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APPLICATION NUMBER:

205625Orig1s000

PHARMACOLOGY REVIEW(S)

Secondary Pharmacology and Toxicology Review for NDA 205-625

TO: NDA 205-625 (GlaxoSmithKline)

FROM: Marcie Wood, Ph.D.

Supervisory Pharmacologist

Division of Pulmonary, Allergy, and Rheumatology Drug Products

DATE: July 25, 2014

Overview: I concur with the recommendation of Dr. Luqi Pei (detailed in a nonclinical review dated July 17, 2014) that the pharmacology and toxicology of Arnuity Ellipta has been adequately studied and the drug product should be approved from a nonclinical perspective.

Arnuity Ellipta, a fluticasone furoate (glucocorticosteroid) dry powder inhaler, is indicated for the treatment of asthma in patients 12 years of age and older. The proposed maximum recommended daily clinical dose of fluticasone furoate (FF) is 200 µg/day. The nonclinical safety program of Arnuity Ellipta is based upon complete FF pharmacology and toxicology studies that were previously submitted and reviewed under existing NDAs for Veramyst Nasal Spray (NDA 20-551) and Breo Ellipta (NDA 204-275). See nonclinical reviews completed on March 7, 2007 (NDA 20-551), March 12, 2013 (NDA 204-275), and April 22, 2013 (NDA 204-275), for complete details. No new, significant nonclinical data was included in the current submission, so a detailed pharmacology and toxicology review of FF was not needed for this NDA.

Labeling: Changes to Section 8.1 (Pregnancy), 12.1 (Mechanism of Action), and Section 13.1 (Carcinogenesis, Mutagenesis, and Impairment of Fertility) were proposed in Dr. Pei's review dated July 17, 2014. As the maximum recommended daily dose of FF is increased in Arnuity Ellipta versus Breo Ellipta (200 µg versus 100 µg), Dr. Pei recommended edits to animal to human dose ratios in Sections 8.1 and 13.1 to reflect decreased animal to human dose ratios. In addition, Dr. Pei recommended edits to Section 12.1 to ensure consistent labeling language across products of the same drug class. See Dr. Pei's review for complete product labeling details.

There are no outstanding Pharmacology and Toxicology issues for this product.

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/s/

MARCIE L WOOD
07/25/2014

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: NDA 205-625

Supporting document/s: Sequences 0000

Applicant's letter date: October 22, 2013

CDER stamp date: October 22, 2013

Product: Arnuity Ellipta (Fluticasone Furoate) Dry Powder Inhaler

Indication: Asthma in patients 12 years of age and older

Applicant: GlaxoSmithKline (GSK)

Review Division: Division of Pulmonary, Allergy, and Rheumatology

Reviewer: Luqi Pei, Ph.D.

Supervisor: Marcie Wood, Ph.D.

Division Director: Badrul Chowdhury, M.D., Ph.D.

Project Manager: Nina Ton, Pharm.D.

Template Version: September 1, 2010

Disclaimer

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1 Executive Summary

1.1 Introduction

This review evaluates nonclinically the safety of the Arnuity Ellipta NDA application (NDA #205-625). GSK proposes to register Arnuity Ellipta (fluticasone furoate dry powder inhaler) for an asthma indication in patients 12 years of age and older.¹ Arnuity Ellipta has two dosage strengths: 100 or 200-μg fluticasone furoate (FF) per actuation. The proposed maximum recommended daily clinical dose of fluticasone furoate (FF) is 200-μg/day. The device product uses lactose as the excipient. See Section 2.3 Drug Formulation for formulation information.

This NDA makes references to the following two existing NDAs: Veramyst Nasal Spray and Breo Ellipta DPI (NDAs 20-551 and 204-275, respectively). The Agency approved Veramyst and Breo NDAs on April 27, 2007, and May 10, 2013, respectively. Veramyst is indicated for allergic rhinitis 12 years of age and older. Breo Ellipta is indicated for chronic obstructive pulmonary disease (COPD). Table 1 presents an overview of the FF products.

Table 1: Overview of Fluticasone Furoate NDAs

Application No.	Drug Name	Indication	FF Dosage (mcg/day)		Reference ^a (DARRTS ID#)
			Adult	Children	
020-551	Veramyst NS	Rhinitis ≥ 2 year	110 mcg ^b	110 mcg	3177618
204-275	Breo Ellipta	COPD in adults	100 mcg ^c	N/A ^e	3306791
205-625	Arnuity Ellipta	Asthma ≥ 12 year	200 mcg ^d	N/A	N/A

a. The approved labeling and reference identification number in the Agency's DARRTS database.

b. A maintenance dose. Each actuation of Veramyst NS releases 55-mcg FF. The maintenance dose is actuation in each nostril once daily. A starting dose of 2 actuations per nostril once daily (i.e., 220 mcg/patient/day) is recommended in adults and may be used in children to manage symptoms. The maintenance dose (1 actuation per nostril once daily, 110 mcg/patient/day) should be used once symptoms are controlled.

c. Each actuation of Breo Ellipta releases 100-mcg FF and 25-mcg vilanterol. The recommended human dose of Breo Ellipta is one actuation per day.

d. The highest proposed FF dose in patients 12 years of age and older. The applicant also proposed doses of 100-mcg FF. The Medical discipline is reviewing the approvability of both doses.

e. N/A, not applicable.

The application contained no new nonclinical data. The applicant resubmitted the FF nonclinical studies that had been submitted to the Veramyst and Breo Ellipta applications. Because the application contained no new, significant nonclinical data, it is unnecessary to generate a detailed nonclinical review for the NDA. A labeling review is necessary because of the potential differences in clinical FF dosage and subsequent differences in dose ratios among applications.

1.2 Brief Discussion of Nonclinical Findings

Not applicable. No new, significant nonclinical data were submitted. Pivotal nonclinical data in support of the safety of FF were previously submitted to and reviewed by the Agency in other applications. Fluticasone furoate possesses a toxicity profile typical of inhaled

¹ The Agency granted this trade name on March 4, 2014 (Ref.: DARRTS ID# 3464364).

corticosteroids, according to the nonclinical reviews completed in the previous applications. See Section 3.3 for these reviews. Briefly, FF is non-genotoxic, non-carcinogenic and non-teratogenic, according to the Breo Ellipta labeling approved on May 10, 2013 (NDA 204-275).

² The target organ of inhaled fluticasone was the respiratory and immune systems.

1.3 Recommendations

1.3.1 Approvability

Approval of the application is recommended from the nonclinical perspective. The applicant has conducted adequate nonclinical characterizations of the toxicity profile of FF in the reference products: Veramyst Nasal Spray and Breo Ellipta (NDAs 22-051 and 204-275, respectively). The characterization included evaluations of the pharmacological, pharmacokinetic, and toxicological profiles of the drug by proper routes of administration. No nonclinical issues were identified in the current application. The review recommends approval of the application from the nonclinical perspective.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

The following is the recommended text for the nonclinical sections of the Arnuity Ellipta labeling. These sections include Section 8.1, 12.1 and 13.1. See Section 12 Labeling Review for rationales and justifications for the recommended edits.

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled studies with ARNUITY ELLIPTA in pregnant women. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Because animal studies are not always predictive of human response, ARNUITY ELLIPTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while taking ARNUITY ELLIPTA.

There were no teratogenic effects in rats and rabbits at approximately 4 times and equal to, respectively, the maximum recommended human daily inhalation dose (MRHDID) in adults (on a mcg/m² basis at maternal inhaled doses up to 91 and 8 mcg/kg/day in rats and rabbits, respectively). There were no effects on perinatal and postnatal development in rats at approximately equal to the MRHDID in adults (on a mcg/m² basis at maternal doses up to 27 mcg/kg/day).

² Breo Ellipta is a drug powder inhaler containing fluticasone furoate and vilanterol furoate as the active pharmaceutical ingredients. The labeling of the product can be accessed at <http://www.accessdata.fda.gov/drugsatfdadocs/label/2011/022051s007lbl.pdf>.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

12.1 Mechanism of Action

Fluticasone furoate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity. Fluticasone furoate has been shown in vitro to exhibit a binding affinity for the human glucocorticoid receptor that is approximately 29.9 times that of dexamethasone and 1.7 times that of fluticasone propionate. The clinical relevance of these findings is unknown.

Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, basophils, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

Though effective for the treatment of asthma, corticosteroids may not affect symptoms immediately. Individual patients will experience a variable time to onset and degree of symptom relief. Maximum benefit may not be achieved for 1 to 2 weeks or longer after starting treatment. When corticosteroids are discontinued, asthma stability may persist for several days or longer.

Trials in subjects with asthma have shown a favorable ratio between topical anti-inflammatory activity and systemic corticosteroid effects with recommended doses of orally inhaled fluticasone furoate. This is explained by a combination of a relatively high local anti-inflammatory effect, negligible oral systemic bioavailability (approximately 1.3%), and the minimal pharmacological activity of the metabolites detected in man.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Fluticasone furoate produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 9 and 19 mcg/kg/day, respectively (less than the MRHDID in adults on a mcg/m² basis).

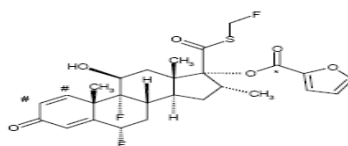
Fluticasone furoate did not induce gene mutation in bacteria or chromosomal damage in a mammalian cell mutation test in mouse lymphoma L5178Y cells in vitro. There was also no evidence of genotoxicity in the in vivo micronucleus test in rats.

No evidence of impairment of fertility was observed in male and female rats at inhaled fluticasone furoate doses up to 29 and 91 mcg/kg/day, respectively (approximately equal to and 4 times, respectively, the MRHDID in adults on a mcg/m² basis).

2 Drug Information

2.1 Drug

CAS Registry Number: 90566-53-3
Product Name: Arnuity Ellipta DPI
Generic Name: Fluticasone Furoate (FF)
Code Name: GW685698
Chemical Name: Androsta-1,4-diene-17-carbothioic acid, 6,9-difluoro-11,17-dihydroxy-16-methyl-3-oxo-, S-(fluoromethyl) ester, (6alpha,11beta,16alpha,17alpha)-
Molecular Formula/Weight: C₂₇H₂₉F₃O₆S/538.6
Structure:



Pharmacologic Class: Corticosteroid

2.2 Relevant INDs, NDAs, and DMFs

IND/NDA	Product	Ingredient	Indication	Date ^a
IND 48,647	-	Fluticasone Furoate (FF)	Rhinitis	10/30/2003
IND 70,297	-	FF	Asthma	10/26/2006
IND 77,855	-	FF/vilanterol (VI)	COPD	6/27/2009
IND (b) (4)	-	(b) (4)	Asthma	(b) (4)
IND (b) (4)	-	(b) (4)	COPD	(b) (4)
NDA 22-051	Veramyst NS	FF	Rhinitis	4/27/2007
NDA 204-275	Breo Ellipta	FF/VI	COPD	5/10/2013

a. These dates are filing and approval dates for IND and NDA applications, respectively.

2.3 Drug Formulation

Fluticasone furoate inhalation powders are supplied in blisters. A blister may contain 100 or 200-mcg fluticasone furoate and (b) (4)-mg lactose (excipient). The drug will be delivered by the Ellipta device.

2.4 Comments on Novel Excipients

Not applicable. The product uses lactose as an inactive ingredient. Lactose is a well-characterized and common excipient in inhalation drug product. Each actuation (daily dose) releases (b) (4)-mg lactose. Breo Ellipta DPI (fluticasone furoate and vilanterol, NDA 204-275 approved on May 10, 2013) contains (b) (4).

2.5 Comments on Impurities/Degradants of Concern

No impurities identified in the product had estimated exposure levels of > 0.15 µg/day. There is no safety concern about any of the impurities that may be present in the product.

2.6 Proposed Clinical Population and Dosing Regimen

Asthmatics 12 years of age and older will be using the maximum recommended dose of 200-mcg fluticasone/day. Patients needing low, mid, and high doses of inhaled corticosteroids (ICS) will receive 100, (b) (4), and 200-mcg FF, respectively.

2.7 Regulatory Background

GSK carried out the development for the Arnuity Ellipta NDA (fluticasone furoate DPI, NDA 205-625) under IND 70,297. All pivotal nonclinical data in support of FF safety was collected in other applications reviewed by the Agency previously. These applications included Veramyst Nasal Spray and Breo Ellipta NDAs (#20-551 and #204,275, respectively) and IND (b) (4). See Section 2.2 Relevant INDs, NDAs, and DMFs for a complete list of FF applications.

The Agency approved Veramyst and Breo applications on April 27, 2007, and May 10, 2013, respectively. Veramyst is indicated for allergic rhinitis in patients 2 years of age and older. Breo Ellipta is indicated for chronic obstructive pulmonary disease (COPD), an adult disease. The proposed indication for Arnuity Ellipta is asthma in patients 12 years of age and older.

DPARP and GSK had numerous interactions discussing the development of Arnuity Ellipta. Key interactions were held under IND 70,297. Some interactions were held under other applications (i.e., NDA 20-551 and IND 77,855). Table 1 lists the major interactions that discussed nonclinical issues.

Table 1: Key Regulatory Events in Relevant Applications

Application	Product	API	Key regulatory events	Dates
I 70,297	-	FF	Filing of the FF asthma IND	10/26/2006
I 70,297	-	FF	EPO2 Meeting for Asthma indication	03/16/2011
I 70,297	-	FF	Pre-NDA meeting for asthma indication	02/11/2013
I 77,855	-	FF/VI	Pediatric developmental program	05/11/2012
N 020-551	Veramyst	FF	Approval of FF NS for rhinitis indication	4/27/2007
N 204-275	Breo Ellipta	FF/VI	Approval of FF/VI for COPD indication	5/10/2013
N 205-625	Arnuity Ellipta	FF	Filing of the NDA for asthma indication	10/22/2013

Two meetings were held under IND 70,297. They were the 16-MAR-2011 End-of-Phase 2 (EOP2) meeting and the 11-FEB-2013 Pre-NDA meeting. Minutes of the meetings can be found in DARRTS Reference ID# 2927083 and 3260105, respectively. The EOP2 Meeting minutes stated that no further nonclinical studies were required to support the filing of an NDA for FF Inhalation Powder (ref.: Question 27). The minutes also stated that the applicant should qualify any impurities or degradants exceeding levels in the ICH Q3A(R) and ICHQ3B(R) guidances, respectively.

The pediatric program for a FF asthma indication was previously discussed in the 11-MAY-2012 Type C Meeting in IND 77,855 (Breo Ellipta) and the 11-FEB-2013 Pre-NDA meeting in IND 70,297, respectively. Breo Ellipta is a combination product (i.e., FF and vilanterol) approved for the COPD indication and is being developed for an asthma indication. Minutes of the meeting (DARRTS ID# 3133118) states that DPARP agreed the following regarding the pediatric program of the FF/VI combination product:

(b) (4)

GSK presented positions (b) (4) in the 11-FEB-2013 Pre-NDA meeting for the Arnuity program in IND 70,297. DPARP requested that GSK submit a pediatric plan in the Arnuity NDA submission.³ GSK submitted its pediatric plan on July 26, 2013 (Serial No. 0359) prior to the NDA submission and reiterated its 26-JUL-2013 position in the NDA submission. Briefly, GSK requested a deferral of clinical studies of Arnuity in children at 5 – 11 years of age and a waiver to studies in children ≤ 5 years of age.

Overall, this NDA contains no significant, new pivotal nonclinical data in support of the safety of the Arnuity Ellipta applications. All pivotal data was submitted to and reviewed by the Agency in the Veramyst and Breo applications.

3 Studies Submitted

3.1 Studies Reviewed

None of the submitted studies were reviewed in this document. All studies evaluating the toxicity profile of fluticasone furoate were submitted to and reviewed by DPARP staff previously. See the nonclinical review completed by D. Huiqing Hao on March 2, 2007 in NDA 22-051 (Veramyst, Nasal Spray) for lists of the fluticasone furoate studies.

3.2 Studies Not Reviewed

See the nonclinical review completed by D. Huiqing Hao on March 2, 2007 in NDA 22-051 (Veramyst, Nasal Spray) for a list of the fluticasone furoate studies.

3.3 Previous Reviews Referenced

This review references the pharmacology and toxicology review completed by Dr. Huiqing Hao on March 2, 2007, in NDA 22-051 (Veramyst Nasal Spray) and by Dr. Luqi Pei on April 22, 2013, in NDA 204-275 (Breo Ellipta DPI, DARRTS ID# 3274683).

³ The minutes stated that “[A]s your EOP2 meeting occurred prior to November 16, 2012, and your application is expected to be submitted prior to January 5, 2014, you should include your pediatric plan with you NDA submission” (Ref.: FDA Response to Question 20)

4 Pharmacology

No new data was submitted. Fluticasone furoate is a synthetic trifluorinated corticosteroid with (b) (4) anti-inflammatory activity.⁴ Inflammation is an important component in the pathogenesis of asthma.⁵ Corticosteroids have been shown to inhibit multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, neutrophils) and mediator production or secretion (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in the asthmatic response. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma (Ref.: Footnote 6).

5 Pharmacokinetics and Toxicokinetics

No new data was submitted for review. See the pharmacology and toxicology review completed by Dr. Huiqing Hao on March 2, 2007, in NDA 22-051 for the pharmacokinetic and toxicokinetic profile of FF in animals.

6 General Toxicology

No new data was submitted for review. See pharmacology and toxicology review completed by Dr. Huiqing Hao on March 2, 2007, in NDA 22-051 for the general toxicity profile of FF in animals. Briefly, FF possesses the toxicity profile typical of glucocorticosteroids.

7 Genetic Toxicology

No new data was submitted for review. FF is non-genotoxic based on the information in the Breo Ellipta labeling approved on May 10, 2013 (DARRTS #3306791): FF did not induce gene mutation in bacteria or chromosomal damage in a mammalian cell mutation test in mouse lymphoma L5178Y cells in vitro. There was also no evidence of genotoxicity in the in vivo micronucleus test in rats, according to the Breo Ellipta labeling. See the pharmacology and toxicology review completed by Dr. Huiqing Hao on March 2, 2007, in NDA 22-051 for the review of these genetic toxicity test reports.

8 Carcinogenicity

No new data was submitted for review. Fluticasone furoate did not produce any treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 9 and 19 mcg/kg/day, respectively. See the pharmacology and toxicology review completed by Dr. Huiqing Hao on March 2, 2007, in NDA 22-051 for the review of these study reports.

⁴ The Breo Ellipta product labeling approved on May 10, 2013, DARRTS # 3306791.

⁵ The Flovent HFA product labeling approved on 07/17/2013, DARRTS ID# 3232188.

9 Reproductive and Developmental Toxicology

No new data was submitted for review. The following information was extracted from the Breo Ellipta labeling approved on May 10, 2013 (DARRTS #33306791). Rats and rabbits at approximately maternal inhaled doses up to 91 and 8 mcg/kg/day, respectively, did not show any teratogenic effects. There were no effects on perinatal and postnatal development at maternal doses up to 27 mcg/kg/day in rats.

10 Special Toxicology Studies

No new data was submitted for review.

11 Integrated Summary and Safety Evaluation

This review recommends approval of the Arnuity Ellipta application (NDA 205-625). Arnuity Ellipta is a fluticasone furoate dry powder inhaler indicated for asthma. GSK proposed to register the drug/device product for an asthma indication. GSK has conducted adequate nonclinical safety evaluations of the active and inactive ingredients of the product. The review recommends approval of the product from the nonclinical perspective.

Arnuity Ellipta is a dry powder inhaler that delivers fluticasone furoate (FF). Arnuity Ellipta has two dosage strengths: 100 and 200-µg fluticasone per actuation. The device contains lactose as the excipient. Each actuation from each device (100 or 200-µg fluticasone presentations) releases (b) (4)-mg lactose.

Nonclinical characterizations and evaluations of FF were completed in previous applications. These applications include Veramyst Nasal Spray and Breo Ellipta NDAs (Nos. 20-551 and 204-275, respectively). The Agency approved Veramyst and Breo on April 27, 2007, and May 10, 2013, respectively. GSK FF in the current submission resubmitted all nonclinical data that it had submitted to the Agency in the previous applications. The Agency had reviewed and evaluated such data. See nonclinical reviews completed by Dr. Huiqing Hao on March 7, 2007, in NDA 22-051 and by Dr. Luqi Pei on April 22, 2013, in NDA 204-275 (DARRTS ID# 3274683) for reviews and evaluations. The following is a brief summary based on the available reviews and product labeling.

Pharmacologically, fluticasone furoate is a synthetic corticosteroid with potent anti-inflammatory activity, according to the Veramyst labeling. Corticosteroids affect a wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation. Fluticasone furoate exhibits a high binding affinity for the human glucocorticoid receptor. Asthma is a chronic inflammatory disease of the airways. A number of inhaled corticosteroids have been approved and marketed for the asthma indication.

Toxicologically, fluticasone furoate is non-mutagenic, non-carcinogenic, and non-teratogenic. General toxicity studies showed that fluticasone furoate possesses a toxicity profile typical of glucocorticosteroid drugs. Treatment-related findings included changes in body weights, clinical pathology, histopathological findings of adrenal atrophy, lymphoid depletion, fatty bone marrow, hair-loss and dermal thinning, liver glycogen deposition, hepatocyte rarefaction and/or hypertrophy, pituitary acidophilic cells, and epiphyseal plate retention. The text below describing fluticasone

furoate toxicity profile is extracted from the Breo Ellipta Labeling (DARRTS ID# 3306791) approved on May 10, 2013.⁶

“8.1 Pregnancy

Teratogenic Effect: Pregnancy Category C. ...

Fluticasone furoate: There were no teratogenic effects in rats and rabbits at approximately 9 and 2 times, respectively, the MRHDID in adults (on a mcg/m² basis at maternal inhaled doses up to 91 and 8 mcg/kg/day in rats and rabbits, respectively). There were no effects on perinatal and postnatal development in rats at approximately 3 times the MRHDID in adults (on a mcg/m² basis at maternal doses up to 27 mcg/kg/day).

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.”

“12.1 Mechanism of Action

Fluticasone furoate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity. Fluticasone furoate has been shown in vitro to exhibit a binding affinity for the human glucocorticoid receptor that is approximately 29.9 times that of dexamethasone and 1.7 times that of fluticasone propionate. The clinical relevance of these in vitro findings is unknown. The precise mechanism through which fluticasone furoate affects COPD symptoms is not known. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation. Specific effects of fluticasone furoate demonstrated in in vitro and in vivo models included activation of the glucocorticoid response element, inhibition of pro-inflammatory transcription factors such as NFκB, and inhibition of antigen-induced lung eosinophilia in sensitized rats.”

“13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Fluticasone furoate produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 9 and 19 mcg/kg/day, respectively (approximately equal to the MRHDID in adults on a mcg/m² basis).

Fluticasone furoate did not induce gene mutation in bacteria or chromosomal damage in a mammalian cell mutation test in mouse lymphoma L5178Y cells in vitro. There was also no evidence of genotoxicity in the in vivo micronucleus test in rats.

No evidence of impairment of fertility was observed in male and female rats at inhaled fluticasone furoate doses up to 29 and 91 mcg/kg/day, respectively (approximately 3 and 9 times, respectively, the MRHDID in adults on a mcg/m² basis).”

Recommendation:

The nonclinical safety program for fluticasone furoate inhalation powder is complete. From a nonclinical perspective, the application is recommended for approval. No additional nonclinical studies are required. Edits to the proposed labeling is recommended. See Section 12 Labeling Review.

⁶ Breo Ellipta is a drug powder inhaler and combination drug product. It contains fluticasone furoate and vilanterol furoate as the active pharmaceutical ingredients.

12 Labeling Review

Edits to the proposed text of the nonclinical sections of the Arnuity Ellipta labeling are recommended. These sections are Sections 8.1 Pregnancy, 12.1 Mechanism of Action, and 13.1 Mutagenesis, Carcinogenesis, and Impairment of Fertility. Major edits are made to Section 12.1. Minor edits were made for Sections 8.1 and 13.1. Edits to Section 12.1 are made to ensure labeling consistency across the same active ingredients. These products include Veramyst Nasal Spray and Breo Ellipta (NDA 22-051 and 204-275, respectively). Minor edits were made to Sections 8.1 and 13.1 because of differences in trade names and recommended human doses among FF products.

12.1 Dose ratios

Edits to dose ratios between animals and humans are recommended. The applicant proposed the same dose ratio between animals and humans for the nonclinical sections of the Arnuity and Breo Labeling. Such ratios are inaccurate because the maximum recommended human daily inhalation doses (MRHDID) of FF differ between Arnuity and Breo. Specifically, the MRHDID of FF will be 200 and 100 mcg for Arnuity and Breo, respectively. As such, dose ratios should be decreased by half. Table 2 presents ratios for the nonclinical sections of Arnuity Ellipta labeling. The table contains the ratios in Breo Ellipta labeling for reference. Dr. Luqi Pei completed the labeling review of Breo Ellipta on April 22, 2013 (DARRTS Reference ID# 3296873).

Table 2: Dose Ratios between Animals and Humans

Section of Labeling	Species	ROA	Dose Ratio (Animal/human) ^a				
			Fluticasone		Arnuity (200 mcg/day)		BREO
			mcg/kg/day	mcg/m ²	Calculated	Round to	(100 mg/day)
Pregnancy	Rat	IH	91	546	4.43	4	9
	Rat	IH	9.5	57	0.46	0.5	1
	Rabbit	IH	8	96	0.78	1	2
P. natal dev. ^b	Rat	IH	27	162	1.31	1	3
Fertility	Rat, M	IH	29	24	1.17	1	2
	Rat, F	IH	91	546	4.43	4	9
Carcinogenicity	Mouse	IH	19	57	0.46	0.5	1
	Rat	IH	9	54	0.44	0.5	1

a. On a mcg/m² basis. The human dose = 12.3 mcg/kg (200 mg/day x 37/60 kg = 12.3 mcg/kg/day)

b. P. natal d. = post natal development.

12.2 Overview and rationales for recommended edits

The review recommends minor edits to Sections 8.1 and 13.1 and major edits to Section 12.1. In Sections 8.1 and 13.1, edits to dose ratios between animals and humans are recommended. These edits are necessary because a new, higher clinical dose of fluticasone furoate is to be approved. The new clinical dose results in lower dose ratios between animals and humans in these sections. The review recommends no text revisions, because the proposed text is identical to that of the Breo Labeling that was approved on May 10, 2013 (DARRTS ID# 3306791).

For Section 12.1, the review recommends significant edits to the proposed text. The edits are made to ensure the concise presentation of relevant data and to maintain consistency in labeling across products of the same drug class. The review references the labeling of three approved and marketed products to maintain constancy. The products are Breo Ellipta DPI (NDA 204,275), Flovent (NDAs 21-433 and 20-833),⁷ and Alvesco MDI (NDA 21-658). These products were chosen because of similarities in pharmacological properties of their APIs and their indications as discussed below:

- Breo Ellipta and Arnuity Ellipta both contain fluticasone furoate as an API and use the same device, although they differ in indications: Breo for COPD and Arnuity for asthma, respectively.⁸
- Flovent HFA and Arnuity Ellipta are indicated for the same disease (i.e., asthma). Also, APIs of the products are two esters of the same active moiety, fluticasone: fluticasone propionate in Flovent and fluticasone furoate in Arnuity, respectively. Further, GSK is the holder of both FP and FF NDAs.⁹
- Alvesco is the most recently approved inhaled corticosteroid of new molecular entities by the Agency.¹⁰

⁷ Flovent has two products (i.e., Flovent HFA metered-dose inhaler and Flovent Diskus). (b) (4), (b) (5)

⁸ (b) (4)

⁹ (b) (4)

¹⁰ The Alvesco labeling (DARRTS ID# 3232188 approved on (b) (4) states: "Ciclesonide, is a prodrug that is enzymatically hydrolyzed to a pharmacologically active metabolite, C21-desisobutryl-ciclesonide (des-ciclesonide or RM1) following oral inhalation. Des-ciclesonide has anti-inflammatory activity with affinity for glucocorticoid

The proposed text for the Arnuity labeling deviates significantly from the labeling for the reference products. Minor differences are expected because of differences in APIs, indications, and other properties among these products. However, the text below should be rejected again because the Agency had rejected it previously in the Breo Ellipta application. See nonclinical labeling review completed by Dr. Luqi Pei on April 22, 2013, and the Breo Labeling approved on May 10, 2013 (DARRTS ID# 3296873 and 3306791, respectively).

(b) (4)

The review also recommends deleting additional sentences from Section 12.1 although they are present in the currently approved labeling of Breo Ellipta. These edits are made to omit information that does not closely reflect the proposed indication of the drug products as indicated earlier. The review recommends deleting the following statements:

(b) (4)

12.3 Recommended edits

Below are the recommended edits to the text of the nonclinical sections of the proposed labeling. Highlights reflect the recommended changes. Strikeouts indicate recommended deletions and underlines indicate additions.

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled studies with ARNUITY ELLIPTA in pregnant women. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Because animal studies are not always predictive of human response, ARNUITY ELLIPTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while taking ARNUITY ELLIPTA.

receptors that is 120 times greater than the parent compound and 12 times greater than dexamethasone. The clinical significance of these findings is unknown.

The precise mechanisms of corticosteroid action in asthma are unknown. Inflammation is recognized as an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in the asthmatic response. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma. Though effective for the treatment of asthma, corticosteroids do not affect asthma symptoms immediately. Individual patients will experience a variable time to onset and degree of symptom relief. Maximum benefit may not be achieved for four weeks or longer after starting treatment. When corticosteroids are discontinued, asthma stability may persist for several days or longer."

(b) (4)

Trials in subjects with asthma have shown a favorable ratio between topical anti-inflammatory activity and systemic corticosteroid effects with recommended doses of orally inhaled fluticasone furoate. This is explained by a combination of a relatively high local anti-inflammatory effect, negligible oral systemic bioavailability (approximately 1.3%), and the minimal pharmacological activity of the metabolites detected in man.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

Fluticasone furoate did not induce gene mutation in bacteria or chromosomal damage in a mammalian cell mutation test in mouse lymphoma L5178Y cells in vitro. There was also no evidence of genotoxicity in the in vivo micronucleus test in rats.

(b) (4)

Luqi Pei, Ph.D.

Senior Pharmacologist/Toxicologist

Marcie Wood, Ph.D.

Supervisory Pharmacologist

13 Appendices

None

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/s/

LUQI PEI
07/17/2014

MARCIE L WOOD
07/17/2014

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 205-625

Applicant: GSK

Stamp Date: October 22, 2013

Drug Name: Fluticasone Furoate
Dry Powder Inhaler

NDA/BLA Type: Original NDA

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	x		The submission contained all nonclinical data of fluticasone furoate, but pivotal data had been submitted to and reviewed by the Agency in NDA 22-051 (Veramyst NS). It is unnecessary to review these studies.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			Not applicable. See comments in Item 1.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			Not applicable. See comments in Item 1.
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	x		A pre-NDA meeting in IND 70297 was held on February 11, 2013. The meeting minutes (Question 27) states that no "further nonclinical studies are required to support the filing of an NDA for FF Inhalation powder."
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Not applicable. The product contained fluticasone and lactose as the API and excipient, respectively. The API was approved for nasal (Veramyst NS, NDA 22-051) and inhalation (Breo Ellipta DPI, NDA 204-275). Breo Ellipta DPI uses lactose as an excipient.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?			Not applicable.
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			Not applicable.
8	Has the applicant submitted all special Studies or data requested by the Division during pre-submission discussions?			Not applicable. See comments in Item 4.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m ² or comparative serum/plasma levels) and in accordance with 201.57?	x		The proposal labeling is in the PLR format.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			To be determined in consultation with the reviewing chemist.
11	Has the applicant addressed any abuse potential issues in the submission?	x		The drug is approved and currently marketed for the same route of the administration in COPD patients.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? __YES.____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

Luqi Pei, Ph.D.

Reviewing Pharmacologist

December 12, 2013

Date

Marcie Wood, Ph.D.

Supervisory Pharmacologist

Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LUQI PEI
12/13/2013

MARCIE L WOOD
12/13/2013
I concur