

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210595Orig1s000

OTHER REVIEW(S)

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

PATIENT LABELING REVIEW

Date: March 21, 2019

To: Sally Seymour, MD
Acting Director
**Division of Pulmonary, Allergy, and Rheumatology
Products (DPARP)**

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

From: Sharon Williams, MSN, BSN, RN
Senior Patient Labeling Reviewer, Patient Labeling
Division of Medical Policy Programs (DMPP)

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

Drug Name (established name): DUAKLIR PRESSAIR (aclidinium bromide and formoterol fumarate)

Dosage Form and Route: inhalation powder, for oral solution

Application Type/Number: NDA 210595

Applicant: AstraZeneca Pharmaceuticals LP

1 INTRODUCTION

On May 31, 2018, AstraZeneca submitted for the Agency's review an original New Drug Application (NDA) 210656 for DUAKLIR PRESSAIR (aclidinium bromide and formoterol fumarate) inhalation powder, for oral solution. DUAKLIR PRESSAIR (aclidinium bromide and formoterol fumarate) is a New Molecular Entity (NME) with a proposed indication for the (b) (4) maintenance treatment of (b) (4) patients with chronic obstructive pulmonary disease (COPD) (b) (4). DPARP recently converted the Medication Guide to the Patient Package Insert (PPI) and requested DMPP to review the PPI.

This review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on March 19, 2019, for DMPP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for DUAKLIR PRESSAIR (aclidinium bromide and formoterol fumarate) inhalation powder, for oral solution.

2 MATERIAL REVIEWED

- Draft DUAKLIR PRESSAIR (aclidinium bromide and formoterol fumarate) PPI and IFU received on May 31, 2018, revised by the Review Division throughout the review cycle, and received by DMPP March 19, 2019
- Draft DUAKLIR PRESSAIR (aclidinium bromide and formoterol fumarate) Prescribing Information (PI) received on May 31, 2018, revised by the Review Division throughout the review cycle, and received by DMPP on March 19, 2019.

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 APFont to make medical information more accessible for patients with vision loss.

In our review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that they are free of promotional language
- ensured that the PPI meets the Regulations as specified in 21 CFR 208.20
- 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 and OPDP on the correspondence.
- Our review of the PPI and IFU are appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHARON W WILLIAMS
03/21/2019 02:10:23 PM

LASHAWN M GRIFFITHS
03/21/2019 02:29:01 PM

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

PATIENT LABELING REVIEW

Date: February 21, 2019

To: Sally Seymour, MD
Acting Director
**Division of Pulmonary, Allergy, and Rheumatology
Products (DPARP)**

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

Sharon Williams, MSN, BSN, RN
Senior Patient Labeling Reviewer, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Kelly Jackson, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Taylor Burnett, PharmD, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and
Instructions for Use (IFU)

Drug Name (established name): DUAKLIR PRESSAIR (aclidinium bromide and formoterol fumarate)

Dosage Form and Route: inhalation powder, for oral solution

Application Type/Number: NDA 210595

Applicant: AstraZeneca Pharmaceuticals LP

1 INTRODUCTION

On May 31, 2018, AstraZeneca submitted for the Agency's review an original New Drug Application (NDA) 210656 for DUAKLIR PRESSAIR (aclidinium bromide and formoterol fumarate) inhalation powder, for oral solution. DUAKLIR PRESSAIR (aclidinium bromide and formoterol fumarate) is a New Molecular Entity (NME) with a proposed indication for the (b) (4) maintenance treatment of (b) (4) patients with chronic obstructive pulmonary disease (COPD) (b) (4).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on June 6, 2018, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for DUAKLIR PRESSAIR (aclidinium bromide and formoterol fumarate) inhalation powder, for oral solution.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft DUAKLIR PRESSAIR (aclidinium bromide and formoterol fumarate) MG and IFU received on May 31, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 6, 2019.
- Draft DUAKLIR PRESSAIR (aclidinium bromide and formoterol fumarate) Prescribing Information (PI) received on May 31, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 6, 2019.

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 MG 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 reformatted the MG and IFU document using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that they are free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KELLY D JACKSON
02/21/2019 02:46:06 PM

TAYLOR B BURNETT
02/21/2019 05:36:22 PM

SHARON W WILLIAMS
02/22/2019 07:46:26 AM

LASHAWN M GRIFFITHS
02/22/2019 07:56:23 AM

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

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

Memorandum

Date: February 20, 2019

To: Ngoc-Linh Do
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Taylor Burnett, Pharm.D., RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Pharm.D., RAC
Team Leader
OPDP

Subject: OPDP Labeling Comments for DUAKLIR[®] PRESSAIR[®] (aclidinium bromide and formoterol fumarate) inhalation powder, for oral inhalation

NDA: 210595

In response to DPARP's consult request dated June 8, 2018, OPDP has reviewed the proposed product labeling (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for the original NDA submission for DUAKLIR[®] PRESSAIR[®] (aclidinium bromide and formoterol fumarate) inhalation powder, for oral inhalation (Duaklir).

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DPARP (Ngoc-Linh Do) on February 6, 2019, and are provided below.

Medication Guide/IFU: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide and IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on February 8, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Taylor Burnett at (240) 402-1349 or Taylor.Burnett@fda.hhs.gov.

52 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TAYLOR B BURNETT
02/20/2019 03:15:06 PM

COMPARATIVE ANALYSIS AND LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	January 28, 2019
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	NDA 210595
Product Name and Strength:	Duaklir Pressair (aclidinium bromide and formoterol fumarate) Inhalation Powder, 400 mcg/12 mcg
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	AstraZeneca
FDA Received Date:	May 31, 2018
OSE RCM #:	2018-1154
DMEPA Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA Safety Evaluator:	Matthew Barlow, RN, BSN
DMEPA Team Leader:	Sarah K. Vee, PharmD
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS

1 REASON FOR REVIEW

This review evaluates the proposed labels and labeling and comparative analysis for Duaklir Pressair (aclidinium bromide and formoterol fumarate) Inhalation Powder for areas of vulnerability that could lead to medication errors. The proposed combination product is comprised of the Pressair inhaler presentation containing the active ingredients aclidinium bromide and formoterol fumarate available in a single strength for the management of chronic obstructive pulmonary disease (COPD) (b) (4).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

3.1 COMPARATIVE ANALYSES: PHYSICAL COMPARISON, TASK ANALYSIS, AND LABELING COMPARISON

AstraZeneca submitted the following comparative analysis for our review of their proposed product Duaklir Pressair compared to the marketed product, Tudorza Pressair: a physical comparison, a task analysis, and a labeling comparison.

The proposed product, Duaklir Pressair, has the same device design and use tasks as the currently marketed Tudorza Pressair. The differences are in the color of the protective cap and dose button, which are used to differentiate the two devices and do not impact critical tasks. We reviewed the submitted product samples to confirm that the device design and use tasks are the same.

We also reviewed the submitted side-by-side Instructions for Use (IFU) comparing the proposed product with the currently marketed Tudorza and found them to be the same except for the color differences and mention of the desiccant in the proposed Duaklir IFU.

3.2 USE-RELATED RISK ANALYSIS (URRA)

The Applicant submitted a URRA as part of this NDA and did not identify any new or unique risks as it is the same Pressair device used in the currently marketed Tudorza. We reviewed the submitted URRA and found the assessment acceptable from a medication error perspective as there are no new or unique risks introduced with their proposed product for Duaklir.

3.3 LABELS AND LABELING

We evaluated the proposed container labels, carton labeling, instructions for use, and prescribing information to determine whether there are any vulnerabilities that may lead to medication errors. We note that the strength of the product does not include the corresponding units on the labels and labeling. Therefore, we provide recommendations in Section 4.1.

4 CONCLUSION & RECOMMENDATIONS

Our review of the Applicant's comparative analyses of Duaklir Pressair compared to Tudorza Pressair and of the URRA showed that the design differences (color of protective cap and dose button) do not impact critical tasks and do not introduce new risks respectively. As such, we find the Applicant's justification that a human factors (HF) validation study is not needed to support the proposed product acceptable.

Our review of the product labels and labeling concludes that the proposed labels and labeling can be improved to promote the safe use of the product and mitigate confusion.

4.1 RECOMMENDATIONS FOR ASTRAZENECA

We recommend the following be implemented prior to approval of this NDA:

- A. General Comments (Container labels & Carton Labeling)
 1. As currently presented, the strength in the colored box does not include units. Include the unit of strength in each location where the strength is listed (i.e. 400 mcg/12 mcg vs. 400/12 mcg) to mitigate confusion.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Duaklir Pressair received on May 31, 2018 from AstraZeneca.

Table 2. Relevant Product Information for Duaklir Pressair	
Initial Approval Date	N/A
Active Ingredient	aclidinium bromide and formoterol fumarate
Indication	(b) (4) maintenance treatment of (b) (4) patients with chronic obstructive pulmonary disease (COPD) (b) (4) . (b) (4)
Route of Administration	Oral Inhalation
Dosage Form	Inhalation Powder
Strength	400 mcg/12 mcg
Dose and Frequency	One inhalation twice daily
How Supplied	Sealed bag with a desiccant sachet and is available in 60 metered doses
Storage	(b) (4) excursions permitted to 15-30°C (59-86°F)
Container Closure	Contained in a cartridge situated in a metered dry powder inhaler (DPI) with an integral dose indicator and removable protective cap

APPENDIX C. HUMAN FACTORS STUDY

The human factors URRAs and comparative analyses can be accessible in EDR via:

<\\cdsesub1\evsprod\nda210595\0001\m3\32-body-data\32r-reg-info\medical-devices-inhaler.pdf>

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Duaklir Pressair labels and labeling submitted by AstraZeneca.

- Container label received on May 31, 2018
- Carton labeling received on May 31, 2018
- Professional Sample Carton Labeling received on May 31, 2018
- Hospital Unit-Dose labels received on May 31, 2018
- Instructions for Use (Image not shown) received on May 31, 2018
- Medication Guide (Image not shown) received on May 31, 2018
- Prescribing Information (Image not shown) received on May 31, 2018

G.2 Label and Labeling Images



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

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MATTHEW J BARLOW
01/28/2019 07:03:23 PM

LISSA C OWENS
01/28/2019 07:47:56 PM

SARAH K VEE
01/30/2019 03:51:35 PM

QUYNHNHU T NGUYEN
01/30/2019 05:11:51 PM