From: Sidney Wolfe
Sent: Wednesday, February 13, 2013 4:10 PM
To:
Cc: Michael Carome
Subject: bedaquiline risks

Guido Rasi, M.D.
Executive Director
European Medicines Agency
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Dear Dr. Rasi,

We strongly urge the European Medicines Agency (EMA) to reject the pending application to the agency for approval of Janssen's new drug for treating multi-drug resistant tuberculosis (MDR TB), bedaquiline. Although there is no question that the drug, in a randomized trial in people with MDR TB in South Africa, South America, Asia, and Eastern Europe, resulted in a more rapid conversion of their sputum from being positive for TB to being negative, there also is no question that this positive outcome came at a terrible price: a five-fold, statistically significant (p=0.017) increase in deaths in subjects who were randomized to get bedaquiline along with other anti-TB drugs (10 deaths), compared with subjects randomized to get a placebo plus these other drugs (two deaths).

In addition, our analysis of those subjects in both groups whose sputum converted from positive to negative found that none of the 56 placebo-treated subjects with sputum conversion died, whereas eight of the 64 bedaquiline-treated subjects with sputum conversion died (p=0.007; Fisher's Exact Test). (The total number of conversions in each group was derived from page 35 of the entire PDF file for the U.S. Food and Drug Administration [FDA] slide set from the November 28, 2012, meeting of the FDA's Anti-Infective Drugs Advisory Committee (AIDAC), accessed at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM332961.pdf, which shows an approximate 80% sputum conversion by 72 weeks in the bedaquiline group and 70% in the placebo group, no longer significantly higher in the bedaquiline group.)

We are attaching a letter we sent to the FDA on December 21, 2012 (prior to performing the analysis of deaths in subjects with sputum conversion) urging the FDA not to approve bedaquiline, based on the agency's own briefing documents on the drug. As you are probably aware, the FDA did, unfortunately, approve it.

As we noted in this letter to the FDA, it is certainly plausible that the higher mortality rate in the bedaquiline-treated subjects could be attributed to, among other things, the failure of the TB drug regimen that included bedaquiline, even if the mechanism for such a detrimental outcome is poorly understood. One possible mechanism may be development of resistance to one or more of the other background TB drugs following exposure to bedaquiline. Indeed, this potential mechanism was apparently recognized by some members of the AIDAC during its November 28, 2012, review of the new drug application for bedaquiline, as reflected in the following excerpt from the meeting transcript (see http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM337696.pdf):

> Dr. Matthew Goetz: And I wonder whether it may be a little bit more challenging in some regards also with bedaquiline because of its long… terminal half-life as to whether that has some residual impact on the sensitivity of cultures after people go off [bedaquiline] therapy. I wonder about that, and I don't think it's a question that we can answer at the present time. But it makes it all the more important, I think, that we have long-term follow-up with patients and a definition of cure rather than just sputum culture conversion. [transcript page 307]
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> Dr. John Teerlink: And so I'm still left with a fivefold increase in mortality no matter how we slice it. And then many of those were TB-related deaths, so how do we not know that this was actually -- because of this unique mechanism of action, the TB came back and actually was more virulent for some reason? [transcript page 349]
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> Ms. Kathleen Young: In terms of data that we need, I would like to see more information on the long half-life of the drug and its effect on resistance, cross-resistance, to other tuberculosis drugs, as well as other drugs used by that population. [transcript page 355]

Clearly, the significantly higher mortality rate of the bedaquiline-treated subjects in the phase 2 randomized, controlled clinical trial of bedaquiline cannot be discounted or explained away, as many have attempted to do. Therefore, we again strongly urge that the EMA not repeat the serious mistake made by the FDA in approving bedaquiline.

Sincerely,

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Director
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