REVIEW ARTICLE

Drugs 2004; 64 Suppl. 1: 27-35
0012-6667/04/0001-0027/$34.00/0

Clinical Experience with Ximelagatran in Orthopaedic Surgery

Bengt Eriksson

Department of Orthopaedics, Sahlgrenska University Hospital/Östra, Gothenburg, Sweden

Abstract

Patients who undergo orthopaedic surgery are at substantially increased risk for venous thromboembolic events. These include proximal and distal deep vein thrombosis, with the former more likely to lead to pulmonary embolism and fatal complications. Anticoagulants are routinely used for venous thromboembolism prophylaxis in patients undergoing total hip or total knee replacement surgery. Although current treatments offer effective prophylaxis, they have disadvantages. Warfarin is limited by the requirement for coagulation monitoring to ensure effective and safe use. Similarly, low-molecular-weight heparins (LMWHs) have disadvantages, including the need for parenteral administration. This article brings together data from clinical trials of the novel oral direct thrombin inhibitor, ximelagatran, in the prevention of venous thromboembolism in patients undergoing elective total hip or total knee replacement. The ximelagatran clinical trial programme in orthopaedic surgery has focused primarily on five large multicentre studies in Europe (the Melagatran Thromboprophylaxis in Orthopaedic surgery II and III and Expanded Prophylaxis Evaluation Surgery Study studies) and in the United States (the Exanta Used to Lessen Thrombosis A and B studies), which enrolled more than 8000 patients. In addition, the USA clinical trial programme included three other trials that investigated ximelagatran in orthopaedic surgery; two of these studies focused on prevention of venous thromboembolism after total knee replacement, and one study investigated prevention of venous thromboembolism after total hip replacement. These studies compared ximelagatran with the LMWHs dalteparin and enoxaparin and with warfarin, and were designed to reflect regional differences in venous thromboembolism prophylaxis and to build on findings from previous studies. Generally, ximelagatran has been shown to possess comparable or greater efficacy relative to comparators. The timing and dose of ximelagatran have been shown to be important determinants of its efficacy and safety. As ximelagatran can be given in fixed oral dosing without coagulation monitoring, it is an attractive choice for the prevention of venous thromboembolism in major elective orthopaedic surgery.

1. Introduction

Venous thromboembolism, which includes deep vein thrombosis (DVT) and pulmonary embolism, can lead to significant morbidity and death, and is difficult to detect. Patients undergoing elective hip replacement or total knee replacement surgery are at increased risk of developing venous thromboembolism after surgery. Indeed, without prophylactic therapy, DVT occurs in as many as 84% of patients undergoing total knee replacement and 57% of those undergoing total hip replacement.[1] Furthermore, proximal DVT, which is more likely to lead to potentially fatal pulmonary embolism than is distal DVT, occurs in up to 70% and 36% of those

undergoing total knee and total hip replacement, respectively.[1]

Anticoagulants are routinely used for venous thromboembolism prophylaxis in patients undergoing total hip or total knee replacement. Current treatments include warfarin and low-molecular-weight heparins (LMWHs) such as dalteparin and enoxaparin.[2,3] Although both warfarin and LMWHs are effective in reducing the risk of venous thromboembolism after orthopaedic surgery, there are drawbacks associated with their use. Warfarin has a slow onset of action, a narrow therapeutic window and inter-patient variability in efficacy. Because of these factors, there is a need for regular coagulation monitoring as a surrogate marker of the efficacy and safety of warfarin. Although such monitoring and the subsequent dose adjustments are not required with LMWHs, they can be administered only parenterally, which limits outpatient use. There is also a minor risk of heparin-induced thrombocytopenia, a serious allergic drug reaction, which can limit the use of LMWHs.[4]

Ximelagatran is a novel, orally administered direct thrombin inhibitor. After administration, ximelagatran is rapidly bioconverted to its active form, melagatran, which can also be administered subcutaneously. Melagatran has stable and predictable pharmacokinetics and pharmacodynamics, and therefore ximelagatran does not require dose adjustment or coagulation monitoring.[5,6] This article gives an overview of the findings from a number of clinical studies involving the use of ximelagatran in the prevention of venous thromboembolism in major elective orthopaedic surgery.

2. Clinical Studies

To assess the efficacy of ximelagatran and melagatran in patients undergoing orthopaedic surgery, several large multicentre clinical studies have been completed. These have examined a range of different dosing regimens and have compared melagatran and ximelagatran with drugs that are currently used in this clinical setting.

2.1 Melagatran Thromboprophylaxis in Orthopaedic Surgery II

After an initial dose-ranging pilot study (**Me**lagatran **Thr**omboprophylaxis in **O**rthopaedic surgery [METHRO] I),[7] the METHRO II study[8] was conducted. This was a large-scale dose–response study comparing four different doses of melagatran/ximelagatran with dalteparin in 1876 patients undergoing elective total hip or total knee replacement.

Patients received melagatran (1, 1.5, 2.25 or 3mg subcutaneously) immediately before the operation. Melagatran was then administered twice daily from 7h to 11h after the operation until oral dosing was possible. At this point, patients received ximelagatran (8, 12, 18 or 24mg orally twice daily) for the remainder of the treatment period (figure 1). Patients not receiving melagatran/ximelagatran received dalteparin 5000IU subcutaneously the night before the operation. This treatment was continued once daily until the night before the end of the study period (7–10 days after surgery for all patients), at which point bilateral venograms were performed in all patients.

Total venous thromboembolism rates (proximal and distal DVT, clinical pulmonary embolism and overall mortality), the primary endpoint of the study, were significantly lower in patients treated with the highest dose of melagatran/ximelagatran than in those patients treated with dalteparin (figure 2). Moreover, a reduction in thromboembolic events relative to dalteparin was observed in the rates of major venous thromboembolisms (proximal DVT, clinical pulmonary embolism and fatal pulmonary embolism). There was also a significant trend towards lower rates of venous thromboembolism in patients treated with higher doses of melagatran/ximelagatran ($p < 0.0001$). The rates of excessive bleeding (as judged by the investigator) increased with increasing doses of ximelagatran, but in the highest dose group (3mg subcutaneously/24mg twice daily by mouth), this difference was not statistically significant compared with findings with dalteparin. In summary, the effects of melagatran/ximelagatran were

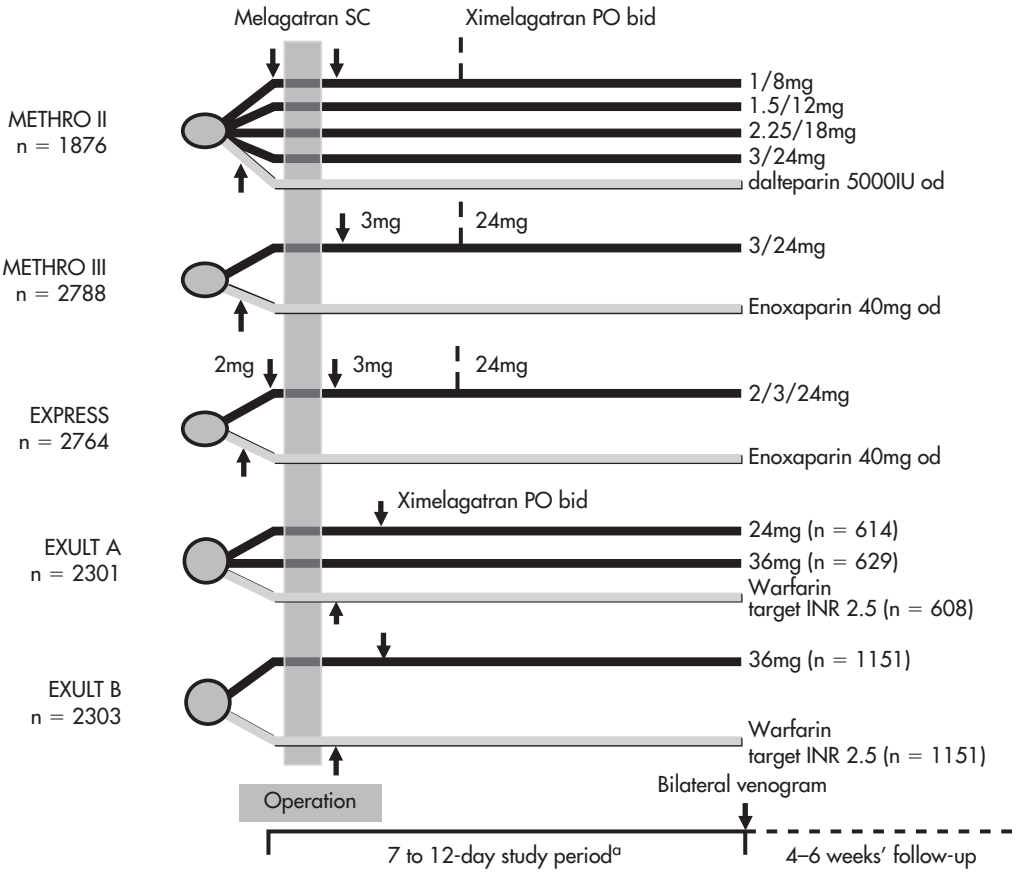

Fig. 1. Study design in the METHRO II, METHRO III, EXPRESS, EXULT A and EXULT B studies. [a]For the METHRO II, METHRO III and EXPRESS studies, the study period was 8–11 days. **bid** = twice daily; **od** = once daily; **PO** = orally; **SC** = subcutaneously.

highly dose-dependent and this combination exhibited superior efficacy to dalteparin in the prevention of venous thromboembolism in patients undergoing elective total hip or total knee replacement.

Thus the results of the METHRO II study demonstrated that the most effective dose of melagatran/ximelagatran was 3mg subcutaneously/24mg twice daily by mouth. To assess further the use of melagatran/ximelagatran and the influence of dose and timing on efficacy and safety, the METHRO III study was subsequently performed.[9]

2.2 METHRO III

The METHRO III study was a postoperative study of parallel-group design similar to the METHRO II study, but only the 3mg subcutaneous/24mg oral dose of melagatran/ximelagatran was used, as this was the most efficacious dose in the METHRO II study (figure 1). A total of 2788 patients undergoing total hip or total knee replacement were enrolled.[9] In an attempt to reduce the rate of severe bleeding that was observed in the METHRO II study, melagatran was administered only postoperatively. Once again, an LMWH

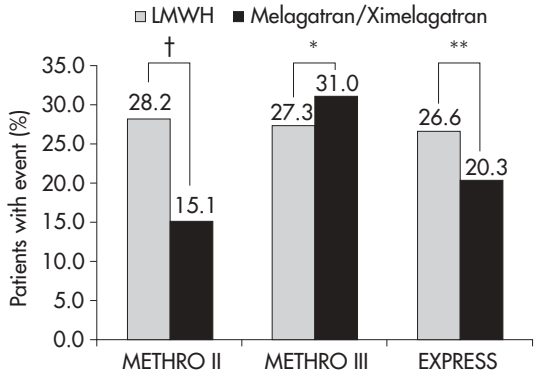

Fig. 2. Total rates of venous thromboembolism in the METHRO II, METHRO III and EXPRESS studies (defined as confirmed overall deep vein thrombosis/pulmonary embolism; in the METHRO III study, this included unexplained death, and in the EXPRESS study, death from any cause). **LMWH** = low-molecular-weight heparin. *$p = 0.053$, **$p < 0.001$, †$p < 0.0001$.

(enoxaparin 40mg once daily instead of dalteparin) was used as a comparator, and it was administered in the same way as in the METHRO II study.

The rate of total venous thromboembolism was slightly lower with enoxaparin than with melagatran/ximelagatran (27.3% and 31.0%, respectively; $p = 0.053$) (figure 2). The rate of major thromboembolic events, including proximal venous thromboembolism, was similar in both treatment groups (melagatran/ximelagatran 5.7%; enoxaparin 6.2%).

A *post-hoc* analysis[10] of the combined total hip replacement and total knee replacement population in METHRO III has shown that patients who received their first dose of melagatran 4–8h after surgery had an incidence of total venous thromboembolism (27.2%) that was lower than that in patients whose first dose was given more than 8h after surgery (35.3%) and similar to that with enoxaparin (27.3%). The risk of major venous thromboembolism was comparable to that with enoxaparin, irrespective of the timing of the first melagatran dose.

Postoperative administration of melagatran/ximelagatran reduced the rate of severe bleeding events relative to that observed in the METHRO II study. The rate of severe bleeding in patients treated with melagatran/ximelagatran was similar to the rate observed in patients treated with enoxaparin. Moreover, there was a significant reduction in blood transfusion requirement in patients treated with melagatran/ximelagatran relative to enoxaparin.

In summary, melagatran/ximelagatran initiated after operation showed efficacy and safety comparable to those of LMWH in patients undergoing major elective orthopaedic surgery.

2.3 Expanded Prophylaxis Evaluation Surgery Study

It was clear from the findings of the METHRO studies that the timing of the first dose relative to surgery is important in determining the efficacy and safety of melagatran/ximelagatran treatment. Preoperative administration (METHRO II) yielded lower rates of venous thromboembolism, but higher rates of excessive bleeding relative to postoperative administration (METHRO III). The design of the **E**xpanded **P**rophylaxis **E**valuation **S**urgery **S**tudy (EXPRESS) allowed further assessment of the balance between the efficacy observed in the METHRO II study and the favourable bleeding rates observed in the METHRO III study.

The EXPRESS study was similar in design to the METHRO III study in that enoxaparin, administered before operation, was used as the comparator. The EXPRESS study differed from the METHRO II study, however, in that the dose used before operation was 2mg (rather than 3mg), with a subsequent postoperative dose of melagatran of 3mg subcutaneously, followed by oral ximelagatran at a dose of 24mg twice daily (figure 1).[11] The trial was designed with two sequentially assessed primary endpoints, as described in recent guidelines for drug development.[11] The first-stage primary endpoint was to demonstrate that ximelagatran was not inferior to enoxaparin in preventing major venous thromboembolism. If non-inferiority was demonstrated, the analysis could proceed to the second stage, which was to

demonstrate that ximelagatran was more effective than enoxaparin in preventing total venous thromboembolism. Secondary endpoints included death, pulmonary embolism or symptomatic DVT during the study period, and severe bleeding rates and changes in laboratory variables.

A total of 2764 patients undergoing total hip or total knee replacement were treated in the EXPRESS study. Patients treated with melagatran/ximelagatran experienced a significantly lower rate of total venous thromboembolism (enoxaparin 26.6% compared with ximelagatran 20.3%; $p = 0.0003$). Similarly, patients treated with melagatran/ximelagatran had a significantly lower rate of major venous thromboembolism (proximal DVT/pulmonary embolism/death: enoxaparin 6.3% compared with melagatran/ximelagatran 2.3%; $p < 0.0001$) (figure 2). There was no difference between treatments in critical site or fatal bleeds or bleeding leading to re-operation; however, investigator-judged excessive bleeds were more common in the ximelagatran group.[11]

In summary, in patients undergoing elective total hip or total knee replacement, preoperatively initiated subcutaneous melagatran followed by oral ximelagatran was significantly more effective in preventing venous thromboembolism than preoperatively initiated subcutaneous enoxaparin.

The results of the METHRO/EXPRESS studies further confirmed recent data indicating that the balance between efficacy and safety for thromboprophylaxis in patients undergoing joint replacement procedures is influenced by the timing of initiation relative to surgery.[12] A pooled analysis[13] of the ximelagatran trials showed that thromboprophylaxis with subcutaneous melagatran followed by oral ximelagatran was effective and well tolerated in all three studies (figure 3). The lowest bleeding rates, and efficacy comparable to that of enoxaparin, were observed in the METHRO III postoperative regimen. The greatest prophylactic efficacy was achieved in METHRO II with a 3mg preoperative dose of melagatran. The balance between venous thromboembolism and bleeding rates in EXPRESS was intermediate between METHRO II and III (which reflects the lower preoperative dose of subcutaneous melagatran), although the efficacy seen with this regimen was significantly greater than with enoxaparin.

2.4 Exanta Used to Lessen Thrombosis Study

Clinical development of ximelagatran has evolved to take into account differences in regional/international clinical practice with respect to venous thromboembolism prophylaxis. For example, in Europe, LMWHs are generally initiated 12h before operation in an attempt to optimise the efficacy of prophylaxis whereas, in North America, prophylaxis is initiated 12–24h after operation in an attempt to minimise bleeding risk. In this respect, the **Ex**anta **U**sed to **L**essen **T**hrombosis study (EXULT A) was a large multicentre investigation with the majority of study centres located in the United States,[14] in contrast to the METHRO/EXPRESS studies, which were based mainly in Europe. In line with prevalent treatment practices in the USA, warfarin was used as a comparator, and there was no pre- or postoperative melagatran treatment, only oral ximelagatran treatment, 24mg or 36mg twice daily, postoperatively (figure 1). The EXULT A study was similar in design to a smaller study by Francis and colleagues,[15] in which ximelagatran 24mg twice daily was compared with warfarin (target international normalised ratio [INR] 2.5) in 680 patients undergoing total hip or total knee replacement. In that study, ximelagatran was found to have an efficacy similar to that of warfarin for reducing the rate of venous thromboembolism. The purpose of the EXULT A study was to determine whether a higher dose of ximelagatran (36mg twice daily) would be superior to warfarin in efficacy and equivalent in safety (bleeding), and to determine which was the optimal postoperative dose of ximelagatran (24mg or 36mg twice daily).

In the EXULT A study, 1851 patients (efficacy population) were treated, all of whom were undergoing total knee replacement surgery. The rates of total venous thromboembolism and all-cause mortality (the primary endpoint of the study) were significantly reduced in patients receiving ximela-

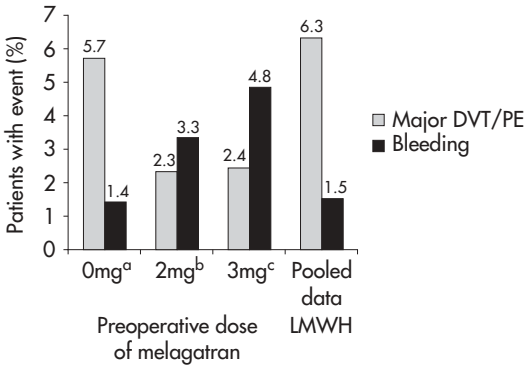

Fig. 3. Major venous thromboembolism (defined as proximal deep vein thrombosis [DVT], pulmonary embolism [PE] or death; in the EXPRESS study, death was included only if pulmonary embolism could not be ruled out) and incidence of adjudicated severe bleeding during treatment with melagatran/ximelagatran or LMW heparin (LMWH; rates from different studies using LMWH were similar). [a]METHRO III; [b]EXPRESS; [c]METHRO II.

gatran 36mg twice daily relative to those receiving warfarin (20.3% compared with 27.6%; $p = 0.003$; figure 4).

In summary, compared with warfarin, ximelagatran 36mg twice daily provides superior prevention of venous thromboembolism to patients undergoing total knee replacement surgery, whereas the 24-mg twice daily dose showed rates of prevention similar to those achieved with warfarin. Furthermore, no significant difference in bleeding was observed between warfarin and ximelagatran use in this patient population. Consequently, the 36-mg twice daily dose of ximelagatran was carried forward into the EXULT B trial.

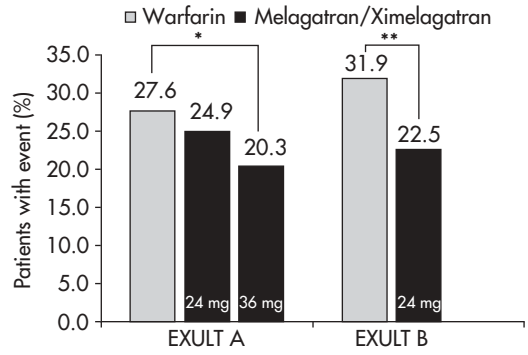

Fig. 4. Deep vein thrombosis/pulmonary embolism and all-cause mortality rates in the EXULT A and B studies. *$p < 0.01$, **$p < 0.001$.

2.5 EXULT B

A second study of similar design, EXULT B, was conducted, again with the majority of centres located in the USA. A total of 2303 patients were allocated randomly to groups to receive treatment with either warfarin (target INR 2.5) or ximelagatran 36mg twice daily (the most effective dose from the EXULT A study; figure 1).[16] As was found in the EXULT A study, ximelagatran 36mg twice daily was significantly more effective than warfarin in reducing total venous thromboembolism and all-cause mortality (figure 4) and showed bleeding rates comparable to those observed with warfarin in this patient population.

2.6 Other Studies in the USA

In addition to EXULT A and EXULT B, the clinical trial programme in the USA included three earlier trials that investigated ximelagatran 24mg twice daily in orthopaedic surgery. Two of these focused on the prevention of venous thromboembolism after total knee replacement,[15,17] and one study investigated the prevention of venous thromboembolism after total hip replacement.[18] The studies by Francis et al.[15] and Heit et al.[17] showed that ximelagatran was well tolerated and at least as effective as warfarin and enoxaparin in preventing venous thromboembolism. In the total hip replacement trial by Colwell et al.,[18] ximelagatran (24mg twice daily) was less effective than enoxaparin, although both agents decreased the overall rate of venous thromboembolism compared with that reported historically. Bleeding rates with ximelagatran were comparable to those observed with enoxaparin.

3. Practical Aspects of Ximelagatran Treatment

Practical experience gained with ximelagatran treatment in major elective orthopaedic surgery has shown that the dosing regimens studied, particularly postoperative initiation of ximelagatran, provide a number of potential benefits. For example, postoperative dosing with ximelagatran avoids the need for patients to be admitted the evening before surgery for prophylaxis to commence. In addition, potential problems with use of neuraxial anaesthesia and the potential risk of spinal bleeding/haematoma are avoided. Where indwelling epidural catheters are used, these should not be removed until 8h after the latest dose of ximelagatran/melagatran (reflecting the half-life of the drug of 4–5h); the next dose of drug should not be given earlier than 1–2h after the removal of the catheter.

Another important benefit of ximelagatran is that the pharmacokinetic and pharmacodynamic profile of the drug lends itself to management of patients with respect to the prevention and treatment of venous thromboembolism. For example, if severe bleeding occurs during venous thromboembolism prevention, haemostasis will be restored within a short time after cessation of ximelagatran. Stopping ximelagatran and ensuring adequate diuresis (bearing in mind the renal clearance of drug) may be all that is required in such cases.

Another benefit, for example within the treatment setting in which duration of treatment is longer, is that, should an acute or elective procedure be required whilst the patient is receiving ximelagatran, administration can be managed to ensure that normal haemostasis is resumed quickly before the procedure, followed by a fast onset of action once ximelagatran is resumed. Thus, risk of bleeding is minimised, as is time without venous thromboembolism protection.

Ximelagatran should not be used in patients with a creatinine clearance of less than 30 ml/min, reflecting the renal route of elimination of the drug. In addition, patients with hepatic impairment, or with a pretreatment alanine aminotransferase (ALT) value greater than twice the upper limit of normal, should not receive ximelagatran; an ALT value should be obtained before surgery. During longer-term use of ximelagatran (more than 35 days), transient increases in liver enzymes, mainly ALT, of more than 3-fold higher than the upper limit of normal have been observed in a proportion of patients. These have mostly occurred between 1 and 6 months of treatment and have resolved either spontaneously or upon discontinuation of treatment.[19,20] In orthopaedic surgery, ximelagatran has not been evaluated beyond 12 days of treatment, and increases in ALT were infrequent, transient and occurred more often with LMWH than with ximelagatran.[9,14]

4. Conclusions

The clinical development of ximelagatran has involved the study of the effects of this agent in more than 8000 patients undergoing orthopaedic surgery and has encompassed regional differences regarding venous thromboembolism prophylaxis. The results from the METHRO, EXPRESS and EXULT clinical studies have shown that ximelagatran has similar or greater efficacy at reducing the rates of venous thromboembolism than LMWHs or warfarin. The EXPRESS study results showed a good efficacy/safety profile for melagatran/ximelagatran, bearing in mind the greater bleeding rates observed in METHRO II, whereas the METHRO III results showed efficacy and safety comparable to those of LMWH, with an overall low rate of major bleeding after total hip and total knee replacement. The importance of the balance between the efficacy and safety profiles of melagatran/ximelagatran treatment was recently highlighted in a meta-analysis of METHRO II/III and EXPRESS. The results showed that prevention of venous thromboembolism with subcutaneous melagatran followed by oral ximelagatran was effective and well tolerated. Furthermore, the timing and dose of melagatran administration are

important clinical considerations, leading to a trade-off of enhanced efficacy at the cost of increased surgical bleeding.

Overall, the efficacy of melagatran/ximelagatran initiated after operation shows comparable rates of DVT/pulmonary embolism compared with LMWHs initiated before operation (enoxaparin). In addition, the safety profile of melagatran/ximelagatran is similar to that of LMWHs and warfarin. The oral ximelagatran and subcutaneous melagatran formulations in Europe allow flexibility in dosing soon after surgery. In addition, the fixed oral dosing and absence of coagulation monitoring associated with the administration of ximelagatran provide advantages over warfarin.

In conclusion, the oral direct thrombin inhibitor, ximelagatran, is an attractive choice for the prevention of venous thromboembolism in major elective orthopaedic surgery.

References

1. Geerts WH, Heit JA, Clagett GP, et al. Prevention of venous thromboembolism. Chest 2001; 119 (1 Suppl.): 132S-75S
2. Paiement GD, Desautels C. Deep vein thrombosis: prophylaxis, diagnosis, and treatment – lessons from orthopaedic studies. Clin Cardiol 1990; 13 (4 Suppl 6.): VI19-22
3. Deitelzweig SB, Vanscoy GJ, Niccolai CS, et al. Venous thromboembolism prevention with LMWHs in medical and orthopaedic surgery patients. Ann Pharmacother 2003; 37 (Pt 3): 402-11
4. Fabris F, Luzzatto G, Stefani PM, et al. Heparin-induced thrombocytopenia. Haematologica 2000; 85 (Pt 1): 72-81
5. Eriksson UG, Bredberg U, Gislen K, et al. Pharmacokinetics and pharmacodynamics of ximelagatran, a novel oral direct thrombin inhibitor, in young healthy male subjects. Eur J Clin Pharmacol 2003; 59 (Pt 1): 35-43
6. Eriksson UG, Mandema JW, Karlsson MO, et al. Pharmacokinetics of melagatran and the effect on ex vivo coagulation time in orthopaedic surgery patients receiving subcutaneous melagatran and oral ximelagatran: a population model analysis. Clin Pharmacokinet 2003; 42 (Pt 7): 687-701
7. Eriksson BI, Arfwidsson AC, Frison L, et al. A dose-ranging study of the oral direct thrombin inhibitor, ximelagatran, and its subcutaneous form, melagatran, compared with dalteparin in the prophylaxis of thromboembolism after hip or knee replacement: METHRO I. MElagatran for THRombin inhibition in Orthopaedic surgery. Thromb Haemost. 2002; 87 (Pt 2): 231-7
8. Eriksson BI, Bergqvist D, Kalebo P, et al. Melagatran for thrombin inhibition in orthopaedic surgery. Ximelagatran and melagatran compared with dalteparin for prevention of venous thromboembolism after total hip or knee replacement: the METHRO II randomised trial. Lancet 2002; 360 (9344): 1441-7
9. Eriksson BI, Agnelli G, Cohen AT, et al. METHRO III Study Group. Direct thrombin inhibitor melagatran followed by oral ximelagatran in comparison with enoxaparin for prevention of venous thromboembolism after total hip or knee replacement. Thromb Haemost 2003; 89 (Pt 2): 288-96
10. Dahl O, Eriksson BI, Agnelli G, et al. Influence of time of first dose on the efficacy and safety of postoperative ximelagatran for prevention of thromboembolism after orthopaedic surgery. Pathophysiol Haemost Thromb 2003; 33 (Suppl. 2): 38 [abstract OC068]. Presented at 18th International Congress on Thrombosis, 20-24 June 2004, Ljubljana, Slovenia
11. Eriksson BI, Agnelli G, Cohen AT, et al. The direct thrombin inhibitor melagatran followed by oral ximelagatran compared with enoxaparin for the prevention of venous thromboembolism after total hip or knee replacement: the EXPRESS study. J Thromb Haemost 2003; 1: 2490-6
12. Hull RD, Pineo GF, Stein PD, et al. Timing of initial administration of low-molecular-weight heparin prophylaxis against deep vein thrombosis in patients following elective hip arthroplasty: a systemic review. Arch Intern Med 2001; 161: 1952-60
13. Cohen AT, Agnelli G, Dahl OE, et al. Efficacy and safety of the treatment regimen of melagatran and ximelagatran for prevention of thromboembolic events after total hip or knee replacement: a meta-analysis of 3 randomized, double-blind studies, to evaluate the influence of time and dose [poster]. XIXth Congress of the International Society on Thrombosis and Haemostatsis (ISTH); 2003 July 12-18; Birmingham, UK
14. Francis CW, Berkowitz SD, Comp PC, et al. EXULT A Study Group. Comparison of ximelagatran with warfarin for the prevention of venous thromboembolism after total knee replacement. N Engl J Med 2003; 349 (Pt 18): 1703-12
15. Francis CW, Davidson BL, Berkowitz SD, et al. Ximelagatran versus warfarin for the prevention of venous thromboembolism after total knee arthroplasty. A randomized, double-blind trial. Ann Intern Med 2002; 137 (Pt 8): 648-55
16. Colwell CW Jr, Berkowitz SD, Comp PC, et al. Randomized double-blind comparison of ximelagatran, an oral direct thrombin inhibitor, and warfarin to prevent venous thromboembolism (VTE) after total knee replacement (TKR): EXULT B [abstract no. 39]. Blood 2003; 102 (Pt 11): 14A, Abs 39
17. Heit JA, Colwell CW, Francis CW, et al. Comparison of the oral direct thrombin inhibitor ximelagatran with enoxaparin as prophylaxis against venous thromboembolism after total knee replacement. Arch Intern Med 2001; 161 (Pt 18): 2215-21
18. Colwell CW Jr, Berkowitz D, Davidson BL, et al. Comparison of ximelagatran, an oral direct thrombin inhibitor, with enoxaparin for the prevention of venous thromboembolism following total hip replacement. A rando-

mized, double-blind study. J Thromb Haemost 2003; 1 (Pt 10): 2119-30
19. Schulman S, Wahlander K, Lundstrom T, et al. THRIVE III Investigators. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. N Engl J Med 2003; 349 (Pt 18): 1713-21
20. Olsson SB, Executive Steering Committee on behalf of the SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. Lancet 2003; 362 (9397): 1691-8

Correspondence and offprints: *Bengt Eriksson*, Department of Orthopaedics, Sahlgrenska University Hospital/Östra, S-416 85 Gothenburg, Sweden.
E-mail: b.eriksson@orthop.gu.se