CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-425

OFFICE DIRECTOR MEMO

Office Director's Memo to File

Date: June 30, 2009

From: Robert Temple, MD
Director, ODE-I

To: Memo to File, NDA 22-425 – Multaq tablets (dronedarone)

Subject: Approval of Multaq(NDA 22-425, dronedarone) for reducing the risk of cardiovascular (CV) hospitalization in patients with paroxysimal AF or AFL; Sponsor – Sanofi-Aventis

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This memo communicates the basis for approving dronedarone (Multaq) for reducing the risk of CV hospitalization in patients with a recent episode of AF/AFL in patients in NSR or about to be cardioverted.

Most issues have been addressed in Dr. Karkowsky's CDTL memo of March 19, 2009 and Dr. Stockbridge's Division Director memo of March 27, 2009. The med/stat review of Drs. Moreschi and Freidlin discusses the clinical data at length.

I. Background

Several drugs (sotolol, dofetilide) are approved for maintenance of NSR (delaying recurrence of AF) in patients with a history of AF/AFL who have been converted to sinus rhythm. Both of those drugs have a significant QT-prolonging effect and can cause Torsade de Pointes arrhythmias at relatively high rates. Neither drug has been shown to affect the need for hospitalization. A drug widely used, and very effective, to prevent recurrence is amiodarone; it is not approved for this use and, at least at 400 mg, has considerable pulmonary, thyroid, and other toxicity. No treatment for AF has improved survival and some studies comparing "rhythm control" with "rate control" in AF have favored the latter with respect to survival.

It has long been Cardio-Renal Division policy (since CAST demonstrated that antiarrhythmic drugs can provoke lethal arrhythmias) to require assurance from clinical studies (not necessarily arrhythmia studies) that the drug does not cause significant harm. Thus, for sotolol such assurance was provided by the Julien post-MI study showing a strong trend for improved survival, and for dofetilide the two Diamond studies provided similar assurance in patients with heart failure and recent myocardial infarction.

As explained in our not approvable letter for Multaq dated 8/29/2006, Sanofi-Aventis conducted the ANDROMEDA study in high risk heart failure population to provide the needed assurance and

support approval on the basis of two studies showing delayed recurrence of AF. Unfortunately, ANDROMEDA showed increased mortality and was stopped early by the DMC for the trial. Our letter suggested need for a study of substantial size in the AF population to provide needed reassurance that any favorable effect on AF was not accompanied by worsened survival. The sponsor therefore conducted the ATHENA study, which provided that reassurance for a population without severe CHF. Making sure dronedarone is not used in that population has led to a REMS that includes a medication guide (Note Dr. Stockbridge did not think that would be useful in his March 27, 2009 review, but on further reflection we concluded it would be) and a communication plan including an information sheet for healthcare professionals and REMS print advertisements as well as labeling that emphasizes in a Box Warning and elsewhere the need to avoid patients with severe heart failure.

II. Effectiveness

A. Early recurrence studies

Dr. Karkowsky's April 6, 2006 review described results of 2 placebo-controlled trials in AF, ADONIS (USA, Canada, Australia, Argentina, and S Africa) and EURIDES (12 E and W European countries. Each study randomized about 600 patients, 2:1 dronedarone: placebo. Patients had had an episode of AF within 3 months but were in NSR and were not in ≥ NYHA Class III heart failure. Recording devices captured rhythms at specified times (days 2, 3, 5, months 3, 5, 7 and whenever a suspect symptom occurred). In both studies, dronedarone significantly delayed recurrence by about 25% (cox regression), with much of that advantage appearing within a month or so, after which it was maintained. The 25% risk reduction translated into a roughly 10-15% absolute reduction in events. Of some interest, a figure shown at the March 18, 2009 Cardiorenal Advisory Committee meeting showed that in each study and pooled data, dronedarone tended to reduce the combined risk of death or cardiovascular hospitalization, HR 0.80 (0.59-1.09) for pooled data. A third study in about 500 patients compared dronedarone 400 mg bid to amiodarone 600 mg/day for 2 weeks, then 200 mg/day, finding amiodarone significantly superior in preventing recurrence HR 1.59 (1.28-1.98). We do not, however, have safety or outcome data for amiodarone for these uses.

B. ATHENA

Support for approval comes primarily from the ATHENA study, a randomized, double-blind comparison of dronedarone 400 mg bid and placebo in patients with AF/AFL within 6 months and who were, at entry, in NSR or about to be cardioverted. Subjects also had to be at high risk (> 70 years or one of: hypertension, diabetes, prior CVA, LA diameter > 50 mm by M-mode echocardiography, or LVEF < 40% by 2D Echo. Patients could not be unstable (pulmonary edema within 12 hours, need for pressors within 4 weeks, or GFR < 10 ml/min).

The primary endpoint was time to first CV hospitalization or death (all cause). Ordered secondary endpoints were:

1. All cause mortality
2. First CV hospitalization
3. CV deaths

As Dr. Stockbridge notes, this made little sense, as, at least in theory, if the first secondary endpoint was NS, the 2nd could not be considered. It is apparent that the order should have been CV hospitalization, CV death, and all cause mortality. Initially, cause-specific mortality was left to investigator judgment, but events were later sent to the blinded steering committee for adjudication.

Sample size was initially 3700 but was increased to 4300 to give a better chance to showing a survival effect after a blinded look at total events. In the end 4628 were randomized.

Results showed a highly significant reduction in death plus CV hospitalization, largely driven by CV hospitalization, which was itself highly significant. Overall mortality trended favorably. The effect on CV hospitalization was driven largely by the effect on hospitalization because of AF, but other CV hospitalization trended favorably (reassuring in view of ANDROMEDA results). Dr. Karkowsky's CDTL review shows the K-M curve for the primary endpoint (p 18) and forest plots for a variety of demographic, concurrent illness, and concomitant illness, and concomitant treatment characteristics. Results were very consistent, not surprising considering the low p-value for this endpoint ($p < 0.0001$).

The major endpoints, taken from labeling, are shown in the following table.

	Placebo n = 2327	Dronedarone n – 2301	HR (95% CI)	p-value
Primary endpoint CV hosp or all cause death	913 (39.2%)	727 (31.6%)	0.76 (0.68-0.83)	< 0.0001
Components of primary endpoint as first event CV hosp All cause death	856 (36.8%) 57 (2.4%)	669 (29.1%) 58 (2.5%)		
Secondary endpoints (any time in study) All cause death CV Hosp	135 (5.8%) 856 (36.8%)	115 (5.0%) 669 (29.1%)	0.86 (0.67-1.11) 0.74 (0.67-0.82)	0.24 < 0.0001
Components of CV hosp AF + SV Other	456 (19.6%) 400 (17.2%)	292 (12.7%) 377 (16.4%)	0.61 (0.53-0.71) 0.89 (0.77-1.03)	< 0.0001 0.11

Labeling does not include cause-specific mortality or cause-specific hospitalization (except for AF/other) because there was concern about classification and because, at least strictly, CV mortality could not be considered statistically after all-cause mortality proved NS. The results are, however, reassuring to a degree.

Among "other" CV hospitalizations, there were more for worsening CHF on placebo (92 to 78). CV deaths favored dronedarone, principally for sudden death, and deaths attributed to heart failure were similar (10 placebo, 13 dronedarone). These results did not support a claim, in our view, but they provide considerable reassurance in light of ANDROMEDA. ATHENA did not include the acutely decompensated patients entered into ANDROMEDA and it is those patients

labeling seeks to have excluded form treatment. Lesser degrees of failure did not appear to represent a problem in ATHENA.

III. Safety

Safety findings are discussed in detail in other reviews. The principal concern is avoiding the ANDROMEDA population, patients recently hospitalized with symptomatic heart failure and severe LV systolic dysfunction. That study was stopped after 627 patients (planned 1000) were randomized and showed mortality of 25 (8.1%) on dronedarone vs 12 (3.8%) on placebo (p-0.027; HR 2.13; CI 1.07-4.25). The main cause of death was increasing heart failure, consistent with dronedarone's negative inotropic effect.

Dronedarone is metabolized by CYP 3A4 and potent 3A4 inhibitors (ketoconazole) give a huge increase (17-fold) in exposure. These drugs are contraindicated. 3A4 inducers (rifampin) decrease dronedarone concentrations by 80%.

Dronedarone is a moderate inhibitor of CYP 3A4 and 2D6, increasing simvastatin levels by 4-fold.

Dronedarone at the recommended dose has a modest (10 msec) QT prolonging effect and should not be used with other QT prolonging drugs or patients with QT > 500 msec.

As noted, by far the greatest concern is avoiding use of dronedarone in patients with decompensated heart failure (Class IV or Class II/III with recent decompensation requiring hospitalization or referral to a specialized heart failure clinic). Labeling warns about worsening heart failure on treatment and urges physician contact and consideration of suspension of drug. The Medguide reminds patients of this and urges physician contact if symptoms of CHF emerge. There is also a Post-Marketing Requirement to carry out 5 epidemiologic studies, four to look for long-term effects characteristic of amiodarone toxicity (pulmonary, neurologic, dermatologic) and one to assess the frequency of use in patients for whom the drug is contraindicated. The safety database did not suggest the amiodarone-like effects but was of insufficient duration to rule them out.

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/s/

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MEDICAL OFFICER