / 56.9* / 45.5 Rescue SABA (puffs/d): -0.8±0.2 / -1.2±0.2* / -0.2±0.2 COPD exacerbation Mild/mod/sev (E-pt/yr): 0.429* / 0.404* / 0.60 COPD exacerbation Mod/sev (E-pt/yr): 0.352 / 0.342 / 0.474 *Significant vs. PBO
Study 38A Phase 3 (supportive) R, DB 12- weeks N=544	See Kerwin et al.	Aclidinium 200 BID (n=183) Aclidinium 400 BID (n=177) Placebo BID (n=182)	**Values for ACL200, 400, and PBO respectively** **Moderate COPD (%):** 52.2; 44.6; 62.1 **Severe COPD (%):** 46.7; 54.2; 36.8 **Pre-bronchodil FEV1 (L):** 1.39; 1.26; 1.45	**A200 BID / A400 BID / PBO** Trough FEV1 (mL): 43±15* / 64±16* / -8.0±15 Trough FVC (mL): 99±25* / 152±25* / 31±25 Trough IC (mL): 44±22* / 72±23* / -42±22 SGRQ total score: -6.0 / -5.4 / -4.3 SGRQ total score ≥4 point improvement (% pts.): 47.2 / 44.8 / 38.8 TDI focal score: 1.0* / 1.3* / 0.3 Rescue SABA (puffs/d): -1.3±0.2 / -1.4±0.2 / -1.1±0.2 COPD exacerbation Mild/mod/sev (E-pt/yr): 0.359 / 0.478 / 0.499 COPD exacerbation Mod/sev (E-pt/yr): 0.285* / 0.412 / 0.501 *Significant vs. PBO