CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203975Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Anoro Ellipta Risk Management Review

Date:	August 27, 2013
Reviewer(s):	Yasmin Choudhry, M.D., Medical Officer, Division of Risk Management (DRISK) Kendra Worthy, Pharm. D., Team Leader, DRISK
Division Director	Claudia Manzo, Pharm. D., DRISK
Drug Name(s):	Anoro Ellipta (umeclidinium/vilanterol) Dry Inhalation Powder
Therapeutic Class:	Long-acting muscarinic antagonist (LAMA) / long-acting beta agonist (LABA)
Dosage and Route:	62.5 mcg/25 mcg one inhalation once daily
Indication(s):	Maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)
Application Type/Number:	NDA 203975 received December 18, 2012
Submission Number:	Sequence #0000
Applicant/sponsor:	GlaxoSmithKline (GSK)
OSE RCM #:	2013-90

1 INTRODUCTION

This review documents the Division of Risk Management (DRISK) evaluation of the New Drug Application (NDA) 203975, for Anoro Ellipta (umeclidinium/vilanterol) inhalation powder, to assess the need for a Risk Evaluation and Mitigation Strategy (REMS).

The Division of Pulmonary, Allergy and Rheumatology Products (DPARP) is recommending approval[1] for NDA 203975 which is subject to change after the Pulmonary-Allergy Drugs Advisory Committee meeting scheduled for September 10, 2013.

1.1 BACKGROUND

Anoro Ellipta is a fixed dose combination of 62.5 mcg of umelidinium (UMEC), a long-acting muscarinic antagonist (LAMA) and 25 mcg of vilanterol (VI), a long-acting beta agonist (LABA) administered by a dry powder inhaler. Mechanism of action of UMEC is through inhibition of M3-receptors at the smooth muscle leading to bronchodilation, while, vilanterol acts via beta-2-adrenergic receptors in the lungs and bronchial smooth muscle.

The proposed indication is COPD including chronic bronchitis and/or emphysema. The proposed dose is one inhalation once daily.

GSK's rationale for the development of a LAMA/LABA combination product is that the use of two bronchodilators with distinct and complementary mechanisms of action will optimize bronchodilator response, providing additional sustained improvements in lung function and symptoms over monotherapy with either component without a clinically significant increase in the incidence of adverse events.

Chronic obstructive pulmonary disease (COPD) is a progressive disease that causes symptoms such as coughing, shortness of breath, and increases risks of disability and death due to worsening of lung function[2].

Inhalation products currently available for COPD are:

- Single ingredient: short-acting anti-cholinergic; and long-acting anti-cholinergic;
- Combination products: short-acting anti-cholinergic/short acting beta-adrenergic agonist; corticosteroid/LABA.

UMEC is a new molecular entity (NME). Vilanterol is currently marketed as Breo Ellipta (fluticasone furoate and vilanterol) inhalation powder. Neither component is currently marketed as a single-ingredient inhalation product.

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[1] Clinical Review NDA 203975 Anoro Ellipta by Jennifer Rodriguez Pippins, MD, MPH dated August 15, 2013

[2] Global Initiative for Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease. Global Initiative for Obstructive Lung Disease (GOLD) 2011. Available from: www.goldcopd.org.

There are no approved LAMA/LABA combination products in United States and to date the proposed combination product is not marketed anywhere in the world.

2 MATERIALS REVIEWED

- GSK Summary of Clinical Efficacy for Anoro Ellipta, received December 18, 2012
- GSK Summary of Clinical Safety for Anoro Ellipta, received December 18, 2012
- Clinical Review for NDA 203975 Anoro Ellipta by Jennifer Rodriguez Pippins, MD, MPH dated August 15, 2013

2.1 OVERVIEW OF CLINICAL PROGRAM OR POSTMARKETING EXPOSURE

2.2 EFFICACY

Efficacy of UMEC/VI (62.5 mcg/25 mcg) as a bronchodilator was demonstrated from Phase 3 program; these trials were 24-week duration and the primary endpoint was change from baseline in pre-dose trough FEV1 on Day 169:

- Studies 361 and 373 were placebo-controlled trials randomized to UMEC/VI, UMEC, VI, and placebo.
- Studies 360 and 374 were tiotropium-controlled trials randomized to one of 4 treatment arms:
    - Study 360: the treatment arms were UMEC/VI 125/25 mcg, UMEC 62.5/25 mcg, VI 25 mcg and tiotropium.
    - Study 374: the treatment arms were UMEC/VI 125/25 mcg, UMEC 62.5/25 mcg, UMEC 125 mcg, and tiotropium.
- Two exercise endurance trials.

Being an NME, efficacy for monotherapy with UMEC was also demonstrated in these clinical trials. Efficacy for VI was previously established with fluticasone and vilanterol inhalation powder, NDA 204275.

The pre-clinical testing for UMEC/VI included:

- A study of general toxicity of inhaled UMEC in dogs and rats which revealed safety margins of 30 and 19 times the maximum recommended human dose.
- Two year carcinogenicity studies in rats and mice which were negative for tumors.
- Reproductive and developmental studies demonstrated no effect of UMEC on fertility in rats, and no teratogenicity in rats or rabbits.
- A 13-week toxicology study with the combination of UMEC and VI was conducted in dogs. The observed toxicity was consistent with the monoproducts and there was no evidence of additive or synergistic toxicity with the combination.

UMEC/VI, consistent with other inhaled products for COPD, will be a pregnancy C category.

2.3 SAFETY

The LAMA class effects include worsening of narrow-angle glaucoma, worsening of urinary retention, stroke and cardiovascular safety. The LABA class effects include hypokalemia, hyperglycemia, and cardiovascular effects i.e., increase in pulse rate, blood pressure, and ECG changes. LABAs are also associated with an increase in asthma-related hospitalizations and deaths (not seen with COPD)[3].

GSK's safety database for UMEC/VI consisted of 17 completed clinical trials with over 6000 patients with COPD.

Adverse events of special interest included cardiovascular events, based largely on the known pharmacological effects of the two classes of drugs (LAMA and LABA).

GSK conducted an analysis of major adverse cardiac events and an evaluation of cardiovascular adverse events of special interest (both from the same safety data).

According to the clinical reviewer, in these analyses, small numerical imbalances favoring placebo were demonstrated for events related to cardiovascular ischemia and for nonfatal myocardial ischemia but not on the broader category of non-fatal cardiac ischemia (primary efficacy trials); the absolute number of events was small and the imbalances were not seen in long-term safety trial. The reviewer concluded that overall, a low number of adverse events were identified.

A total of 48 deaths were reported for the 17 COPD trials and according to the clinical reviewer, in the primary efficacy trials, the percentage of patients with fatal events was <1% across all treatment groups and causality could not be determined due to the limited information provide.

Common adverse events included headache, nasopharyngitis, cough, upper respiratory tract infections, back pain, hypertension, oropharyngeal pain, arthralgia, dyspnea, tachycardia and atrial fibrillation.

The Anoro Ellipta Prescribing Information will address the risks associated with UMEC/VI. DPARP, at this time, is not recommending postmarketing risk management activities (subject to change per September 10, 2013 AC decision).

2.4 RISK MANAGEMENT PROPOSED BY APPLICANT

GSK's risk management proposal for UMEC/VI includes routine pharmacovigilance including labeling and a Medication Guide. A proposed REMS was not submitted by GSK.

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[3] The REMS for the LABA class to address the risk of asthma-related deaths, intubations and hospitalizations has been eliminated after REMS Oversight Committee concurrence dated June 18, 2012 that a REMS for the LABAs was not required since the REMS assessments results demonstrated that information regarding LABA safety and asthma-related death has been widely distributed to physicians with demonstrated uptake of the information into clinical practice.

3 DISCUSSION

As of August 15, 2013, the preliminary recommended regulatory action for Anoro Ellipta (UMEC/VI) by the clinical reviewer is Approval. As noted above this regulatory action is subject to change after the Advisory Committee meeting scheduled for September 10, 2013.

Based on the medical officer's review of the available data, the benefits of UMEC/VI for the proposed indication outweigh the risks of UMEC/VI. Additionally, the safety profile of UMEC/VI is consistent with the known pharmacological effects LAMA/LABA.

The risks associated with UMEC/VI, particularly the cardiovascular risks, can be mitigated through professional labeling.

While approved LAMA and LABA monotherapy products are available in the United States there are no approved LAMA/LABA combination products. Thus approval of UMEC/VI, with a favorable benefit-risk profile, will provide an additional treatment option for COPD patients.

4 CONCLUSION AND RECOMMENDATIONS

In conclusion, at this time, risk mitigation measures beyond labeling do not appear warranted for Anoro Ellipta (UMEC/VI). DPARP and DRISK are in agreement that a REMS for UMEC/VI will not be required and that the risks can safely be communicated via product labeling. Additionally, the approved drug products in the classes of LAMA and LABA for the proposed indication do not have a REMS.

Should DPARP, after the Advisory Committee meeting raise further concerns regarding safety of Anoro Ellipta and believe that a REMS may be necessary to mitigate the risk, we will re-evaluate our recommendation. DRISK will continue to follow this NDA.

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/s/

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08/27/2013

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