73. Exanta (=Ximelagatran)

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The new oral blood thinner Exanta® (=Ximelagatran) (see also Q/A 2 on www.fvleiden.org) will likely not come to the market soon, possibly never. On Sept 10th, 2004, a medical advisory panel recommended the FDA against approval of the drug for the 3 indications that the drug's company (Astra-Zeneca) is seeking:

1. Long-term prevention of DVT in patients who have already had one leg clot,
2. Stroke prevention in patients with irregular heart beat (atrial fibrillation),
3. Prevention of leg clots (deep vein thrombosis = DVT) after major orthopedic surgery (hip and knee replacement).

Usually the FDA follows the recommendations of the advisory panel. The reasons for the recommendation not to approve the drug are concerns about its safety, and, to a lesser degree, its efficacy:

1. More patients treated with Exanta® developed severe liver injury and heart attacks than patients treated with warfarin (=coumadin®). The panel felt that the risk outweighed the benefit.
2. In the short-term trials, no severe liver injury was seen, but some mild injury was reported. In long-term trials, there were 37 cases of severe injury with Exanta® versus 5 in the comparison groups, a statistically significant increase. The rate of severe liver injury was one case for every 200 patients treated, or 0.5%.
3. Three deaths occurred that were judged by the investigators and the FDA to be related to treatment with Exanta®, i.e. one death in 2300 patients treated.
4. First signs of liver injury in patients who then developed severe liver injury were noted during the first month of Exanta® therapy in 6 patients from long-term trials. It was therefore criticized that the company's recommendation to monitor liver test once every month was not frequent enough to detect patients who would develop liver problems.
5. For short-term treatment in the orthopedic DVT prevention trials it was pointed out that Exanta® was actually less effective than other methods of DVT prevention: death, blood clots to the lung (PE = pulmonary embolism), and heart attack together occurred more frequently in the Exanta®- treated patients than in the comparison group.
6. For the long-term DVT prevention indication there were discrepant opinions in the advisory panel: while there was some thought that the risk of fatal liver toxicity did not warrant the approval of Exanta®, particularly since long-term warfarin could be used without the liver toxicity, one member of the advisory board felt that it would be appropriate to make Exanta® available for the long-term use for DVT prevention, because, in the real world outside of well-controlled clinical studies, people are just hesitant to put patients on warfarin long-term.

It is not clear what Astra-Zeneca will do now – whether they will terminate development of the drug or whether they will follow-up with additional studies. The final FDA decision on Exanta® approval is pending, but no surprises are really expected.

The good news for patients and health care providers is: Several other oral blood thinners are in development and are entering clinical trials, even though they are all still early in development. May be in 2, 3 or 4 years we will have an oral blood thinner available that (a) is effective, (b) safe, and (c) does not require monitoring.

Personal comment: I was not present at the FDA advisory board meeting; the information above was brought to me by other people. I can therefore not guarantee its accuracy.