Ximelagatran and Oral Direct Thrombin Inhibition

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[Rev Cardiovasc Med. *2004;5(suppl 5):S1*]

Ximelagatran is a novel oral direct thrombin inhibitor that, when converted to its active form, melagatran, works directly as an inhibitor of thrombin, a key mediator of thrombosis. Direct thrombin inhibitors act in a manner contrasting to that of heparin and its derivatives, which inhibit thrombin and other coagulation serine proteases via antithrombin, and to warfarin and similar drugs, which interfere with the synthesis of the precursors of the coagulation serine proteases. Ximelagatran, administered orally, is the most promising and extensively evaluated drug in its class.

The data summarized in this supplement, along with longer-term outcomes and additional details on safety, were presented to the US Food and Drug Administration (FDA) Cardiovascular and Renal Drugs Advisory Committee in September 2004. The 12-member panel advised against approval of ximelagatran for the following indications: 1) short-term use in the prevention of venous thromboembolism (VTE) in patients undergoing elective total knee replacement; 2) secondary VTE prevention after 6 months of standard therapy for an acute episode of VTE; and 3) prevention of stroke and systemic embolic events in patients with atrial fibrillation.

The Advisory Committee stated that the benefits of ximelagatran did not outweigh the risks for any of the 3 indications for which approval was sought. AstraZeneca, LP, the manufacturer of ximelagatran (Exanta™), received an official USFDA action letter to this effect, in October of 2004. However, the acting chair of the panel, Dr. Jeffrey Borer, stated that it was difficult to discuss the drug's safety without considering its benefit in comparison to the only currently available alternative, warfarin. The USFDA generally follows the recommendations of the advisory panels. A statement issued by AstraZeneca indicated that the company would continue discussion with USFDA regulators, regarding the additional research necessary to move forward with the approval process. Ximelagatran has been approved in a number of European countries, for the prevention of blood clots in patients undergoing hip- or knee-replacement surgeries, and investigation of additional potential indications is on-going. AstraZeneca is committed to gaining approval for ximelagatran in the US market.

This supplement will evaluate the known safety and efficacy data on this new and important compound as it relates to cardiovascular medicine. The worldwide use of ximelagatran, and its potential replacement of warfarin in the marketplace, will have profound ramifications for generalists and specialists caring for patients in need of short- and longer-term anticoagulation. ■