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FDA Drug Safety Communication: Multaq (dronedarone) and increased risk of death and serious cardiovascular adverse events

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Safety Announcement

[07-21-2011] The U.S. Food and Drug Administration (FDA) is reviewing data from a clinical trial that was evaluating the effects of the antiarrhythmic drug Multaq (dronedarone) in patients with **permanent** atrial fibrillation. The study was stopped early after the data monitoring committee found a two-fold increase in death, as well as two-fold increases in stroke and hospitalization for heart failure in patients receiving Multaq compared to patients taking a placebo. Currently Multaq is approved for use in a different, but related patient population (see Facts about Multaq box). The approval of Multaq was based on another trial (ATHENA) in which use of Multaq was associated with a decreased number of deaths compared to placebo.¹

The **Permanent Atrial fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy**

(PALLAS)² study, sponsored by Sanofi Aventis (the maker of Multaq), was being conducted to assess the potential clinical benefit of Multaq in patients over 65 years of age with permanent atrial fibrillation in the reduction of:

- Major cardiovascular (CV) events (stroke, systemic arterial embolism, myocardial infarction or cardiovascular death), or
- Unplanned cardiovascular hospitalization or death from any cause

A critical question is whether and how the unfavorable results of the PALLAS study, obtained in patients with permanent atrial fibrillation, apply to patients who use Multaq for the approved indications (non-permanent atrial fibrillation, also known as paroxysmal or persistent atrial fibrillation). [see Data Summary for more information]

At this time, patients taking Multaq should talk to their healthcare professional about whether they should continue to take Multaq for non-permanent atrial fibrillation. Patients should not stop taking Multaq without talking to a healthcare professional. Healthcare professionals should not prescribe Multaq to patients with permanent atrial fibrillation.

FDA previously issued a Drug Safety Communication (DSC) in January 2011³ regarding cases of rare but severe liver injury that have been reported with the use of Multaq.

Today's communication is in keeping with FDA's commitment to inform the public about its ongoing safety review of drug. FDA will update the public when more information is available.

Additional Information for Patients

- Talk to your healthcare professional about whether you should continue to take Multaq for paroxysmal or persistent atrial fibrillation. Do not stop taking Multaq without talking to your healthcare professional.
- Discuss any questions or concerns about Multaq with your healthcare professional.
- Report any side effects you experience to the FDA MedWatch program using the information in the "Contact Us" box.

Facts about Multaq

- Used to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent episode of AF/AFL and associated cardiovascular risk factors, who are in sinus rhythm or who will be cardioverted [Refer to Multaq label¹]
- From approval in July 2009 through June 2011, approximately 1 million Multaq prescriptions were dispensed and approximately 241,000 patients received Multaq prescriptions from U.S. outpatient retail pharmacies.²

at the bottom of the page.

Additional Information for Healthcare Professionals

- Do not prescribe Multaq to patients with permanent atrial fibrillation.
- FDA is evaluating whether and how the preliminary results of the PALLAS study apply to patients taking Multaq for paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL).
- The PALLAS study results are considered preliminary at this time because the data have not undergone quality assurance procedures and have not been completely adjudicated.
- Report adverse events involving dronedarone to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of the page.

Data Summary

Sanofi Aventis conducted "A randomized, double blind, placebo controlled, parallel group trial for assessing the clinical benefit of dronedarone 400 mg BID on top of standard therapy in patients with permanent atrial fibrillation and additional risk factors" (PALLAS). This study was a large outcome trial intended to evaluate the effectiveness of dronedarone in patients with permanent atrial fibrillation.

The patients eligible to enroll in PALLAS were 65 years or older, in permanent atrial fibrillation (defined by the presence of atrial fibrillation/atrial flutter for at least 6 months prior to randomization without plans to restore sinus rhythm), and had at least one additional cardiovascular (CV) risk criterion.

In July 2011, the data monitoring committee reviewed the preliminary data and concluded that there was a significant excess of CV events in the Multaq group for both co-primary endpoints (CV death/myocardial infarction/stroke/systemic embolism; death/unplanned CV hospitalization) as well as other CV events (see Table 1 below). As a result, the PALLAS study was stopped.

Table 1: Events during the PALLAS study as of June 30, 2011.

	Multaq N=1572 n (%)	Placebo N=1577 n (%)	Hazard Ratio	p- value
CV Death, Myocardial Infarction, Stroke, Systemic Embolism*	32 (2)	14 (0.9)	2.3	0.009
Death, Unplanned CV Hospitalization*	118 (7.5)	81 (5.1)	1.5	0.006
Death	16 (1)	7 (0.4)	2.3	0.065
Myocardial Infarction	3 (0.2)	3 (0.2)	1.0	1
Stroke	17 (1.1)	7 (0.4)	2.4	0.047
Heart Failure Hospitalization	34 (2.2)	15 (1)	2.3	0.008

*coprimary endpoints

Note: These are preliminary data provided by the manufacturer; therefore, the data have not undergone quality assurance procedures and have not been completely adjudicated.

FDA has received and is currently reviewing preliminary results from the PALLAS study and will review the final results when they become available. Because the review is ongoing, FDA has not concluded whether the results of the PALLAS study are applicable to patients taking Multaq for paroxysmal or persistent atrial fibrillation or atrial flutter. However, healthcare professionals should not prescribe Multaq to patients with permanent atrial fibrillation. FDA will update the public when further information is available.

References

1. Hohnloser SH, Crijns HJ, van Eickels M, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med* 2009 Feb 12;360(7):668-78.
2. Source: SDI, Vector One®: National (VONA) and Total Patient Tracker (TPT). July 2009 – June 2011. Extracted 7-18-2011.

Related Information

- [Multaq \(dronedarone\) Information](#)⁴
- [FDA Drug Safety Communication: Severe liver injury associated with the use of dronedarone \(marketed as Multaq\)](#)⁵
1/14/2011
- [Permanent Atrial fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy \(PALLAS\) study](#)⁶
- [Multaq \(dronedarone\) label \(6/21/2011\)](#)⁷
- [FDA Drug Safety Podcast for Healthcare Professionals: Multaq \(dronedarone\) and increased risk of death and serious cardiovascular adverse events](#)⁸
- [Comunicado de la FDA sobre la seguridad de los medicamentos: Multaq \(dronedarona\) y el aumento en el riesgo de muerte y graves problemas cardiovasculares](#)⁹

Contact Us

- **Report a Serious Problem**

- 1-800-332-1088
- 1-800-FDA-0178 Fax
- [MedWatch Online](#)¹⁰

Regular Mail: Use postage-paid FDA Form 3500¹¹

Mail to: MedWatch 5600 Fishers Lane
Rockville, MD 20857

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1. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022425s010lbl.pdf
2. <http://clinicaltrials.gov/ct2/show/NCT01151137?term=pallas&rank=1>
3. </Drugs/DrugSafety/ucm240011.htm>
4. </Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm240024.htm>
5. </Drugs/DrugSafety/ucm240011.htm>
6. <http://clinicaltrials.gov/ct2/show/NCT01151137?term=pallas&rank=1>
7. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022425s010lbl.pdf
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