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**Testimony before the FDA's Pulmonary and Allergy Drugs Advisory Committee
on NDA 203-975: umeclidinium/vilanterol for the long-term, maintenance treatment
of airflow obstruction in patients with chronic obstructive pulmonary disease
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My name is Sammy Almashat, a physician with Public Citizen's Health Research Group. I have no conflicts of interest.

You are being asked today to consider the approval of umeclidinium/vilanterol (UMEC/VI; proposed trade name Anoro Ellipta) combination therapy for the treatment of chronic obstructive pulmonary disease (COPD). Public Citizen opposes this approval because of the uncertainty surrounding the alarming cardiac safety signal seen in the pre-approval studies.

While no definitive conclusions can be made as to whether or not the safety signal represents a real risk of heart attack in COPD patients, it is clear that this is an unanswered question that should not be taken lightly given the presence of a plausible mechanism, similar concerns with other long-acting muscarinic antagonists (LAMAs), and the fact that COPD patients are at higher risk for heart attacks than the general population.¹ We strongly believe that this signal must be addressed prior to approving a combination drug that is neither a breakthrough nor life-saving advance in the treatment of COPD.

Inhaled anticholinergics and cardiovascular events: recent evidence and controversy

That inhaled anticholinergics, such as umeclidinium, may be associated with cardiovascular side effects has been the subject of speculation and controversy for decades. A 2008 meta-analysis by Singh et al.² reignited the debate when it found an increased risk of MI and cardiovascular death with inhaled anticholinergics in 17 trials reporting on cardiovascular outcomes published to that date. The UPLIFT trial, published

¹ Lange P, Mogelvang R, Marott JL, et al. Cardiovascular morbidity in COPD: A study of the general population. *COPD*. 2010 Feb;7(1):5-10.

² Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA*. 2008 Sep 24;300(12):1439-50.

shortly afterwards, found no increased cardiovascular risk with tiotropium,³ reassuring many, including the FDA⁴ that such an association did not exist, at least for tiotropium.

However, an FDA review noted that atrial tachycardia and tachyarrhythmias were markedly increased (RR 7.39 [0.92, 59.1] and 3.70 [0.79, 17.4], respectively) in those receiving tiotropium.⁵ In addition, the UPLIFT trial excluded subjects with a recent history of MI or hospitalization for heart failure and arrhythmias requiring a recent change in drug therapy,⁶ thus precluding definitive conclusions about the safety of tiotropium in COPD patients most vulnerable to a cardiovascular event.

The subsequent publication of the POET-COPD trial showed a 50% increased rate of MI in subjects on tiotropium compared with those on salmeterol.⁷ As with UPLIFT, subjects at highest risk for cardiovascular events were excluded from the trial.⁸

The FDA's residual (and appropriate) concern about the potential cardiovascular effects of this class of drugs was apparent in its 2012 approval of aclidinium, the second LAMA to be approved in the U.S. The pre-approval studies aclidinium comprised a total of 1,921 subjects, evaluated for the prespecified endpoint of cardiovascular deaths and non-fatal myocardial infarctions and strokes.⁹ Two cardiovascular deaths in the aclidinium arms, compared with none in the placebo arm, were concerning enough to prompt the FDA to require a large post-marketing study to clarify whether aclidinium increases the risk of cardiovascular death.¹⁰

Non-fatal MIs and arrhythmias with umeclidinium/vilanterol

Fast forward one year and this committee is faced with an even more concerning MI signal with umeclidinium/vilanterol. The pre-approval safety dataset for this combination therapy is more extensive than existed for aclidinium, with over 6,000 subjects in all

³ Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008 Oct 9;359(15):1543-54.

⁴ Michele TM, Pinheiro S, Iyasu S. The safety of tiotropium--the FDA's conclusions. 2010 Sep 16;363(12):1097-9.

⁵ FDA. Clinical Briefing Document, NDA# 21-395 (Spiriva HandiHaler). November 19, 2009, p. 75.

<http://www.fda.gov.ezproxy.welch.jhmi.edu/downloads/advisorycommittees/committeesmeetingmaterials/drugs/pulmonary-allergydrugsadvisorycommittee/ucm190463.pdf>. Accessed on September 9, 2013.

⁶ Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008 Oct 9;359(15):1543-54. [Supplementary Appendix, p. 21]

⁷ Vogelmeier C, Hederer B, Glaab T, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. *N Engl J Med*. 2011 Mar 24;364(12):1093-1103. [Supplementary Appendix, Section 12]

⁸ *Ibid.*

⁹ FDA. Aclidinium Summary Review. Page 8, Table 3.

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202450Orig1s000SumR.pdf. Accessed on September 8, 2013.

¹⁰ FDA Approval Letter. Aclidinium. July 23, 2012.

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202450Orig1s000Approv.pdf. Accessed on September 9, 2013.

arms.¹¹ After COPD exacerbations, myocardial infarction and ischemic disease were the most commonly reported serious adverse events.¹² A total of 13 subjects receiving the combination or one of its component drugs experienced a non-fatal MI, compared with a single subject in the placebo arm and no subjects on tiotropium. The incidence of non-fatal MIs was 1.7 times higher than placebo in those receiving vilanterol 25 mcg monotherapy, 1.8 times higher in those on umeclidinium 62.5 mcg, and 2.7 times higher for those on the combination dose being considered for approval today.¹³

To our knowledge, this is the strongest cardiovascular signal yet seen in pre-approval trials of LAMA therapies, greater than those seen for either of the two LAMAs (tiotropium and aclidinium) currently on the market.

Of further concern is the large number of dropouts seen across the pre-approval trials and particularly the reasons for early withdrawals. In the long-term safety trial, 5-6% of subjects on umeclidinium alone and in combination with vilanterol withdrew early due to an ECG abnormality, compared to none in the placebo group.¹⁴ And in the only trial to include Holter monitoring in all randomized subjects, 16% of subjects on umeclidinium and umeclidinium/vilanterol dropped out because of ECG and/or Holter abnormalities compared with only 7% of placebo subjects.¹⁵

No urgency for approval

The central question pertinent to your decision today is not over the certainty of this cardiovascular safety signal. This cannot be clarified on the basis of the data available and another, larger study will be necessary to reveal whether such a serious risk truly exists. The fundamental question is whether this drug should be approved before such data become available.

A post-marketing study will take years to complete (the post-marketing study for aclidinium will not be finalized until 2018, six years after the drug's approval¹⁶). Therefore, should an increased risk of myocardial infarction eventually be confirmed, thousands of heart attacks will likely have occurred before we know of the drug's dangers.

¹¹ FDA Pulmonary and Allergy Drugs Advisory Committee Meeting. NDA 203-975: umeclidinium and vilanterol inhalation powder for the long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). FDA Briefing Document. p. 29.

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM367411.pdf>. Accessed on September 9, 2013. p. 29.

¹² FDA UMEC/VI Briefing Document, p. 27

¹³ FDA UMEC/VI Briefing Document, p. 29.

¹⁴ FDA UMEC/VI Briefing Document, p. 32.

¹⁵ FDA UMEC/VI Briefing Document, p. 253.

¹⁶ FDA Approval Letter. Aclidinium. July 23, 2012.

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202450Orig1s000Approv.pdf.

Accessed on September 9, 2013.

Is this a risk we are willing to take? Is the approval of a drug that is neither a breakthrough drug nor a life-saving advance in the treatment of COPD so urgent that we cannot wait until such a vital question is resolved? There is no prior clinical experience with fixed-combination LAMA/LABA therapies, or with either of this specific combination's individual components. With a plethora of similarly effective drugs already on the market, with more established safety records, we urge you to oppose approval until the uncertainty over this novel combination therapy's cardiovascular safety is addressed.