

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202450Orig1s000**

**OFFICE DIRECTOR MEMO**

## Summary Basis for Regulatory Action

<b>Date</b>	July 23, 2012
<b>From</b>	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
<b>Subject</b>	Summary Review
<b>NDA/BLA #</b>	202450
<b>Supp #</b>	
<b>Applicant Name</b>	Forest Laboratories
<b>Proprietary / Established (USAN) Names</b>	Tudorza Pressair (aclidinium bromide inhalation powder)
<b>Dosage Forms / Strength</b>	400 mcg inhalation powder BID
<b>Proposed Indication(s)</b>	Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema
<b>Action:</b>	<i>Approval</i>

### 1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding aclidinium bromide. Please refer to the action package for other reviews containing more detailed discussion. Aclidinium is a new molecular entity (NME) belonging to the subclass of long-acting antimuscarinics (LAMA) seeking an indication for bronchospasm associated with COPD.

Aclidinium bromide belongs to the anticholinergic class of drugs and is considered an M3 antagonist. There are several drug classes available for the treatment of COPD, including anticholinergic agents, beta-adrenergic agonists, PDE-4 inhibitors, and various combinations of beta-adrenergic agonists with anticholinergics or inhaled corticosteroids.

Other currently available anticholinergics for COPD include ipratropium bromide (short-acting) and tiotropium (long-acting; Spiriva Handihaler). As Dr. Limb discusses, anticholinergic agents have well-recognized common side-effects, but there has been some added concern regarding possible cardiovascular (CV) effects based on a meta-analysis of 17 clinical trials in COPD.<sup>1</sup> This concern was lessened in some part with the conclusion of the UPLIFT<sup>2</sup> study which contradicted the findings of the meta-analysis and has given reassurance with Spiriva Handihaler. However, to confuse the issue further, an alternate tiotropium formulation delivered by the Respimat device, which is not approved in the US, has demonstrated numerical imbalances in all-cause mortality over placebo with no specific cause of death standing out. Presently, a large, prospective safety trial is underway to further evaluate potential CV risks with tiotropium Respimat.

<sup>1</sup> Singh S, et al. JAMA 2008; 300:1439-50.

<sup>2</sup> Tashkin DP, et al. NEJM 2008 ; 359 :1543-54.

Acclidinium bromide demonstrated efficacy and the safety profile is consistent with other approved anticholinergic drugs in this class. I agree with the review team that this application should receive an Approval action.

### Efficacy

Efficacy and safety are based on three trials, Trial 33, 34 and 38A. All were of similar design and included acclidinium bromide 400 mcg BID, acclidinium bromide 200 mcg BID, and placebo in subjects with moderate to severe COPD. Results are summarized in the table below from Dr. Chowdhury's review (Page 6).

**Table 1. Change from baseline in trough FEV1 (L) at week 12 (LOCF in ITT population)**

	n	Baseline Mean *	Change from Baseline † LS Mean	Treatment Different from placebo ‡		
				LS Mean	95% CI	p-value
<b>Study 33 or Trial B</b>						
Tudorza Pressair 400 mcg BID	19 0	1.33	0.10	0.12	0.08, 0.16	<0.001
Tudorza Pressair 200 mcg BID	18 4	1.36	0.06	0.09	0.04, 0.13	<0.001
Placebo	18 5	1.38	-0.02			
<b>Study 38 A or Trial C</b>						
Tudorza Pressair 400 mcg BID	17 7	1.25	0.06	0.07	0.03, 0.12	0.001
Tudorza Pressair 200 mcg BID	18 2	1.40	0.04	0.05	0.01, 0.09	0.019
Placebo	18 2	1.46	-0.01			
<b>Study 34 or Trial D ‡</b>						
Tudorza Pressair 400 mcg BID	26 9	1.51	0.06	0.11	0.07, 0.14	<0.001
Tudorza Pressair 200 mcg BID	27 7	1.51	0.03	0.08	0.04, 0.12	<0.001
Placebo	27 3	1.50	-0.05			
* Mean baseline scores are calculated based on observed data. † P-value, LS mean, and LSMD were obtained from an ANCOVA model with change from baseline in trough FEV <sub>1</sub> as response, with treatment group and sex as factors and baseline trough FEV <sub>1</sub> and age as covariates. Last observation carried forward (LOCF) approach was applied to missing data. Similar findings were observed when Mixed Model Repeated Measures analysis was applied to the data ‡ In the 6-month Study 34 (Trial D), placebo-adjusted change from baseline in trough FEV <sub>1</sub> at 24 weeks was 0.13 (0.09, 0.17).						

Secondary measures of respiratory function were similar to the results above and favorable for acclidinium compared to placebo.

Changes in St. George’s Respiratory Questionnaire (SGRQ) demonstrated numerically greater decreases in total score for acclidinium compared to placebo, although a treatment difference exceeding the minimally important different of 4 units was not consistently observed. COPD exacerbations, while an imprecise measure that relies on individual investigator discretion, also demonstrated trends in favor of acclidinium use as did rescue medication use.

Acclidinium bromide demonstrated replicated, statistically significant differences between acclidinium bromide 400 mcg BID and placebo for the primary endpoint. Secondary endpoints also demonstrated trends supporting efficacy. Acclidinium bromide has demonstrated efficacy for the proposed indication.

### Safety

As mentioned above, CV concerns have been noted for anticholinergic drugs used in the treatment of COPD patients. There were few events noted in the application and the controlled trial data and uncontrolled long-term extension data are summarized below in tables from Dr. Limb’s review (Page 17).

<b>Table 1 MACE score: Placebo-controlled trials</b>						
	<b>Placebo N=641 ET=190.6</b>		<b>Acclidinium 200 N=644 ET=199.4</b>		<b>Acclidinium 400 N=636 ET=198.4</b>	
	<b>n (%)</b>	<b>Incidence Rate</b>	<b>n (%)</b>	<b>Incidence Rate</b>	<b>n (%)</b>	<b>Incidence Rate</b>
<b>MACE Score</b>	4 (0.6)	21.0	2 (0.3)	10.0	2 (0.3)	10.1
<i>CV Death</i>	0	0	1 (0.2)	5.0	1 (0.2)	5.0
<i>Non-fatal myocardial infarction</i>	1 (0.2)	5.2	0	0	0	0
<i>Non-fatal stroke</i>	3 (0.5)	15.7	1 (0.2)	5.0	1 (0.2)	5.0

Note: N=number of patients in the Safety Population; ET=total exposure time in years; n=number of patients in the specific category. Percentages are calculated as 100 x (n/N). Incidence Rate (IR)=n/ET\*1000.

<b>Table 2 MACE score: Long-term safety trials</b>				
	<b>Acclidinium 200 N=448 ET=340.6</b>		<b>Acclidinium 400 N=891 ET=644.2</b>	
	<b>n (%)</b>	<b>Incidence Rate</b>	<b>n (%)</b>	<b>Incidence Rate</b>
<b>MACE Score</b>	8 (1.8)	23.5	19 (2.1)	29.5
<i>CV Death</i>	0	0	4 (0.4)	6.2
<i>Non-fatal myocardial infarction</i>	5 (1.1)	14.7	8 (0.9)	12.4
<i>Non-fatal stroke</i>	3 (0.7)	8.8	8 (0.9)	12.4

Note: N=number of patients in the Safety Population; ET=total exposure time in years; n=number of patients in the specific category. Percentages are calculated as 100 x (n/N). Incidence Rate (IR)=n/ET\*1000.

The data above neither confirms or repudiates any contribution of acclidinium bromide to CV risk as there are too few events.

Adverse events were low in incidence and there was not a signal of imbalance in serious adverse events. However, the database is small and the limited number of events prohibits any definitive conclusions. Dr. Limb opined that the number of CV deaths during the placebo controlled phase and long-term data suggests a possible dose-dependent CV death effect. For the placebo controlled phase, there was one death in each of the acclidinium bromide arms compared to none in the placebo group. This is too few events to make any conclusions. For the long-term extension, while I agree the percentages are different (1.8% acclidinium bromide 200 vs. 2.1% for acclidinium bromide 400), changing one death between groups gives identical percentages of events. I do not find this very compelling but it is the quandary we face with limited numbers of events and we must always be careful not to over- (or under) interpret results. I agree that an outcome trial should shed further light on the issue.

The adverse events were low in incidence and for the most part reflect what would be expected from this category of drug.

### **Advisory Committee Meeting**

A meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) was convened February 23, 2012. Dr. Limb has a nice summary of the meeting in her review. For the overall question regarding approval, the committee voted 12 yes, 2 no.

### **Conclusions and Recommendations**

Acclidinium bromide has demonstrated efficacy on the clinical endpoint of 12-hour post-dose trough FEV1 after 12-weeks of therapy. Secondary endpoints trended in a favorable direction. Adverse events were low and expected for the drug class. I do not find the CV events in the application of a sufficient number to make any conclusions. However, pending the final results of the Respimat safety study discussed above, it is not unreasonable to be concerned that different types of formulations, or anticholinergics, may have different effects on the cardiovascular system. As such, and considering that we have required outcome studies for a variety of drugs used in a variety of disorders, it is reasonable to require a study that generates enough events upon which to form conclusions. I do not find the data compelling enough to require an outcome study prior to approval.

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/s/  
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CURTIS J ROSEBRAUGH  
07/23/2012