The FDA will offer generally positive but also highly mixed advice to the FDA's Cardiovascular and Renal Drugs Advisory Committee when it meets on Wednesday to consider the supplemental new drug application for rivaroxaban (Xarelto, Johnson & Johnson) for use in patients with acute coronary syndrome (ACS) already taking dual antiplatelet therapy. The FDA posted the briefing documents on its website this morning.

Although the primary clinical review and the statistical review support approval for the new indication (the drug is already approved for venous thromboembolism prophylaxis and stroke prevention in AF), one reviewer, Thomas Marciniak, the Medical Team Leader, issued a blistering memorandum suggesting that the supporting data, plagued by missing and inconsistent records in the pivotal ATLAS ACS 2-TIMI 51 trial , "may not support the favorable statistical results."

The primary clinical reviewer, Karen Hicks, recommended approval for the 2.5 mg BID dose (but not the 5 mg dose) of rivaroxaban for ACS. She noted that the lower dose reduced the combined endpoint of CV death, nonfatal MI, or nonfatal stroke in the ATLAS trial, with most of the benefit driven by a reduction in CV death, with little or no difference in MI or stroke. The higher 5 mg dose increased bleeding risk in the trial without providing additional efficacy, she concluded. She did not recommend a mortality indication for the label. Her views generally coincide with the reception of the ATLAS trial following its presentation and publication in the *New England Journal of Medicine* .

It should be noted that Hicks hedged her endorsement with a potentially significant caveat:

For the reasons stated above, I recommend approval. Should additional information become evident in the next two months that affect overall trial interpretability, I may choose to reconsider this recommendation.

The reasons for her statement are spelled out by Marciniak in his memorandum near the end of the FDA briefing document. Marciniak raises concerns about the high 12% rate of incomplete

followup in ATLAS, writing that “because of the extent of missing follow-up in ATLAS we cannot have confidence in either the calculated mortality or CV endpoint benefits.” Marciniak raises a number of other issues, including, most ominously, an audit that uncovered 3 uncounted deaths in the trial which “may be the trip of the iceberg regarding problems with missing data.”

Marciniak has been down this path before, with mixed results. During the marathon two day Avandia meeting
Marciniak thoroughly discredited the RECORD trial, and this played a role in the generally unfavorable committee recommendations. By contrast, although Marciniak and others were highly critical of the pivotal PLATO trial during the ticagrelor (Brilinta) advisory committee meeting, the committee and the FDA ultimately approved ticagrelor. Finally, we should remember that
the FDA reviewers initially recommended against approval of rivaroxaban for the AF indication due to concerns about the ROCKET trial but that the committee ultimately recommended approval, based on
their support of large, pragmatic trials
. Compared to the drama of
that
hearing, Wednesday’s session is likely to be much less contentious.

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