



Issue 62  
November 2004

# Issues in Emerging Health Technologies

## Ximelagatran in Prevention of Cardiovascular Events

### Summary

- ✓ **Ximelagatran (Exanta®) is the first oral anticoagulant in a new class of drugs called direct thrombin inhibitors.**
- ✓ **Two studies suggest that ximelagatran is at least as effective as warfarin in preventing stroke in high risk patients with atrial fibrillation. Ximelagatran may also reduce the rate of major cardiovascular events after a myocardial infarction, compared to placebo.**
- ✓ **Ximelagatran does not require dose adjustments or routine blood monitoring.**
- ✓ **As with warfarin, bleeding risks increase with higher doses of ximelagatran. There is, however, no specific antidote to help manage bleeding.**
- ✓ **The safety of ximelagatran will not be fully known without further evaluation and surveillance for potential liver toxicity and drug interactions.**

### The Technology

Ximelagatran (Exanta®) is the first oral agent in a new class of anticoagulants called direct thrombin inhibitors.<sup>1</sup> After absorption, it is converted to its active form, melagatran.<sup>1</sup> Ximelagatran reduces blood clotting by binding directly to thrombin (free and clot-bound), thereby preventing fibrinogen from converting to fibrin, the primary component of blood clots.<sup>2</sup> Unlike warfarin, ximelagatran has a low potential for drug interactions and can be given in fixed doses, without close monitoring.<sup>1,3</sup>

### Regulatory Status

Ximelagatran has been approved in Europe for the prevention of venous thromboembolism (VTE) following total hip or total knee replacement (TKR) surgery.<sup>4</sup> The product has been launched in seven European countries for this indication.<sup>4</sup> In the US, the Food and Drug Administration (FDA) recently declined granting approval for VTE prevention in TKR, long-term secondary prevention of VTE and stroke prevention in patients with atrial fibrillation (AF).<sup>4</sup>

### Patient Group

#### Atrial Fibrillation

AF is the most common sustained arrhythmia,<sup>5</sup> increasing in men and women after age 40 and rising rapidly after age 65. Roughly 10% of people over 80 have AF.<sup>5</sup> It is a major risk factor for stroke;<sup>6</sup> on average, 5% of patients with non-valvular AF have an ischemic stroke per year.<sup>5,6</sup> In high risk groups, this can reach 12% to 15%.<sup>6</sup> High risk factors include prior thromboembolism, age >75 years, mitral valve disease, prosthetic heart valve, hypertension and heart failure.<sup>5,7</sup> Diabetes mellitus, coronary artery disease, age 65 to 75 years, and thyrotoxicosis are moderate risk factors.<sup>5,7</sup>

#### Post-Myocardial Infarction

There are two types of acute myocardial infarction (MI): ST-segment elevation (STEMI) or non-ST-segment elevation (NSTEMI). NSTEMIs are smaller and less extensive than STEMI. The mortality rate during hospitalization for acute MI ranges from 5% to 15%, depending on age.<sup>8</sup>

## Current Practice

### Atrial Fibrillation

Studies have shown that an oral anticoagulant decreases the risk of stroke in patients with AF and that it is more effective than daily acetylsalicylic acid (ASA) alone in high risk patients.<sup>5,9</sup> Bleeding, however, is more frequent with anticoagulants than with ASA.<sup>5</sup> Intra-cranial hemorrhage is most feared, because it is often fatal or permanently disabling.<sup>5</sup> In selecting AF patients for anticoagulation, the individual risk of stroke and bleeding must be considered.<sup>5,9</sup> Adjusted-dose warfarin [target international normalized ratio (INR) 2 to 3] is recommended for AF patients with any high risk factor or >1 moderate risk factors.<sup>7,10</sup> Warfarin requires regular INR monitoring and special attention to drug interactions.<sup>10</sup> ASA is appropriate for lower risk AF patients.<sup>7,10</sup>

### Post-Myocardial Infarction

Antiplatelet and anticoagulant agents are part of the initial treatment of an acute MI, but ischemia may occur once anticoagulants are stopped.<sup>11</sup> Controversy exists regarding whether to continue anticoagulant therapy with warfarin after an acute MI.<sup>8</sup> Moderate intensity warfarin combined with ASA may be better than ASA alone to prevent recurrent ischemia, with a marginal increase in major bleeding.<sup>10</sup>

## The Evidence

Two phase III trials investigated ximelagatran for preventing stroke in patients with AF. One phase II trial studied secondary prevention in post-MI patients.

### Prevention of stroke in AF

The SPORTIF III and V (Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation) trials were designed to test the non-inferiority of ximelagatran relative to warfarin based on a <2% difference in event rates.<sup>12</sup> SPORTIF III was conducted at 259 sites in 23 countries in Europe, Asia and Australasia.<sup>12</sup> It was a randomized, open-label, parallel group trial, with blinded endpoint assessment.<sup>12</sup> In addition, preliminary results from SPORTIF V, a North American, multicentre, randomized,

double-blind, double-dummy trial, were recently presented.<sup>13</sup> In both studies, patients with non-valvular AF and one or more risk factors for stroke were randomized to receive either a fixed dose of ximelagatran (36 mg twice daily) or adjusted-dose warfarin (target INR 2 to 3).<sup>12,13</sup> Up to 100 mg of ASA was allowed daily in SPORTIF III;<sup>12</sup> information on ASA use is unavailable for SPORTIF V. The primary endpoint in both SPORTIF studies was the incidence of all strokes (ischemic or hemorrhagic) and systemic embolic events, based on an intention to treat analysis. Secondary endpoints included all cause mortality, transient ischemic attack, MI and composites of these outcomes.<sup>12,13</sup> There was no statistically significant difference in event rates between the SPORTIF groups, in both primary endpoints (Table 1) and primary endpoints or death (ARD: -0.9%, p=0.15 for SPORTIF III; ARD: 0.10%, p=0.86 for SPORTIF V). Based on this evidence, ximelagatran may be considered at least as effective as warfarin in preventing stroke in high-risk AF patients, although the use of a non-inferiority margin of 2% was considered too liberal by the FDA.<sup>14</sup>

**Table 1:** Efficacy of ximelagatran in stroke prevention

Trial	Primary Endpoint <sup>a</sup>		
	Ximelagatran %	Warfarin %	ARD (p value)
SPORTIF III <sup>12</sup> n=3407	1.6*	2.3*	-0.7% (p=0.10)
SPORTIF V <sup>13</sup> n=3922	1.6**	1.2**	+0.45% (p=0.13)

<sup>a</sup>Incidence of all strokes and systemic embolic events, ARD=absolute risk difference, \*per patient-year, \*\*per year.

### Prevention of cardiovascular events post-MI

The ESTEEM (Efficacy and Safety of the oral direct Thrombin inhibitor ximelagatran in patients with recent Myocardial damage) trial was a phase II, randomized, placebo-controlled, double-blind, dose-guiding study of 1,883 patients in 18 countries.<sup>15</sup> Patients who experienced an acute MI (STEMI or NSTEMI) in the past 14 days received either ximelagatran orally at doses of 24 mg, 36 mg, 48 mg or 60 mg twice daily or placebo for six months. The drug was initiated within six to 12 hours of

heparin cessation. All patients received 160 mg of ASA once daily. The combined four ximelagatran groups had significantly reduced risk for the primary endpoints (all-cause mortality, non-fatal MI and severe recurrent ischemia) compared with placebo [16.3% versus 12.7% (hazard ratio (HR)=0.76, 95% CI 0.59 to 0.98)]. Efficacy did not change with dose.<sup>15</sup>

## Adverse Effects

In the SPORTIF trials, rates of major bleeding were similar between treatment groups (Table 2a). However, the overall rate of bleeding (major and minor) was significantly lower in patients receiving ximelagatran (Table 2b). In SPORTIF III, 18% of the study population was taking ASA concurrently and had significantly higher rates of combined bleeding compared with those not on ASA.<sup>12</sup> In the ESTEEM trial, the frequency of major bleeding did not differ between the placebo and combined ximelagatran groups (HR: 1.97, 95% CI: 0.80 to 4.84).

**Table 2a:** Safety of ximelagatran – major bleeding

Trial	Major* Bleeding		
	Ximelagatran %	Control % (comparator)	p value
SPORTIF III <sup>12</sup> n=3407	1.3 <sup>α</sup>	1.8 <sup>α</sup> (warfarin)	p=0.2281
SPORTIF V <sup>13</sup> n=3922	2.4	3.1 (warfarin)	NR
ESTEEM <sup>15</sup> n=1883	2 <sup>β</sup>	1 (placebo)	NR

**Table 2b:** Safety of ximelagatran – combined bleeding

Trial	Combined Bleeding (major and minor**)		
	Ximelagatran %	Control % (comparator)	p value
SPORTIF III <sup>12</sup> n=3407	25.8 <sup>α</sup>	29.8 <sup>α</sup> (warfarin)	p=0.0065
SPORTIF V <sup>13</sup> n=3922	37	47 (warfarin)	p<0.0001
ESTEEM <sup>15</sup> n=1883	22 <sup>β</sup>	13 (placebo)	NR

\*Major bleeding: fatal, involving critical anatomical sites, significant reduction in hemoglobin, requiring transfusion;  
\*\*minor bleeding: other bleeding, including that causing the cessation of treatment; <sup>α</sup>per patient-year, based on on-treatment analysis; <sup>β</sup>combined ximelagatran groups; NR=not reported.

The overall bleeding rates, however, were higher in the combined ximelagatran group (HR: 1.76, 95% CI: 1.38 to 2.25) and the risk increased with dose.<sup>15</sup> Taking ASA or a higher dose of ximelagatran may increase the risk of bleeding.

In the SPORTIF trials, 6% of ximelagatran patients had elevations in serum alanine aminotransferase (ALT) of >3 times the upper limit of normal (ULN), compared to about 1% of warfarin patients<sup>12,13</sup> (Table 3). In the ESTEEM trial, 11% of patients in the combined ximelagatran groups had an overall ALT >3 times ULN (4% at three to five times ULN, 7% at >5 times ULN) as compared to 2% of placebo patients (1% at three to five times ULN, 1% at >5 times ULN).<sup>15</sup> The ALT increase was proportional to the ximelagatran dose, ranging from 7% with the 24 mg dose to 13% with the 60 mg dose.<sup>15</sup> In each trial, increases were typically asymptomatic, detected after two to six months of treatment, returned toward baseline levels (even when the drug was continued) and were not associated with any serious adverse events.<sup>12,15</sup> The FDA review of the two SPORTIF trials, however, revealed two deaths likely related to ximelagatran-induced liver toxicity.<sup>14</sup>

**Table 3:** Safety of ximelagatran - rates of elevated ALT

Trial	ALT elevation >3 times ULN		
	Ximelagatran %	Control %	p value
SPORTIF III <sup>12</sup>	6	1	p<0.0001
SPORTIF V <sup>13</sup>	6	0.8	p<0.001
ESTEEM <sup>15</sup>	11	2	p<0.0001

## Administration and Cost

Based on the two stroke prevention trials, 36 mg of ximelagatran taken orally, twice daily, will likely be the recommended dose, while 24 mg twice daily may be tested in future post-MI secondary prevention trials. No cost information is available for Canada.

## Concurrent Developments

Another oral direct thrombin inhibitor, BIBR 1048, is undergoing phase II testing for stroke prevention in AF.<sup>6,16</sup>

## Rate of Technology Diffusion

Given the aging population and improved survival of cardiac patients, the potential use of anticoagulants is increasing.

Ximelagatran, similar to warfarin, reduces thrombosis but increases bleeding. Given the precautions necessary for the safe use of warfarin, ximelagatran may have the potential to replace warfarin for some patients with AF. Ximelagatran is also being studied in the prevention<sup>17-23</sup> and treatment<sup>24</sup> of VTE.

## Implementation Issues

Evidence suggests that ximelagatran is comparable to warfarin in preventing stroke. Phase III secondary prevention trials are needed to further assess the safety and efficacy of this drug in post-MI patients. The bleeding risk appears to be similar to that of warfarin, but when there is bleeding, there is no specific antidote to reverse its anticoagulant effect.<sup>16</sup> The safety of ximelagatran, when used with other drugs such as non-steroidal anti-inflammatory agents and statins, must still be evaluated. If ximelagatran is to be used broadly, it will need to be studied in special populations (such as those with renal failure or pregnant women). After marketing, surveillance will be needed in case there is a potential for liver toxicity. As the cost of the drug is unknown, its cost-effectiveness is yet to be determined.

## References

1. Boos CJ, et al. *Curr Controlled Trials Cardiovasc Med* 2004;5(1):3.
2. Weitz J. *Semin Vasc Med* 2003;3(2):131-7.
3. Hrebickova L, et al. *Heart Dis* 2003;5(6):397-408.
4. AstraZeneca receives action letter from FDA for Exanta® (ximelagatran) [news release]. London: AstraZeneca International; 2004 Oct 11. Available: <http://www.astrazeneca.com/pressrelease/3285.aspx> (accessed 2004 Oct 28).
5. Albers GW, et al. *Chest* 2001;119(1 Suppl):194S-206S.
6. Donnan GA, et al. *Lancet Neurol* 2004;3(5):305-8.
7. Fuster V, et al. *J Am Coll Cardiol* 2001;38(4):1231-66.
8. Stringer KA, et al. In: DiPiro JT, et al, editors. *Pharmacotherapy: a pathophysiologic approach*. 5th ed. New York: McGraw-Hill; 1999. p.251-71.
9. Man-Son-Hing M, et al. *Arch Intern Med* 2003;163(13):1580-6.
10. Hirsh J, et al. *Chest* 2001;119(1 Suppl):8S-21S.
11. Granger CB, et al. *Circulation* 1995;91(7):1929-35.
12. Executive Steering Committee on behalf of the SPORTIF III Investigators. *Lancet* 2003;362(9397):1691-8.
13. Halperin J. Presentation at American Heart Association Scientific Sessions 2003; 2003 Nov9-12; Orlando (FL).
14. Desai M. NDA 21-686. *ximelagatran (H376/95)*. Indication: prevention of stroke and thromboembolic complications associated with atrial fibrillation. Rockville (MD): Center for Drug Evaluation and Research, U.S. Food and Drug Administration; 2004. Available: [http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4069B1\\_06\\_FDA-Background-C-R-MOR.pdf](http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4069B1_06_FDA-Background-C-R-MOR.pdf) (accessed 2004 Oct 7).
15. Wallentin L, et al. *Lancet* 2003;362(9386):789-97.
16. Gustafsson D. *J Intern Med* 2003;254(4):322-34.
17. Eriksson BI, et al. *Thromb Haemost* 2003;89(2):288-96.
18. Eriksson BI, et al. *J Thromb Haemost* 2003;1(12):2490-6.
19. Colwell CW, et al. *J Thromb Haemost* 2003;1(10):2119-30.
20. Francis CW, et al. *Ann Intern Med* 2002;137(8):648-55.
21. Francis CW, et al. *N Engl J Med* 2003;349(18):1703-12.
22. Colwell CW, et al. Presentation at American Society of Hematology 45th Annual Meeting and Exposition; 2003 Dec 6-9; San Diego. Available: <http://www.hematology.org/meeting/abstracts.cfm>.
23. Schulman S, et al. *N Engl J Med* 2003;349(18):1713-21.
24. Francis CW, et al. Presentation at American Society of Hematology 45th Annual Meeting and Exposition; 2003 Dec 6-9; San Diego. Available: <http://www.hematology.org/meeting/abstracts.cfm>.

**Cite as:** Molckovsky D, Boucher M. *Ximelagatran in prevention of cardiovascular events* [Issues in emerging health technologies issue 62]. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2004.

\*\*\*\*\*

CCOHTA takes sole responsibility for this bulletin and appreciates comments from its reviewers.

**Reviewers:** Chantal Pharand PharmD, Faculty of Pharmacy, Université de Montréal, Montréal QC, Muhammad Mamdani PharmD MA MPH, Institute of Clinical Evaluative Sciences, North York ON.

ISSN 1488-6324 (online)  
ISSN 1488-6316 (print)  
PUBLICATIONS MAIL AGREEMENT NO: 40026386  
RETURN UNDELIVERABLE CANADIAN ADDRESSES TO  
CANADIAN COORDINATING OFFICE FOR  
HEALTH TECHNOLOGY ASSESSMENT  
600-865 CARLING AVENUE  
OTTAWA ON K1S 5S8