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APPLICATION NUMBER:

22-425

OTHER ACTION LETTER(s)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-913

Sanofi-Aventis U.S. Inc.
Attention: Nancy Barone Kribbs, Ph.D.
Senior Director, Drug Regulatory Affairs
11 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Kribbs:

Please refer to your new drug application (NDA) dated June 10, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Multaq (dronedarone hydrochloride) 400 mg Tablets.

We acknowledge receipt of your submissions dated July 22, August 9, 17, October 4, 11, December 6, 22, 2005, January 3, 26, 27, February 16, 27, March 6, and 8, 2006.

We have completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

1. There is no doubt that dronedarone HCl 400 mg twice daily increases the time to recurrent AF modestly and slows the ventricular response by about 10 beats per minute. The data, however, do not indicate a favorable risk-benefit relationship for either rate control or prevention of AF recurrence. As all antiarrhythmic agents raise concerns of pro-arrhythmic or other adverse cardiovascular effects, their use to control symptoms needs to be supported by an assessment of their potential for serious harm. The ANDROMEDA study was intended to provide reassurance about this potential by showing a low upper bound for dronedarone's possible adverse effect on mortality in a high-risk population. ANDROMEDA did not provide such reassurance, instead showing increased mortality, causing the Data Monitoring Committee for the trial to urge its interruption. Apart from ANDROMEDA's failure to provide general reassurance, as patients with AF commonly have underlying heart disease, the ANDROMEDA result seems particularly applicable to that population. Conceivably, a study of substantial size in the target population could provide reassurance.
2. While dronedarone reduced the ventricular rate in patients with atrial fibrillation, most of those patients remained tachycardic. Therefore, the Agency is not convinced that the reductions in ventricular rate will lead to symptomatic improvement. This could be addressed in a study of symptoms in patients in atrial fibrillation.
3. Apart from the questions raised by ANDROMEDA, approval on the basis of any symptomatic benefit would also need to be weighed against other safety concerns, including carcinogenicity, teratogenicity, and endocrine effects (thyroid, female cyclicity).
4. You have not provided sufficient permeability information to support dronedarone's designation as BCS 2.

5. The dissolution methodology is acceptable, however, we do not agree with your dissolution specification. Based on the data provided the following specification is more appropriate: 1) Not less than (b) (4) and not more than (b) (4) is dissolved within 30 minutes 2) Q = (b) (4) at 90 minutes.
6. In order to define and control the drug substance particle size distribution, you will need to add an acceptance criterion for (b) (4) in addition to the current (b) (4) criterion, or justify why it is not necessary to have an acceptance criterion for (b) (4).
7. We will have to reach agreement on the content of the labeling after the above issues have been addressed.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Cardiovascular and Renal Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please contact:

Mr. Russell Fortney
Regulatory Health Project Manager
(301) 796-1068

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Robert Temple

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