Food and Drug Administration
Center for Drug Evaluation and Research
Hilton College Park, 4095 Powder Mill Road, Beltsville, Maryland.

Meeting Minutes of the Cardiovascular and Renal Drugs Advisory Committee meeting on December 12, 2007.

On December 12, 2007, the committee discussed new drug application (NDA) 22-123, PULZIUM® (tedisamil sesquifumarate) IV solution 2 milligrams per milliliter, Solvay Pharmaceuticals, Incorporated, for the proposed indication of use for conversion of atrial fibrillation or atrial flutter to normal sinus rhythm.

These summary minutes for the December 12, 2007 meeting of the Cardiovascular and Renal Drugs Advisory Committee were approved on Monday, December 17, 2007.

I certify that I attended the December 12, 2007 meeting of the Cardiovascular and Renal Drugs Advisory Committee and that these minutes accurately reflect what transpired.

_____//S//_____	_____//S// _____	12/17/2007
Cathy A. Miller, M.P.H., R.N.	William R. Hiatt, M.D.	Date
Designated Federal Official	Committee Chair	

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

The Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on December 12, 2007 at the Sheraton College Park, 4095 Powder Mill Road, Beltsville, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background material from Astellas Pharma US, Inc. The meeting was called to order by William Hiatt, M.D. (Committee Chair); the conflict of interest statement was read into the record by Cathy A. Miller, M.P.H. (Designated Federal Official). There were approximately 125 persons in attendance. There were no Open Public Hearing speakers for this session.

Issue: On December 12, 2007, the committee discussed new drug application (NDA) 22-123, PULZIUM® (tedisamil sesquifumarate) IV solution 2 milligrams per milliliter, Solvay Pharmaceuticals, Incorporated, for the proposed indication of use for conversion of atrial fibrillation or atrial flutter to normal sinus rhythm.

Attendance:

Cardiovascular and Renal Drugs Advisory Committee Members Present (Voting):
William Hiatt, M.D. (Chair); Frederick J. Kaskel, M.D. Robert A. Harrington, M.D., F.A.C.C.; Abraham Michael Lincoff, M.D., F.A.C.C.;

Special and Federal Government Employee Consultants (Voting):
Richard Cannon, M.D.; Barry M. Massie, M.D.; Thomas Simon (Patient Representative)

Cardiovascular and Renal Drugs Advisory Committee Members Not Present:
Henry Black, M.D.; John M. Flack, M.D.; Lynn Warner Stevenson, M.D.; Emil Paganini, M.D.; Jonathan Fox, M.D.; John Teerlink, M.D.; James Neaton, Ph.D.; Steven Findlay, M.P.H.

FDA Participants (Non-Voting):
Norman Stockbridge, Ph.D., M.D.
Thomas Marciniak, M.D.

Designated Federal Official:
Cathy A. Miller, M.P.H., R.N.

Open Public Hearing Speakers:
None Registered

The agenda was as follows:

Call to Order and Introductions	**William R. Hiatt, M.D.** Committee Chair Cardiovascular and Renal Drugs Advisory Committee
Conflict of Interest Statement	**LCDR Cathy A. Miller, M.P.H., R.N.** Designated Federal Official Cardiovascular and Renal Drugs Advisory Committee
Introduction and Background	**Norman Stockbridge, M.D., Ph.D.** Director, Division of Cardiovascular and Renal Products FDA Center for Drug Evaluation and Research

Solvay Pharmaceuticals Sponsor Presentation:

Introduction	**Victor Raczkowski, M.D., M.S.**

	Vice President US Regulatory Affairs Solvay Pharmaceuticals
Unmet Medical Need	**Peter R. Kowey, M.D**. President, Main Line Health Heart Center William Wikoff Smith Chair in Cardiovascular Research Professor of Medicine and Clinical Pharmacology Jefferson Medical College of Thomas Jefferson
Efficacy and Safety	**Matthias Straub, M.D.** Vice President, Global Clinical Development Solvay Pharmaceuticals
Risk Minimization Plan	**Earl Sands, M.D.** Vice President and Chief Medical Officer U.S. Research & Development Solvay Pharmaceuticals
Risk Benefit	**Peter R. Kowey, M.D.**
Conclusions	**Victor Raczkowski, M.D., M.S.**

FDA Division of Cardiovascular and Renal Products Presentation:

Tedisamil for Conversion of Atrial Fibrillation	**Thomas Marciniak, M.D.** Medical Team Leader Division of Cardiovascular and Renal Products CDER, FDA
	Questions/Discussion from the Committee
	Lunch
	Open Public Hearing
	Questions to the Committee Part 2
	Adjournment

Questions to the Committee:

1. What clinical benefits were *demonstrated* in the development program for tedisamil? For which of them are there beneficial and meaningful trends?

   - Reduction in thromboembolic events?

   The Committee commented that there was a slight numeric excess thromboembolic events observed with tedisamil treatment.

   - Reduction in hemorrhagic events (reduced need for warfarin)?
     The Committee had no evidence from the trials to support a reduction (or any other changes) in hemorrhagic events.

   - Reduction in the need for hospitalization?

   The Committee did not feel there was data to support reduction in the need for hospitalization

- Reduction in symptoms attributable to atrial fibrillation?

The Committee commented that there were no demonstrated reduction in symptoms attributable to atrial fibrillation since symptoms were not evaluated in the studies.

- Avoidance of electrical cardioversion?

The Committee agreed that the data supported an avoidance of cardioversion, especially in males.

- Others?

(See transcripts for detailed discussion)

2. What clinical benefits do you believe should be *expected* through the use of tedisamil? Compared with what treatment (electrical cardioversion, rate control, or another drug) are these clinical benefits expected?

The Committee had the following comments on clinical benefits 'expected' from the use of tedisamil:

- ***The Committee felt that the sample size needed to prove that a shorter time in AF with drug therapy would have a measurable clinical outcome was not feasible. The risk for thromboembolic events is cumulative the longer one is in atrial fibrillation, therefore shortening the period of AF by a few hours may not translate into a reduction in events given the low absolute risk for that very short interval.***
- ***Hemorrhagic events would be driven by the duration and management of anticoagulation. Since most patients would be anticoagulated, it was not anticipated that tedisamil would reduce the risk of bleeding.***
- ***There was considerable discussion around reduction in hospitalization. While an effective drug to convert AF to normal sinus would theoretically reduce the length of time in the hospital, the need to a long monitoring window may cancel out that potential benefit. Some of the committee felt that an observational study could provide some helpful data.***
- ***The Committee agreed that tedisamil would be expected to provide reduction in symptoms attributable to atrial fibrillation as (well as the avoidance of cardioverson) but noted that symptoms were not assessed in the trials.***

(See transcripts for detailed discussion)

3. Cited conversion rates excluded patients who underwent early electrical conversion, those who converted prior to receiving study drug, and those who otherwise did not receive study drug. Are these exclusions reasonable? If not, how should these cases be handled?

- ***Overall, the committee felt these exclusions were handled acceptably and there was transparency in analyzing the data. There was some discussion, about torsades patients being handled as failures.***

(See transcripts for detailed discussion)

4. In a restricted sense, tedisamil is clearly more effective than is placebo. Among patients who had been in atrial fibrillation for 3 hours to 45 days, the rates of spontaneous conversion on placebo *within a 2.5-h window* were 3-10%, while conversion rates on drug were 18-55% at proposed doses.

- How well characterized is the relationship between time in atrial fibrillation and spontaneous conversion? Note that 3% of patients converted spontaneously after randomization but before study drug administration.

The Committee felt that this relationship was fairly well. Spontaneous conversion rates within 24 hours are relatively well known and the committee anticipated that additional patients would have converted had the run-in period been 24 hours.

- How well characterized is the relationship between time in atrial fibrillation and conversion on tedisamil?

The Committee did not see an analysis of response to drug as correlated with duration of AF. However a curvi-linear relationship would have been anticipated. The committee agreed that the drug was more effective when used within the first 48 hours of AF, with diminishing effectiveness after that.

- What length of time in atrial fibrillation is clinically meaningful?

The Committee felt that for symptomatic patients or patients who were hemodynamically unstable, any length of time in AF was clinically meaningful. In terms of response to therapy, most agreed that the length of time should be no more than 48 hours.

- For patients who have been in atrial fibrillation for what duration is the time savings attributable to tedisamil clinically meaningful?

The Committee agreed that time savings is meaningful though there was considerable debate about quantifying this time savings. They agreed that the longer patients were in atrial fibrillation, the lower the efficacy of the drug and at 48 hours or greater, safety becomes a bigger concern. Most agreed that after 48 hours, the benefit drops off substantially.

(See transcripts for detailed discussion)

5. What effect does unsuccessful conversion with tedisamil have upon subsequent attempts at electrical conversion?

The Committee agreed that unsuccessful conversion with tedisamil had no effect on subsequent attempts to electrically cardiovert.

6. How is atrial hemodynamic function affected by tedisamil? Does this matter?

The Committee commented that there was not adequate data to assess drug effects on atrial hemodynamics. When asked to expand on whether it matter, the Committee commented that they were unsure if it matters any more than with other treatments to convert atrial fibrillation.

(See transcripts for detailed discussion)

7. How much of a safety concern is torsade de pointes?

The Committee felt that torsades represented a significant safety concern. The committee also expressed that concomitant antiarrythmic medications might increase the risk.. The committee also cited concerns about the significant uncertainty about the true torsades risk and the percentage of bad outcomes of torsades. They cautioned that the real world frequency of torsades could be considerably greater.

- Have the rates of torsades been adequately characterized in the patient population and at the doses for which tedisamil should be used?

The Committee agreed there was significant concerned and the rates were not well characterized. Concerns included rates of torsades in women.

For how long (either hours or QT prolongation) should rhythm be monitored after exposure to tedisamil? Does this time need to be adjusted for 2D6 inhibitors or for poor metabolizer phenotypes?

Many of the Committee felt the QT measurement criterion was not realistic and would be prone to error in analysis or being overlooked altogether. They felt the criteria should be set as a 'time period' rather than a QT measurement. There was a suggestion to employ a 2-fold observational period: one for successful conversion and one for unsuccessful conversion. In either case the committee felt that much longer observation periods would be required, perhaps up to 8-9 hours.

- The sponsor recommends a lower dose in women to try to avoid some risk of torsade de pointes, and a lower dose showed a trend for lower risk of torsade. However, women also tended to have lower rates of conversion on drug at any given dose than did men. Does this trade-off (lower effectiveness, lower risk) make sense?

There was considerable discussion surrounding efficacy versus risk in women when considering the dose. Some of the Committee felt that it was acceptable to equalize risk between men and women by decreasing the dose even if it decreased efficacy. The Committee agreed that we need more events on drug to get a better sense of the risk for women. Overall the committee could not reach a recommendation on a safe and effective dose, particularly in women.

(See transcripts for detailed discussion)

8. How much of a safety concern is bradycardia?

The Committee agreed that bradycardia was not a major concern in the group studied in the trials.

9. How much of a safety concern are thromboembolic events, including strokes?

Though there were a few events seen on drug, the Committee felt that these events may be drug-related and therefore could represent a significant safety concern. The Committee did suggest, though, that thromboembolic events needed to be better characterized and more events would need to be acquired to allow for an adequate interpretation.

10. Are there other safety concerns?

No other safety concerns were cited by the Committee other than the one death that seemed to be definitely drug related.

11. Is the risk management plan proposed by the sponsor appropriate for the safety concerns?

The Committee discussed lingering safety concerns and the need for more information before the risk management plan proposed by the sponsor can be thoroughly evaluated.

12. Is another study necessary to confirm the appropriateness of the dosing recommendations? If so, in what population should it be conducted?

A few of Committee suggested that another study needs to be conducted to confirm dosing in women. Many of the Committee, though, complimented the Sponsor on their efforts to address dosing in their studies and recognizing the challenges presented to the Sponsor in formulating the dosing strategy. The Committee has concerns, though, about the complexity of the dosing regimen.

(See transcripts for detailed discussion)

13. **VOTE**: Should tedisamil be approved for the conversion of atrial fibrillation?

YES: 0 **NO: 7**

The Committee provided supplementary comments to their 'No' votes including:

Variation in the voting trends for tedisamil compared to the previous days vote on vernakalant could, in fact, be because there was actually more data presented for tedisamil.

- ***When asked what information the Committee would need to reevaluate their decision, recommendations included:***
- ***More USA representation***
- ***Increased number of patients on anti-arrythmic therapy to assess drug interactions***

- ***Increased patients where we are confident about the estimates and a need for more safety events for confidence in dosing***

- ***Suggestion for a trial randomizing patients to DC cardioversion or tedisamil, though there would be challenges with agreeing on primary endpoints***

(See transcript for detailed discussion)

14. If you conclude that tedisamil should be approved, …
    - … to what range of durations of atrial fibrillation should approval apply?
    - … should use extend to patients with recent MI or heart failure?
    - … should the claim extend to atrial flutter?
    - … are any post-marketing commitments appropriate, such as …
        - … to study use with beta-blockers?
        - … to study the effect on ventricular defibrillatory threshold?
        - … to study use in non-Caucasians?
        - … to study use in patients with structural heart disease?
        - … to study use in patients with hepatic impairment?
        - … to study use with inhibitors of P-glycoprotein or other transporters?
        - Others?

Since there were no votes for approval, the Committee did not address Question #14.

The committee adjourned at approximately 5:00 pm

(See transcript for detailed discussion)