

Cardiovascular and Renal Drugs Advisory Committee Meeting

September 10, 2004

Holiday Inn, Versailles Ballrooms, Bethesda, MD

Questions to the Committee

Safety:

1. What is your level of concern (none, low, moderate, high) for the risk of liver toxicity with use of ximelagatran:
 - a) For prevention of stroke and systemic embolic events in patients with atrial fibrillation?
 - b) For secondary prevention of venous thromboembolism (VTE) after 6 months standard treatment for an episode of acute VTE?
 - c) For prevention of VTE in patients undergoing elective total knee replacement surgery (TKR)?For each response please explain.
2. Based on currently available data, is it possible to identify patients who are at risk for developing severe liver toxicity after exposure to ximelagatran?
3. Did the sponsor's study procedures for monitoring and managing patients with regard to liver function adequately minimize the risk of severe liver injury and liver failure in the clinical studies?
4. Do you have other safety concerns regarding the long-term use of ximelagatran (e.g. cardiac)? Regarding the short-term use of ximelagatran?

Short-term Use: prevention of VTE in patients undergoing elective total knee replacement surgery

5. Do you recommend additional safety studies with longer follow-up to address the possibility of delayed occurrence of liver toxicity following short-term use?
6. Regarding the potential risk of myocardial infarction/coronary artery disease (MI/CAD) with short-term exposure to ximelagatran (mean 8 days) in patients undergoing TKR, do you recommend further studies to assess the risk of acute MI/CAD? If yes, what type of study(ies) do you recommend?
7. Based on the currently available data, do you conclude that the benefits of ximelagatran for short-term use for prevention of VTE in patients undergoing elective total knee replacement surgery outweigh its risk?

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Questions to the Committee
Cont.

Long-term Use: secondary prevention of VTE after 6 months standard treatment for an episode of acute VTE

8. Based on the currently available data, do benefits of ximelagatran for secondary prevention of VTE (18 months) after 6 months standard treatment for an episode of acute VTE outweigh the risks for this indication?

Long-term Use: prevention of stroke and systemic embolic events in patients with atrial fibrillation

9. Is the non-inferiority margin of 2% compared to warfarin adequate to ensure that ximelagatran is non-inferior to warfarin with respect to efficacy? If no, what should the non-inferiority margin be for the indication of prevention of stroke and systemic embolic events in patients with atrial fibrillation?
10. Based on the currently available data, do you conclude that the benefits of ximelagatran for long-term use for prevention of stroke and systemic embolic events in patients with atrial fibrillation outweigh its risk?