

Integrated Executive Summary of FDA Review for NDA 21-686 Exanta (Ximelagatran)

NDA: 21-686

Sponsor: AstraZeneca

Drug name: Exanta (ximelagatran) Tablets

Indications:

- 1) Prevention of venous thromboembolism in patients undergoing knee replacement surgery;
- 2) Long-term secondary prevention of VTE after standard treatment for an episode of acute VTE;
- 3) Prevention of stroke and other thromboembolic complications associated with atrial fibrillation (AF).

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Executive Summary Section

I. Introduction and Background

A. EXANTA (ximelagatran)

EXANTA® (ximelagatran) is an oral anticoagulant and a prodrug of melagatran, a potent, reversible, competitive and direct inhibitor of thrombin.

Marketing approval of ximelagatran is being sought for the following 3 indications: prevention of venous thromboembolism (VTE) (defined as deep vein thrombosis [DVT], pulmonary embolism [PE], or both), in patients undergoing knee replacement surgery; long-term secondary prevention of VTE after standard treatment for an episode of acute VTE; and prevention of stroke and other thromboembolic complications associated with atrial fibrillation (AF). All 3 indications are for the adult population only.

For the indication of prevention of VTE in patients undergoing knee replacement surgery, the proposed dosing is EXANTA 36 mg twice-daily for a treatment period of 7 to 12 days. Provided hemostasis has been established, the first dose should be given the morning after surgery, but no sooner than 12 hours from the time of surgery. For the indication of long-term secondary prevention of VTE, it is proposed that patients who have received standard anticoagulant treatment for DVT or PE be treated with EXANTA 24 mg twice-daily for an additional 18 months. For the indication of prevention of stroke and other thromboembolic complications associated with atrial fibrillation, the proposed dosing is EXANTA 36 mg twice-daily. The first indication (in patients undergoing knee replacement surgery) is a short-term therapy (7 to 12 days); however, the 2nd indication (secondary prevention of VTE) and 3rd indication (in patients with AF) are long-term therapy (18 months or life-long, respectively).

B. State of Armamentarium for Indication(s)

Warfarin is approved for:

- ?? the prophylaxis and/or treatment of venous thrombosis and its extension, and PE;
- ?? the prophylaxis and/or treatment of the thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement;
- ?? reducing the risk of death, recurrent myocardial infarction (MI), and thromboembolic events such as stroke or systemic embolization after MI.

The “Dosage and Administration” section of warfarin labeling refers to “longer term therapy” for indications such as VTE, in patients with A-Fib or mechanical and bioprosthetic heart valves. It also states that the duration of therapy in each patient should be individualized and anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed. Thus, the indications and dosing recommendations for warfarin are sufficiently broad to encompass extended prophylaxis of DVT.

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Other drugs approved for the indication of the prophylaxis of VTE in patients undergoing knee replacement surgery include Lovenox (enoxaparin sodium) injection, a low molecular weight heparin, and Arixtra (fondaparinux sodium) injection, a synthetic inhibitor of activated Factor X (Xa). Both Lovenox and Arixtra are for subcutaneous injection. No oral medication has been approved so far for this short-term use to prevent VTE in patients undergoing elective knee replacement surgery.

Except warfarin, no other agents are approved for long-term thrombo-prophylaxis after treatment of DVT or PE, or for chronic thrombo-prophylaxis in patients with atrial fibrillation.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The clinical studies were designed to demonstrate that fixed doses of ximelagatran, without coagulation monitoring or dosage adjustment, offer superiority to placebo (long-term secondary prevention of VTE), superiority to warfarin (prevention of VTE in patients undergoing knee replacement surgery), and non-inferiority to warfarin (prevention of stroke associated with atrial fibrillation).

The development program includes 5 major efficacy and safety studies for the indications being sought and 77 additional clinical studies with ximelagatran and/or melagatran (a total of 60 Phase 1 studies and 22 Phase 2 and 3 studies). These studies have involved a total of 30,698 subjects of whom 17,593 received the oral prodrug ximelagatran, or the active drug melagatran. In the long-term treatment populations, 6931 patients received ximelagatran (5024 for at least 6 months and 3509 for at least a year).

All 5 major Phase 3 studies were conducted as a multi-center, randomized, parallel-group, comparator-controlled design. All studies were double-blind except for SH-TPA-0003 (SPORTIF III for the indication of prevention of stroke in patients with AF; which was open-label in design). All studies used a central laboratory for all protocol-specified laboratory measurements.

For the indication of prevention of VTE in patients undergoing elective knee replacement surgery, the sponsor conducted three Phase 3 studies in comparison with warfarin in patients undergoing primary, elective total knee replacement (TKR) surgery (EXULT A, EXULT B and SH-TPO-0006). Ximelagatran 36 mg bid was used in both studies EXULT A and EXULT B. Ximelagatran 24 mg was used in study SH-TPO-0006. A total of 5284 patients were randomized in these three studies (1927 to ximelagatran 36 mg bid, 2247 to warfarin, and 1110 to ximelagatran 24 mg bid).

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To support the indication of prolonged prophylaxis of VTE after a six-month anticoagulation treatment for VTE, the sponsor provided only one 18-month study, SH-TPV-0003 (THRIVE III). A total of 1233 patients were randomized, with 903 completing the study (468 on ximelagatran 24 mg bid and 435 on placebo).

For the indication of prevention of stroke and systemic embolic events in patients with nonvalvular atrial fibrillation, two pivotal Phase 3 studies, one double-blind and one open-label, have been submitted in support of the stated indication. In the atrial fibrillation development program a total of approximately 7,300 patients were followed for an average of 1.4 years. The two studies were active controlled studies designed to show that ximelagatran is “non-inferior” to treatment with warfarin, the current standard of care. The two studies compared the effectiveness of fixed doses of ximelagatran 36 mg administered twice a day versus warfarin, targeting an INR of 2 – 3 in patients with nonvalvular atrial fibrillation and at least one additional risk factor for stroke.

B. Efficacy

Indication 1: Prevention of VTE in patients undergoing elective total knee replacement (TKR) surgery

In study EXULT A ximelagatran 24 mg and 36 mg were compared to warfarin. In EXULT B ximelagatran 36 mg was compared to warfarin. Oral ximelagatran 36 mg bid was superior to warfarin in reducing total VTE and/or all-cause mortality at end of 7-12 days therapy among patients undergoing TKR surgery in these two Phase 3 studies.

In the pooled analyses (study EXULT A and study EXULT B), the incidence of total VTE and/or all-cause mortality among patients undergoing TKR was 21.7% for patients in the ximelagatran 36 mg group and 30.2% for patients in the warfarin group ($p < 0.001$). However, the benefit was mainly due to a reduction in asymptomatic distal DVT diagnosed by venography which is not clinically meaningful. There were no clinically or statistically significant differences between ximelagatran and warfarin groups in reducing the frequency of proximal DVT, PE, and/or all-cause mortality in this population (Table 1).

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Table 1 Objectively confirmed symptomatic and asymptomatic thromboembolic events over the entire study (efficacy ITT population) – EXULT A and EXULT B 36 mg bid

Component of the primary endpoint ^a	EXULT A		EXULT B	
	Ximelagatran 36 mg % (n/N)	Warfarin % (n/N)	Ximelagatran 36 mg % (n/N)	Warfarin % (n/N)
Asymptomatic total DVT ^b	19.8 (124/625)	27.4 (166/606)	21.9 (214/976)	31.4 (301/960)
Proximal DVT	2.1 (13/625)	3.8 (23/601)	3.1 (30/969)	3.4 (33/957)
Distal DVT ^c	19.2 (120/625)	26.7 (161/604)	21.4 (209/976)	31.1 (298/959)
Symptomatic total DVT				
Proximal DVT	0.5 (3/629)	0.7 (4/608)	0.4 (4/982)	0.2 (2/967)
Distal DVT	0.8 (5/629)	0.8 (5/608)	0.7 (7/982)	1.4 (14/967)
Pulmonary embolism	0.3 (2/629)	0.2 (1/608)	0.3 (3/982)	0.5 (5/967)
Death	0.5 (3/629)	0.2 (1/608)	0.7 (7/982)	0.3 (3/967)

Data derived from [Tables 5.3.5OS.3\(36\) – 2.3 and 2.14.2](#).

^a Each patient is counted only once within the categories of Asymptomatic DVT and Symptomatic DVT using the worst case principle.

^b Asymptomatic DVT recorded at mandatory venography. N excludes patients included in efficacy ITT solely because of a symptomatic event or death (these patients are counted in the N for the symptomatic events).

^c Distal DVT = Total DVT minus proximal DVT.

DVT deep vein thrombosis; ITT intention-to-treat.

Sponsor's table from Module 2; vol. 1, page 90.

There are several major problems with using warfarin as an active comparator in these two studies. Warfarin is not approved for this short-term indication. The comparison is unfair, because warfarin will take about 3-5 days to reach therapeutic level, while EXANTA reaches therapeutic levels within hours. Mean days of exposure were 8.1 days for ximelagatran and 6.7 days for warfarin in these two studies. The results show that 33.1% - 35.2% of patients receiving warfarin had an INR less than 1.8 at postoperative day 3, and 24.0 - 26.9% of patients receiving warfarin had an INR less than 1.8 at end of treatment (day 7 - 12). Because of the superiority study design, however, efficacy results for ximelagatran in these studies may still be acceptable, since warfarin may be considered to be placebo.

In EXULT A ximelagatran 24 mg bid was not superior to warfarin in reducing total VTE and/or all-cause mortality (27.6% warfarin vs 24.9% ximelagatran 24 mg) at end of 7-12 days therapy.

For detailed efficacy evaluation on the indication of prevention of VTE in patients undergoing elective TKR surgery, please see Appendix A, Medical Officer's Review by Dr. Ruyi He, and Appendix B, Statistical Review by Dr. Dionne Price.

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Indication 2: Long-term secondary prevention of VTE after standard treatment for an episode of acute VTE

Ximelagatran significantly reduced the recurrence rate of symptomatic, objectively confirmed VTE (the primary variable of the study) as compared to placebo over 18 months of treatment (cumulative risk of 2.8% versus 12.6%; hazard ratio 0.16; $p < 0.0001$). The number of patients with a VTE event was 12 in the ximelagatran group and 71 in the placebo group. The number of patients with a PE event was lower in the ximelagatran group compared to the placebo group (2 and 23) respectively. The results for the secondary variable, all-cause mortality, showed no significant difference between the treatment groups (1.1% vs 1.4% for patients on ximelagatran and placebo, respectively) during the 18 months.

For detailed efficacy evaluation on the indication of long-term secondary prevention of VTE, please see Appendix A, Medical Officer's Review by Dr. Ruyi He, and Appendix B, Statistical Review by Dr. Dionne Price.

Indication 3: Prevention of stroke and other thromboembolic complications associated with atrial fibrillation

SPORTIF III and SPORTIF V are two Phase 3, active control, non-inferiority studies that were provided in support of EXANTA for long-term use in patients with atrial fibrillation. Both studies compared the effectiveness of a fixed dose of ximelagatran, 36 mg administered twice a day to warfarin targeting an INR of 2 to 3 in patients with nonvalvular atrial fibrillation and at least one additional risk factor for stroke. The studies were very similar in design except that SPORTIF III was open label while SPORTIF V was double-blind. The primary endpoint was the composite of all strokes (fatal and non-fatal) and systemic embolic events. The sponsor pre-specified a non-inferiority margin of 2 percentage points in the event rate in both studies. However, the margin was not agreed to by the Agency and its derivation from referenced historical trials is unclear. A margin of that size could leave open the possibility that ximelagatran is only half as effective as warfarin and still be considered "non-inferior."

In both studies, the efficacy of ximelagatran was within the sponsor's pre-specified non-inferiority margin of 2% and it was concluded by the sponsor that ximelagatran was as efficacious as warfarin. While the two studies could be considered "successes" based on the sponsor's pre-specified margin, the margin chosen was too liberal.

The two SPORTIF studies produced divergent results despite their similar designs and patient populations studied. In SPORTIF V, the event rate was higher in the ximelagatran arm compared to the warfarin arm (Table 2) while in SPORTIF III, the event rate was higher in the warfarin arm compared to the ximelagatran arm (Table 3). Comparing the event rates in common arms of both studies, the event rate in the ximelagatran arm of both SPORTIF studies were similar at approximately 1.6%. However, the event rate in the warfarin arm varied by almost two-fold: 1.2% in SPORTIF V versus 2.3% in SPORTIF III. Differences in the patient populations in the two studies at baseline could be a possible explanation of the differences in the

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event rate in the treatment arms. However, it is difficult to explain why such differences would lead to differences in event rates in the warfarin arm while leaving the event rate in the ximelagatran arm unaffected. In a setting where two similarly designed studies produce divergent results, the results from the double-blind study could be considered more reliable. The event rate in both studies was primarily driven by the occurrence of ischemic strokes and more than 80% of the events in both studies were ischemic strokes.

The results of the primary pre-specified endpoint from SPORTIF V and SPORTIF III are summarized in Table 2 and Table 3 below, respectively.

Table 2: Number of patients with stroke and/or systemic embolic event (SEE) by treatment group (SPORTIF V)^a

Treatment group	Events ^{b,c}	Patient Years	Event Rate (%/year)	95% CI		p-value
				Lower	Higher	
Ximelagatran	51	3160	1.61	1.17	2.06	
Warfarin	37	3186	1.16	0.79	1.54	
Ximelagatran – warfarin			0.45	-0.13	1.03	0.133

^aData in this table obtained from Table 45 of SPORTIF V CSR

^bEvents represent CEAC adjudicated events

^cThis table only informs of the number of patients with their first event. If a patient had more than one event, it is not reflected in this table.

Table 3: Number of patients with stroke and/or SEE by treatment group (SPORTIF III)^a

	Events ^b	Patient years	Event rate (%/year)	95% CI		p-value
				Lower	Higher	
Ximelagatran	40	2446	1.64	1.13	2.14	
Warfarin	56	2440	2.29	1.69	2.9	
Ximelagatran-Warfarin			-0.66	-1.45	0.13	0.100

^aData in this table obtained from Table 39 of SPORTIF III CSR

^bEvents represent CEAC adjudicated events

For detailed efficacy evaluation on the indication of prevention of stroke associated with atrial fibrillation, please see Appendix C, Medical Officer's Review by Dr. Mehul Desai, and Appendix D, Statistical Review by Dr. John Lawrence.

C. Safety

C.1. Safety of ximelagatran in patients undergoing a surgical procedure (use \leq 35 days)

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A total of 1913 patients were exposed to ximelagatran 36 mg bid, 1097 patients were exposed to ximelagatran 24 mg bid, and 2226 patients were exposed to warfarin with a mean duration of exposure of 8 days for the ximelagatran groups.

Overall, more than 55% of patients in each treatment group experienced at least 1 adverse event (AE). Post-operative complications were mostly related to bleeding and were reported at a higher frequency in the ximelagatran groups (17% at 36 mg, 23% at 24 mg) than in the warfarin groups (15% and 20%, respectively).

There were 18 deaths (12 patients exposed to ximelagatran and 6 patients exposed to warfarin). Of the 12 deaths reported among the 3010 patients who received ximelagatran, 2 were fatal bleeding events (both on ximelagatran 36 mg). Six were fatal events in which 'PE could not be excluded'. The remaining 4 deaths in patients who received ximelagatran were adjudicated by the sponsor as 'death not associated with VTE or bleeding'. For these the investigators reported the causes of death in 1 patient on treatment as sudden death, and in the other 3 patients after treatment as intestinal perforation, acute MI, and pneumonia. Of the 6 deaths reported among the 2226 patients who received warfarin (0.3%), 2 were fatal events in which 'PE could not be excluded'. The causes of death in 2 patients on treatment were arrhythmia and MI and in the other 2 after treatment were colon carcinoma and AMI.

There were more discontinuations of study drug due to adverse events in the ximelagatran 36 mg group (2.6%) than in the warfarin group (2.0%) and in the ximelagatran 24-mg group compared to warfarin group (3.1% versus 2.1%, respectively). The most common adverse event leading to study drug discontinuation was postoperative complication.

With respect to on-treatment adjudicated events, major bleeding occurred in 0.9% of patients treated with ximelagatran 36 mg, compared to 0.5% of patients treated with warfarin. There were 2 fatal bleeding events (both on ximelagatran 36 mg). Major/minor bleeding occurred in 5.1% of patients treated with ximelagatran 36 mg and 4.1% of patients treated with warfarin.

Incidences of alanine aminotransferase (ALAT) elevation reported as adverse events (AEs) were higher in the 36 mg ximelagatran group (2.1%) than other groups (1.3-1.5% warfarin; 1.4% ximelagatran 24 mg). There were no hepatobiliary fatal adverse events, non-fatal severe AEs or discontinuation of study drug due to adverse events in either ximelagatran group. During the follow-up period (4-6 weeks), 8 patients in the ximelagatran group, and 1 in the warfarin group had their first ALAT elevation >3x upper limit of normal (ULN). However, patients were followed up for only 4-6 weeks post operation. Drug effects on liver toxicity beyond 4-6 weeks are unknown. It should be noted that in studies with long-term exposure to ximelagatran elevation of hepatic enzymes was typically seen between the 2nd and 6th month after starting ximelagatran.

In both studies Exult A and Exult B, the proportion of patients with coronary artery disease adverse events (MI or ischemia/angina) was significantly higher in the ximelagatran groups than in the warfarin groups. In patients undergoing TKR surgery (Exult A and Exult B), the proportion of patients with coronary artery disease adverse events was statistically significantly

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higher in the ximelagatran group (20/2677, 0.75%) than in the warfarin group (5/1907, 0.26%) ($p=0.02800$). The proportion of patients with myocardial infarction (MI) was also higher in the ximelagatran group (16/2677, 0.60%) than in the warfarin group (4/1907, 0.21%) in the TKR population ($p=0.04951$). There were no appreciable differences between the treatment groups for underlying diseases including hypertension, hypercholesterolemia, diabetes mellitus, coronary atherosclerosis, as well as age, gender and weight. Considering ximelagatran as an anticoagulant with potential to treat MI, these results are unexpected and worrisome.

Overall, these studies raised some safety concerns for use of oral ximelagatran 36 mg bid for 7 to 12 days after surgery (beginning the morning after surgery) in the prevention of VTE in patients undergoing elective knee replacement surgery. There is a potential risk of higher coronary artery disease adverse events including acute myocardial infarction. Potential for long-term use (>12 days) that will cause liver toxicity is high. Also, major bleeding events were more common in patients treated with ximelagatran than in patients treated with warfarin. A study with longer follow up (6 months) may also be considered in the assessment of liver toxicity with short-term use of ximelagatran.

For detailed safety evaluation of ximelagatran in patients undergoing a surgical procedure (use \leq 35 days), please see Appendix A, Medical Officer's Review by Dr. Ruyi He.

C.2. Safety of ximelagatran in patients with long-term exposure (> 35 days)

A total of 6931 patients received doses of 20 to 60 mg of ximelagatran, for a median of 370 days. A total of 5024 patients were exposed to ximelagatran for at least 6 months and 3509 for at least 12 months. A total of 6216 patients were exposed for a median of 455 days to warfarin ($n=4967$) and placebo ($n=1249$).

C.2.1. Deaths

There were 224 deaths during active treatment, 112 in the ximelagatran treatment groups and 112 in the comparator groups. A further 331 patients died after stopping study drug (166 in the ximelagatran group and 165 in the comparator group). There were no differences between the treatment groups. The most common fatal SAE was myocardial infarction. Nine ximelagatran-treated patients died with concomitant ALAT $>3xULN$ and bilirubin $>2xULN$.

C.2.2. Non-fatal Severe Adverse Events (SAE)

A total of 26.3% of patients in the ximelagatran group and 27.1% of patients in the comparator group experienced a non-fatal SAE during treatment. A further 5.5% of patients in the ximelagatran group and 4.3% of patients in the comparator group experienced a non-fatal SAE after stopping study drug. The most common non-fatal SAEs were cardiovascular events. The most common non-fatal SAEs considered to be causally related to ximelagatran were increases in hepatic transaminases.

C.2.3. Discontinuation

The proportion of patients who discontinued study drug was higher in the ximelagatran group (1189/6931, 17.2%) than in the comparator group (801/6216, 12.9%). This was mostly due to the discontinuation of study drug due to elevated hepatic transaminases. Data from

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discontinuation of ximelagatran secondary to adverse events indicate that “coronary artery disorders (CAD)” were more common in the ximelagatran group than in the comparator group (0.6% vs. 0.3%, respectively) whereas thromboembolic events were less common in the ximelagatran group (0.4% vs. 1.3%, respectively), because of a placebo control. Other common causes of discontinuations included bleeding events, with no difference between ximelagatran and the comparators, except for hematuria and rectal hemorrhage/ melaena, which caused slightly more discontinuations in the ximelagatran group than in the comparator groups.

C.2.4. Bleeding Events

In patients with atrial fibrillation (AF), in terms of major bleeding events, the total number of bleeds was numerically lower in the ximelagatran arms of both SPORTIF studies. However, there were no significant differences for major bleeding events between the groups in each of the 2 pivotal studies (SH-TPA-0003 and STP-0005). In patients with acute venous thromboembolism (VTE), ximelagatran 36 mg was associated with numerically fewer major bleeding events than enoxaparin/warfarin. In patients undergoing extended secondary prophylaxis for VTE, ximelagatran 24 mg was associated with a similar incidence of major bleeding events compared to placebo. A total of 38 patients experienced bleeding-related severe AEs with a fatal outcome, 19 cases in each treatment group (ximelagatran or comparator).

C.2.5. Hepatobiliary Toxicity

In patients receiving long-term administration of ximelagatran (>35 days) an increase in ALAT >3xULN occurred in 6-13% (average 7.6%, 531/6948) compared to 0-2% (average 1.1%, 68/6230) of patients receiving comparator treatments. Including local laboratory data, 620 patients showed an ALAT elevation >3xULN during the studies, 546 patients in the ximelagatran group (cumulative incidence 7.8%) and 74 patients in the comparator group (cumulative incidence 1.1%). Among the 531 patients in the ximelagatran group who presented with an ALAT >3xULN, 206 (39%) completed the study on study drug. The remaining 325 patients (61%) discontinued study drug prematurely.

The time pattern of ALAT elevations was consistent across patients. The increase typically occurred between 1 and 6 months after the initiation of ximelagatran. Before and after this time frame, the incidence of ALAT increase was similar to that in the comparator groups. Of the 531 ximelagatran-treated patients who had an ALAT elevation >3xULN recorded by the central laboratory, 502 (95%) had their ALAT return to <2xULN (235 with study drug continued). Most cases show a peak of ALAT within the first 2 to 3 months post-randomization and a decline back towards baseline within about 6 months post-randomization in patients who discontinued or in patients continued on ximelagatran.

Eighteen patients who discontinued study drug with elevations of ALAT subsequently resumed treatment after ALAT had returned to the normal range. Of these 18 patients, 2 again experienced elevations of ALAT after drug was resumed.

An evaluation of potential risk factors for increase in ALAT indicated an increased risk in the post acute coronary syndrome (ACS) population ($p=0.0009$), VTE-treatment (VTE-T) ($p=0.0003$) populations, in female patients ($p=0.0002$) patients, in low BMI ($<27 \text{ kg/m}^2$)

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population ($p < 0.0001$), and in patients receiving concomitant treatment with statins ($p = 0.019$). Asian patients were found to have a decreased risk ($p = 0.0038$). Although a single factor identified above may not be strong enough to eliminate the subgroup population, consideration may be given to contraindicating ximelagatran in patients who have 2 or more risk factors, such as, female patients with low body weight or who are taking statin.

ALAT $> 3xULN$ was associated with bilirubin $> 2xULN$ (within one month following the rise in ALAT) in 0.53% (37/6948) of all patients who were exposed to ximelagatran > 35 days as compared to 0.08% (5/6230) of patients exposed to comparators. Nine ximelagatran-treated patients (24.3%, 9/37) died with concomitant ALAT $> 3xULN$ and bilirubin $> 2xULN$. Among these, 3 died from heart failure; 3 died from carcinomas with hepatic metastases; 2 (ID# 7259, and 7859) died from GI bleeding with coagulopathy (1 with biopsy documented hepatic necrosis) and 1 (ID# 5442) died from hepatitis B. Liver failure/toxicity by ximelagatran might have caused or at least contributed to these deaths. Only one autopsy was done in these 9 deaths and it showed a small, friable and diffusely mottled liver suggestive of severe diffuse hepatic necrosis.

C.2.6. Adverse Events of Coronary Artery Disease

In all study populations except the post acute coronary syndrome, the proportion of patients with coronary artery disease adverse events was higher in the ximelagatran groups than in the comparator groups (7.0% and 6.7% for the AF pool, 1.3% and 0.1% for the VTE-treatment (VTE-T) pool and 2.6% and 2.0% for the VTE-prevention (VTE-P) pool, for the ximelagatran and comparator groups, respectively). This trend was consistent across the pools for myocardial infarction.

The proportion of patients with coronary artery disease adverse events was statistically significantly higher in the ximelagatran group (32/1848, 1.7%) than in the warfarin/placebo group (12/1859, 0.7%) in the VTE population ($p = 0.00411$, the combination of VTE-Treatment and + VTE-Prevention population). The proportion of patients with MI was also significantly higher in the ximelagatran group (13/1848, 0.7%) than in the warfarin/placebo group (3/1859, 0.16%) in the VTE population ($p = 0.01183$). There were no appreciable differences between the treatment groups for underlying diseases including hypertension, diabetes mellitus, hypercholesterolemia, coronary atherosclerosis, as well as age, gender and weight. Considering ximelagatran as an anticoagulant with potential to treat MI, these results are worrisome.

For detailed safety evaluation of ximelagatran in patients with long-term exposure (use > 35 days), please see Appendix A, Medical Officer's Review by Dr. Ruyi He and Appendix C, Medical Officer's Review by Dr. Mehul Desai.

III. Review of risk minimization action plan

The Office of Drug Safety (ODS) has reviewed the EXANTA (ximelagatran) Risk Minimization Action Plan (RiskMAP) submitted by AstraZeneca as part of its new drug application (NDA 21-686) to address the risk of hepatotoxicity associated with long-term ximelagatran therapy. The

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RiskMAP does not address the possible risks of delayed hepatotoxicity after short-term use with ximelagatran, or the risk of myocardial infarction (MI) that was identified in the FDA Clinical Safety Review. In addition, reversal of excessive ximelagatran-induced bleeding was not addressed by the sponsor.

Ximelagatran is an anticoagulant and if approved, will be the first available oral direct thrombin inhibitor. The sponsor is seeking approval for three indications: 1) for the short term prevention of venous thrombo-embolism (VTE) in patients undergoing knee replacement surgery; 2) for the long-term prevention of stroke and other thromboembolic complications associated with atrial fibrillation; and 3) for the long term secondary prevention of VTE after standard treatment for an episode of acute VTE. In this document, we occasionally refer to the combined safety experience with long term exposure (LTE), which includes the treatment populations for indications (2) and (3).

A. Long-term Use (>35 days)

During clinical development, at least 37 cases of severe liver injury [defined as alanine aminotransferase (ALAT) > 3 x upper limit of normal (ULN) with concurrent increase in total bilirubin (TBL) >2 x ULN] were observed among patients randomized to ximelagatran. The relative risk of severe liver injury was 6.6 (95% CI 2.6 – 16.9) compared to warfarin/placebo, with one affected person in 200 treated with ximelagatran. Preliminary analyses suggest the risk of severe liver injury begins within the first month of therapy.

Based on the observation of Hy Zimmerman¹ that at least 10% of individuals with severe drug-induced liver injury (as defined above) progress to liver failure, liver transplant, or death, ximelagatran-associated fatal liver injury or liver failure could occur in as many as 1 in 2,000 patients treated long-term (i.e., 10% of 1 in 200). Consistent with this prediction, three deaths associated with severe liver injury occurred in the ximelagatran long-term exposure clinical development program, for a proportion of one fatal liver injury in 2,300 patients exposed to ximelagatran (n=6948 ximelagatran treated patients, mean treatment duration of 357 days).

To address ximelagatran-induced hepatotoxicity associated with long-term use, the sponsor proposes an ALT-monitoring program similar to the program used during clinical development. This program consisted of baseline and monthly ALT assessments, with more frequent testing and discontinuation linked to different thresholds of ALT elevation relative to the upper limit of normal. The initial algorithm specified an ALT >7 times the ULN as a threshold for drug discontinuation, but this was revised to 5 times the ULN after the occurrence of a death associated with severe liver injury. Cases of severe liver injury and a case of fatal liver injury continued to be observed after the implementation of the revised algorithm. More conservative algorithms were not tested, so it remains unknown whether timely discontinuation with any ALT elevation can prevent irreversible life-threatening liver injury with ximelagatran.

¹ Zimmerman HJ. Drug-induced liver disease. In: Hepatotoxicity The Adverse Effects of Drugs and Other Chemicals on the Liver. Appleton-Century-Crofts, New York, 1978, 1999.

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The sponsor's proposed RiskMAP targets [] compliance with ALT monitoring and algorithm-triggered discontinuation. In the clinical development program, severe liver injury, including fatal liver injury occurred even though compliance with ALT testing and discontinuation met or exceeded 83%. The sponsor has not provided sufficient evidence about whether timely transaminase monitoring and early discontinuation of the drug at the first signs of liver toxicity could prevent severe liver injury and associated fatalities with ximelagatran. Even if evidence were sufficient to support the claim that monitoring can reduce the risk of severe liver injury and associated fatalities, the sponsor's projected lower adherence with recommended ALT monitoring in clinical use has the potential to result in a *higher* rate of severe liver injury and liver failure/fatal liver injury than was observed in clinical development.

The demonstrated severity and rate of hepatotoxicity is substantial with long term treatment with ximelagatran. Since no adequate mechanism to prevent or limit this toxicity has been demonstrated, there is no basis for proposing RiskMAP tools to reliably limit hepatotoxicity risk in individual patients.

Should it be determined that ximelagatran offers selected populations of patients sufficient benefits to counter the hepatotoxicity risk, consideration should be given to a restrictive RiskMAP that would limit risk on a population basis. One example might be a performance-linked access system with a registry for patients entering long-term ximelagatran therapy. Such a system should focus on appropriate education of patients and providers about risk, and appropriate patient selection. We would also advocate further quantification of the risk of hepatotoxicity over time, and clarification of the ability of ALT monitoring and early discontinuation of the drug to mitigate the risk of severe liver injury and liver failure/fatal liver injury.

B. Short-term Use

In comparison to warfarin controls, there does not appear to be an elevated risk of severe liver injury during the short-term use (<12 days) of ximelagatran. However, in the two pivotal studies of total knee replacement (TKR) patients, an imbalance in ALT > 3 x ULN was observed at the follow-up visit approximately 6 weeks after surgery in ximelagatran-treated patients (8 ximelagatran- vs. 1 warfarin-treated subject). Whether delayed onset of severe liver injury after short-term ximelagatran treatment could occur is unknown, since no additional routine study visits were conducted.

Analysis of data from the long-term exposure population shows that initial signs of liver injury (ALT > 3 x ULN) were observed during the first month of ximelagatran therapy in 6 of 37 patients who went on to develop severe liver injury (ALT > 3 x ULN and TBL > 2 x ULN). This suggests that severe liver injury can potentially begin during the first month of treatment with ximelagatran. Since practice guidelines recommend anticoagulation of certain high risk patients with TKR for more than 12 days, we anticipate physicians will want to treat some TKR patients for a longer period with ximelagatran. Since the risk of severe liver injury could increase with

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longer duration of ximelagatran therapy, even during the first month, “short-term” duration of use after TKR would need to be strictly limited to prevent potential severe liver injury.

The sponsor did not submit a RiskMAP to constrain ximelagatran use to a defined period (i.e., 7-12 days). Again, we remain concerned about the intrinsic risk and poorly characterized pace of hepatotoxicity with ximelagatran. Should the benefit of ximelagatran therapy be sufficient to warrant approval for short-term prevention of VTE in patients undergoing TKR, we recommend implementation of a RiskMAP to assure that total duration of therapy in individual patients does not exceed 12 days or whatever interval is found to be appropriate.

We note other safety risks of ximelagatran may merit serious consideration. These include (1) the risk of MI identified in the FDA Clinical Safety Review, and (2) the absence of clear methods to control excessive bleeding with ximelagatran should it occur. Neither of these risks was addressed by the sponsor, and one or both may warrant exploration of various risk management tools.

For detailed risk evaluation of ximelagatran, please see Appendix E, Review of Risk Minimization Action Plan by the Division of Drug Risk Evaluation and the Division of Surveillance, Research and Communication Support, Office of Drug Safety. Please also see Appendix F, Clinical White Paper, CDER-PHRMA-AASLD Conference 2000 for more information regarding evaluation of drug-induced liver toxicity.

IV. Summary of Pre-clinical Evaluation

Ximelagatran (H 376/95) is quickly metabolized to melagatran (H 319/68). Two intermediates, hydroxy-melagatran (H 415/04) and ethyl-melagatran (H 338/57) are formed during conversion of ximelagatran to melagatran. They are measurable in human plasma. In vitro studies indicated that melagatran is a potent and selective thrombin inhibitor. Ethyl-melagatran is also pharmacologically active and its potency is similar to that of melagatran. Ximelagatran and hydroxy-melagatran are less potent.

The results of the cardiovascular pharmacology studies with ximelagatran did not reveal any significant effects at oral doses up to 95 mg/kg in rats and i.v. doses up to 36 mg/kg in dogs. Intravenous administration of melagatran did not reveal any significant effects at doses up to 6.5 mg/kg in rats and dogs.

The toxicity profiles of ximelagatran and melagatran have been characterized in 1- to 6-month oral toxicity studies in rats and 1- to 12-month oral toxicity studies in dogs. The toxicity profiles of melagatran have been also characterized in 4-week i.v. toxicity studies in rats and dogs. The major treatment-related toxicity identified in these studies was the exaggerated pharmacological activity including prolongation of clotting times and hemorrhages. In these studies, there were no toxicological effects on the liver.

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Ximelagatran and its intermediate, ethyl-melagatran, were positive in the mouse lymphoma cell (L5178Y/TK[±]) forward gene mutation tests. Ximelagatran was not genotoxic in the following tests: Ames, rat hepatocyte unscheduled DNA synthesis (UDS) test, and *in vivo* mouse micronucleus test. Melagatran was not genotoxic in the following tests: Ames, human lymphocyte chromosome aberration test, mouse lymphoma cell (L5178Y/TK[±]) forward gene mutation test, and mouse micronucleus test. The intermediate, hydroxy-melagatran, was not genotoxic in the mouse lymphoma (L5178Y/TK[±]) forward gene mutation test.

In a 2-year oral carcinogenicity study in rats, ximelagatran at doses of 19, 38, 76 or 114 mg/kg/day produced pancreatic acinar cell hyperplasia, adenoma, and carcinoma. The dose of 19 mg/kg/day was about 3 times the recommended human maintenance dose of 48 mg/day based on body surface area. Ximelagatran was not tumorigenic in the 2-year oral carcinogenicity study in mice at doses up to 85 mg/kg/day, which was about 7 times the recommended human maintenance dose of 48 mg/day based on body surface area.

Ximelagatran was found to have no adverse effects in the reproductive toxicology studies in rats, rabbits, and mini-pigs.

V. Summary of Clinical Pharmacology Evaluation

Data from 60 Clinical Pharmacology studies, 23 Biopharmaceutics-related studies and several *in vitro* mechanistic studies were submitted in support of this application.

Following oral administration, ximelagatran is rapidly absorbed with a mean absolute bioavailability of melagatran estimated at 20%. Ximelagatran is activated to melagatran by hydrolysis of the ethyl ester (H338/57) and reduction of the N-hydroxyamidine function (H415/04). The conversion of ximelagatran to melagatran does not appear to be mediated by CYP 450 enzymes. Following oral administration of ¹⁴C-labeled ximelagatran, approximately 71% and 25% of the administered radioactivity were recovered in feces and urine, respectively.

Melagatran is a potent direct inhibitor of thrombin with a Ki of 2 nmol/L. H 338/57, one of the two intermediates, was shown to have potent direct thrombin inhibition activity *in vitro* (Ki 1.3 nmol/L). However, the mean AUC value for H 338/57 corresponds to only 3.2% of melagatran AUC. Melagatran is not highly bound to plasma proteins (15%) and is mainly excreted unchanged in urine (~80%) with the renal clearance corresponding to glomerular filtration rate. Dose linearity of melagatran was demonstrated following administration of single oral doses of ximelagatran ranging from 5 to 98 mg. There was also minimal accumulation (10-15%) of melagatran following administration of BID doses of ximelagatran oral solution 20 mg for 5 days to healthy subjects.

The clinical trial- and Phase 2 formulations were shown to be bioequivalent while the To-Be-Marketed commercial ximelagatran tablet formulation was deemed equivalent to the Phase 3 tablet based on *in vitro* dissolution data. Concomitant administration of ximelagatran with food has no significant effect on AUC and C_{max} of melagatran. Crushed ximelagatran tablet contents

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sprinkled in applesauce and ximelagatran tablet dissolved in water and administered via nasogastric tube were shown to be bioequivalent to the intact ximelagatran tablet.

Administration of ximelagatran in patients with hepatic disease is not recommended in the package insert due to the potential hepatotoxic adverse events associated with ximelagatran. Administration of ximelagatran in patients with severe renal impairment increases C_{max} and AUC by five fold and two fold, respectively, relative to patients with mild renal impairment. The proposed labeling for ximelagatran states that use of ximelagatran in patients with severe renal impairment is not recommended. There are no recommendations, however for dosage adjustment in patients with mild to moderate renal impairment.

Oral administration of ximelagatran in patients resulted in higher melagatran systemic exposure and longer half-life ($t_{1/2} \sim 5$ hours) relative to that in healthy subjects ($t_{1/2} \sim 3$ hours). This was attributed by the sponsor to age-related lower renal function in patients. In addition, the inter-individual variability in melagatran exposure was markedly higher in patients (50%) relative to healthy subjects (20%).

C_{max} and AUC of melagatran were elevated in elderly subjects relative to young male subjects. The oral bioavailability, C_{max} and AUC values of melagatran in healthy elderly subjects increased by 23%, 47% and 38%, respectively relative to young subjects. The decrease in CL in elderly subjects is likely due to reduced renal function with age.

No clinically significant pharmacokinetic drug-drug interactions were observed between ximelagatran and either CYP 3A4 substrates (nifedipine, atorvastation, amiodarone and diazepam), CYP 2C9 substrates (diclofenac) or CYP 2C19 substrates (diazepam). Co-administration of melagatran 36 mg with erythromycin increased mean AUC and C_{max} values of melagatran by 82% and 74%, respectively. No potentially clinically significant pharmacodynamic drug-drug interactions were observed between ximelagatran and either acetylsalicylic acid, diclofenac, amiodarone or clopidogrel.

Exposure response (E/R) analysis of melagatran with respect to efficacy and safety using pooled data from long-term studies (treatment > 6 months) showed that there was a relationship between melagatran exposure and both bleeding events and ALAT > 3 X ULN.

VI. Considerations for the Committee

A. Short-term Use: prevention of VTE in patients undergoing elective total knee replacement surgery

1. In studies with long-term exposure to ximelagatran, elevation of hepatic enzymes was typically seen between the 2nd and 6th month after starting ximelagatran. The initial signs of liver injury (ALT > 3 x ULN) were observed during the first month of ximelagatran therapy in 6 of 37 patients who went on to develop severe liver injury (ALT > 3 x ULN and TBL > 2 x ULN). This suggests that severe liver injury can potentially begin during

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the first month of treatment with ximelagatran. For study Exult A and Exult B in patients undergoing TKR, during the follow-up period (4-6 weeks), 8 patients in the ximelagatran group, and 1 in the warfarin group had their first ALAT elevation $>3\times$ ULN. However, patients were followed up for only 4-6 weeks post operation. Drug effects on liver toxicity beyond 4-6 weeks are unknown.

Do you recommend additional safety studies with longer follow-up to address this issue?

2. Because severe liver toxicity is associated with long-term use of ximelagatran, do you recommend a risk management program to restrict distribution and use to short-term use (≤ 12 days) in this indication?
3. Regarding the potential risk of myocardial infarction/coronary artery disease (MI/CAD) with short-term exposure to ximelagatran (≤ 12 days) in patients undergoing TKR, do you recommend a study to further investigate the risk of MI/CAD? If yes, should the study be done prior to approval or as a Phase 4 commitment (post-marketing)? What type of study do you recommend?
4. No oral medication has been approved for short-term use to prevent VTE in patients undergoing TKR. EXANTA will provide an alternative choice to patients who prefer oral medication to subcutaneous injection. However, the demonstrated efficacy benefit is mainly reduction of asymptomatic distal DVT diagnosed by venography and there are some safety concerns as list above.

Do benefits of EXANTA exceed risks for this indication?

B. Long-term Use: secondary prevention of VTE after 6 months standard treatment for an episode of acute VTE

5. Ximelagatran significantly reduced the recurrence rate of symptomatic, objectively confirmed VTE as compared to placebo over 18 months of treatment. However, ximelagatran-associated fatal liver injury or liver failure could occur in as many as 1 in 2,000 patients treated long-term, MI/CAD may be a potential risk of ximelagatran in the VTE population and warfarin is currently available therapy.

Do benefits of EXANTA exceed risks for this indication?

C. Long-term Use: prevention of stroke and systemic embolic events in patients with atrial fibrillation

The sponsor is seeking an indication for ximelagatran to prevent stroke and systemic embolic events in patients with atrial fibrillation. This claim is based upon two "non-inferiority" trials

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with warfarin. SPORTIF III was an open-label comparison in 3407 subjects and SPORTIF V was a double-blind study with 3922 subjects.

The expected effect of warfarin was based on 6 placebo-controlled studies (4 open-label) performed 10 to 15 years ago. The sponsor's meta-analysis of these data concluded that warfarin reduced the risk of stroke by 64% (95% CI of 52 to 73%). The sponsor proposed that ximelagatran be considered "non-inferior" if the absolute event rate was not 2% higher on ximelagatran than on warfarin, i.e., if ximelagatran preserved nominally about 50% of the effect of warfarin.

	Stroke/SEE (# events/ 100 patient-years)			Discontinued		Major bleed (# events/ 100 patient-years)		Hy's Law cases: ALT >3xULN followed by bili > 2xULN within one month	
	Xim	War	Delta (95% CI)	Xim	War	Xim	War	Xim	War
SPORTIF III	1.64%	2.30%	-0.66 (-1.45, 0.13)	10.9%	5.9%	1.3%	1.7%	0.5%	0.06%
SPORTIF V	1.61%	1.16%	0.45 (-0.13, 1.03)	18.1%	15.4%	2.4%	3.1%	0.5%	0.05%

Event rates on warfarin in the two studies were 2.3% (SPORTIF III) and 1.2% (SPORTIF V), quite different from one another despite similar study designs, and not similar to the expected event rate of 3.1%, from which the non-inferiority margin was derived.

In SPORTIF III, there were 96 events, with nominal risk reduction of 29% on ximelagatran (95% CI for relative risk is 48% to 106%). In SPORTIF V there were 88 subjects with events, nominally 39% more on ximelagatran (95% CI for relative risk is 91% to 212%).

7. Without monitoring, major bleeding was reduced by about 0.7% absolute with ximelagatran. However, ximelagatran is associated with hepatotoxicity, which can be expected to be sometimes fatal. Does the margin of 2% ensure ximelagatran is non-inferior to warfarin with respect to efficacy and in light of safety concerns? Do benefits exceed risks for this indication?

D. General

8. Based on currently available data, is it possible to identify patients who are at risk for developing severe liver toxicity after exposure to ximelagatran?
9. Does the RiskMAP as proposed by the sponsor effectively mitigate the risk of severe liver injury and liver failure?