Questions

Dronedarone for AF

March 18, 2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

The Advisory Committee is asked to opine on the approvability of and appropriate target population for dronedarone for use to delay recurrence of and hospitalization for atrial fibrillation.

Dronedarone is an analog of amiodarone. Dronedarone was originally submitted as an NDA in 10 June 2005. Based on the results of two placebo-controlled studies ADONIS and EURIDIS, dronedarone delayed the time to the first recurrence of arrhythmia and also decreased symptomatic recurrence of these events in a patient population with a history of either atrial fibrillation or atrial flutter who were in sinus rhythm at the time of randomization.

The application was not approved, largely because of adverse outcomes in ANDROMEDA. ANDROMEDA was a placebo-controlled study of dronedarone 400 mg BID in patients with NYHA Class II-IV. Intended to provide reassurance regarding safety in a high-risk population, ANDROMEDA was stopped, with N=627 of a planned enrollment of 1000, for an adverse effect on mortality (25 vs. 12), hospitalization for heart failure (39 vs. 31), and hospitalization for cardiovascular causes (71 vs. 50).

The sponsor then performed ATHENA, placebo-controlled study of dronedarone 400 mg BID in patients who during the last six months had at least one episode of atrial fibrillation or flutter and at least one normal ECG during the same period (in either order). Patients with 'permanent' atrial arrhythmias were precluded from enrollment. Those who were in atrial fibrillation at the time of enrollment were to be converted after a suitable anticoagulation interval. The primary end point was time to first event of cardiovascular hospitalization or death from any cause.

CV hospitalizations or death in ATHENA

	Placebo N=2327	**Dronedarone N=2301**
Any	917	734
Cardiovascular hospitalization	859	675
Death as first event	58	59
Death at any time during study	134	115

There were 24% fewer such events on dronedarone, a difference that was highly statistically significant. The groups separated early and remained separated through 24 months of follow-up. The results were largely homogeneous across a variety of planned subgroups, including US vs. non-US.

1. The sponsor postulated that adverse effects in ANDROMEDA were the result of dronedarone's presumably innocuous inhibition of renal tubular creatinine secretion, which led to inappropriate and harmful discontinuation of ACE inhibitors or ARBs. Does the Committee find this explanation plausible?

   1.1. Causes of death in ANDROMEDA are shown in the table below:

Deaths in ANDROMEDA

	Placebo	**Dronedarone**
Any	12	25
Cardiovascular	9	23
Heart failure	2	10
Arrhythmia	2	6
(Presumed)	3	5
Myocardial infarction	2	0
Other	0	3
Non-cardiovascular	3	1

   Are these differences consistent with the sponsor's hypothesis?

   1.2. Deaths by use of ACEI/ARB at baseline are shown below:

Deaths by ACEI/ARB usage in ANDROMEDA

	Placebo	**Dronedarone**
Not on ACEI/ARB at baseline	1 / 50	6 / 36
ACEI/ARB maintained	10 / 267	10 / 274
ACEI/ARB discontinued	1 / 12	9 / 19
Total	12 / 329	25 / 329

   Are these differences consistent with the sponsor's hypothesis?

   1.3. Dr. Karkowsky's memo describes the course of the 9 subjects who died on dronedarone following discontinuation of ACEI/ARB.

Do the decisions to discontinue ACEI/ARB appear to have been related to small, benign increases in serum creatinine?

1.4. In ATHENA, during the specified period of follow-up, there were 134 deaths on placebo (xx%) and 115 deaths on dronedarone (xx%; RR=0.xx; 95% CI=0.xx, 0.xx). Are these results compatible with mortality in ANDROMEDA, when you compare …

… confidence limits?

… populations enrolled?

… patient management?

2. ATHENA's planned enrollment was 4300, but the actual enrollment was 4637. Why was that?

3. Some analyses categorized hospitalizations and deaths as cardiovascular or non-cardiovascular. Please comment on …

… the categories of events that were considered cardiovascular or non-cardiovascular.

… the adequacy of the information on the case report form to support categorization.

4. The major categories of cardiovascular hospitalizations are shown in the table below.

Categories of CV hospitalizations in ATHENA

	Placebo N=2327	**Dronedarone N=2301**
Any	859	675
AF or supraventricular arrhythmia	457	296
Worsened heart failure	92	78
Unstable angina or MI	61	48
Stable angina or atypical chest pain	41	45
TIA or stroke	35	28
ICD or pacemaker	29	32
Arterial procedures	31	27
12 less common categories	113	121

Is the effect on cardiovascular hospitalizations more than an effect on symptomatic atrial fibrillation?

5. Is there an effect of dronedarone on atrial flutter
6. Have dose and regimen been adequately studied? If not, does further study need to be done prior to approval?
7. Who should not receive dronedarone? For each such restriction, please indicate …

   … how *important* it is to restrict use.

   … how *feasible* it is to restrict use.
8. How concerned are you about adverse effects of dronedarone on …

   … renal function?

   … bradycardia?

   … QT prolongation?

   … heart failure?

   … other safety issues?
9. VOTE: Should dronedarone be approved to treat patients with non-permanent atrial fibrillation? After the vote, please comment on whether you believe the claim should be any broader or narrower than ATHENA's primary end point.