

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205382Orig1s000

**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**

Risk Management Review

Date: December 31, 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): Umeclidinium bromide oral inhalation via dry powder inhaler

Therapeutic Class: Long-acting muscarinic antagonist (LAMA)

Indication(s): Chronic obstructive pulmonary disease (COPD)

Dose(s): The proposed dose is 62.5 mcg once daily

Application Type/Number: NDA 205382

Applicant/sponsor: GlaxoSmithKline (GSK)

OSE RCM #: 2013-1260

1 INTRODUCTION

This review documents the Division of Risk Management (DRISK) evaluation of the New Drug Application (NDA) 205382, for umeclidinium (hereafter referred to as UMEC) inhalation powder, to assess the need for a Risk Evaluation and Mitigation Strategy (REMS).

The application was considered a new molecular entity (NME); but since the approval of Anoro Ellipta (umeclidinium/vilanterol) on December 17, 2013, it is no longer an NME¹.

2 BACKGROUND

UMEC is a long-acting muscarinic antagonist (LAMA) administered by oral inhalation at a dose of 62.5 mcg once daily. UMEC inhibits M3-receptors at the smooth muscle which leads to bronchodilation. The proposed indication is for maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

According to the sponsor², COPD is a progressive disease with worsening lung function over time. Pharmacological management of COPD is primarily aimed at improving symptoms and quality of life, optimizing lung function, reducing exacerbations and improving exercise tolerance. LABAs and LAMAs are recommended for the treatment of symptomatic patients with moderate to severe COPD and are considered more efficacious and safer to use than short-acting bronchodilators. The benefits of LAMAs include control of symptoms, improvement in lung function and hyperinflation, exercise performance, COPD exacerbations, and health status. GSK believes that UMEC will provide an additional treatment option to marketed LAMAs such as tiotropium bromide and aclidinium bromide for COPD.

UMEC, in combination with vilanterol, a LABA, was recently approved for COPD as Anoro Ellepta in a fixed dose combination (UMEC 62.5 mcg and vilanterol 25 mcg). Currently, UMEC is not available for marketing in any country.

3 MATERIALS REVIEWED

- GSK's Summary of Clinical Efficacy for UMEC received April 30, 2013
- GSK's Summary of Clinical Safety for UMEC received April 30, 2013

4 OVERVIEW OF CLINICAL PROGRAM

4.1 EFFICACY

¹ Risk Management review completed by Yasmin Choudhry, dated August 27, 2013.

² GSK's Clinical Overview Umeclidinium NDA 205382 dated April 30, 2013.

Efficacy of UMEC 62.5 mcg dose as a bronchodilator in patients with moderate to very severe COPD was demonstrated in two placebo-controlled clinical trials: A 12-week trial evaluated two doses of UMEC, 62.5 mcg and 125 mcg; and one 24-week trial evaluated UMEC 125 mcg. The primary endpoint was trough FEV1 at the end of treatment.

4.2 SAFETY CONCERNS

The safety database of UMEC consists of 2,706 patients from a total of 8 clinical trials; over 1,400 patients were treated with either UMEC 62.5 mcg or 125 mcg dose.

Class effects of LAMAs include worsening of narrow-angle glaucoma, worsening of urinary retention, cardiovascular events, and stroke. According to the clinical reviewer³, more recent controlled clinical data regarding cardiovascular safety have been reassuring; GSK's analyses of major adverse cardiac events showed small numerical imbalances and small numbers (<1%) of these events were observed in the UMEC long-term safety trial. A total of 16 deaths (<1%) were reported in the UMEC clinical trials for which the clinical reviewer stated that a dose-related pattern was not observed⁴.

5 RISK MANAGEMENT PROPOSED BY APPLICANT

GSK's risk management proposal for UMEC includes routine pharmacovigilance including labeling. A proposed REMS was not submitted by GSK.

6 DISCUSSION

The safety profile of UMEC is considered acceptable by the clinical reviewer. The clinical reviewer is not recommending a REMS for UMEC at this time. The approved LAMA products do not have a REMS. The UMEC prescribing information will address the risks associated with UMEC.

As of December 11, 2013, the recommended regulatory action for UMEC by the clinical reviewer is Approval. Based on the medical officer's review of the available data, the benefits of UMEC for the proposed indication outweigh its risk. Additionally, the safety profile of UMEC is consistent with the known pharmacological effects of LAMA, and as with the approved LAMA products, the risks associated with UMEC can be mitigated through professional labeling.

7 CONCLUSION AND RECOMMENDATIONS

In conclusion, at this time, risk mitigation measures beyond labeling do not appear warranted for UMEC. DPARP and DRISK are in agreement that a REMS for UMEC will not be required and that the risks can safely be communicated via product labeling.

Should DPARP raise further concerns regarding safety of UMEC 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.

⁴ Clinical Review NDA 205382 Umeclidinium by Jennifer Rodriguez Pippins, MD, MPH dated December 19, 2013

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/s/

KENDRA C WORTHY
01/06/2014