

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202450Orig1s000

OTHER REVIEW(S)

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information	
NDA # 202450 BLA#	NDA Supplement #:S- BLA STN #
Proprietary Name: Acridinium Bromide Established/Proper Name: (b) (4) Dosage Form: Inhalation Powder (oral) Strengths: 400 mcg	
Applicant: Forest Laboratories, Inc. Agent for Applicant (if applicable): Amjad Iqbal	
Date of Application: June 23, 2011 Date of Receipt: June 23, 2011 Date clock started after UN:	
PDUFA Goal Date: April 23, 2012	Action Goal Date (if different):
Filing Date: August 22, 2011 (74 Day Filing Issues Sept 02, 2011)	Date of Filing Meeting: August 12, 2011
Chemical Classification: (1,2,3 etc.) (original NDAs only) Class 1	
Proposed indication(s)/Proposed change(s): COPD	
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input checked="" type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input checked="" type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): IND 68,653				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p>X</p>																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															<p>X</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>			<p>X</p>																	

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>				

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	X			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			(b) (4) was denied by OSE under IND 68653. The sponsor submitted a new proposed proprietary name of (b) (4) to the original application but not separately.
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	X			
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>			?	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>			?	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>				

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 04, 2011

BLA/NDA/Supp #: NDA 202-450

PROPRIETARY NAME: (b)(4)

ESTABLISHED/PROPER NAME: Acclidinium Bromide

DOSAGE FORM/STRENGTH: 400 mcg powder inhalation

APPLICANT: Forst Laboratories

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): COPD

BACKGROUND: IND 68,653

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Sadaf Nabavian	N
	CPMS/TL:	Sandy Barnes	N
Cross-Discipline Team Leader (CDTL)	Susan Limb		Y
Clinical	Reviewer:	Jennifer Pippins	Y
	TL:	Susan Limb	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Partha Roy	N
	TL:	Suresh Doddapaneni	Y
Biostatistics	Reviewer:	Feng Zhou	Y
	TL:	Joan Buenconsejo	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Grace Lee	Y
	TL:	Tim A. Robison	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Yong Hu	Y
	TL:	Alan Schroeder/Prasad Peri	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Nichelle Rashid	Y
	TL:	Sean Bradley	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> 	<input checked="" type="checkbox"/> YES Date if known: February 23, 2012 <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Curtis Rosebraugh	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

<input type="checkbox"/>	<ul style="list-style-type: none"> • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

SADAF NABAVIAN
06/28/2012

**REGULATORY PROJECT MANAGER LABELING REVIEW
(PHYSICIAN LABELING RULE)**

Division of Pulmonary, Allergy, and Rheumatology Products

Application Number: NDA 202450

Name of Drug: [REDACTED]^{(b) (4)} (aclidinium bromide)

Applicant: Forest Pharmaceuticals, Inc.

Material Reviewed:

Submission Date(s): June 23, 2011

Receipt Date(s): June 23, 2011

Submission Date of Structure Product Labeling (SPL): June 23, 2011

Type of Labeling Reviewed: Word/SPL

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in the proposed labeling.

General Comments

1. For specific requirements on the content and format of labeling for human prescription drug and biologic products refer to 21 CFR 201.57. Also see Draft Guidance for Industry: Labeling for human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements (Implementation Guidance).
2. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling format.

Table of Contents

3. There should be no periods after the numbers for the section and subsection headings.

Full Prescribing Information Contents

4. To Section 17 of the Full Prescribing Information, in parenthesis add “Patient Information and Instructions for Use” after the statement “*See FDA-approved Patient Labeling.*”
5. The proprietary and established names can be repeated at the beginning of the FPI, or at the beginning of each page of the FPI (e.g., as a header), if this enhances product identification on subsequent pages of labeling.

Recommendations

Please address the identified deficiencies/issues and re-submit labeling by September 23, 2011. This updated version of labeling will be used for further labeling discussions.

Sadaf Nabavian
Regulatory Health Project Manager

Supervisory Comment/Concurrence:

Sandy Barnes
Chief, Project Management Staff

Drafted: SNabavian/08.24.2011
Revised/Initialed: SBarnes/08.24.2011
Finalized: SNabavian/08.24.2011
Filename: CSO Labeling Review Template (updated 1-16-07).doc
CSO LABELING REVIEW OF PLR FORMAT

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/s/

SADAF NABAVIAN

06/08/2012

Sandy, the only change I noticed in the review is that the proposed trade name has been changed to Tudorza Pressair (vs. (b) (4))

SANDRA L BARNES

06/26/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 15, 2012

TO: Forest laboratories

THROUGH: Amjad Iqbal
Associate Director

FROM: Susan Limb, M.D., Clinical Team Leader
Sally Seymour, M.D., Deputy Director of Safety
Jennifer Pippins, M.D., Clinical Reviewer
Joan Buenconsejo, Ph.D., Statistical Team Leader
Angela Ramsey, R.N., M.S.N, Senior Regulatory Project Manager

SUBJECT: **Proposed PMR submission dated, April 6, 2012**

APPLICATION/DRUG: **NDA 202450 aclidinium bromide powder**

The Division requested a teleconference to provide Forest Laboratories feedback on a proposed PMR safety trial submitted April 6, 2012. The Division noted that the proposal addressed two objectives: cardiovascular safety (b) (4). Although both objectives are meaningful, addressing the cardiovascular issue is the primary objective of the PMR. The Division provided Forest with the following points of consideration for the proposed PMR:

1. (b) (4)
2. Address the potential ethical concerns regarding the inclusion of patients who are on a long-acting antimuscarinic agent (LAMA) at baseline. If such patients are included and are washed off their LAMA prior to randomization, specify how this change in treatment will be handled to minimize risk to the patient.
3. Propose a broader population at risk for cardiovascular events.
4. Consider how the planned interim analysis for efficacy might compromise the safety assessment.

Forest submitted the following proposed timeline:
Final Protocol Submission: January 2013

Study Completion: January 2018
Final Study Report: October 2018

The Division requested reconsideration of the proposed timeline. The Division stated that Fall 2012 is reasonable for submission of the final protocol. The Division reiterated that the goal is to assess safety therefore; it is a PMR, not a PMC.

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/s/

ANGELA H RAMSEY
05/18/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: March 15, 2012

To: Angela Ramsey, Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Matt Falter, Regulatory Review Officer
Division of Direct-to-Consumer Promotion (DDTCP)
Office of Prescription Drug Promotion (OPDP)

Roberta Szydlo, Regulatory Review Officer
Division of Professional Promotion (DPP), OPDP

CC: Sadaf Nabavian, Regulatory Project Manager, DPARP
Lisa Hubbard, Group Leader, DPP
Robyn Tyler, Group Leader, DDTCP
Olga Salis, Project Manager, OPDP

Subject: NDA 202450
OPDP labeling comments for Tudorza[®] Pressair[®] (aclidinium
bromide inhalation powder)

OPDP has reviewed the proposed Package Insert (PI), proposed Patient Package Insert (PPI), and proposed Instructions for Use (IFU) for Tudorza[®] Pressair[®] (aclidinium bromide inhalation powder) submitted for consult on September 13, 2011, and offers the following comments.

OPDP's comments on the PI are based on the proposed draft marked-up labeling titled "NDA202450_ForestProposedLabeling_Final Updated Team .doc" that was sent via e-mail from DPARP to OPDP on March 2, 2012.

OPDP's comments on the PPI and IFU are based on the proposed draft labeling titled "3 12 12 aclidinium bromide PPI IFU (clean).doc" that was sent via e-mail from DMPP to DPARP and OPDP on March 13, 2012.

OPDP's comments on the PI, PPI, and IFU are provided directly in the marked-up document attached (see below).

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions regarding the PI, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.

If you have any questions regarding the PPI or IFU, please contact Matt Falter at (301) 796-2287 or matthew.falter@fda.hhs.gov.

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/s/

ROBERTA T SZYDLO
03/15/2012

MATTHEW J FALTER
03/15/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: March 13, 2012

To: Badrul Chowdhury, M.D., Director
**Division of Pulmonary, Allergy and Rheumatology
(DPARP)**

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Associate Director, Patient Labeling Team
Division of Medical Policy Programs (DMPP)

Melissa Hulett, RN, BSN, MSBA
Team Leader, Patient Labeling Team
Division of Medical Policy Programs (DMPP)

Robin Duer, RN, BSN, MBA
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Twanda Scales, RN, MSN/Ed.
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling, Patient Package Insert
(PPI), and Instructions for Use (IFU)

Drug Name: Tudorza Pressair (aclidinium bromide inhalation powder)

Dosage Form and Route: For Inhalation

Application
Type/Number: NDA 202450

Applicant: Forest Laboratories, Inc.

1 INTRODUCTION

On June 23, 2011, the Applicant submitted an original New Drug Application (NDA) for acclidinium bromide inhalation powder for the long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD).

This review is written in response to a request by the Division of Division of Pulmonary, Allergy and Rheumatology (DPARP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for acclidinium bromide inhalation powder.

Following the submission of this NDA the proprietary name "Tudorza Pressair (acclidinium bromide inhalation powder)" was approved.

2 MATERIAL REVIEWED

- Draft Tudorza Pressair (acclidinium bromide inhalation powder) PPI and IFU received on June 23, 2011 and received by DMPP on February 27, 2012
- Draft Tudorza Pressair (acclidinium bromide inhalation powder) prescribing information (PI) received on June 23, 2011, revised by the Review Division throughout the review cycle and received by DMPP on February 27, 2012

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI and IFU documents using the Verdana font, size 11.

In our review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the PPI and IFU are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI or IFU.

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
03/13/2012

MELISSA I HULETT
03/13/2012

LASHAWN M GRIFFITHS
03/13/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: February 6, 2012

Reviewer: Jung Lee, RPh
Division of Medication Error Prevention and Analysis

Team Leader Irene Z. Chan, PharmD, BCPS
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Acridinium Bromide Inhalation Powder
400 mcg per actuation

Application Type/Number: NDA 202450

Applicant/sponsor: Forest Laboratories

OSE RCM #: 2011-2779

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the labels and labeling of Acclidinium Bromide Inhalation Powder submitted on June 23, 2011, for areas of vulnerability that can lead to medication error in response to a request from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP).

1.1 REGULATORY HISTORY

Tudorza Pressair is the third proprietary name for this application, and it is being evaluated under a separate cover (OSE Review # 2011-4488). DMEPA previously reviewed the proposed proprietary names, (b) (4) (IND 068653), which was found unacceptable from both a promotional and safety perspective, and (b) (4) (NDA 202450), which was found unacceptable from a safety perspective.

In response to an information request sent on January 11, 2012, Forest Laboratories provided the following information with respect to the labeling and packaging for Acclidinium Bromide:

- The Early Experience Program (EEP) kit consists of the following elements: A “sleeve” which slips over the “tray” containing 5 “outer cartons.” Each “outer carton” opens like a book and contains one “carton” inserted in a hollowed out area on the right side and a slit on the left side, into which a co-pay card will be inserted. The “carton” contains a “pouch” (with the 60 actuations inhaler enclosed), a package insert and the “Patient Information and Instructions for Use Booklet.”
- The EEP samples will be distributed during the initial period following launch. The EEP samples contain 30 days of therapy (60 actuations) to provide an adequate time period for physicians and patients to gain experience with the product. After the initial period following launch, Forest plans to transition to the 15 day professional samples (30 actuations).

1.2 PRODUCT INFORMATION

The following product information is provided in the September 22, 2011 labeling submission.

- Active Ingredient: Acclidinium Bromide
- Indication of Use: A long-acting muscarinic antagonist indicated for the long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including bronchitis and emphysema
- Route of Administration: Oral Inhalation
- Dosage Form: Inhalation Powder
- Strength: 400 mcg per actuation
- Dose: One oral inhalation of 400 mcg twice daily
- How Supplied: In a sealed labeled aluminum pouch available in 60 metered doses

- Storage: Store in a dry place at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)
- Container and Closure Systems: Acclidinium Bromide Inhalation Powder 400 mcg is in a non-refillable, breath-actuated, multi-dose and device-metered dry powder inhaler (DPI) specifically designed to reliably deliver a minimum of 60 nominal doses of the drug product. The inhaler is enclosed in a heat-sealed aluminum pouch and the pouch is packaged in an outer carton.

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis,¹ principles of human factors, and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted June 23, 2011
- Carton Labeling submitted June 23, 2011
- Insert Labeling submitted September 22, 2011
- Demonstration Inhaler Carton Labeling submitted September 22, 2011

In the cover letter, Forest Labs stated “Forest is not submitting revised draft labels and labeling at this time. As agreed with DMEPA in the August 12, 2011 email communication, “Forest will revise the proprietary name on all draft labels and labeling once a proposed name is found to be acceptable to DMEPA or closer to the PDUFA date.”

3 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling introduce vulnerability that can lead to medication errors. The established name, strength and other statements on the proposed label and labeling lack prominence or require relocation. The patient labeling also lacks emphasis of important warnings and notes under the Patient Information and Patient’s Instructions for Use sections. We advise the following recommendations be implemented prior to approval:

A. General Comment (all labels and labeling)

Minimize the graphic located to the right of the proprietary name so it does not distract from the prominence of the proprietary name.

B. Professional Samples and Trade Device Labels

1. Increase the prominence of the established name to be in accordance with 21 CFR 201.10(g)(2). Ensure the established name has prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing features.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2. Revise the strength statement to state 400 mcg per actuation and increase the font size for increased prominence.
3. Relocate the route of administration statement “For Oral Inhalation” to appear below the statement of strength.
4. Debold the “Rx Only” statement so it is less prominent.

C. Professional Sample Device Label

Debold the font for “Professional Sample Not for Sale” so it is less prominent.



E. Professional Samples Carton Labeling, Trade Carton Labeling and EEP (Early Experience Program) Professional Sample Labeling (tray, sleeve, and carton)

1. See comments B1 to B4 above.
2. Revise and bold the statement “Discard Tradename inhaler 45 days after removing from the pouch...” to read “**Discard Tradename inhaler 45 days after opening the pouch...**” for clarity and increased prominence, respectively.
3. Debold the statement “See Package Insert...Instructions for Use.”

F. Professional Sample Carton Labeling, EEP Professional Sample Sleeve, and EEP Sample Carton Labeling

See comment C above.

G. Aluminum Pouch Labeling (Professional Samples and Trade)

1. See comments B1 to B4 and E2 to E3 above.
2. Relocate the discard statement above the storage statement so that it immediately follows the statement to keep the inhaler inside the sealed pouch

until the administration period starts. This will allow related information to read sequentially.

H. EEP Professional Sample Sleeve & Sample Carton Labeling

1. See comments B1 to B4, E2 to E3 and G2 above.
2. Identify where the expiration date and lot number will be printed on the sleeve and sample package labeling.

I. Demonstration Inhaler Carton and Aluminum Pouch Labeling

See comments D1 through D4 above.

J. Insert Labeling

1. General Comments

- a. The applicant utilizes trailing zeros within the insert labeling. Trailing zeros can lead to 10-fold errors in dosing. DMEPA recommends removing all trailing zeros with the exception of when it is required to demonstrate the level of precision of the value being reported, such as for laboratory results, imaging studies that report size of lesions, or catheter/tube sizes.
- b. The symbols $<$, \leq , $>$, \geq were utilized in the insert labeling to represent “less than,” “less than or equal to,” “greater than,” or “greater than or equal to,” respectively. These symbols can be misinterpreted as the opposite of the intended symbol or mistakenly used as the incorrect symbol.² Please revise the labeling to replace all symbols with text.
- c. When presenting numbers with symbols or units, insert a space between the number and the symbol, or unit, to provide better readability. An example can be found in Section 11 (line 247). Instead of “2L,” consider revising to read “2 L.”
- d. We recommend adding a unit of measure immediately following all numbers, as appropriate. For example (line 190), revise “doses of up to 4.8 and 3.6 mg/kg/day” to read “doses of 4.8 mg/kg/day and 3.6 mg/kg/day.”
- e. We recommend keeping numbers next to units or symbols within the same line of text. For example (line 190, line 246, line 302, and line 337), revise the layout so the 3.6, 6, 400, and 400 are not at the end of the line of text, respectively.
- f. Consider stating numbers greater or equal to 1,000 with a comma to prevent the reader from misinterpreting thousands “1000” as hundreds

² Institute for Safe Medication Practices (ISMP). ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations. ISMP: 2010.

“100.” For example (line 230), “6000 mcg” should be written as “6,000 mcg.”

2. Full Prescribing Information

a. How Supplied/Storage and Handling (Section 16)

1). (Line 471) In order to increase clarity, consider revising the statement [REDACTED] (b) (4) to “...and only open immediately before use.”

2). (Line 474) In order to increase clarity, consider revising the statement [REDACTED] (b) (4) to “...45 days after opening the pouch...”

K. Patient Information Labeling

1. (Line 558 to 560) In order to further emphasize the correct use of the inhaler, consider bolding the statement “[REDACTED] (b) (4) is not a rescue medicine....”
2. (Line 620 to 621) In order to increase clarity and minimize confusion, revise the statement [REDACTED] (b) (4) to read “Each dose should be about 12 hours apart.”
3. (Line 680) Refer to comment J.2.a.1) above.
4. (Line 687) Refer to comment J.2.a.2) above.
5. Consider adding a warning under the question “How do I store [REDACTED] (b) (4) to never take the inhalation device apart.”

L. Patient’s Instruction for Use

(Line 808) Increase the font size to be similar to the font size on line 851.

If you have further questions or need clarifications, please contact Nichelle Rashid, project manager, at 301-796-3904.

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/s/

JUNG E LEE
02/06/2012

IRENE Z CHAN
02/06/2012

CAROL A HOLQUIST
02/07/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: December 15, 2011

TO: Sadaf Navabian, Regulatory Project Manager
Jennifer Pippins, M.D., Medical Officer
Susan Limb, M.D., Team Leader
Division of Pulmonary, Allergy and Rheumatology Products (DPARP)

FROM: Anthony Orenca, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations (*formerly* Division of Scientific Investigations)

THROUGH: Susan Leibenhaut, M.D.
Acting Team Leader, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Acting Division Director
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 202450

APPLICANT: Forest Laboratories, Inc.

DRUG: aclidinium bromide
NME: Yes

THERAPEUTIC CLASSIFICATION/REVIEW: Standard Review
INDICATION: COPD

CONSULTATION REQUEST DATE: August 18, 2011
DIVISION ACTION GOAL DATE: April 23, 2012
PDUFA DATE: April 23, 2012

I. BACKGROUND:

Forest Laboratories submitted this application for the use of aclidinium bromide for the maintenance of bronchodilator treatment to relieve symptoms in patients with Chronic Obstructive Pulmonary Disease (COPD) including chronic bronchitis and emphysema. Aclidinium bromide is a muscarinic antagonist with a longer residence time at M3 receptors and shorter residence time at M2 receptors.

The protocols inspected were:

Protocol #LAS-MD-33, entitled "Efficacy and Safety of Aclidinium Bromide at Two Dose Levels (200 µg Twice Daily, 400 µg Twice Daily) vs. Placebo When Administered to Patients With Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)," and

Protocol #M-34273-34, entitled "Efficacy and Safety of Aclidinium Bromide at Two Dose Levels vs. Placebo When Administered to Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)."

LAS-MD- 33 and M-34273-34 were both prospective, randomized, parallel group, placebo-controlled, double-blind, multinational and multicenter, clinical studies. The primary efficacy was change in morning pre-dose (trough) FEV₁ from baseline to Week 12. Protocol LAS-MD- 33 was conducted at 100 centers in the US and 6 centers in Canada. Protocol M-34273-34 was conducted outside the US at 106 centers in 10 countries in Europe and in South Africa.

Two foreign clinical sites, one for each protocol, and the sponsor files for Protocol #LAS-MD-33 were inspected in support of this application. The sites had enrollment of large numbers of study participants and/or large drop out rates.

II. RESULTS:

Name of CI City, State	Protocol/site	Insp. Date	Final Classification*
Anthony D'Urzo, MD Toronto, Canada	LAS-MD- 33 Site #2203	November 14 to 16, 2011	Pending (Preliminary: NAI)
Susanne Mindt-Prüfert, M.D. Hamburg, Germany	M-34273-cl34 Site #4042	October 31 to November 4, 2011	Pending (Preliminary: NAI)
Forest Laboratories, Inc. Jersey City, NJ	LAS-MD- 33	September 12 to 20, 2011	NAI

*Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable/Critical findings may affect data integrity.

Preliminary= The Establishment Inspection Report (EIR) has not been received and findings are based on preliminary communication with the field.

CLINICAL STUDY SITE INVESTIGATOR

1. Anthony D'Urzo, MD/Protocol LAS-MD- 33 Site #2203

Primary Care Lung Clinic

1670 Dufferin Street STE 107, Toronto, Ontario, M6H 3M2 CANADA

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from November 14-16, 2011. A total of 13 subjects were screened, 11 were randomized, and 11 completed the study. An audit of 11 randomized subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

Source documents for randomized subjects were verified against the case report forms and NDA subject line listings. No discrepancies were noted. There was no under-reporting of serious adverse events.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection.

d. Data acceptability/reliability for consideration in the NDA review decision.

Data submitted by this clinical site appear acceptable for this specific indication.

NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.

2. Susanne Mindt-Prüfert, M.D./ Protocol M-34273-cl34 Center 3589/Site #4042

Klinische Forschung

Hamburg GmbH Hoheluftchaussee 18, Hamburg, 20253 GERMANY

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from October 31 to November 4, 2011. A total of 25 subjects were screened, 17 subjects were randomized, and 9 subjects completed the study. An audit of 11 of randomized subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and NDA subject line listings.

No discrepancies were noted. There was no under-reporting of serious adverse events noted. This clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued.

d. Data acceptability/reliability for consideration in the NDA review decision.

The data, in support of clinical efficacy and safety from this clinical site, appear acceptable for this specific indication.

NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.

SPONSOR INSPECTION

Forest Laboratories, Inc.

Jersey City, NJ

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.810, from September 12-20, 2011.

The Sponsor inspection evaluated the following: documents related to Sponsor's study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed FDA forms 1572, monitoring reports, communication with the Sponsor and drug accountability, staff training and site monitors. Regulatory files for Anthony D'Urzo, M.D. (Site #2203) in Protocol LAS-MD-33 at Sponsor's New Jersey site were reviewed also during the inspection.

In contrast, Protocol M-34273-34 was conducted by Sponsor's partner, Forest Research Institute's, Almirall Sofotec, at their Barcelona, Spain headquarters. No Sponsor (Almirall) inspection was conducted, but the European site selected for clinical site audit, Site #4042 (Susan Mind-Prüfert), monitored by this Spanish Sponsor, had no data integrity or data reliability issues.

Based on DPARP's determination, there was no relevant rationale to inspect two separate Sponsors. The U.S. Sponsor, as applicant holder, mattered for NDA approvability decisions and was thus inspected. There were no discordant findings in efficacy between Protocol LAS-MD-33 and Protocol M-34273-cl34, which were short-term clinical trials.

b. Limitations of inspection

None.

c. General observations/commentary

Sponsor maintained adequate oversight of the clinical trial. There were no noncompliant sites, and monitoring of the investigator sites was considered adequate. No salient issues pertinent to data reliability or human subject protection were identified. There was no evidence of under-reporting of adverse events. No discrepancies were noted. This clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued at the end of the Sponsor inspection.

d. Data acceptability/reliability for consideration in the NDA review decision.

The data in support of efficacy and safety from this Sponsor oversight appear acceptable for this specific indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two foreign clinical sites, one for each protocol, and the sponsor files for Protocol #LAS-MD-33 were inspected in support of this application. No regulatory violations were noted. Based on review of inspectional findings for these clinical investigators, the study data collected appear generally reliable in support of the requested indication.

Note: Observations noted above, for the clinical investigator sites (Anthony D'Urzo, M.D. and Susanne Mindt-Prüfert, M.D.) are based on the preliminary communications from the field investigator. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final Establishment Inspection Report.

{See appended electronic signature page}

Anthony Orenca, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Leibenhaut, M.D.
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CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Acting Division Director
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Office of Scientific Investigations

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/s/

ANTHONY J ORENCIA
12/16/2011

SUSAN LEIBENHAUT
12/16/2011

TEJASHRI S PUROHIT-SHETH
12/16/2011

Executive CAC

Date of Meeting: November 15, 2011

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Dan Mellon, Ph.D., DAAAP, Alternate Member
Timothy Robison, Ph.D., DPARP, Team Leader
Grace Lee, Ph.D., DPARP, Presenting Reviewer

Author of Draft: Grace Lee, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA # 202-450

Drug Name: Aclidinium Bromide

Applicant: Forest Laboratories, Inc

Background: Two-year mouse and rat carcinogenicity studies with aclidinium bromide were conducted by [REDACTED] ^{(b) (4)}. Dose levels in these studies were concurred with FDA's ECAC recommendations (See meeting minutes dated March 30, 2004). Aclidinium bromide was positive in the Ames assay (2 of 5 batches) and in the mouse lymphoma assay (all 5 batches). However, aclidinium bromide was negative in the *in vivo* mouse micronucleus study at the limit dose of 2000 mg/kg by oral administration and in the *in vivo/in vitro* unscheduled DNA synthesis test in male rats using subcutaneous doses up to 20 mg/kg.

Mouse Carcinogenicity Study:

In a 2-year carcinogenicity study, mice received aclidinium bromide by inhalation (nose only) at achieved doses of 0.29, 0.79 and 2.4 mg/kg/day. There were also air control and vehicle control (lactose) groups in the study. There were no drug-related effects on mortality. At the end of the treatment period (week 104), mean absolute body weights were decreased in a dose-related manner in the males and females (decreases of 2-8% in males and 8-12% in females, relative to the respective air control groups). No statistically significant drug-related tumor findings were observed in the study.

Rat Carcinogenicity Study:

In a 2-year carcinogenicity study, rats received aclidinium bromide by inhalation (nose only) at achieved doses of 0.019, 0.069 and 0.2 mg/kg/day. There were also air control and vehicle control (lactose) groups in the study. There were no drug-related effects on mortality. At the end of the treatment period (week 103), mean absolute body weights were decreased by 13-19% in males and 5-9% in females in all drug-dosed groups, relative to the respective air control groups. No statistically significant drug-related tumor findings were observed in the study.

Executive CAC Recommendations and Conclusions:

Rat:

- The Committee agreed that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concluded that the study was negative for drug related tumors.

Mouse:

- The Committee agreed that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concluded that the study was negative for drug related tumors.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\n
/NDA 202-450 Division File, DPARP
/TRobison, DPARP
/GLee, DPARP
/SNabavian, DPARP
/ASeifried, OND IO

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/s/

ADELE S SEIFRIED
11/16/2011

DAVID JACOBSON KRAM
11/16/2011

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 202-450
Product Name: Tudorza Pressair (aclidinium bromide inhalation powder)

PMR/PMC Description: Conduct a randomized, controlled trial to evaluate the risk of major adverse cardiac events with aclidinium bromide in patients with COPD

PMR/PMC Schedule Milestones: Final Protocol Submission: 11/2012
Study/Trial Completion: 09/2017
Final Report Submission: 06/2018

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The application includes adequate data to support safety for the proposed indication.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the PMR is to evaluate the risk of major adverse cardiac events. This is in response to a small imbalance in cardiovascular deaths observed for aclidinium 400 mcg BID in the clinical development program. The low number of overall events in the development program limits the interpretability of these data.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Randomized, controlled clinical trial in patients with COPD

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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/s/

SALLY M SEYMOUR
07/11/2012