Ximelagatran (Exanta™): A Product Review and Update

Olga Hilas, BS, PharmD, and Nino Marzella, BS, PharmD

INTRODUCTION

Since its discovery in the early 1940s, warfarin (Coumadin®, Bristol-Myers Squibb) has been the leading oral anticoagulant agent for various thromboembolic events. A vitamin K antagonist, warfarin is the only clinically available oral anticoagulant.1–4 Although it is effective, warfarin has certain limitations (Table 1) that make its use complex.5–7

As a result of these limitations, clinical efforts have focused on the development of more specific agents.7,8 One approach has been to examine the activation of the coagulation cascade, a key pathophysiological mechanism involved in a number of cardiovascular conditions.

In December 2003, AstraZeneca submitted ximelagatran (Exanta™) for regulatory review in the U.S. and European Union. Ximelagatran, the first oral direct thrombin inhibitor, is the first clinically tested oral anticoagulant since the introduction of warfarin. This new agent works on thrombin, a major regulator of thrombogenesis, which leads to the formation and stabilization of clots, the re-

Table 1  Limitations of Warfarin Use

1. Slow onset of action, prompting the concurrent use of a parenteral anticoagulant
2. Variation in metabolism, requiring dosage adjustments
3. Multiple drug and food interactions, requiring frequent drug monitoring
4. Narrow therapeutic index, necessitating frequent drug monitoring
primary endpoint was evaluation of the rate of deep vein thrombosis (DVT) and pulmonary embolism (PE).

The overall rate of DVT and PE in the ximelagatran patients (2.3%) was lower than that in the enoxaparin group (6.3%). The total rate of VTE was lower in the ximelagatran arm (20.3%) than in the enoxaparin arm (26.6%). It is interesting that no differences in clinically significant bleeding were reported among the two groups. However, bleeding events were higher in the patients in the ximelagatran arm (3.3%) than those in the enoxaparin arm (1.2%).

The authors of the study concluded that subcutaneous melagatran, in combination with oral ximelagatran, was more effective in preventing VTE than enoxaparin alone in patients with total hip or total knee replacement surgery.

The EXULT A Trial10,14

The Exanta Used to Lessen Thrombosis (EXULT) study was a multicenter, randomized, double-blind trial consisting of three treatment arms. A total of 2,301 patients underwent total knee replacement surgery.

In one group, ximelagatran 24 mg was given twice daily; the patients in the second arm received ximelagatran 36 mg twice daily. Both dosages were initiated on the morning after surgery. A third study arm consisted of patients who received warfarin, initiated during the evening of the day of surgery. The doses in the warfarin arm were titrated to a goal International Normalized Ratio (INR) of 2 to 3. All treatments in each study arm were continued for seven to 12 days.

The study endpoints evaluated the incidence of VTE, all causes of mortality, and bleeding. Combined incidences of DVT and PE with all causes of mortality showed that ximelagatran 36 mg twice daily (20.3%) was more effective than warfarin (27.6%). No differences were reported between endpoints that were independently assessed among the three study arms.

Bleeding was evaluated, and no major differences were reported among the groups. The bleeding incidence was noted to be associated with the dosage: ximelagatran 24 mg (4.8%), ximelagatran 36 mg (5.3%), and warfarin (4.5%).

In conclusion, ximelagatran showed superior effects over traditional warfarin therapy in preventing VTE after total knee replacement.

The THRIVE III Trial2,10,15

The Oral Direct Thrombin Inhibitor, ximelagatran, for Venous Thromboembolism (THRIVE) study, a multicenter, double-blind trial, included 1,233 patients with documented DVT and PE and appropriate anticoagulation therapy for six months’ duration. This study evaluated the efficacy and safety of ximelagatran in preventing secondary events associated with VTE. Inclusion criteria were based on the receipt of either placebo or ximelagatran 24 mg twice daily for 18 months after the initial six-month anticoagulation period. The primary endpoint was the evaluation of any recurrences of VTE.

Patients receiving ximelagatran experienced a significantly lower incidence of VTE recurrence than did patients receiving placebo. Bleeding, described as a major hemorrhage, was not significant between study groups.

Overall, ximelagatran was safe and effective in preventing the secondary events of VTE.

The SPORTIF III and V Trials10,16–18

The Stroke Prevention by Oral Thrombin Inhibitor in Atrial Fibrillation III (SPORTIF III) study was a randomized, open-label, parallel-group trial with blinded event assessment. The trial included 3,407 patients at 259 study centers in 23 countries.

SPORTIF V was also a randomized, open-label, parallel-group trial with a similar design in utilizing double-blind treatment investigation. This trial involved 3,922 patients in 409 North American study centers.

For both studies, the primary endpoint was the incidence of all strokes and systemic embolic events among the ximelagatran and warfarin treatment groups. Secondary endpoints included stroke, embolism, myocardial infarction, ischemic stroke, transient ischemic attack (TIA), bleeding, treatment discontinuation, and death.

In an intent-to-treat analysis of SPORTIF III, 3,407 patients received ximelagatran 36 mg twice daily and 1,703 received warfarin with an INR of 2–3. A mean follow-up period of 17.4 months demonstrated 40 documented cases of increased risk of stroke and systemic embolism with ximelagatran and 56 cases of increased risk with warfarin. The data confirmed the non-inferiority of ximelagatran over warfarin.

In SPORTIF V, patients were followed for a mean of 20 months. The data from this trial also verified the non-inferiority of ximelagatran over warfarin.

Bleeding was observed in both treatment groups, and the incidence was higher in the ximelagatran group. Patients receiving ximelagatran demonstrated an increase in alanine aminotransferase (ALT) levels greater than three times the upper limits of normal (ULN) (at 6%) compared with the warfarin patients (at 0.7–0.8%).

Liver enzyme concentrations were elevated within the first six months of therapy and decreased with or without drug discontinuation. Long-term safety over
35 days and liver enzyme levels were also evaluated. Liver enzymes of ALT were more than three times the ULN with ximelagatran in contrast to comparator agents with more than twice the ULN of bilirubin.

Of nine patients who died, three were in the ximelagatran group.

ADVERSE DRUG REACTIONS\(^2,7,10,11\)

The most common and expected adverse drug event (ADE) associated with ximelagatran is bleeding. Clinical trials have shown that the risk of bleeding associated with ximelagatran is comparable to that of traditional anticoagulants. However, the incidence is reported to be less than with other conventional therapies.

Elevations of liver enzymes have also been noted in clinical trials. Within the first two to six months of treatment with ximelagatran, up to 6% of patients had elevated serum ALT levels as high as three times the ULN. However, these levels returned to normal in most of the patients whether or not they continued therapy.

Because of the uncertainty of the significance of liver enzyme elevations, authorities have recommended that liver function tests, in particular ALT testing, be performed before the initiation of ximelagatran and every two months thereafter for at least the first six months, then periodically. Recommendations have been implemented to monitor patients clinically, and patients are urged to adhere to protocols in order to prevent possible ADEs.

DRUG/FOOD INTERACTIONS\(^2,10,11,19\)

The potential for drug interactions with ximelagatran has been described in various in vitro and in vivo studies. In general, ximelagatran demonstrated a low potential for drug interactions based on several factors:

- The mechanism of action of ximelagatran was not affected by vitamin K-dependent clotting factors.
- The plasma protein binding of melagatran was relatively low.
- The elimination route of systemic melagatran was via glomerular filtration.
- CYP450 enzymes did not appear to affect the metabolism of ximelagatran.

In vitro studies demonstrated no evidence of metabolism or inhibition of CYP enzymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, or 3A4. Various CYP450 substrates and inhibitors have also been used to conduct in vivo studies of healthy subjects. No significant interactions were observed with the concomitant administration of ximelagatran and amiodarone (Cordarone®, Wyeth), angiotensin-converting enzyme (ACE)–inhibitors, angiotensin II receptor antagonists, aspirin, atorvastatin (Lipitor®, Pfizer), beta blockers, calcium-channel blockers, clopidogrel bisulfate (Plavix®, Bristol-Myers Squibb/Sanoﬁ), diazepam (Valium®, Roche), diclofenac (e.g., Cataflam®, Voltaren®, Novartis), digoxin, HMG–CoA reductase inhibitors (statins), loop diuretics, nifedipine (Procardia®, Pfizer), or nitrates.

However, clinically significant elevated levels of melagatran were observed with the concomitant use of erythromycin, azithromycin (Zithromax®, Pfizer), and cefuroxime axetil (Ceftin®, Glaxo-SmithKline). Other antibiotics tested were ciprofloxacin (Cipro®, Bayer), amoxicillin (e.g., Amoxil®, Glaxo-SmithKline), and doxycycline (e.g., Vibramycin®, Pfizer); none of these showed any interactions with ximelagatran.

Ximelagatran demonstrated no clinical interactions with food or alcohol.

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**Figure 1** Schematic diagram of the coagulation cascade showing the effects of warfarin versus those of ximelagatran.
CONTRAINDICATIONS2,10,11

Ximelagatran is contraindicated in patients with a history of hypersensitivity to ximelagatran, melagatran, or any of its components. The use of ximelagatran is prohibited in patients with any type of severe, active bleeding.

PRECAUTIONS AND WARNINGS2,10,11

Appropriate precautions should be implemented with ximelagatran administration, for example, in patients with known risk factors for bleeding, including uncontrolled hypertension, thromboembolism, a history of gastric and/or duodenal ulcer, a recent history of major surgery or trauma, bacterial endocarditis, malignancy, or stroke.

Its concurrent use with thrombolytics, antiplatelet agents, and nonsteroidal anti-inflammatory drugs (NSAIDs) increases the potential for clinically significant bleeding.

For patients with renal insufficiency, dose adjustments of ximelagatran are needed; otherwise, there is an enhanced risk of bleeding.

Currently, there is no evidence available to support the use of ximelagatran in pregnancy or breast-feeding.

DOSE AND ADMINISTRATION1,2,10,11

Although optimal doses and dosing schedules have not been determined, clinical trials have reflected efficacy with fixed doses of 24 to 36 mg orally twice a day (morning and evening). As a result of the few drug interactions associated with ximelagatran and its wide therapeutic index, no routine coagulation monitoring is necessary.

CONCLUSION2,10,11,20–22

Ximelagatran offers some advantages over warfarin (Table 2). Despite the FDA’s rejection of this product, the FDA advisory committee has made recommendations to AstraZeneca for its possible future approval. These recommendations include providing the FDA with more well-defined studies of ximelagatran’s benefit–risk ratio, its efficacy, and its proof of superiority over warfarin.

As AstraZeneca decides how to move forward with ximelagatran, the search for an ideal oral anticoagulant continues. Good bioavailability, the absence of food or drug interactions, a rapid onset of action, a wide therapeutic index, a predictable anticoagulant response, a fixed dosage, limited side effects, and the availability of an antidote are among the most important factors to be considered in developing an oral anticoagulant.

Currently, four other oral anticoagulants are in phase 2 clinical trials:

- dabigatran etexilate (a direct thrombin inhibitor)
- razaxaban (a selective Xa inhibitor)
- BAY 59-739 (a selective Xa inhibitor)
- DX-9065a (an antithrombin III inhibitor)

Depending on what happens with the possible new oral anticoagulation therapies and with AstraZeneca’s and the FDA’s future actions regarding ximelagatran, it remains to be seen which product will be next to play an important role in oral anticoagulation and which one might replace warfarin as the mainstay therapy.

REFERENCES