CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202450Orig1s000

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	July 20, 2012
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology, Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	202450, SN000
Applicant Name:	Forest Pharmaceuticals, Inc.
Date of Submission:	June 23, 2011
PDUFA Goal Date:	July 23, 2012 (original goal date was April 23, 2012)
Proprietary Name:	Tudorza Pressair
Established Name:	Aclidinium bromide
Dosage form:	Inhalation Powder
Strength:	Aclidinium bromide 400 mcg
Proposed Indications:	Chronic Obstructive Pulmonary Disease
Action:	Approval

1. Introduction

Forest Pharmaceuticals submitted this 505(b)(1) new drug application for use of Tudorza Pressair (aclidinium bromide inhalation powder) for the long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. The proposed dose is one inhalation of Tudorza Pressair 400 mcg twice daily. The application is based on clinical efficacy and safety studies. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

Forest Pharmaceuticals submitted an amendment on March 15, 2012, containing corrected tables and datasets pertaining to a key secondary efficacy variable, the St. George's Respiratory Questionnaire (SGRQ). Since the SGRQ data provide an important alternative assessment of efficacy that is independent of spirometry, the submission was considered to be a major amendment, and the review clock was extended by three months.

2. Background

There are several drug classes available for the relief of airflow obstruction in patients with COPD. These include beta-2 adrenergic agonists, anticholinergic agents, combination products containing beta-2 adrenergic agonists and anticholinergic agents, combination products containing long-acting beta-2 adrenergic agonists and inhaled corticosteroids, and methylxanthines. Aclidinium is a new molecular entity and is categorized as an anticholinergic agent, specifically an M3 muscarinic receptor antagonist. Due to its duration of action and its specific action on muscarinic receptors, aclidinium belongs to the subclass of long-acting antimuscarinic agents (LAMAs).

Inhaled anticholinergic agents are widely used in the US and worldwide. In the US, a short-acting anticholinergic, ipratropium bromide, has been approved as a bronchodilator for patients with COPD since 1986. A long-acting anticholinergic, tiotropium bromide (Spiriva HandiHaler), has been available in the US since 2004. Inhaled anticholinergic agents are associated with adverse events expected due to their pharmacology, such as dry mouth, constipation, and urinary retention. There are also potential safety concerns with anticholinergic agents regarding risk of stroke, cardiovascular death, and myocardial infarction (MI) in patients with COPD using tiotropium. A meta-analysis of 17 clinical trials with tiotropium showed potential for such a signal,[1] however, a large 4-year controlled trial with tiotropium (UPLIFT) did not show such a safety signal.[2, 3]

Forest Laboratories and the Division had various regulatory interactions, such as a pre-IND meeting, an End-of-Phase 2 meeting, and two Pre-NDA meetings. Forest Laboratories initially conducted a phase 2 program and a subsequent phase 3 program that evaluated aclidinium bromide at a dose of 200 mcg once daily with trough FEV1 as the endpoint for evaluation of bronchodilatory efficacy. The phase 3 program showed a difference of 60 mL between aclicinium bromide 200 mcg once daily and placebo. Although the difference was statistically significant, the 60 mL effect size is approximately half or less than half of the effect size observed in the phase 2 program for aclidinium bromide and also the effect size typically seen with other bronchodilators in COPD patients. Noting the small effect size with aclidinium bromide 200 mcg once daily, Forest Laboratories subsequently conducted another phase 3 program with aclidinium bromide at doses of 200 mg twice daily and 400 mcg twice daily and finally concluded that 400 mcg twice daily provides optimum, consistent efficacy.

3. Chemistry, Manufacturing, and Controls

Tudorza Pressair (aclidinium bromide inhalation powder) 400 mcg is comprised of a formulation of aclidinium bromide with lactose for inhalation delivery via the Pressair device. Each actuation of Tudorza Pressair provides a metered dose of 13 mg of powder that contains 400 mcg of aclidinium bromide and lactose carrier. This results in delivery of 375 mcg aclidinium bromide from the mouthpiece based on in vitro testing at an average flow rate of 63 L/min. Tudorza Pressair consists of a detachable green protective cap, a white color inhaler with mouthpiece, a colored control window, a dose indicator, and a green color button. To deliver a dose, patients press and release the green button that meters the inhalation powder into a chamber inside the inhaler (at that point the color control window changes from red to green) and then breathe in quickly and deeply through the mouthpiece. Each Tudorza Pressair has 60 metered doses. Forest Laboratories has submitted adequate stability data to support expiry periods of 24 months.

The drug substance is manufactured by [redacted] (b) (4) and [redacted] (b) (4) [redacted]. The inhaler device is manufactured for

[1] Singh S, Loke YK, Furberg CD. JAMA 2008; 300: 1439-50.
[2] Tashkin DP, Celli B, Senn S, et al. N Engl J Med 2008; 359: 1543-54.
[3] Michele TM, Pinheiro S, Iyasu S. N Engl J Med 2010; 363:1097-99.

(b) (4). The final product is manufactured by Forest Laboratories in Dublin, Ireland. The drug substance and device DMFs were deemed adequate. All manufacturing and testing facilities associated with this product have acceptable establishment evaluation status.

4. Nonclinical Pharmacology and Toxicology

Forest Laboratories submitted results from a full preclinical program, including single dose toxicology, subchronic toxicology, chronic toxicology, reproductive toxicology, genotoxicity, and carcinogenicity studies. The program included studies in which animals were dosed with the drug via inhalation to evaluate local and systemic toxicities. Repeat-dose inhalation toxicity studies of up to 3 months duration in the mouse, 6 months in the rat, and 39 weeks in the dog were conducted. Most of the observed effects in these studies were related to the pharmacological action of an anticholinergic, including increased heart rate, mydriasis, decreased tear production, and tremor. In the rat, non-dose-related deaths were observed, which were attributed to exaggerated anticholinergic effects and found to be specific to rats and of little or no clinical significance.

Studies for genotoxicity, reproductive toxicity, and carcinogenicity did not show any major findings of concern. Aclidinium was positive in the Ames bacterial mutation assay and in the mouse lymphoma assay, but negative in the in vivo mouse micronucleus assay and the in vivo/in vitro unscheduled DNA synthesis assay in male rats. Two-year carcinogenicity studies in mice and rats were negative. Reproductive and developmental toxicity studies showed impairment of several fertility and reproductive performance indices. The teratology study in rabbits showed an increased incidence of additional liver lobes and decreased fetal body weights when aclidinium was administered by the oral route, but no structural alterations were observed in rats and rabbits when aclidinium was administered by inhalation. Aclidinium is designated as Pregnancy Category C.

5. Clinical Pharmacology and Biopharmaceutics

Forest Laboratories submitted results from a comprehensive clinical pharmacology program that included studies to assess protein binding and metabolism, pharmacokinetics after single and multiple inhaled doses, pharmacokinetics in COPD patients, effect of renal impairment, and QTc effect. Studies in hepatic impairment were not conducted as aclidinium is metabolized via chemical and enzymatic hydrolysis. In vitro studies indicated that aclidinium and its major metabolites do not inhibit CYP450 enzymes. Given these results and the low plasma levels achieved at clinically relevant doses, aclidinium is not anticipated to interact with co-administered drugs, and formal drug-drug interaction studies were not conducted.

Inhaled aclidinium bromide has approximately 6% bioavailability resulting from both pulmonary and intestinal absorption. The major route of metabolism of aclidinium bromide is hydrolysis, which occurs both chemically and enzymatically by esterases. The estimated effective half-life of aclidinium is ~5-8 hours. Elimination of the hydrolyzed residues occurs through urine and feces. In vitro studies using human liver microsomes show that aclidinium bromide and its major metabolites do not inhibit

common CYP450 enzymes. Therefore, aclidinium bromide is not expected to alter the disposition of drugs metabolized by the human CYP450 enzymes. No clinically significant differences were observed with renal impairment or age, and no dose adjustment for aclidinium bromide is recommended for these subgroups of patients. A study to assess the QTc effect on aclidinium bromide was reviewed by the QT/IRT team and was determined to be negative.

6. Clinical Microbiology

There are no outstanding clinical microbiology issues.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the clinical studies that form the basis of review and regulatory decision for this application are shown in Table 1. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

As discussed in Section 2 above, Forest Laboratories initially conducted a clinical program to support 200 mcg once daily dose of aclidinium bromide, which failed to show clinically meaningful efficacy. Clinical studies with the 200 mcg once daily are not covered in this review because this dose is lower than the 400 mcg twice daily dose that is proposed for marketing.

Table 1. Relevant COPD clinical studies with aclidinium bromide inhalation powder

ID Year *	**Study Characteristics** **- Study design** **- Study duration** **- Patient age, yr**	**Treatment groups †**	**N ‡**	**Primary efficacy variable §**	**Regions**
Dose ranging studies					
CL 23 2009	- Cross over, double blind - 15 day - ≥ 40	Acl 400 mcg BID Tio 18 mcg QD Placebo	30	FEV1 $AUC_{0\text{-}12hr}$	Germany
CL 29 Trial A 2010	- Cross over, double blind - 7 day - ≥ 40	Acl 400 mcg BID Acl 200 mcg BID Acl 100 mcg BID For 12 mcg BID Placebo	79	FEV1 $AUC_{0\text{-}12hr}$	Germany, Belgium
Confirmatory efficacy and safety studies					
MD 33 Trial B 2009	- Parallel arm, double blind - 12 weeks - ≥ 40	Acl 400 mcg BID Acl 200 mcg BID Placebo	190 184 186	Trough FEV1 at week 12	US, Canada
CL 34 Trial D 2010	- Parallel arm, double blind - 24 weeks - ≥ 40	Acl 400 mcg BID Acl 200 mcg BID Placebo	269 277 273	Trough FEV1 at week 12 and 24	W and E Europe, Peru, S Africa
MD 38 A Trial C 2010	- Parallel arm, double blind - 12 weeks - ≥ 40	Acl 400 mcg BID Acl 200 mcg BID Placebo	177 183 182	Trough FEV1 at week 12	US, Canada
Long term safety studies					

ID Year *	**Study Characteristics** **- Study design** **- Study duration** **- Patient age, yr**	**Treatment groups †**	**N ‡**	**Primary efficacy variable §**	**Regions**
MD 35 2011	- Parallel arm, double blind - 52 weeks - ≥ 40	Acl 400 mcg BID Acl 200 mcg BID	291 311	None	US, Canada
MD 36 2010	- Parallel arm, double blind - 52 weeks - ≥ 40	Acl 400 mcg BID Acl 200 mcg BID	153 138	None	US, Canada
MD 38 B 2011	- Single arm, open label - 40 weeks - ≥ 40	Acl 400 mcg BID	448	None	US, Canada

* Study ID shown (from top to bottom) abbreviated from Forest Laboratories study number, and as referred to in the Tudorza Pressair product label. Year shows when study subject enrollment completed. For long term safety studies: MD 36 is extension of MD 33, study MD 38 has two parts – A for efficacy and safety assessment and B for long term safety assessment.
† Acl = Aclidinium bromide inhalation powder; Tio = Tiotropium; For = Formoterol
‡ Number randomized
§ FEV1 = Forced Expiratory Volume in 1 second in Liters (L)

b. Design and conduct of the studies

All studies were conducted in patients with a clinical diagnosis of COPD with a history of cigarette smoking of at least 10 pack-years. In the confirmatory efficacy and safety studies, there was a 2-week run-in period, followed by a double-blind treatment period. The primary efficacy endpoint was change from baseline in morning trough FEV1 at week 12. Other efficacy variables included peak FEV1, St. George's Respiratory Questionnaire (SGRQ), reliever medication use, and COPD exacerbation. Safety assessment included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, ECG, and Holter monitoring in a subset of patients.

c. Efficacy findings and conclusions

The clinical program supports the efficacy of Tudorza Pressair (aclidinium bromide inhalation powder) as a maintenance treatment of airflow obstruction in patients with COPD at a dose of 400 mcg twice daily.

Dose selection and dosing frequency selection for aclidinium bromide were based on previously conducted studies that evaluated a dose of 200 mcg once daily and two additional studies, Study 23 and Study 29, that used tiotropium and formoterol for benchmark comparison. Data generated from these studies support a twice daily dosing frequency, and the 400 mcg twice daily dose demonstrated a greater change in trough FEV1 and time profile serial FEV1 measurement compared to lower doses of 100 mcg and 200 mcg twice daily. The 400 mcg twice daily doses in these studies generally performed better than lower doses and in a similar range to the two active comparators. Based on these data and previous experience with the 200 mcg once daily dose, the selection of the 400 mcg twice daily dose for Tudorza Pressair for further evaluation in confirmatory phase 3 studies was reasonable.

In all three confirmatory studies, a statistically significant increase from baseline in morning trough FEV1 for Tudorza Pressair compared to placebo was seen (**Error! Reference source not found.**). The effect size for the 400 mcg twice daily dose ranged from 72 ml to 124 ml across the three studies at week 12, and the treatment effect appeared to persist when assessed at week 24 in Study 34. The 200 mcg twice daily dose also demonstrated a statistically significant difference from placebo, although the magnitude of the treatment difference was 51 to 86 ml, which was smaller than the effect size observed for the 400 mcg twice daily dose. Other spirometry based efficacy variables, such as peak FEV1 and time profile serial FEV1 curve, also support 400 mcg twice daily as the appropriate bronchodilator dose for Tudorza Pressair.

The change from baseline in the SGRQ total symptom score was assessed as another efficacy variable in the three confirmatory studies. Greater decreases in total score were observed for Tudorza Pressair compared to placebo and were generally supportive of efficacy, but only Study 34 demonstrated a treatment difference between the 400 mcg twice daily dose and placebo that exceeded the minimum clinical important difference (MCID) threshold of a 4-unit change (data not shown in this document). (b) (4)

COPD exacerbations were categorized by severity and defined as increased COPD symptoms of at least 2 consecutive days requiring one of the following: 1) increased rescue medications and/or inhaled corticosteroid use (mild exacerbation); 2) treatment with antibiotics and/or systemic corticosteroids (moderate exacerbation), or 3) hospitalization or emergency room treatment (severe exacerbation). Exacerbation results from the six-month Study 34 suggested a decrease in exacerbations with Tudorza Pressair treatment. Results from the three-month studies were less consistent, although this variability may be due in part to a low background rate of exacerbations overall (data not shown in this document). (b) (4)

Table 2. Change from baseline in trough FEV1 (L) at week 12 (LOCF in ITT population)

	n	Baseline	Change from Baseline †	Treatment Different from placebo †		
		Mean *	LS Mean	LS Mean	95% CI	p-value
Study 33 or Trial B						
Tudorza Pressair 400 mcg BID	190	1.33	0.10	0.12	0.08, 0.16	<0.001
Tudorza Pressair 200 mcg BID	184	1.36	0.06	0.09	0.04, 0.13	<0.001
Placebo	185	1.38	-0.02			
Study 38 A or Trial C						
Tudorza Pressair 400 mcg BID	177	1.25	0.06	0.07	0.03, 0.12	0.001
Tudorza Pressair 200 mcg BID	182	1.40	0.04	0.05	0.01, 0.09	0.019
Placebo	182	1.46	-0.01			
Study 34 or Trial D ‡						
Tudorza Pressair 400 mcg BID	269	1.51	0.06	0.11	0.07, 0.14	<0.001
Tudorza Pressair 200 mcg BID	277	1.51	0.03	0.08	0.04, 0.12	<0.001
Placebo	273	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_1 as response, with

	n	Baseline	Change from Baseline †	Treatment Different from placebo †		
		Mean *	LS Mean	LS Mean	95% CI	p-value
treatment group and sex as factors and baseline trough FEV_1 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 FEV1 at 24 weeks was 0.13 (0.09, 0.17).						

8. Safety

a. Safety database

The safety assessment of Tudorza Pressair for COPD patients is based on three confirmatory efficacy and safety studies, two long term extension safety studies, one dedicated one-year safety study, and small short-term phase 2 studies (Table 1). The size of the safety database is adequate.

b. Safety findings and conclusion

The submitted data support the safety of Tudorza Pressair for use as a maintenance treatment of airflow obstruction in patients with COPD at a dose of 400 mcg twice daily.

A total of 17 deaths were reported in the aclidinium twice daily program: 8 deaths in the placebo-controlled portion of the studies and 9 in the long-term safety studies. In the placebo-controlled portion of the studies, 4 deaths were reported in the aclidinium 400 mcg arm, compared to 2 deaths in the aclidinium 200 mcg and placebo arms each. In the long-term safety studies, 6 and 3 deaths occurred in the aclidinium 400 and 200 mcg arms, respectively. The causes of death varied. Some cases appeared unlikely to be related to aclidinium (e.g., lung cancer, sepsis occurring a month after discontinuation, etc.,), but in other cases, causality could neither be confirmed nor ruled out.

Serious adverse events and discontinuation due to adverse events do not raise any concern for Tudorza Pressair. In the placebo-controlled trials, the overall incidence rate of serious adverse events was greater in the placebo group (105 events/1000 patient-years) compared to aclidinium 200 mcg (70 events/1000 patient-years) and 400 mcg (76 events/1000 patient-years). A wide range of events was reported and most events occurred in just 1 or 2 patients. COPD cited as an SAE was an exception, with a higher incidence reported in the placebo-treated patients (89 events/1000 patient-years) compared to aclidinium-treated patients (45-50 events/1000 patient-years).

Cardiovascular adverse events are a specific safety event of interest for anticholinergic drugs given the previous findings with tiotropium as discussed in Section 2 above. To assess cardiovascular safety of aclidinium bromide, an analysis of major adverse cardiac events (MACE) was done. The MACE score is defined as the total number of cardiovascular deaths, nonfatal myocardial infarctions, and nonfatal strokes. Table 3 shows the summary of the analysis. These results do not indicate an increased overall MACE score for aclidinium bromide and do not show a definite signal of imbalance for any of the individual categories of events, but the strength of this assessment is limited by the 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.

These data neither confirm nor prove any contribution of aclidinium bromide to cardiovascular risk. While no definite cardiovascular signal was seen, the quandary here is the limited number of events that were seen in the program. Forest Laboratories will conduct a post-marketing required study of a larger size that will address this issue.

Table 3. Major adverse cardiac events (MACE) scores *

	Placebo N=641 ET=190.6		**Aclidinium 200 mcg** N=644 ET=199.4		**Aclidinium 400 mcg** N=636 ET=198.4	
	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate
Placebo-controlled studies						
MACE score	4 (0.6)	21.0	2 (0.3)	10.0	2 (0.3)	10.1
CV Death	0	0	1 (0.2)	5.0	1 (0.2)	5.0
Non-fatal myocardial infarction	1 (0.2)	5.2	0	0	0	0
Non-fatal stroke	3 (0.5)	15.7	1 (0.2)	5.0	1 (0.2)	5.0
Long-term safety studies						
MACE score			8 (1.8)	23.5	19 (2.1)	29.5
CV Death			0	0	4 (0.4)	6.2
Non-fatal myocardial infarction			5 (1.1)	14.7	8 (0.9)	12.4
Non-fatal stroke			3 (0.7)	8.8	8 (0.9)	12.4

* 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.

Other safety assessments, such as ECGs, Holter monitoring and a thorough QT study, did not show any cardiac safety signals. Adverse events, such as stroke, pneumonia, and symptoms associated with anticholinergic events did now show any increased risk associated with aclidinium bromide. Laboratory parameters and common adverse events also did not show any specific findings of concern.

c. REMS/RiskMAP

No post-marketing risk evaluation and mitigation strategies are recommended.

9. Advisory Committee Meeting

A meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) was held on February 23, 2012, to discuss this application. The major issues for discussion were the adequacy of the efficacy data to support the proposed indication, the adequacy of the safety database for making an informed benefit-risk assessment, and the benefit-risk assessment for aclidinium bromide 400 mcg twice daily for its proposed indication. In general, the panel members concluded that there were sufficient data to support the efficacy of aclidinium bromide 400 mcg twice daily for the proposed indication. On voting questions, the Committee voted favorably regarding whether there was substantial evidence of efficacy (14 yes, 0 no), and the safety of aclidinium bromide had been adequately assessed (10 yes, 3 no, 1 abstention). Regarding the approvability question,

which is essentially the sum of the demonstration of efficacy and safety, the results were in favor of approval (12 yes, 2 no). Several members stated that data on COPD exacerbations would be helpful for determining how best to use aclidinium bromide. In terms of safety, several members voiced concerns regarding the need for further information in patients at risk for cardiovascular disease. At the meeting Forest Laboratories provided a general outline of their planned post-marketing study. Committee members provided some comments on the proposed study.

10. Pediatric

COPD is an adult disease; therefore, specific pediatric studies would not be required that relate to this action specific to COPD. PeRC agreed that a full waiver should be granted because studies would be impossible or highly impracticable since the disease does not exist in pediatric patients.

11. Other Relevant Regulatory Issues

a. DSI Audits

DSI audited two sites recommended by the clinical review team. These two sites enrolled larger number of patients compared to other sites. No irregularities were identified that would impact data integrity. During review of this application, the review team did not identify any irregularities that would raise concerns regarding data integrity. All studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. One investigator had a financial interest in Forest Laboratories. The number of subjects that this investigator enrolled was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that one center with a possible interest could have influenced or biased the results of these studies.

c. Other

There are no outstanding issues with consults received from OPDP (formerly known as DDMAC), DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

The proposed proprietary name Tudorza Pressair was reviewed by DMEPA and found to be acceptable. The name was also found to be acceptable to OPDP from a promotional perspective.

b. Physician Labeling

Forest Laboratories submitted a label in the Physician Labeling Rule format. The label was reviewed by various disciplines of this Division, the Office of Medical Policy Programs (OMPP), the Office of Surveillance and Epidemiology (OSE)/DMEPA, and by

OPDP. Various changes to different sections of the label were done to reflect the data accurately and better communicate the findings to healthcare providers. The Division and Forest Laboratories have agreed on the final label language.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division, ONDQA, OPMP, and DMEPA, and were found to be acceptable.

d. Patient Labeling and Medication Guide

There is patient labeling (Instructions for Use and Patient Package Insert) that has been reviewed by the Division, OMPP, and other groups within the Center and was to be acceptable. There will not be a Medication Guide for this product.

13. Action and Risk Benefit Assessment

a. Regulatory Action

Forest Laboratories has submitted adequate data to support approval of Tudorza Pressair (aclidinium bromide inhalation powder) 400 mcg for the long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema at a dose of 400 mcg twice daily. The recommended regulatory action for this application is approval.

b. Risk Benefit Assessment

The overall risk-benefit assessment supports approval of Tudorza Pressair at 400 mcg twice daily for long-term once daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema.

The submitted safety data do not raise any specific safety concerns. Cardiovascular adverse events are a specific safety event of interest for anticholinergic drugs given the previous findings with tiotropium as discussed in Section 2 above. Analysis of major adverse cardiac events (MACE) do not indicate an increased overall MACE score for aclidinium bromide, but the strength of this assessment is limited by the relatively limited sample size and a low event rate. From an efficacy standpoint, the clinical program showed that aclidinium bromide at 400 mcg twice daily dose provided statistically significant bronchodilator effect in patients with COPD with replicate findings. Secondary efficacy endpoints, including peak FEV1, time profile FEV1, rescue medication use, and COPD exacerbation, provide additional support. Tudorza Pressair will provide patients with COPD a choice of a second LAMA. Currently, the only other LAMA available in the US market is tiotropium. Forest Laboratories will conduct a post-marketing required study of a larger size that will further assess cardiovascular safety and may also provide additional efficacy data.

c. Post-marketing Risk Management Activities

No post-marketing risk evaluation and management strategies are recommended.

d. Post-marketing Study Commitments

There will be a clinical post-marketing requirement (PMR) study as mentioned in Section 8 above. The PMR study will be a randomized, controlled trial to evaluate the risk of major adverse cardiac events with aclidinium bromide in patients with COPD. Forest Laboratories will submit the study protocol by November 2012. The study will be completed by September 2017, and the final report will be submitted to the Agency by June 2018.

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/s/

BADRUL A CHOWDHURY
07/20/2012