



DRAFT
Questions
NDA 22-123
Tedisamil

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Cardio-Renal Advisory Committee

The Advisory Committee is asked to opine on the use of tedisamil to effect conversion of atrial fibrillation (AF) to normal sinus rhythm.

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?
 - Reduction in hemorrhagic events (reduced need for warfarin)?
 - Reduction in the need for hospitalization?
 - Reduction in symptoms attributable to atrial fibrillation?
 - Others?
2. What clinical benefits do you believe should be *expected* through the use of tedisamil? Compared with what treatment are these clinical benefits expected?
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?
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.
 - How well characterized is the relationship between time in atrial fibrillation and conversion on tedisamil?
 - What length of time in atrial fibrillation is clinically meaningful?
 - For patients who have been in atrial fibrillation for what duration is the time savings attributable to tedisamil clinically meaningful?

5. What effect does unsuccessful conversion with tedisamil have upon subsequent attempts at electrical conversion?
6. How is atrial hemodynamic function affected by tedisamil? Does this matter?
7. How much of a safety concern is torsade de pointes?
 - Have the rates of torsades been adequately characterized in the patient population and at the doses for which tedisamil should be used?
 - 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?
 - 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?
8. How much of a safety concern is bradycardia?
9. How much of a safety concern are thromboembolic events, including strokes?
10. Is the risk management plan proposed by the sponsor appropriate for the safety concerns?
11. VOTE: Should tedisamil be approved for the conversion of atrial fibrillation?
12. 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?

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- ... 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?

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