

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205382Orig1s000**

**PHARMACOLOGY REVIEW(S)**

## Pharmacology and Toxicology Secondary Review for NDA 205-382

TO: NDA 205-382 (INCRUSE ELLIPTA; Umeclidinium bromide)

FROM: Timothy W. Robison, Ph.D., D.A.B.T.  
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Division of Pulmonary, Allergy, and Rheumatology Products

DATE: January 13, 2014

INCRUSE ELLIPTA is a dry powder inhaler containing umeclidinium bromide for the treatment of airflow obstruction in chronic obstructive pulmonary diseases (COPD) in adults. INCRUSE ELLIPTA delivers 62.5 mcg of umeclidinium bromide in each actuation. The formulation includes magnesium stearate and lactose as excipients.

Dr. Whittaker's review focused on the nonclinical safety assessment of umeclidinium bromide alone.

I concur with the recommendations of Dr. Whittaker's review dated December 12, 2013 that the nonclinical pharmacology and toxicology of the drug product, umeclidinium bromide, have been adequately studied and INCRUSE ELLIPTA should be approved from the nonclinical perspective.

Pharmacology: Umeclidinium is a long-acting, antimuscarinic agent, which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, it exhibits pharmacological effects through inhibition of M3 receptor at the smooth muscle leading to bronchodilation.

Secondary Pharmacology: Umeclidinium at 1  $\mu$ M was screened against a panel of receptors, ion channels, and transporters using radioligand binding. The  $K_i$  values for the five targets, which were not muscarinic M<sub>1</sub>-M<sub>4</sub> receptors, were Kappa opioid receptor (69 nM), Sigma (non-selective) receptor (220 nM), Ca<sup>2+</sup> channel [L, verapamil site] (330 nM), Na<sup>+</sup> channel [site 2] (170 nM), and Dopamine transporter (780 nM).

Safety Pharmacology: Umeclidinium bromide was assessed for effects on CNS, cardiovascular, and respiratory functions in safety pharmacology studies with rats and dogs following inhalation exposure. Moderately dilated pupil was observed for rats at inhaled doses of 322 and 1994 mcg/kg, which was an expected pharmacological effect, but no other changes in CNS were observed. An inhaled dose of 10  $\mu$ g/kg administered to dogs increased heart rate up to 49 bpm from a predose average of 65 bpm, which recovered 30 min after infusion. In agreement with increased heart rate, RR interval decreased, but returned to predose values by 30 min postdose. Changes in heart rate and RR interval were associated with the tachycardia seen following dosing with 10 mcg/kg. Second degree atrioventricular (AV) block was observed in 3 of 4 animals treated with 10 mcg/kg. Increased heart rate, decreased RR interval, and AV block can

be attributed to the antimuscarinic effects of umeclidinium. Single inhaled doses of umeclidinium at 215 and 2260 mcg/kg administered to rats produced increases in respiratory rate (18 to 45%) and decreases in tidal volume (3 to 17%).

ADME: The absorption, distribution, metabolism, and excretion of umeclidinium were examined in mice, rats, dogs, and humans. The half-lives of umeclidinium in rats and dogs following intravenous administration were 1.42 and 11.6 hr, respectively. The half-life of umeclidinium at an inhaled dose of 62.5 µg in human subjects was 11 to 15 hr. Plasma protein binding in mouse, rat, rabbit, dog, and human ranged from 74.7 to 88.8% and was concentration-independent. Studies in rats and dogs suggested extensive distribution into tissues and rapid clearance suggestive of metabolic clearance. Umeclidinium was a substrate for p-glycoprotein. Metabolism was examined *in vitro* using hepatocytes from mouse, rat, rabbit, dog and human. Studies with human hepatocytes and microsomes found that the main routes of metabolism of umeclidinium were O-dealkylation and hydroxylation. Other routes were conjugation with glutathione and methylation and/or glucuronidation of the hydroxylated metabolite. The main routes of metabolism in humans were also present in rat and dog. Metabolism of umeclidinium in human liver microsomes was mediated primarily by CYP2D6, with some contribution from CYP3A4; umeclidinium was an inhibitor of both enzymes.

Inhalation Toxicology: Pivotal general toxicology studies to support the use of umeclidinium were 26 and 39 week inhalation studies in rats and dogs, respectively. NOAELs were identified in both studies. Relevant target organs were the lung and tracheal bifurcation in the rat and the heart, lung, larynx, and nasal turbinates in the dog.

Genotoxicity: Umeclidinium was negative in genetic toxicology testing based on results from the *in vitro* bacterial reverse mutation assay, *in vitro* mouse lymphoma assay, and *in vivo* rat micronucleus test.

Carcinogenicity: The sponsor determined the carcinogenic potential of umeclidinium in 2-year nose-only inhalation bioassays conducted with mice and rats. Both bioassays were negative for test-article related tumors.

Reproductive and developmental toxicology: Reproductive and developmental studies showed that umeclidinium had no effects on fertility or reproductive performance in rats and was not teratogenic in rats or rabbits. Umeclidinium did not have any effects on pre- or post-natal development in rats.

Excipients: The drug product includes lactose and magnesium stearate as excipients. There are no safety concerns for either compound.

Established Pharmacological Class (EPC): INCRUSE ELLIPTA is an anticholinergic. The EPC for umeclidinium as an anticholinergic was discussed with Dr. Paul Brown.

Labeling: Dr. Whittaker's review recommends changes to product labeling in Section 1 (Indications and Usage), Section 8.1 (Pregnancy), Section 8.3 (Nursing Mothers),

Section 12.1 (Mechanism of Action), and Section 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility). I concur with Dr. Whittaker's recommendations for changes to the product label. See Dr. Whittaker's review for additional details of changes to the product labeling.

Control of potential genotoxic impurities: Genotoxic impurities in the drug substance were controlled to the Threshold of Toxicological Concern (TTC) of less than 1.5 µg/day.

**Recommendation:** From the nonclinical perspective, approval of the application is recommended.

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

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/s/  
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TIMOTHY W ROBISON  
01/13/2014

**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 205,382

**Supporting document/s:** SD-1 (New NDA)  
SD-5 (Labeling/Package Insert Draft)  
SD-9 Proprietary name/request for review

**Applicant's letter date:** SD-1: 4/29/13  
SD-5: 7/26/13  
SD-9: 9/6/13

**CDER stamp date:** SD-1: 4/30/13  
SD-5: 7/26/13  
SD-9: 9/6/13

**Product:** Umeclidinium bromide powder for inhalation

**Indication:** Maintenance treatment of airflow obstruction in chronic obstructive pulmonary disease (COPD)

**Applicant:** GlaxoSmithKline

**Review Division:** Division of Pulmonary, Allergy, and Rheumatology Products

**Reviewer:** Matthew Whittaker, Ph.D.

**Supervisor/Team Leader:** Timothy Robison, Ph.D.

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

**Project Manager:** Angela Ramsey

*Template Version: September 1, 2010*

## **Disclaimer**

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 205,382 are owned by GlaxoSmithKline or are data for which GlaxoSmithKline has obtained a written right of reference. Any information or data necessary for approval of NDA 205,382 that GlaxoSmithKline does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 205,382.

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## Executive Summary

### 1.1 Introduction

GlaxoSmithKline (GSK) submitted NDA 205,382 on April 30, 2013 for registration of INCRUSE ELLIPTA for maintenance treatment of airflow obstruction in chronic obstructive pulmonary disease (COPD). INCRUSE ELLIPTA is a dry powder inhaler that delivers micronized umeclidinium bromide (62.5 mcg per actuation) with the excipients magnesium stearate and lactose monohydrate. The proposed dose is 1 actuation per day. Umeclidinium bromide is a high affinity muscarinic antagonist with subnanomolar binding affinity at M1, M2, M3, M4, and M5 metabotropic acetylcholine receptors.

Nonclinical studies to support the use of GSK573719A (umeclidinium bromide salt) were submitted to IND 104,479. These studies were reviewed under IND 104,479 and NDA 203,975 (ANORO ELLIPTA, umeclidinium bromide and vilanterol combination). NDA 203,975 is pending approval by the FDA (approximately 12/18/13). The dose of umeclidinium bromide in INCRUSE ELLIPTA (62.5 mcg/day) is identical to that in ANORO ELLIPTA.

### 1.2 Brief Discussion of Nonclinical Findings

Umeclidinium bromide is a long acting muscarinic antagonist (LAMA). It is being recommended to be labeled as an anticholinergic drug to maintain consistency with the established pharmacological classification for similar approved drugs in its class. A complete and extensive nonclinical program has been conducted to support the safety of umeclidinium bromide.

Pivotal toxicology studies included a 26 week inhalation study in rats and a 39-week inhalation study in beagle dogs. Relevant target organs in the rat included the lung and tracheal bifurcation. Target organs in the dog included the heart, lung, larynx, and nasal turbinates. Safety margins were 25 and 16 times the maximum recommended human daily inhalation dose (MRHDID) on an AUC basis for rats and dogs, respectively.

Two-year carcinogenicity studies were conducted with umeclidinium in rats and mice. Both bioassays were negative for treatment-related tumors. Safety margins were 22 and 18 times the MRHDID on an AUC basis for male and female mice, respectively. The safety margin in male and female rats was 18 times the MRHDID.

Reproductive and developmental studies showed that umeclidinium did not affect fertility in rats, and was judged to be non-teratogenic in rats or rabbits at the doses tested. With regard to fertility, safety margins were 84 and 44 times the MRHDID on an AUC basis in studies in rats using subcutaneous (SC) and inhalation (IH) routes of administration respectively. For teratogenicity, safety margins were 165 and 44 times the MRHDID on an AUC basis for rabbits (SC) and rats (IH), respectively. The peri- and postnatal study in rats (SC) provided a safety margin of 67 times the MRHDID on an AUC basis.

### 1.3 Recommendations

#### 1.3.1 Approvability

The applicant has provided complete nonclinical pharmacology and toxicology data for umeclidinium to support the safety of the proposed clinical dose of 62.5 mcg/day for the treatment of airflow obstruction in COPD. The application is recommended for approval from the nonclinical perspective.

#### 1.3.2 Additional Non Clinical Recommendations

See Recommended Labeling Edits (1.3.3).

#### 1.3.3 Recommended Labeling Edits

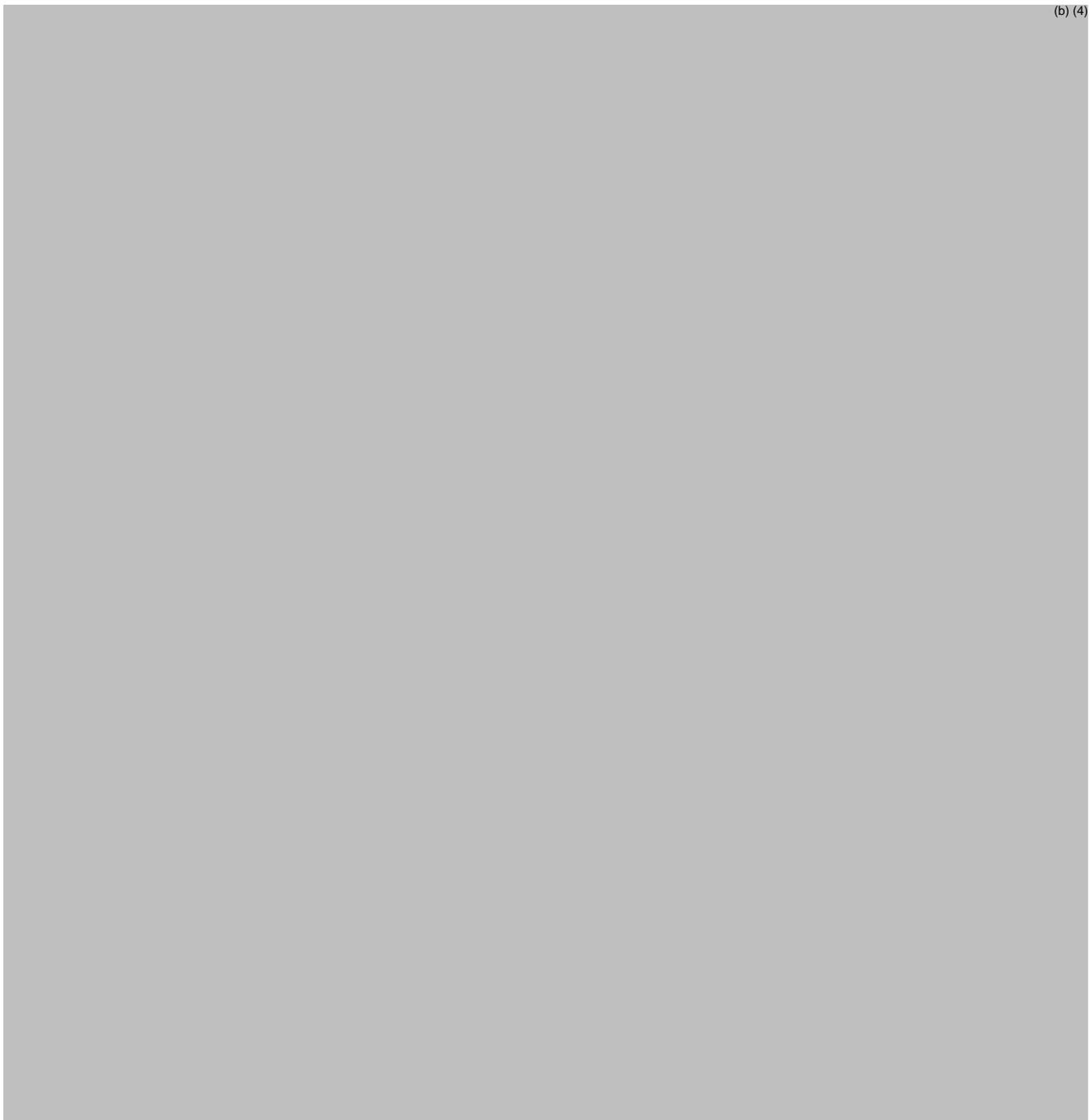
Recommended edits to the proposed text for the nonclinical sections of the INCRUSE ELLIPTA label are provided below. Additions are presented as red underlined text, while deletions are seen as strikethroughs.

Changes to the current label reflect the relevant language used in the current label for NDA 203,975 (umeclidinium + vilanterol; label date: 11/15/2013). Exposure multiples are also adjusted for the increase in clinical umeclidinium exposure at the maximum recommended human dose of 62.5 mcg/day (0.3716 ng\*h/ml) when administered as a monoproduct compared to umeclidinium exposure when administered in combination with vilanterol (0.3124 ng\*h/ml).

(b) (4)

(b) (4)





## **2 Drug Information**

### **2.1 Drug**

CAS Registry Number (Optional):  
869113-09-7

Generic Name:  
Umeclidinium bromide

Code Name:

GSK 573719A (bromide salt); GSK573719 (b) (4)

Chemical Name:

4-[Hydroxy(diphenyl)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide

Molecular Formula/Molecular Weight:C<sub>29</sub>H<sub>34</sub>NO<sub>2</sub> • Br

508.5 g/mol

(b) (4) 438.6 g/mol

Structure or Biochemical Description:Pharmacologic Class:

Anticholinergic

**2.2 Relevant INDs, NDAs, BLAs and DMFs**

- NDA 203,975 [GSK, ANORO ELLIPTA (umeclidinium bromide/vilanterol combination) Dry Powder Inhaler]
- IND 104,479 (GSK, GSK573719)
- DMF 26,339 (GSK, GSK573719)

**2.3 Drug Formulation**

The drug product is a plastic inhaler which contains one strip of either 30 or 7 regularly distributed blisters containing Umeclidinium Inhalation Powder (Table 1). Each dose contains 62.5 mcg of umeclidinium bromide per inhalation. The sponsor proposes inclusion of up to (b) (4) overage of the blend to compensate for losses during blister filling. The quantity of umeclidinium bromide per blister may be adjusted based on the assigned purity of the drug substance.

Table 1. Formulation for 62.5 microgram dose of Umeclidinium Inhalation Powder

Ingredient	Quantity per blister <sup>1</sup>	Function
Umeclidinium bromide, micronized	74.2 mcg <sup>2</sup>	Active
Magnesium stearate	75 mcg	(b) (4)
Lactose monohydrate	to 12.5 mg	(b) (4)

<sup>1</sup> Manufacturing overage of up to (b) (4) of the blend may be included

<sup>2</sup> 74.2 mcg of umeclidinium bromide is equivalent to 62.5 mcg of umeclidinium ( (b) (4)

## 2.4 Comments on Novel Excipients

Daily exposures to magnesium stearate and lactose monohydrate are lower than exposures in ANORO ELLIPTA, an inhaled product that is pending approval by the FDA (approximately 12/18/13).

## 2.5 Comments on Impurities/Degradants of Concern

There are no concerns for impurities or degradants from the nonclinical perspective.

## 2.6 Proposed Clinical Population and Dosing Regimen

INCRUSE ELLIPTA is intended for adults with chronic obstructive pulmonary disease (COPD). The proposed dosage is 62.5 mcg once daily.

## 2.7 Regulatory Background

NDA 205,382 relies on data submitted to IND 104,479 (umeclidinium alone) and NDA 203,975 (umeclidinium + vilanterol) for nonclinical support. The 62.5 mcg/day dose of umeclidinium in the combination product is identical to the proposed umeclidinium dose in the proposed monoproduct. Further discussion of the regulatory background of umeclidinium alone can be found in the nonclinical review for NDA 203,975 (pg. 19, Sohn, 6/25/13).

Table 2. Key regulatory events relevant to nonclinical review of umeclidinium.

Application	Drug	Regulatory event	Date
NDA 203,975	Umeclidinium (62.5 mcg) + vilanterol (25 mcg)	NDA Filing	12/18/2012
	Umeclidinium (62.5 mcg) + vilanterol (25 mcg)	Pulmonary Allergy Drugs Advisory Committee (PADAC)	9/10/2013
IND 104,479	Umeclidinium	pre-IND meeting	5/26/2009

Application	Drug	Regulatory event	Date
		Review of rat & mouse carcinogenicity protocols	6/3/2009
		IND Filing	7/14/2009
		Review of amendments to rat & mouse carcinogenicity protocols	2/18/2011
NDA 205,382	Umeclidinium (62.5 mcg)	NDA Filing	4/30/2013
		Proprietary name granted	11/21/2013

### 3 Studies Submitted

#### 3.1 Studies Reviewed

No new studies were reviewed for NDA 205,382.

#### 3.2 Studies Not Reviewed

Not applicable.

#### 3.3 Previous Reviews Referenced

NDA 203,975: Nonclinical review for Umeclidinium bromide (62.5 mcg)/Vilanterol (25 mcg) combination, Jane Sohn, Ph.D., 6/25/13.

NDA 203,975: FDA comments regarding proposed labeling for ANORO ELLIPTA; 11/5/13.

NDA 203,975: Cross-Discipline Team Leader review; Susan Limb, MD., 11/9/13.

NDA 205,382: Proprietary Name Review; Lissa Owens, 11/19/13.

### 4 Pharmacology

#### 4.1 Primary Pharmacology

Umeclidinium bromide is a high affinity muscarinic antagonist with subnanomolar binding affinity at M1, M2, M3, M4, and M5 metabotropic acetylcholine receptors.

See NDA 203,975 nonclinical review (6/25/13) for detailed discussion of umeclidinium bromide pharmacology.

## 4.2 Secondary Pharmacology

See NDA 203,975 nonclinical review (6/25/13)

## 4.3 Safety Pharmacology

See NDA 203,975 nonclinical review (6/25/13)

# 5 Pharmacokinetics/ADME/Toxicokinetics

## 5.1 PK/ADME

See NDA 203,975 nonclinical review (6/25/13)

# 6 General Toxicology

Toxicology studies for umeclidinium alone were carried out in rats, dogs, and mice. These studies were reviewed under IND 104,479. Pivotal toxicology studies included a 26 week inhalation study in rats and a 39-week inhalation study in beagle dogs. The results of these studies are described in the Nonclinical review for NDA 203,975 (pg. 88, 6/25/13). Safety margins are based on clinical exposure of umeclidinium alone dosed at the maximum recommended human inhaled dose of 62.5 mcg/day in COPD patients (Table 3).

Table 3. Safety margins for proposed maximum clinical dose of umeclidinium alone based on AUC

Study Type	Route	NOAEL dose (µg/kg/day)	Mean AUC <sub>0-t</sub> (ng*h/ml)	Clinical AUC <sub>ss</sub> at proposed UMEC dose of 62.5 µg/d (ng*h/ml)	Safety margin
26 week rat	Inhalation	87.1	9.49	0.3716 <sup>a</sup>	25
39 week dog	Inhalation	109	5.89		16

<sup>a</sup> Steady state UMEC alone clinical exposure value is from study DB2116975. This study predicted steady state UMEC exposures in COPD patients based on data from study DB2113373, a 24 week study in COPD patients. UMEC alone dose was 62.5 µg /day.

Safety margins with respect to pulmonary deposited dose are seen in Table 4. Note that clinical pulmonary deposited dose is calculated based on 100% dose deposition in humans and a lung weight of 1000 g.

Table 4. Safety margins for the proposed maximum clinical dose of umeclidinium alone based on pulmonary deposited dose.

Study Type	Route	NOAEL dose (µg/kg/day)	Pulmonary deposited dose (µg/g lung weight)	Clinical pulmonary deposited dose (µg/g lung weight)	Safety margin
26 week rat	Inhalation	87.1	2.44	0.0625	39
39 week dog	Inhalation	109	3.0		48

Please see the nonclinical review for NDA 203,975 (pgs. 24 – 28) for references to reviews of all nonclinical studies submitted to IND 104,479.

## 7 Genetic Toxicology

### 7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

See NDA 203,975 nonclinical review (6/25/13).

### 7.2 *In Vitro* Assays in Mammalian Cells

See NDA 203,975 nonclinical review (6/25/13).

### 7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

See NDA 203,975 nonclinical review (6/25/13).

### 7.4 Other Genetic Toxicity Studies

None.

## 8 Carcinogenicity

2 year inhalation carcinogenicity studies with umeclidinium were carried out in rats (Study 2012N131619) and mice (Study 2012N131664). Both bioassays were negative for treatment related tumors.

For detailed reviews of these studies, see Nonclinical reviews for NDA 203,975 dated 4/25/13 and 6/25/13. Safety margins for the proposed umeclidinium dose with respect to carcinogenicity are seen in Table 5.

Table 5. Safety margins for proposed maximum clinical umeclidinium dose based on carcinogenicity studies.

Study Type	Sex	Achieved NOAEL dose ( $\mu\text{g}/\text{kg}/\text{day}$ ) <sup>a</sup>	Mean $\text{AUC}_{0-t}$ ( $\text{ng}\cdot\text{h}/\text{ml}$ )	Clinical $\text{AUC}_{ss}$ at proposed UMEC dose of $62.5 \mu\text{g}/\text{d}$ ( $\text{ng}\cdot\text{h}/\text{ml}$ )	Safety margin
2 year mouse	Male	295	8.21	0.3716 <sup>b</sup>	22
	Female	200	6.87		18
2 year rat	Male & Female	137	6.75		18

<sup>a</sup> Doses were decreased at week 67 in male mice and at week 73 in male and female rats. Achieved doses listed in table reflect the reduced doses after the dose change.

<sup>b</sup> Steady state UMEC alone clinical exposure value is from study DB2116975. This study predicted steady state UMEC exposures in COPD patients based on data from study DB2113373, a 24 week study in COPD patients. UMEC alone dose was  $62.5 \mu\text{g}/\text{day}$ .

## 9 Reproductive and Developmental Toxicology

### 9.1 Fertility and Early Embryonic Development

See NDA 203,975 nonclinical review (6/25/13).

## 9.2 Embryonic Fetal Development

### 9.2.1 Inhaled Embryo-Fetal Development Study in Rats

Study no.:	WD2007/00764/00
Study report location:	Volume 23, pages 1-145
Conducting laboratory and location:	 (b) (4)
Date of study initiation:	
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	See original review by T. Robison, Ph.D. IND 104,479 May 25, 2010

#### Key Study Findings

- See the review in the nonclinical NDA review for NDA 203,975 (umeclidinium + vilanterol) completed by Jane Sohn, Ph.D. on 6/25/13.
- UMEC was administered by nose only **inhalation** for 1 hour each day from gestational days 6 – 17 in pregnant Sprague-Dawley rats
  - Achieved inhaled doses were estimated to be: 31.7, 96.9, and 278 µg/kg/day
- UMEC was not teratogenic in rats at inhaled doses up to 278 µg/kg/day
- No systemic exposure data was included with this study
  - For NDA 203,975 labeling purposes: systemic exposure values from a 28 day inhalation study in rats (Study #WD2005/0142) were proposed by FDA to establish safety margins
  - Sponsor used AUC data from a 13 week rat inhalation study to establish safety margins. AUC value is **16.2 ng\*h/ml**
  - Sponsor's AUC value was more conservative than the value initially used by the FDA and thus accepted for the label.

**9.2.2 GSK573719A: Subcutaneous Embryo-Fetal Development Study in Rabbits**

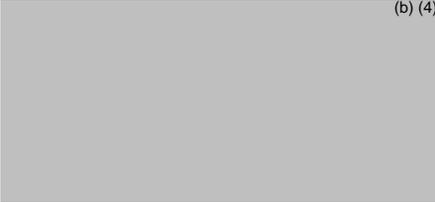
Study no.: CD2010/00253/00  
Study report location: SD-1, eCTD 4.2.3.5.2  
Conducting laboratory and location: GlaxoSmithKline  
UK Research & Development  
PCD-DMPK  
Park Road  
Ware, Hertfordshire  
SG12 0DP  
United Kingdom  
Date of study initiation: May 24, 2010  
GLP compliance: Yes  
QA statement: Yes  
Drug, lot #, and % purity: GSK 573719A bromide salt  
Batch R360972  
99.8%

**Key Study Findings**

- This study tested **subcutaneous** umeclidinium alone at doses of 0.04, 0.1, and 0.18 mg/kg/day in pregnant New Zealand white rabbits.
  - Animals were treated on gestational days 7 -19 and sacrificed on GD 29.
- See the complete review of this study in the nonclinical review for NDA 203,975 (umeclidinium + vilanterol), completed by Jane Sohn, Ph.D. on 6/25/13.
- Umeclidinium was not teratogenic in rabbits at doses up to 0.18 mg/kg/day.
  - Systemic exposure at the 0.18 mg/kg/day dose: **AUC<sub>0-t</sub> = 61.4 ng\*h/ml**

### 9.3 Prenatal and Postnatal Development

**Study title:**

Study no.: GSK # 2011N118595-00  
Study report location: SD-1, eCTD 4.2.3.5.2  
Conducting laboratory and location:  (b) (4)  
Date of study initiation:   
GLP compliance: Yes  
QA statement: Yes  
Drug, lot #, and % purity: GSK573719A (bromide salt of GSK573719)  
Batch #081168623  
83.8% purity  
Sponsor included a correction factor of 1.194  
for dose calculations

**Key Study Findings**

- See the complete review of this study in the nonclinical review for NDA 203,975 (umeclidinium + vilanterol), completed by Jane Sohn, Ph.D. on 6/25/13.
- Female rats received 0, 0.01, 0.06, or 0.18 mg/kg/day (SC) from gestation day 6 – postnatal day 20
- There were no effects on perinatal and postnatal development in rats at any of the doses tested
  - $AUC_{0-t}$  in dams at the highest dose tested on postnatal day 20 was 24.9 ng\*h/ml
  - This dose is equivalent to 67 times the MRHDID in adults (on an AUC basis at maternal subcutaneous doses up to 180 mcg/kg/day).

## 11 Integrated Summary and Safety Evaluation

### 11.1 Umeclidinium bromide

The nonclinical studies submitted in support of umeclidinium bromide adequately assessed the pharmacology, pharmacokinetics, and toxicology of umeclidinium. The nonclinical development program for umeclidinium is summarized in detail in section 11.1 of the Nonclinical Review for NDA 203,975 (6/25/13). Individual reviews of nonclinical studies submitted to IND 104,479 are referenced in the current review and in the Nonclinical review for NDA 203,975.

### 11.2 Excipients

INCRUSE ELLIPTA drug product contains lactose monohydrate and magnesium stearate as excipients. Lactose monohydrate is present as an excipient in currently marketed inhalation drug products at doses exceeding the approximately 12.5 mg dose in INCRUSE ELLIPTA. Support for the safety of magnesium stearate as an excipient is provided by a 26 week rat inhalation toxicity study (WD2006/03154; reviewed by Dr. Luqi Pei; 6/7/2000). No treatment related effects were observed at pulmonary deposited doses of magnesium stearate up to 180 mcg/kg/day. The expected exposure to magnesium stearate in patients taking INCRUSE ELLIPTA is 1.25 mcg/kg/day (75 mcg/day for 60 kg individual), thus providing a safety margin of 144.

**Unresolved toxicology issues:** None.

### 11.3 Labeling Evaluation

The maximum recommended human daily inhaled dose (MRHDID) for umeclidinium bromide is established as 62.5 mcg/day. This dose is associated with a human systemic exposure of 0.3716 ng\*h/ml in COPD patients (Study DB2116975). Doses referred to in nonclinical studies reflect the dose administered by the subcutaneous route or the estimated achieved dose via the inhalation route.

The proposed changes to the draft label for INCRUSE ELLIPTA reflect the current language in the label for ANORO ELLIPTA, and have been made to maintain consistency between the labels. The adjusted exposure multiples presented in the current draft label for INCRUSE ELLIPTA are due to the increased human systemic exposure of umeclidinium when administered alone (0.3716 ng\*h/ml) vs. when administered in combination with vilanterol in ANORO ELLIPTA (0.3124 ng\*h/ml). These changes are summarized in Table 6. The NOAEL and nonclinical AUC<sub>0-t</sub> values in this table are derived from the Nonclinical review of NDA 203,975 (Sohn, 6/25/13). In studies where toxicokinetic data was not available, AUC values were estimated based on values from studies in which animals were treated with similar doses and for a similar duration.

Table 6. Summary of relevant exposure multiples for inclusion in label for INCRUSE ELLIPTA.

Study Type	Study #	Species	Route	NOAEL dose (µg/kg/day)	AUC <sub>0-t</sub> (ng*h/ml)	Clinical AUC <sub>ss</sub> at proposed UMEC dose of 62.5 µg/d (ng*h/ml)	Exposure multiple
EFD	WD2007/00764	Rat	Inhalation	278	16.2 <sup>a</sup>		44
EFD	CD2010/00253	Rabbit	SC	180	61.4		165
PPND	2011N118595	Rat	SC	180	24.9		67
PPND	2011N118595	Rat	SC	60 <sup>c</sup>	8.07		22
Carcinogenicity	2012N131619	Rat	Inhalation	137	6.75	0.3716 <sup>b</sup>	18
Carcinogenicity	2012N131664	Mouse, Males	Inhalation	295	8.21		22
Carcinogenicity	2012N131664	Mouse, Females	Inhalation	200	6.87		18
Fertility	CD2010/00187	Rat	SC	180	31.1 <sup>d</sup>		84
Fertility	WD2007/00763	Rat	Inhalation	294	16.2 <sup>a</sup>		44

EFD = embryo-fetal development study

PPND = prenatal & postnatal development study

<sup>a</sup> AUC value is extrapolated from 13 week rat inhalation study (#WD2007/02012)

<sup>b</sup> Steady state UMEC alone clinical exposure value is from study DB2116975. This study predicted steady state UMEC exposures in COPD patients based on data from study DB2113373, a 24 week study in COPD patients. UMEC alone dose was 62.5 µg /day.

<sup>c</sup> 60 µg/kg/day dose refers to dose at which UMEC was detected in pups, reflecting potential excretion in breast milk

<sup>d</sup> AUC value is extrapolated from study RD2009/01099 (14 day SC toxicity & TK study in rats)

### 11.3.1 Labeling Recommendations

The most recent version of the label for INCRUSE ELLIPTA was submitted by GSK on July 26, 2013. This label was essentially the same as the sponsor's initially proposed label for ANORO ELLIPTA, with the portions related to vilanterol removed. Multiple changes have subsequently been agreed upon for the ANORO ELLIPTA label. Recommended changes to the nonclinical sections of the INCRUSE ELLIPTA label are presented to maintain consistency with the language used in the current label for ANORO ELLIPTA (12/10/13) and to adjust the animal:

human exposure multiples to reflect human systemic exposure values with 62.5 mcg/day UMEC alone.

The complete labeling recommendations pertaining to nonclinical data are presented below:

## **1 INDICATIONS AND USAGE**

INCRUSE™ ELLIPTA™ is an anticholinergic indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled trials with INCRUSE ELLIPTA in pregnant women. Because animal reproduction studies are not always predictive of human response, INCRUSE 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 INCRUSE ELLIPTA.

There was no evidence of teratogenic effects in rats and rabbits at approximately 44 and 165 times, respectively, the MRHDID (maximum recommended human daily inhaled dose) in adults (on an AUC basis at maternal inhaled doses up to 278 mcg/kg/day in rats and maternal subcutaneous doses up to 180 mcg/kg/day in rabbits).

Nonteratogenic Effects: There were no effects on perinatal and postnatal developments in rats at approximately 67 times the MRHDID in adults (on an AUC basis at maternal subcutaneous doses up to 180 mcg/kg/day).

### **8.3 Nursing Mothers**

It is not known whether INCRUSE ELLIPTA is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when INCRUSE ELLIPTA is administered to a nursing woman.

Subcutaneous administration of umeclidinium to lactating rats at approximately 22 times the MRHDID in adults resulted in a quantifiable level of umeclidinium in 2 pups, which may indicate transfer of umeclidinium in milk. Since there are no data from well-controlled human studies on the use of INCRUSE ELLIPTA by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue INCRUSE ELLIPTA, taking into account the importance of INCRUSE ELLIPTA to the mother.

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

Umeclidinium is a long-acting, antimuscarinic agent, which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, it exhibits pharmacological effects through the inhibition of M3 receptors on smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical *in vitro* as well as *in vivo* studies, prevention of methacholine and acetylcholine-induced

bronchoconstrictive effects was dose-dependent and lasted longer than 24 hours. The clinical relevance of these findings is unknown. The bronchodilation following inhalation of umeclidinium is predominantly a site-specific effect.

### **13 NONCLINICAL TOXICOLOGY**

#### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Umeclidinium produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 137 mcg/kg/day and 295/200 mcg/kg/day (male/female), respectively (approximately 18 and 22/18 times the MRHDID in adults on an AUC basis, respectively).

Umeclidinium tested negative in the following genotoxicity assays: the *in vitro* Ames assay, *in vitro* mouse lymphoma assay, and *in vivo* rat bone marrow micronucleus assay.

No evidence of impairment of fertility was observed in male and female rats at subcutaneous doses up to 180 mcg/kg/day and inhaled doses up to 294 mcg/kg/day, respectively (approximately 84 and 44 times, respectively, the MRHDID in adults on an AUC basis).

#### **11.3.2 Labeling Discussion**

##### **Introduction**

INCRUSE ELLIPTA is a dry powder inhaler that contains umeclidinium bromide (UMEC) as the active ingredient. Each actuation of INCRUSE ELLIPTA delivers 62.5 mcg of UMEC. The nonclinical data in support of the safety of 62.5 mcg UMEC has been reviewed in detail in the nonclinical review for ANORO ELLIPTA (NDA 203,975; Sohn, 6/25/13)

The proposed changes to the nonclinical sections of the draft label for INCRUSE ELLIPTA reflect the language used in the most recent version of the label for ANORO ELLIPTA (11/15/13). In addition, dose ratios between animal vs. human data have been adjusted from the recent ANORO ELLIPTA label to reflect the increased systemic exposure of UMEC when administered alone (INCRUSE ELLIPTA) vs. in combination with vilanterol (ANORO ELLIPTA).

##### **Exposure Ratios**

The animal: human UMEC exposure ratios used in the current label were calculated on an AUC basis, and are summarized in Table 6. In fertility and embryofetal development studies where toxicokinetic data was not available, AUC values were estimated based on values from studies in which animals were treated with similar doses and for a similar duration. These studies are noted in Table 6. All doses reflect the dose administered by the subcutaneous route or the estimated achieved dose for the inhalation route. The NOAEL and nonclinical AUC<sub>0-t</sub> values in this table are derived from the Nonclinical review of NDA 203,975 (Sohn, 6/25/13).

The value used for human systemic exposure is based on the maximum recommended human dose of UMEC: 62.5 mcg/day. Study DB2116975 predicted steady state UMEC exposures in patients treated with 62.5 µg /day UMEC based on data from clinical study DB2113373, a 24 week study in COPD patients. This dose is associated with an estimated steady state human systemic exposure of 0.3716 ng\*hr/ml.

**Indications and Usage**

GSK proposed the following sentence to describe the indications and usage of their product:

“(b) (4)<sup>TM</sup> ELLIPTA<sup>TM</sup> is indicated for the long-term, once-daily, maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema”

The proposed proprietary name “(b) (4) ELLIPTA” was denied by the FDA Division of Medication Error Prevention and Analysis on 6/11/13. The proprietary name was subsequently changed to “INCRUSE ELLIPTA”. This name was considered acceptable on 11/21/13.

The recommended language in this section also includes the term ‘anticholinergic’ in order to reference the established pharmacologic class of UMEC:

“INCRUSE ELLIPTA is an anticholinergic indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.”

**Reproductive and Developmental Toxicity**

The standard battery of reproductive and developmental toxicity studies were completed with UMEC in rats and rabbits. The results of these studies are summarized in the nonclinical review of NDA 203,975 (Sohn; 6/25/13). Briefly, UMEC did not affect fertility rats, it was not teratogenic in rats or rabbits, and it did not have any pre-or postnatal effects in rats.

***Fertility*****Section 13.1**

The sponsor’s language regarding the effects of UMEC on fertility is as follows:

(b) (4)

Revised dose ratios are recommended based on extrapolated AUC data from studies RD2009/01099 (14 day SC toxicity & TK study in rats) and #WD2007/02012 (13 week rat inhalation study) as described in Table 6. Recommended changes to language are mainly stylistic in nature.

“No evidence of impairment of fertility was observed in male and female rats at subcutaneous doses up to 180 mcg/kg/day and inhaled doses up to 294 mcg/kg/day, respectively (approximately 84 and 44 times, respectively, the MRHDID in adults on an AUC basis).”

***Teratogenicity*****Section 8.1**

UMEC was determined to be non-teratogenic in rats (IH; study WD2007/00764) and rabbits (SC; study CD2010/00253) based on the lack of test article related malformations in Embryofetal Development (EFD) studies in both species. These studies are reviewed in the nonclinical review for NDA 203,975 (Sohn; 6/25/13). GSK proposed the following text regarding teratogenic effects of UMEC based on EFD studies



The recommended language is consistent with ANORO ELLIPTA, and adjustments were made to the dose ratios to present them in terms of AUC rather than mcg/m<sup>2</sup>. The dose ratio for rats is derived from AUC data in study WD2007/02012, a 13 week rat inhalation study as there was no TK data provided in study WD2007/00764.

“There was no evidence of teratogenic effects in rats and rabbits at approximately 44 and 165 times, respectively, the MRHDID (maximum recommended human daily inhaled dose) in adults (on an AUC basis at maternal inhaled doses up to 278 mcg/kg/day in rats and maternal subcutaneous doses up to 180 mcg/kg/day in rabbits).”

***Post-natal development*****Section 8.1**

Study 2011N118595 evaluated the effects of UMEC on parturition and postnatal development of rat pups of dams dosed during pregnancy and lactation (GD6 – PND 21). Results of this study are described in the nonclinical review of NDA 203,975 (Sohn; 6/25/13). There were no treatment-related adverse effects observed in this study.

GSK proposed the following text regarding pre-and postnatal effects of UMEC:



As in the ANORO ELLIPTA label, the recommended text for this portion of the label is moved to a subheading within section 8.1 labeled “Non-teratogenic Effects”, and the dose ratio is expressed on an AUC basis.

“Non-teratogenic effects: There were no effects on perinatal and postnatal developments in rats at approximately 67 times the MRHDID in adults (on an AUC basis at maternal subcutaneous doses up to 180 mcg/kg/day).”

The statement regarding detection of UMEC in 2 pups is moved to section 8.3 (Nursing Mothers) as it is in the label for ANORO ELLIPTA.

### ***Excretion in milk***

#### **Section 8.3**

GSK references data from rat PPND study 2011N118595 to describe transfer of UMEC to breast milk in section 8.1

(b) (4)

Reference to excretion of UMEC in breast milk was moved to section 8.3 (Nursing Mothers) to be consistent with the label for ANORO ELLIPTA. The dose ratio is based upon the exposure in dams administered 60 µg/kg/day UMEC. This is the dose at which UMEC was detected in pups, reflecting potential excretion in breast milk.

“Subcutaneous administration of umeclidinium to lactating rats at approximately (b) (4) times the MRHDID in adults resulted in a quantifiable level of umeclidinium in 2 pups, which may indicate transfer of umeclidinium in milk.”

### **Clinical Pharmacology**

#### ***Mechanism of Action***

##### **Section 12.1**

UMEC is a long-acting inhibitor of muscarinic (metabotropic) acetylcholine receptors. Agents that inhibit acetylcholine receptors are often referred to under the general term anticholinergic. The proposed language in this section is consistent with what is included in the label for ANORO ELLIPTA. The rationale for the proposed language is based upon the review of multiple *in vitro* and *in vivo* functional studies with UMEC (nonclinical review for NDA 203,975; 6/25/13). The proposed text also maintains consistency with the labels for other approved inhaled anticholinergic agents including tiotropium bromide (Spiriva, NDA 21,395) and aclidinium bromide (Tudorza, NDA 202,450).

GSK’s proposed text is as follows:

(b) (4)

(b) (4)

The recommended text for section 12.1 is:

“Umeclidinium is a long-acting, antimuscarinic agent, which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, it exhibits pharmacological effects through the inhibition of M3 receptors on smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical *in vitro* as well as *in vivo* studies, prevention of methacholine and acetylcholine-induced bronchoconstrictive effects was dose-dependent and lasted longer than 24 hours. The clinical relevance of these findings is unknown. The bronchodilation following inhalation of umeclidinium is predominantly a site-specific effect.”

### **Nonclinical toxicology**

#### ***Carcinogenesis***

##### **Section 13.1**

UMEC was negative for carcinogenicity in 2-year inhalation studies conducted in rats and mice. GSK proposed the following text pertaining to carcinogenesis:

(b) (4)

Changes are recommended for this section to maintain consistency with the ANORO ELLIPTA label and to express dose ratios on an AUC basis:

“Umeclidinium produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 137 mcg/kg/day and 295/200 mcg/kg/day (male/female), respectively (approximately (b) (4) and (b) (4) times the MRHDID in adults on an AUC basis, respectively).”

#### ***Mutagenesis***

##### **Section 13.1**

UMEC tested negative in a standard battery of genetic toxicology assays including the (1) *in vitro* bacterial reverse mutation assay, (2) *in vitro* mouse lymphoma assay, and (3) *in vivo* rat micronucleus assay. These studies were evaluated in the nonclinical review of IND 104,479 (Robison; 6/3/09).

GSK proposed the following text regarding mutagenesis:

Changes are recommended for this section to maintain consistency with the ANORO ELLIPTA label:

“Umeclidinium tested negative in the following genotoxicity assays: the *in vitro* Ames assay, *in vitro* mouse lymphoma assay, and *in vivo* rat bone marrow micronucleus assay.”

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MATTHEW T WHITTAKER  
12/12/2013

TIMOTHY W ROBISON  
12/12/2013  
I concur

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number:** NDA 205,382 **Applicant:** GlaxoSmithKline **Stamp Date:** 4/30/2013

**Drug Name:** Umeclidinium bromide **NDA/BLA Type:** Original NDA  
(GSK 573719)

On **initial** overview of the NDA/BLA 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		Studies are submitted in eCTD format.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
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		
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).	X		UMEC was formulated with lactose and magnesium stearate in chronic inhalation toxicology studies in rat (26 weeks, FD2009/00467) and dog (39 weeks, FD2009/00466)
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?	X		All studies were by the inhalation route unless otherwise justified.
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?	X		The sponsor states in their Nonclinical Written Summary that all pivotal toxicology studies were carried out in full compliance with GLP regulations.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		No additional nonclinical studies were requested based on the pre-NDA meeting minutes for IND 106,616 (UMEC + Vilanterol combination) dated 2/3/2012.

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement  
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA/BLA or Supplement**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		The proposed labeling is in Physician Labeling Rule (PLR) format.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		To be determined in consultation with the reviewing chemist.
11	Has the applicant addressed any abuse potential issues in the submission?	NA		There appear to be no issues regarding abuse potential.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	NA		

**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.

*The NDA is fileable from the pharmacology/toxicology perspective.*

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. *There are no potential review issues at this time.*

Matthew Whittaker 6/11/13  


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 Reviewing Pharmacologist Date

Timothy Robison 6/11/13  


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 Team Leader/Supervisor Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MATTHEW T WHITTAKER  
06/13/2013

TIMOTHY W ROBISON  
06/13/2013  
I concur