CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-425

SUMMARY REVIEW

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memo

NDA: 22-425 (Multaq; dronedarone for atrial fibrillation and atrial flutter)

Sponsor: sanofi-aventis

Review date: 27 March 2009

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

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HFD-110/Fortney/Karkowsky

This memo conveys the Division's recommendation to approve dronedarone to prolong the time to recurrence and time to hospitalization for atrial fibrillation or atrial flutter.

Most issues have been addressed in Dr. Karkowsky's CDTL memo (19 February 2009; revised 25 March 2009). I summarize very briefly.

Dronedarone is a structural analog of amiodarone, with a similar spectrum of pharmacological (beta-adrenergic, sodium channel, and IKr potassium channel) effects. Either dronedarone's activities are not in the same proportion as those of amiodarone or the dose selection kept dronedarone from being close to the effectiveness of amiodarone in DIONYSOS (N=504; highly significant 59% increase in time to recurrence of AF/AFL compared with amiodarone).

The early development program demonstrated modest effectiveness in AF/AFL. Two similar placebo-controlled studies, EURIDIS (n=612) and ADONIS (n=625) demonstrated statistically significant increases in time to recurrence of AF/AFL (22% and 27%, respectively) on dronedarone 400 mg bid in patients with non-permanent (AF/AFL within 3 months, but sinus rhythm at randomization) atrial arrhythmias.

It is interesting that in all three studies (EURIDIS, ADONIS, and DIONYSOS) about half of the recurrences of atrial arrhythmias occur in the first few weeks after randomization. The remaining occur over a year and total only about 60%. This probably reflects the distribution of times between conversion and randomization, with many of them in the days prior to randomization, but obviously many people—even untreated—go a very long time between recurrences.

Because of concerns about possible adverse effects of antiarrhythmic drugs on mortality, the sponsor was tasked with obtaining reassuring data. They elected to study a heart failure population because these patients are at high risk of sudden death, so there was some possibility of benefit. The resulting ANDROMEDA study was stopped at n=617/1000 with a nominally significant 25 deaths on dronedarone vs. 12 on placebo. The result is plausibly true (increased heart failure deaths and dronedarone is a negative inotrope), but could as well be chance (stopping boundary of $p<0.05$ and many interim looks much inflated the false-positive error rate). An early hypothesis that dronedarone's block of creatinine secretion led to inappropriate withdrawal of ACE inhibitor therapy has been thoroughly discredited.

The sponsor then conducted ATHENA (n=4628) among patients who had been in both atrial arrhythmia and sinus rhythm within 6 months, at increased cardiovascular risk, but not NYHA Class IV within 4 weeks. The primary end point was cardiovascular hospitalization or death from any cause. Dronedarone was associated with a highly

statistically significant 24% reduction, almost all of which was cardiovascular hospitalization, and most of that was hospitalizations for atrial arrhythmias.

Secondary end points in ATHENA were not well chosen. The first, all-cause mortality, was not significantly different, and should have been a safety end point only, not formally tested. The second was cardiovascular hospitalization, highly significant, but a guaranteed interpretation of the primary end point and thus should not have been in the list of formally tested secondaries. The third was cardiovascular death, and the nominally significant favorable effect might have supported a claim. The Advisory Committee concluded it is not persuasive, and I concur, but it is at least reassuring.

All-cause mortality, 255 total events, showed a nominal 16% reduction on dronedarone, which ruled out about an 8% increase, and this too is reassuring.

The Advisory Committee favored (10 to 3) approval of dronedarone, and I concur. They recommended that patients with advanced (NYHA Class III or IV) heart failure or those recently hospitalized with heart failure be excluded, and I concur in that, too. The restriction needs to be in a boxed warning, and the focus of the sponsor's REMS. The primary component of the REMS should be a communications plan to ensure that prescribers know whom to avoid treating. A Medications Guide does not appear to be useful. The review team is attempting to formulate a plan to collect information on the effectiveness of the REMS.

Pediatric studies should be waived; AF is rare in children.

Financial disclosure is covered in the clinical/statistical review. Eight of 551 investigators reported significant payments or interests. The review does not comment on whether this is a problem, but I believe it is not, as this is a small proportion of sites, they enrolled a small fraction of the subjects in ATHENA, and the end point was not much at risk of bias.

As of this writing, the EER is pending. The sponsor is making their revisions to the label as a result of the Advisory Committee meeting.

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/s/

Norman Stockbridge
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