CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-345

MEDICAL REVIEW(S)

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA:	21-345 (000: BZ, AZ)
Sponsor:	Fonda BV
Drug name:	Arixtra (Org31540/SR90107A, fondaparinux sodium injection)
Class:	Antithrombotic, Synthetic Pentasaccharide
Indication:	Prophylaxis of Deep Vein Thrombosis following Hip Fracture, Hip Replacement and Knee Replacement Surgeries
Date submitted:	August 31, 2001; October 9, 2001
Date assigned:	October 16, 2001
Review completed:	November 16, 2001
Medical reviewer:	Min Lu, M.D., M.P.H.

Introduction

This NDA was submitted to the Agency on February 15, 2001 for the approval of ARIXTRA for the indication of prophylaxis of deep vein thrombosis following hip fracture, hip replacement and knee replacement surgeries. The Agency issued an Approvable Letter on August 15, 2001 including Draft Labeling, Phase IV commitments, and issues in CMC, Clinical Pharmacology and Labeling.

In this submission, the sponsor has submitted a full response to 15 August Agency Approval Letter with revised draft labeling, safety update report and responses to Phase IV commitments.

Revised Draft Labeling

In the sponsor's response to the Agency's Approvable Letter, the revised draft labeling has been changed significantly. The most important change is deletion of [redacted] in Contraindications section. The following are the main changes made by the sponsor in the revised draft labeling followed by this reviewer's comments.

I. Black Box Warning on Spinal/Epidural Hematomas

Deletion of "low molecular weight heparin or heparinoid" in the first paragraph. The sponsor's main reason for deletion is "neither of these terms encompass fondaparinux sodium".

Reviewer's comments: The phrase "low molecular weight heparin, heparinoid, or *fondaparinux sodium" should be added in the first paragraph.*
Reasons:
1) This Black Box Warning is standard for LMWHs and similar products.
2) The term "Heparinoid" is not well defined and may not apply to fondaparinux sodium. Therefore, listing fondaparinux sodium in the warning sentence is more appropriate.

II. Clinical Studies section

1. **Addition of a sentence giving the total number of patients studied in overall clinical trials at the beginning of this section.**

Reviewer's comments: This is unacceptable.
Reasons:
1) This sentence is not needed. The Clinical Studies section should include and give numbers of patients involved in the clinical studies that provide primary support for effectiveness of Arixtra.
2) The number of patients studied in pivotal trials providing primary support for effectiveness for each indication has been included in subsections under Clinical Studies section.
3) This recommendation is consistent with current FDA thinking as reflected in the draft guidance "Clinical Studies Section of Labeling for Prescription Drugs and Biologics—Content and Format, May 2001".

2. **Addition of the term of ———— in the trial design description and a comparative conclusion between Arixtra and enoxaparin sodium in the results.**

Reviewer's comments: This is unacceptable.
Reasons:
1) These are superiority claims.
2) Superiority claims can not be made based on these trials because of the following reasons:
a) [ ]
b) For prophylaxis of thromboembolic events following hip replacement surgery, Study 1 (EFC2442) demonstrated no significant difference in the incidence of VTE, the primary efficacy endpoint, between Atrixtra 2.5 mg once daily SC post-operatively and enoxaparin sodium 30 mg every 12 hours SC post-operatively. In Study 2 (63118), enoxaparin sodium (comparator) was administered in a suboptimal regimen (only 88% patients received enoxaparin 40 mg once daily SC pre-operatively and the mean

time between the last active pre-operative injection and start of surgery was 13±14 hours). The approved and recommended dosage for enoxaparin sodium (Lovenox) for the indication for prophylaxis of DVT following hip replacement is 30 mg every 12 hour SC post-operatively. A dose of 40 mg once a day SC, given initially 12±3 hours prior to surgery, may be considered.

c) *For prophylaxis of thromboembolic events following knee replacement surgery, in a single clinical trial (95002), enoxaparin sodium 30 mg every 12 hours SC was administered at 21±2 hours after surgical closure. The approved and recommended dosage for enoxaparin sodium (Lovenox) for the indication for prophylaxis of DVT following knee replacement surgery is 30 mg every 12 hours SC with a initial dose given 12 to 24 hours after surgery. Because most patients received the first dose of enoxaparin at later time in the clinical trial, which may not be optimal condition for the comparator, superiority claim should not be included in the labeling.*

3. Deletion of "Symptomatic PE" results in the efficacy Tables (1-3).

Reviewer's comments: This is unacceptable.
Reasons:

1) *VTE is a composite endpoint. Effects on all components of a composite endpoint should be presented. This recommendation is consistent with current FDA thinking as reflected in the draft guidance "Clinical Studies Section of Labeling for Prescription Drugs and Biologics—Content and Format, May 2001".*
2) *In four pivotal trials, 11 patients in Arixtra group and 10 patients in enoxaparin group developed symptomatic PE up to 11 days. Of these, most patients (7 in each group) developed symptomatic PE during the study treatment period. A similar number of patients (4 in Arixtra group and 3 in enoxaparin group) developed symptomatic PE after study treatment was stopped.*

4. Replace "knee replacement surgery" with [redacted]

Reviewer's comments: This is unacceptable.
Reason: It appears that most patients enrolled in knee surgery clinical trial underwent knee replacement surgery although [redacted] *a broader term, was required in the inclusion criteria. In the NDA submission, all narratives submitted (i.e., for 45 patients who experienced death, SAEs, and/or discontinuation due to AEs) indicated that knee replacement surgeries were performed in all these patients. Therefore, a more specific patient population, patients undergoing knee replacement surgery, instead of* [redacted] *should be used in the labeling.*

5. Addition of p value in the footnotes of each efficacy Tables (1-3).

Reviewer's comments: This is acceptable provided 95% confidence interval also is included.
Reason: A p-value used alone is potentially misleading. This recommendation is consistent with current FDA thinking as reflected in the draft guidance "Clinical Studies Section of Labeling for Prescription Drugs and Biologics—Content and Format, May

2001".

6. Addition of a [redacted] across all indications in the end of Clinical Studies section.

Reviewer's comments: This is unacceptable.
Reasons:
1) This is not pre-defined analysis.
2) The information in the Figure could be misleading (i.e., [redacted] in Study 1 under hip replacement surgery on the Figure but no significant difference was found in pre-defined analysis) and is not clinically useful.
3) Efficacy results for each indication have been presented in efficacy tables.

Reviewer's additional comments regarding the efficacy tables: Presentations of the efficacy results based on all-treated patients are inappropriate based on available data.

Reasons:

1) About 20-30% of all-treated patients were missing for efficacy assessment due to non-evaluable or no venography in clinical trials.

2) All-treated patients with missing efficacy assessment are considered as no VTE event in the efficacy tables (best case scenario analysis for handling missing patients).

3) The rates of endpoint events for all-treated patients in the efficacy tables may be significantly underestimated, which may provide false impression regarding absolute effectiveness of this product.
4) That significant number of patients were missing efficacy assessment in these trials should be conveyed by providing the number of all-treated patients in the top of table and number of evaluable patients in the table along with the actual trial results.

III. Indications and Usage section

1. Replacement of knee replacement surgery" with [redacted]

Reviewer's comments: This is unacceptable.
Reason: See comments in II (4).

IV. Contraindications section

1. Deletion of Box Contraindication for [redacted] severe renal impairment.

Reviewer's comments: This is unacceptable.
Reasons:
1) There was a higher incidence of major bleeding in patients with [redacted] severe renal impairment [redacted]

2) The sponsor is unable to provide a dose-adjustment schedule for these patients and unable to provide graduated prefilled syringe for possible dose-adjustment.

Reviewer's additional comments for Box Contraindications:
Low body weight (<50 kg) should be added in this section because major bleeding rate was much higher in patients with low body weight (<50 kg) as compared to those with body weight ≥50 kg (5.4% vs. 2.1%) in clinical trials. The sponsor is unable to provide dose adjustment schedule for this population.

2. Deletion of patients with thrombocytopenia associated with a positive in vitro test for anti-platelet antibody in the presence of fondaparinux sodium in Contraindications section.

Reviewer's comments: This is unacceptable.
Reasons:
1) A similar percentage of patients with thrombocytopenia was observed between Arixtra and enoxaparin sodium (known to be associated with heparin-induced thrombocytopenia) groups in clinical trials (3.0% vs. 3.2%).
2) A slightly higher percentage of patients with the presence of anti-platelet antibody was observed in patients treated with Arixtra than those treated with enoxaparin sodium (4.4% vs. 3.3% based on ELISA test; 16.5% vs. 12.4% based on serotonin release test in ELISA positive patients).
3) The frequency of patients having both thrombocytopenia and anti-platelet antibody was similar between Arixtra and enoxaparin sodium treatments (0.13% vs. 0.10%).
4) Possible association between the presence of anti-platelet antibody and Arixtra treatment cannot be excluded based on current data available.

3. Addition of bacterial endocarditis in this section.

Reviewer's comments: This is acceptable.
Reason: Bacterial endocarditis was in Warnings section under hemorrhage subsection.

V. Warnings section

1. Deletion of the paragraph describing that the product can not be used interchangeably with other similar products.

Reviewer's comments: This is unacceptable.
Reason: This is a standard paragraph in the labeling for other similar products.

2. Hemorrhage subsection: deletion of the paragraph regarding the risk of hemorrhage in patients with renal impairment.

Reviewer's comments: This is unacceptable.
Reason: See above IV (1).

Reviewer's additional comments for this subsection: Instruction on discontinuation of Arixtra treatment in case of bleeding should be added in this section because no test is available to physician to monitor anti-Factor Xa activity of Arixtra in clinical practice (international standard test of anti-Factor Xa activity for LMWH can not be used for this product).

3. **Thrombocytopenia subsection: incorporated rate of moderate thrombocytopenia (platelet counts between 100,000/mm^3 and 50,000/mm^3) in clinical trials per FDA request.**

Reviewer's comments: This is acceptable. Rate of severe thrombocytopenia (platelet counts <50,000/mm^3) in clinical trials should also be included in this section. Instruction on monitoring platelet count and discontinuation of treatment if moderate or severe thrombocytopenia occurs should be added in this section as other similar product labeling.

VI. Precautions section

1. **General subsection: Deletion of the paragraph regarding use of the drug in elderly patients and in patients with a history of heparin-induced thrombocytopenia.**

Reviewer's comments: This is unacceptable.
Reasons:
1) Major bleeding rate was higher in elderly patients as compared to younger patients in clinical trials.
2) Elderly patients are more likely to have decreased renal function.
3) Anti-platelet antibody has been identified in patients receiving Arixtra in clinical trials. Possible association between the presence of anti-platelet antibody and Arixtra treatment can not be excluded based on current data available (See also IV:2).

2. **Laboratory Tests subsection: Deletion of platelet count and stool occult blood tests in periodic routine laboratory tests.**

Reviewer's comments: This is unacceptable.
Reasons:
1) This is recommended by College of American Pathologists in 1998 Conference on Laboratory Monitoring of Anticoagulant Therapy for anticoagulants that do not have available tests for monitoring.
2) This is a standard paragraph in labeling for other similar products.

Reviewer's additional comments for this subsection: monitoring of serum creatinine level should be included in this subsection.

3. **Geriatric Use subsection: Deletion of the paragraph of monitoring renal function in elderly patients.**

Reviewer's comments: This is unacceptable.
Reason: This statement is required for a drug that is known to be substantially excreted by the kidney according to 21 CFR §201.57(10) (iii)(B).

VII. Adverse Reactions section

1. **Deletion of the major exclusion criteria of patients with serum creatinine >2.0 mg/dL in clinical trials in this section.**

Reviewer's comments: This is unacceptable.
Reason: Any critical exclusion from safety database should be provided. Because a high major bleeding rate is associated with renal impairment, this exclusion criteria of patients with serum creatinine >2.0 mg/dL should be considered as a critical exclusion for current safety database. This recommendation is consistent with current FDA thinking as reflected in the draft guidance "Clinical Studies Section of Labeling for Prescription Drugs and Biologics—Content and Format, May 2001".

2. **Hemorrhage subsection: Deletion of table of major bleeding rate by indication.**

Reviewer's comments: This is unacceptable.
Reasons:
1) This safety information is important to the physician.
2) A significantly higher incidence of major bleeding has been observed in patients following knee replacement surgery in Arixtra-treated patients as compared to enoxaparin sodium-treated patients in clinical trial. This important safety information should be provided clearly in the labeling.

3. **No information provided for thrombocytopenia.**

Reviewer's comments: Thrombocytopenia should be listed as a subsection and the reader referred to Warnings section as in the labeling for other similar products.

4. **Incorporated subsection on Elevated of Serum Aminotransferases per FDA request.**

Reviewer's comments: This is acceptable.

5. **Listed only adverse reactions that occurred in —— of patients and that were assumed possibly or probably related to treatment by the sponsor in the adverse event table.**

Reviewer's comments: This is unacceptable.
Reason: All adverse reactions that occurred in ≥2% of patients in clinical trials regardless of attribution of causality should be listed in the table. Other serious adverse reactions reported in ongoing studies should be listed in the text.

VIII. Overdosage section

1. Inclusion of [redacted]

Reviewer's comments: This is unacceptable.
Reasons:
1) This information is irrelevant to indicated patient populations.
2) This information may provide misimpression on the safety of this product.

IX. Dosage and Administration section

1. Replaced "6 hour" with [redacted] as the time of administration for Arixtra after surgical closure.

Reviewer's comments: This is unacceptable.
Reason: Major bleeding rate was higher in patients who received Arixtra < 6 hours in clinical trials as compared to those who received the drug ≥6 hours in clinical trials.

2. Addition of [redacted]

Reviewer's comments: This is unacceptable.
Reasons:
1) See above 1. All patients should receive the first treatment 6 hours after surgical closure.
2) Only one-third of major bleeding occurred following the first injection of treatment. The restriction of the time of the first treatment is not adequate in these subpopulations.
3) These dosing recommendations are not adequately supported. No studies were designed to address dosing in these [redacted]
4) [redacted] should be included in the Contraindications section.

Safety Update

This NDA Safety Update Report provides cumulative data up to 15 August 2001, for studies that were ongoing on, or begun since, 01 March 2001 (120-Day Safety Update cutoff date, 28 February 2001).

Safety data include one ongoing Phase IIB study (63119) and three ongoing Phase III studies (EFC2441, 63123 and EFC4582). An overview of the ongoing studies with enrolled patients is provided in the following table.

Ongoing Clinical Studies

Ongoing Studies	Study Design	Study population	Initially planned for inclusion	Number of subjects		
				Entered[a] Age/Gender/ Race	Completed[a]	Permanently discontinued for any reason[a]
63119	Phase IIB Dose ranging study of once daily Org31540/ SR90107A (2.5, 4, 8, and 12 mg – adjusted to body weight category)	Patients [redacted]	1075	Entered = 1147 654 ADUL; 493 ELD 772 M; 375F 1118 C; 15 B; 8 OE; 6 OTH	1147	212*
EFC2441	Phase III Efficacy and safety of once daily Org31540/ SR90107A (5 mg or 7.5 mg or 10 mg – dose according to body weight category) versus twice daily enoxaparin (1 mg/kg)	Patients with [redacted]	2200	Entered = 1746 881 ADUL; 855 ELD; 10 MD 925 M; 821 F; 1694 C; 32 B; 3 OE; 14 OTH; 3 MD	1649	89
63123	Phase III Efficacy and safety of once daily Org31540/ SR90107A (5 mg or 7.5 mg or 10 mg -according to body weight category) versus adjusted-dose IV UFH in [redacted]	Patients with [redacted]	2200	Entered = 1197 575 ADUL; 622 ELD; 205 M; 253 F; 739 MD 417 C; 31 B; 1 OE; 8 OTH; 740 MD	322	62
[redacted]	[redacted]	[redacted]	670	Entered = 10 4 ADUL; 6 ELD; 3 M; 7 F; 9 C; 1 OTH	2	2

May include blinded and unaudited data [a] Since study start
*. Based on status evaluation at discharge or on AE/SAE with action taken stopped Age: ADUL = Adults (16 to 65 years); ELD = Elderly (65 years and older) Gender: M =Male; F = Female Race: C = Caucasian; B = Black; OE = Oriental; OTH = Other.
Reviewer's table based on NDA Safety Update Report pp. 6-9 submitted on 10/9/2001.

A total of 4100 patients entered the 4 ongoing studies and 3120 of these have completed the studies.

Patient Exposure

A summary of the duration of exposure for the ongoing studies in this safety update is provided in the following table.

For the Phase IIB Study (63119), patients were to be treated with study drug (fondaparinux 2.5 mg, 4.0 mg, 8.0 mg, or 12.0 mg, or enoxaparin 1 mg/kg) for 3-7 days.

For the two Phase III VTE treatment studies (EFC2441 and 63123), the study drug (fondaparinux 5.0 mg, 7.5 mg, or 10.0 mg according to body weight, or UFH 1250 IU/hour) were to be administered for at least 5 days until a therapeutic INR effect was observed with INR values above 2 on two consecutive days.

[ ]

Table 3.1 - Summary of Duration of Exposure to Study Drug - All Treated Patients

	NDA 21-345		Safety Update	NDA 21-345	Safety Update	Safety Update	Safety Update
	MOSLL Studies with Pre-op Randomization Fondaparinux 2.5 mg o.d. EFC2698 and 63118	MOSLL Studies with Post-op Randomization Fondaparinux 2.5 mg o.d. EFC 2442 and 995-002	[ ]	Treatment Dose Ranging Study Fondaparinux 5.0, 7.5 or 10.0 mg o.d. DRI2440	Treatment Study Fondaparinux 7.5 mg od** or enoxaparin 1 mg/kg EFC2441	Treatment Study Fondaparinux 7.5 mg** or UFH *** 63123	Study Fondaparinux 2.5, 4.0, 8.0 or 12.0 mg or enoxaparin 1 mg/kg 63119
	N = 1950	N = 1645	N = 10	N = 334	N = 1746	N = 1197	N = 1147
Duration of therapy (days) *							
1 day	19 (1.0%)	9 (0.5%)	0	3 (0.9%)	7 (0.4%)	27 (6.0%)	11 (1.0%)
1 < day < 5	73 (3.7%)	61 (3.7%)	1 (11.1%)	4 (1.2%)	41 (2.3%)	59 (13.1%)	539 (47.1%)
5 ≤ day ≤ 9	1777 (91.1%)	1564 (95.1%)	2 (22.2%)	310 (92.8%)	1498 (85.8%)	336 (74.8%)	594 (51.9%)
>9	81 (4.2%)	11 (0.7%)	6 (66.7%)	17 (5.1%)	200 (11.5%)	27 (6.0%)	0
Total ****	1950 (100.0%)	1645 (100.0%)	9 (100.0%)	334 (100.0%)	1746 (100%)	449 (100%)	1144 (100.0%)

* For the ongoing studies in the safety update [ ], EFC2441, 63123, 631191, data are still blind and data cleaning and validation are in progress. For the studies in NDA 21-345 where some of them used double-dummy technique, duration or therapy is presented for active study drug.
** Large step body weight adjustment: patients < 50 kg – 5.0 mg, patients between 50 and 100 kg – 7.5 mg, patients >100 kg – 10.0 mg
*** Continuous intravenous UFH of at least 1250 IU/h adjusted to maintain the aPTT at 1.5 to 2.5 x control
**** For ongoing studies: Treated patients with data on treatment duration available. For study 63123, the information about treatment duration was based on the study database whereas the higher number of entered patients was taken from a separate blinded randomization database that more closely resembled the population with SAE information.

Sponsor's table in NDA safety update report pp. 11 submitted on 10/9/2001.

Major bleeding

Major bleeding was the main safety parameter identified in NDA 21-345.

For this safety update, EFC2441 [ ] treatment) and 63119 ([ ] are close to completion. The bleeding adjudication is approximately two-thirds finished for both EFC2441 and 63119. A summary of the patients who experienced an adjudicated major bleeding event in ongoing studies EFC2441 (blind) and 63119 (blind) is provided in the following table. Data for adjudicated major bleeding events in ongoing studies 63123 [ ] treatment) and [ ] are not available.

Reviewer's comments: Sixteen patients experienced major bleeding events including one fatal bleeding in EFC2441 — treatment) trial and 6 patients experienced major bleeding in 63119 ——— trial based on incomplete bleeding adjudication process.

Table 4.1.1 - Number (%)of Patients with Adjudicated Major Bleeding during treatment period- All Treated Patients

	NDA 21-345		NDA 21-345	Safety Update*	Safety Update*
	MOSLL Studies with Pre-op Randomization Fondaparinux 2.5 mg o.d. EFC2698 and 63118	MOSLL Studies with Post-op Randomization Fondaparinux 2.5 mg o.d. EFC2442 and 095-002	— Treatment Dose Ranging Study Fondaparinux 5.0, 7.5 or 10.0 mg o.d. DRI2440	— Treatment Study Fondaparinux 7.5 mg o.d.** or enoxaparin 1 mg/kg EFC2441	——— Study Fondaparinux 2.5, 4.0, 8.0 or 12.0 mg or enoxaparin 1 mg/kg 63119
	N = 1971	N = 1645	N = 334	N = 1746	N =1147
Major Bleeding	65 (3.3%)	31 (1.9%)	6 (1.8%)	16 (1.0%)	6 (0.5%)
Fatal bleeding	0	0	0	1 (0.1%)	****
Non-fatal bleeding at critical site	0	0	0	0	****
Re-operation due to bleeding	8 (0.4%)	4 (0.2%)	NA	NA	****
BI ≥ 2 ***	57 (2.9%)	27 (1.6%)	6 (1.8%)	15 (0.9%)	****

* These studies in the safety update are ongoing. Data are still blind and data cleaning and validation are in progress.
** Large step body weight adjustment: patients < 50 kg – 5.0 mg, patients between 50 and 100 kg – 7.5 mg, patients >100 kg – 10.0 mg
*** The definition of BI ≥ 2 differs between study type (see criteria above table).
**** For ongoing study 63119, the detailed adjudication criteria were not part of the CRFs and not entered into the central study database

Sponsor's table in NDA safety update report pp. 14 submitted on 10/9/2001.

In accordance with NDA 21-345, adjudicated major bleeding rates during the treatment period are presented by baseline covariate in the following table.

Reviewer's comments: Major bleeding results for EFC2441 and 63119 are consistent with those of the NDA studies. Major bleeding rate increased with decreasing creatinine clearance and body weight, and with increasing in age. In EFC2441 — treatment) study, major bleeding was much higher in patients with severe renal impairment (5.7%), moderate renal impairment (2.5%) as compared to those with mild renal impairment (1.2%) and normal renal function (0.1%). Similar results were found in 63119 (unstable angina) trial. In EFC2441 trial, there was a higher major bleeding rate in patients with body weight <50 kg (2.5%) as compared to those with body weight ≥50 kg (1% in 50-100 kg and 0% in ≥100 kg groups, in spite of dose adjustment treatment schedule was used.

Table 4.2.1 - Number (%)of Patients with Adjudicated Major Bleeding During Treatment Period by Covariate - All Treated Patients

Covariate	NDA 21-345		NDA 21-345	Safety Update*	Safety Update*
	MOSLL Studies with Pre-op Randomization Fondaparinux 2.5 mg o.d. EFC2698 and 63118	MOSLL Studies with Post-op Randomization Fondaparinux 2.5 mg o.d. EFC2442 and 095-002	Treatment Dose Ranging Study Fondaparinux 5.0, 7.5 or 10.0 mg o.d. DRI2440	Treatment Study Fondaparinux 7.5 mg o.d.** or enoxaparin 1 mg/kg EFC2441	Fondaparinux 2.5, 4.0, 8.0 or 12.0 mg or enoxaparin 1 mg/kg 63119
	N = 1971	N = 1645	N = 334	N = 1746	N = 1147
Age					
Missing	0/4 (0.0%)	0/0	0/0	0/1 (0.00%)	0/0
< 65	15/604 (2.5%)	13/658 (2.0%)	1/169 (0.6%)	2/890 (0.2%)	1/654 (0.2%)
[65-75]	17/556 (3.1%)	11/561 (2.0%)	3/92 (3.3%)	4/432 (0.9%)	4/411 (1.0%)
≥ 75	33/807 (4.1%)	7/426 (1.6%)	2/73 (2.7%)	10/423 (2.4%)	1/82 (1.2%)
Gender					
Male	20/680 (2.9%)	23/760 (3.0%)	1/174 (0.6%)	11/821 (1.3%)	4/772 (0.5%)
Female	45/1291 (3.5%)	8/885 (0.9%)	5/160 (3.1%)	5/925 (0.5%)	2/375 (0.5%)
Race					
Missing	0/1 (0.0%)	0/0	0/0	0/3 (0.0%)	0/0
Caucasian	63/1954 (3.2%)	27/1524 (1.8%)	6/331 (1.8%)	16/1694 (0.9%)	6/1118 (0.5%)
Black	0/8 (0.0%)	3/84 (3.6%)	0/1 (0.0%)	0/32 (0.0%)	0/15 (0.0%)
Asian	2/5 (40.0%)	0/6 (0.0%)	0/1 (0.0%)	0/3 (0.0%)	0/8 (0.0%)
Others	0/3 (0.0%)	1/31 (3.2%)	0/1 (0.0%)	0/14 (0.0%)	0/6 (0.0%)
Weight					
Missing	1/37 (2.7%)	0/1 (0.0%)	0/0	0/0	0/0
< 50	7/109 (6.4%)	0/21 (0.0%)	0/1 (0.0%)	1/40 (2.5%)	0/11 (0.0%)
[50,100]	56/1739 (3.2%)	23/1310 (1.8%)	6/309 (1.9%)	15/1519 (1.0%)	6/1048 (0.6%)
≥ 100	1/86 (1.2%)	8/313 (2.6%)	0/24 (0.0%)	0/187 (0.0%)	0/88 (0.0%)

* All studies in the safety update are ongoing. Data are still blind and data cleaning and validation are in progress
** Large step body weight adjustment: patients < 50 kg – 5.0 mg, patients between 50 and 100 kg – 7.5 mg, patients > 100kg – 10.0 mg
*** The definition of BI ≥ 2 differs between study type (see criteria above table).

Table 4.2.1 - Number (%)of Patients with Adjudicated Major Bleeding During Treatment Period by Covariate - All Treated Pati (continued)

Covariate	NDA 21-345		NDA 21-345	Safety Update*	Safety Update*
	MOSLL Studies with Pre-op Randomization Fondaparinux 2.5 mg o.d. EFC2698 and 63118	MOSLL Studies with Post-op Randomization Fondaparinux 2.5 mg o.d. EFC2442 and 095-002	Treatment Dose Ranging Study Fondaparinux 5.0, 7.5 or 10.0 mg o.d. DRI2440	Treatment Study Fondaparinux 7.5 mg o.d** or enoxaparin 1 mg/kg EFC2441	Fondaparinux 2.5, 4.0, 8 12.0 mg or enoxapari 1 mg/kg 63119
	N = 1971	N = 1645	N = 334	N = 1746	N = 1147
Creatinine Clearance					
Missing	1/78 (1.3%)	0/79 (0.0%)	2/54 (3.7%)	1/42 (2.4%)	0/13 (0.0%)
< 30	4/72 (5.6%)	0/11 (0.0%)	0/6 (0.0%)	2/35 (5.7%)	0/6 (0.0%)
[30,50]	30/386 (5.2%)	0/121 (0.0%)	4/48 (8.3%)	5/203 (2.5%)	3/87 (3.4%)
[50,80]	26/788 (3.3%)	14/502 (2.8%)	0/92 (0.0%)	7/576 (1.2%)	2/497 (0.4%)
≥ 80	14/647 (2.2%)	17/932 (1.8%)	0/134 (0.0%)	1/890 (0.1%)	1/544 (0.2%)

* All studies in the safety update are ongoing. Data are still blind and data cleaning and validation are in progress
** Large step body weight adjustment: patients < 50kg – 5.0 mg, patients between 50 and 100 kg – 7.5 mg, patients > 100 kg – 10.0 mg
*** The definition of BI ≥ 2 differs between study type (see criteria above table)

Sponsor's tables in NDA safety update report pp. 16-17 submitted on 10/9/2001.

Deaths

(63119)

The number (%) of patients with SAEs during the treatment period leading to death is summarized in the table below. Among the 1147 patients included before the safety update cut-off date, 12 (1.0%) died following an SAE that occurred during the treatment period.

Reviewer's comments: The majority of deaths were attributable to myo-, endo-, pericardial and valve disorders and heart rate and rhythm disorders.

Table (3.3.1) 1 - Number of Patients with SAEs During the Treatment Period Leading to Death in Ongoing Study 63119

WHO Organ Class Adverse Events (WHO Preferred Term)	Fondaparinux sodium or enoxaparin sodium (N = 1147)
Any event	12 (1.0%)
Myo-, endo-, pericardial and valve disorders	
Total	7 (0.6%)
Myocardial infarction	5 (0.4%)
Angina pectoris aggravated	1 (0.1%)
Cardiac tamponade	1 (0.1%)
Heart rate and rhythm disorders	
Total	6 (0.5%)
Cardiac arrest	3 (0.3%)
AV block	1 (0.1%)
Bradycardia	1 (0.1%)
Fibrillation ventricular	1 (0.1%)
Body as a whole - general disorders	
Total	1 (0.1%)
Condition aggravated	1 (0.1%)
Cardiovascular disorders, general	
Total	1 (0.1%)
Cardiac failure	1 (0.1%)
Respiratory system disorders	
Total	1 (0.1%)
Cyanosis	1 (0.1%)

May include blinded and unaudited data

Sponsor's table in NDA safety update report pp. 11 submitted on 8/31/2001.

— Treatment (EFC2441)

The number (%) of patients experiencing serious adverse events during the treatment period is summarized in the table below. Among the 1746 patients included before the safety update cut-off date, 7 (0.4%) died following an SAE that occurred during the treatment period.

Reviewer's comments: One patient died of retroperitoneal bleeding and was adjudicated as major bleeding event (fatal bleeding). One patient died of cardiac arrest in the trial.

Table (3.3.1) 2 - Number (%) of Patients With SAEs During Treatment Period Leading t
Death in Ongoing Study EFC2441

WHO Organ Class Serious Adverse Events (WHO Preferred Term)	Fondaparinux sodium or enoxaparin sodium Double-blind (N=1746)
Any event	7 (0.4%)
Neoplasm	
Total	2 (0.1%)
Hepatic neoplasm	1 (0.1%)
Neoplasm malignant	1 (0.1%)
Gastro-intestinal system disorders	
Total	1 (0.1%)
Intestinal obstruction	1 (0.1%)
Heart rate and rhythm disorders	
Total	1 (0.1%)
Cardiac arrest	1 (0.1%)
Platelet, bleeding and clotting disorders	
Total	1 (0.1%)
Haemorrhage retroperitoneal	1 (0.1%)
Reproductive disorders, female	
Total	1 (0.1%)
Endometrial neoplasm malignant	1 (0.1%)
Respiratory system disorders	
Total	1 (0.1%)
Pneumonia	1 (0.1%)

May include blinded and unaudited data

Sponsor's table in NDA safety update report pp. 12 submitted on 8/31/2001.

Treatment (63123)

The number (%) of patients with SAEs during the treatment period leading to death is summarized in the table below. Among the 1197 patients included before the safety update cut-off date, 15 (1.3%) died following an SAE that occurred during the treatment period.

Reviewer's comments: The most frequent causes of deaths were attributable to platelet, bleeding and clotting disorders (0.4%), and cardiovascular disorders (0.3%).

Table (3.3.1) 3 - Number of Patients with SAEs During Treatment Period (plus extension of 9 days) Leading to Death in Ongoing Study 63123

WHO Organ Class Adverse Events (WHO Preferred Term)	Fondaparinux sodium or unfractionated heparin (N = 1197)
Any event	15 (1.3%)
Platelet, bleeding and clotting disorders	
Total	4 (0.3%)
Embolism pulmonary[1]	3 (0.3%)
GI haemorrhage	1 (0.1%)
Cardiovascular disorders, general	
Total	3 (0.3%)
Cardiac failure	2 (0.2%)
Circulatory failure	1 (0.1%)
Body as a whole - general disorders	
Total	2 (0.2%)
Death	2 (0.2%)
Metabolic and nutritional disorders	
Total	1 (0.1%)
Hypercalcaemia	1 (0.1%)
Myo-, endo-, pericardial and valve disorders	
Total	1 (0.1%)
Myocardial infarction	1 (0.1%)
Reproductive disorders, female	
Total	1 (0.1%)
Ovarian carcinoma	1 (0.1%)
Respiratory system disorders	
Total	1 (0.1%)
Dyspnoea	1 (0.1%)
Secondary terms	
Total	1 (0.1%)
Metastases nos	1 (0.1%)
Vascular (extracardiac) disorders	
Total	1 (0.1%)
Cerebrovascular disorder	1 (0.1%)

Study is open label, but all AE data reported as blind to minimize bias
[1] Pulmonary embolism is a component of study primary efficacy endpoint

Sponsor's table in NDA safety update report pp. 13 submitted on 8/31/2001.

Serious Adverse Events

[redacted] (63119)

The number (%) of patients experiencing serious adverse events during treatment period is summarized in the sponsor's Table below. Among the 1147 patients included before the safety update cut-off date, 40 (3.5%) reported SAEs during the treatment period.

Reviewer's comments: The majority of reported SAE were myo-, endo-, pericardial and valve disorders (2.1%), and heart rate and rhythm disorders (0.8%). Four patients reported bleeding events (0.3%) as SAEs including one case of intracranial hemorrhage.

Table (3.4.1) 1 - Number (%) of Patients Experiencing SAEs During the Treatment Period in Ongoing Study 63119

WHO Organ Class Adverse Events (WHO Preferred Term)	Fondaparinux sodium or enoxaparin sodium (N = 1147)
Any event	40 (3.5%)
Myo endo pericardial & valve disorders	
Total	24 (2.1%)
Myocardial infarction	22 (1.9%)
Angina pectoris aggravated	1 (0.1%)
Cardiac tamponade	1 (0.1%)
Heart rate and rhythm disorders	
Total	9 (0.8%)
Cardiac arrest	3 (0.3%)
Fibrillation ventricular	3 (0.3%)
AV block	1 (0.1%)
Bradycardia	1 (0.1%)
Sinoatrial block	1 (0.1%)
Platelet, bleeding and clotting disorders	
Total	4 (0.3%)
Haematoma	1 (0.1%)
Haemorrhage intracranial	1 (0.1%)
Haemorrhage nos	1 (0.1%)
Haemorrhage rectum	1 (0.1%)
Cardiovascular disorders, general	
Total	2 (0.2%)
Cardiac failure	1 (0.1%)
Circulatory failure	1 (0.1%)
Liver and biliary system disorders	
Total	2 (0.2%)
Hepatic function abnormal	1 (0.1%)
Hepatic neoplasm	1 (0.1%)
Respiratory system disorders	
Total	2 (0.2%)
Cyanosis	1 (0.1%)
Pneumonia	1 (0.1%)

May include blinded and unaudited data

Table (3.4.1) 1 - Number (%) of Patients Experiencing SAEs During the Treatment Period in Ongoing Study 63119 (continued)

WHO Organ Class Adverse Events (WHO Preferred Term)	Fondaparinux sodium or enoxaparin sodium (N = 1147)
Autonomic nervous system disorders	
Total	1 (0.1%)
Syncope	1 (0.1%)
Body as a whole - general disorders	
Total	1 (0.1%)
Condition aggravated	1 (0.1%)
Gastro-intestinal system disorders	
Total	1 (0.1%)
Rectal carcinoma	1 (0.1%)
Metabolic and nutritional disorders	
Total	1 (0.1%)
Hyponatraemia	1 (0.1%)
Red blood cell disorders	
Total	1 (0.1%)
Anaemia normocytic	1 (0.1%)
Resistance mechanism disorders	
Total	1 (0.1%)
Sepsis	1 (0.1%)
Vascular (extracardiac) disorders	
Total	1 0.1%)
Cerebrovascular disorder	1 (0.1%)

May include blinded and unaudited data

Sponsor's tables in NDA safety update report pp. 14-15 submitted on 8/31/2001.

—Treatment (EFC2441)

The number (%) of patients experiencing serious adverse events during the treatment period is summarized in the sponsor's Table below. Among the 1746 patients included before the safety update cut-off date, 68 (3.9%) reported SAEs during the treatment period.

Reviewer's comments: The most frequent reported SAEs were platelet, bleeding and clotting disorders (1.8%). Of these, there were 26 serious bleeding events including one case of cerebral hemorrhage and one case of retroperitoneal hemorrhage.

Table (3.4.1) 2 - Number of Patients Experiencing SAEs During the Treatment Period in Ongoing Study EFC2441

WHO Organ Class Adverse Events (WHO Preferred Term)	Fondaparinux sodium or enoxaparin sodium Double blind (N = 1746)
Any event	68 (3.9%)
Platelet, bleeding and clotting disorders	
Total	31 (1.8%)
Haematoma	7 (0.4%)
Haematuria	5 (0.3%)
Haemorrhage nos	5 (0.3%)
GI haemorrhage	4 (0.2%)
Bleeding time increased	1 (0.1%)
Cerebral haemorrhage	1 (0.1%)
Epistaxis	1 (0.1%)
Haemorrhage retroperitoneal	1 (0.1%)
Melaena	1 (0.1%)
Prothrombin decreased	1 (0.1%)
Thrombosis	1 (0.1%)
Thrombosis arterial leg	1 (0.1%)
Thrombosis venous arm	1 (0.1%)
Vaginal haemorrhage	1 (0.1%)
Neoplasm	
Total	6 (0.3%)
Neoplasm nos	3 (0.2%)
Neoplasm malignant	2 (0.1%)
Hepatic neoplasm	1 (0.1%)
Central and peripheral nervous system disorders	
Total	4 (0.2%)
Stupor	2 (0.1%)
Coma	1 (0.1%)
Convulsions	1 (0.1%)
Headache	1 (0.1%)
Hypertension intracranial	1 (0.1%)
Metabolic and nutritional disorders	
Total	4 (0.2%)
Diabetes mellitus	2 (0.1%)
Gout	1 (0.1%)
Hyperglycaemia	1 (0.1%)
Body as a whole - general disorders	
Total	3 (0.2%)
Condition aggravated	1 (0.1%)
Fever	1 (0.1%)
Pain	1 (0.1%)
Gastro-intestinal system disorders	
Total	3 (0.2%)
Intestinal obstruction	2 (0.1%)
Duodenal ulcer haemorrhagic	1 (0.1%)

May include blinded and unaudited data

Table (3.4.1) 2 - Number of Patients Experiencing SAEs During the Treatment Period in Ongoing Study EFC2441 (continued)

WHO Organ Class Adverse Events (WHO Preferred Term)	Fondaparinux sodium or enoxaparin sodium Double blind (N = 1746)
Respiratory system disorders	
Total	3 (0.2%)
Pneumonia	2 (0.1%)
Respiratory insufficiency	1 (0.1%)
Upper respiratory tract infection	1 (0.1%)
Cardiovascular disorders, general	
Total	2 (0.1%)
Cardiac failure	1 (0.1%)
Not coded	1 (0.1%)
Heart rate and rhythm disorders	
Total	2 (0.1%)
Cardiac arrest	1 (0.1%)
Tachycardia supraventricular	1 (0.1%)
Musculo-skeletal system disorders	
Total	2 (0.1%)
Arthrosis	2 (0.1%)
Resistance mechanism disorders	
Total	2 (0.1%)
Infection	1 (0.1%)
Otitis media	1 (0.1%)
Secondary terms	
Total	2 (0.1%)
Inflicted injury	1 (0.1%)
Post-operative wound infection	1 (0.1%)
Urinary system disorders	
Total	2 (0.1%)
Bladder carcinoma	1 (0.1%)
Cystitis	1 (0.1%)
Application site disorders	
Total	1 (0.1%)
Cellulitis	1 (0.1%)
Collagen disorders	
Total	1 (0.1%)
LE syndrome	1 (0.1%)
Liver and biliary system disorders	
Total	1 (0.1%)
Cholelithiasis	1 (0.1%)
Myo-, endo-, pericardial and valve disorders	
Total	1 (0.1%)
Angina pectoris	1 (0.1%)
Red blood cell disorders	
Total	1 (0.1%)
Anaemia	1 (0.1%)

May include blinded and unaudited data

Table (3.4.1) 2 - Number of Patients Experiencing SAEs During the Treatment Period in Ongoing Study EFC2441 (continued)

WHO Organ Class Adverse Events (WHO Preferred Term)	Fondaparinux sodium or enoxaparin sodium Double blind (N = 1746)
Reproductive disorders, female	
Total	1 (0.1%)
Endometrial neoplasm malignant	1 (0.1%)
Skin and appendages disorders	
Total	1 (0.1%)
Rash	1 (0.1%)
Vascular (extracardiac) disorders	
Total	1 (0.1%)
Cerebrovascular disorder	1 (0.1%)

May include blinded and unaudited data

Sponsor's tables in NDA safety update report pp. 16-18 submitted on 8/31/2001.

— Treatment (63123)

The number (%) of patients experiencing serious adverse events during the treatment period is summarized in the sponsor's Table below. Among the 1197 patients included before the safety update cut-off date, 70 (5.8%) reported SAEs during the treatment period.

Reviewer's comments: Most frequent SAEs class was platelet, bleeding and clotting disorders (1.9%), followed by respiratory system disorders (0.8%) and cardiovascular disorders (0.6%). There were 18 serious bleeding events including one case of cerebral hemorrhage. One patient reported Torsade Des Pointes in this trial. The case report form of this patient has been reviewed by Dr. Farrell (Safety update review, dated July 13, 2001). This case was unblinded and the patient received Arixtra 7.5 mg SC once daily for 6 days. This patient had a past medical history of ischemic heart disease with a recent graft infection after bypass surgery, hypertension, diabetes, and asthma. No conclusive evidence was identified for a causative relationship between the Torsade Des Pointes and Arixtra treatment by Dr. Farrell. Continued adverse event surveillance was recommended.

Table (3.4.1) 3 - Number (%) of Patients Experiencing SAEs During the Treatment Period (plus extension of 9 days) in Ongoing Study 63123

WHO Organ Class Adverse Events (WHO Preferred Term)	Fondaparinux sodium or unfractionated heparin (N = 1197)
Any event	70 (5.8%)
Platelet, bleeding and clotting disorders	
Total	23 (1.9%)
Haemorrhage nos	5 (0.4%)
Embolism pulmonary[1]	4 (0.3%)
Haematoma	4 (0.3%)
GI haemorrhage	3 (0.3%)
Haematuria	2 (0.2%)
Melaena	2 (0.2%)
Cerebral haemorrhage	1 (0.1%)
Haemarthrosis	1 (0.1%)

Study is open label, but all AE data reported as blind to minimize bias
[1] Pulmonary embolism is a component of study primary efficacy endpoint

Table (3.4.1) 3 - Number (%) of Patients Experiencing SAEs During the Treatment Period (plus extension of 9 days) in Ongoing Study 63123 (continued)

WHO Organ Class Adverse Events (WHO Preferred Term)	Fondaparinux sodium or unfractionated heparin (N = 1197)
Platelet, bleeding and clotting disorders, continued	
Thrombocytopenia	1 (0.1%)
Thrombophlebitis	1 (0.1%)
Thrombosis	1 (0.1%)
Vaginal haemorrhage	1 (0.1%)
Respiratory system disorder	
Total	10 (0.8%)
Dyspnoea	4 (0.3%)
Pleural effusion	2 (0.2%)
Pneumonia	2 (0.2%)
Bronchitis	1 (0.1%)
Respiratory insufficiency	1 (0.1%)
Cardiovascular disorders, genera	
Total	7 (0.6%)
Cardiac failure	3 (0.3%)
Aneurysm	1 (0.1%)
Circulatory failure	1 (0.1%)
Hypertension	1 (0.1%)
Hypotension	1 (0.1%)
Body as a whole - general disorders	
Total	5 (0.4%)
Death	2 (0.2%)
Chest pain	1 (0.1%)
Oedema	1 (0.1%)
Purulent discharge	1 (0.1%)
Central and peripheral nervous system disorders	
Total	5 (0.4%)
Confusion	3 (0.3%)
Brain stem disorder	1 (0.1%)
Convulsions	1 (0.1%)
Monoplegia	1 (0.1%)
Gastro-intestinal system disorders	
Total	5 (0.4%)
Intestinal obstruction	2 (0.2%)
Abdominal pain	1 (0.1%)
Gastric ulcer	1 (0.1%)
Pancreas neoplasm malignant	1 (0.1%)
Red blood cell disorders	
Total	5 (0.4%)
Anaemia	5 (0.4%)

Study is open label, but all AE data reported as blind to minimize bias

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Table (3.4.1) 3 - Number (%) of Patients Experiencing SAEs During the Treatment Period (plus extension of 9 days) in Ongoing Study 63123 (continued)

WHO Organ Class Adverse Events (WHO Preferred Term)	Fondaparinux sodium or unfractionated heparin (N = 1197)
Myo-, endo-, pericardial and valve disorders	
Total	4 (0.3%)
Myocardial infarction	3 (0.3%)
Cardiomyopathy	1 (0.1%)
Resistance mechanism disorders	
Total	3 (0.3%)
Infection	2 (0.2%)
Sepsis	1 (0.1%)
Application site disorders	
Total	2 (0.2%)
Cellulitis	2 (0.2%)
Heart rate and rhythm disorders	
Total	2 (0.2%)
Tachycardia supraventricular	1 (0.1%)
Tachycardia ventricular	1 (0.1%)
Torsade de pointes[2]	1 (0.1%)
Liver and biliary system disorders	
Total	2 (0.2%)
Cholecystitis	1 (0.1%)
Hepatic cirrhosis	1 (0.1%)
Metabolic and nutritional disorders	
Total	2 (0.2%)
Hypercalcaemia	1 (0.1%)
Hypokalaemia	1 (0.1%)
Neoplasm	
Total	2 (0.2%)
Adenocarcinoma nos	1 (0.1%)
Neoplasm nos	1 (0.1%)
Secondary terms	
Total	2 (0.2%)
Joint dislocation	1 (0.1%)
Metastases nos	1 (0.1%)
Urinary system disorders	
Total	2 (0.2%)
Renal carcinoma	1 (0.1%)
Urinary tract infection	1 (0.1%)
Vascular (exuracardiac) disorders	
Total	2 (0.2%)
Cerebrovascular disorder	1 (0.1%)
Pulmonary infarction	1 (0.1%)

Study is open label, but all AE data reported as blind to minimize bias

[2] This case of Torsades de Pointes was included in the 120-Day Safety Update. Additional details on this case were submitted to NDA 21-345, 03 July 2001, Amendment No. 008.

Table (3.4.1) 3 - Number (%) of Patients Experiencing SAEs During the Treatment Period (plus extension of 9 days) in Ongoing Study 63123 (continued)

WHO Organ Class Adverse Events (WHO Preferred Term)	Fondaparinux sodium or unfractionated heparin (N = 1197)
Psychiatric disorders	
Total	1 (0.1%)
Aggressive reaction	1 (0.1%)
Reproductive disorders, female	
Total	1 (0.1%)
Ovarian carcinoma	1 (0.1%)

Study is open label, but all AE data reported as blind to minimize bias

Sponsor's table in NDA safety update report pp. 19-21 submitted on 8/31/2001.

The number (%) of patients experiencing serious adverse events during the study period is summarized in the Table below. Among the 10 patients included before the safety update cut-off date, 2 reported SAEs (cerebrovascular disorder and hemorrhage in operation site) during the treatment period.

Table (3.4.1) 4 - Number of Patients Experiencing SAEs During the Period 1 in Ongoing Study

WHO Organ Class Adverse Events (WHO Preferred Term)	(N = 10)
Any event	2 (20%)
Vascular (extracardiac) disorders	
Total	1 (10%)
Cerebrovacsular disorders	1 (10%)
Platelet, bleeding and clotting disorders	
Total	1 (10%)
Haemorrhage of operative wound	1 (10%)

May include blinded and unaudited data

Sponsor's table in NDA safety update report pp. 21 submitted on 8/31/2001.

Discontinuations Due to Adverse Events

(63119)

The number (%) of patients who permanently discontinued study drug is summarized in Table below. Among the 1147 patients included before the safety update cut-off date, 24 (2.1%) permanently discontinued due to an adverse event.

Reviewer's comments: The most frequent adverse events leading to discontinuation were myo-, endo-, pericardial and valve disorders (1.0%), followed by bleeding events (0.6%).

Table (3.5.1) 1 - Number (%) of Patients Who Permanently Discontinued Study Drug Due to an AE in Ongoing Study 63119

WHO Organ Class Adverse Events (WHO Preferred Term)	Fondaparinux sodium or enoxaparin sodium (N = 1147)
Any event	24 (2.1%)
Myo-, endo-, pericardial and valve disorders	
Total	12 (1.0%)
Myocardial infarction	11 (1.0%)
Pericarditis	1 (0.1%)
Platelet, bleeding and clotting disorders	
Total	7 (0.6%)
Haemorrhage nos	3 (0.3%)
Haematoma	1 (0.1%)
Haematuria	1 (0.1%)
Haemorrhage rectum	1 (0.1%)
Oral haemorrhage	1 (0.1%)
Cardiovascular disorders, general	
Total	1 (0.1%)
Circulatory failure	1 (0.1%)
Heart rate and rhythm disorders	
Total	1 (0.1%)
Fibrillation atrial	1 (0.1%)
Liver and biliary system disorders	
Total	1 (0.1%)
Hepatic function abnormal	1 (0.1%)

May include blinded and unaudited data

Table (3.5.1) 1 - Number (%) of Patients Who Permanently Discontinued Study Drug Due to an AE in Ongoing Study 63119 (continued)

WHO Organ Class Adverse Events (WHO Preferred Term)	Fondaparinux sodium or enoxaparin sodium (N = 1147)
Red blood cell disorders	
Total	1 (0.1%)
Anaemia	1 (0.1%)
Respiratory system disorders	
Total	1 (0.1%)
Dyspnoea	1 (0.1%)
Urinary system disorders	
Total	1 (0.1%)
Renal failure acute	1 (0.1%)

May include blinded and unaudited data

Sponsor's table in NDA safety update report pp. 22-23 submitted on 8/31/2001.

— Treatment (EFC2441)

The number (%) of patients who permanently discontinued study drug is summarized in the sponsor's Table below. Among the 1746 patients included before the safety update cut-off date, 20 (1.1%) permanently discontinued due to an adverse event.

Reviewer's comments: The majority of withdrawals were due to platelet, bleeding and clotting disorders (19 patients, 0.9%) and most of them were bleeding events (14 events).

Table (3.5.1) 2 - Number (%) of Patients Who Permanently Discontinued Study Drug Due to an Adverse Event in Ongoing Study EFC2441

WHO Organ Class Adverse Events (WHO Preferred Term)	Fondaparinux sodium or enoxaparin sodium Double blind (N = 1746)
Any event	20 (1.1%)
Platelet, bleeding and clotting disorders	
Total	16 (0.9%)
GI haemorrhage	4 (0.2%)
Haematoma	4 (0.2%)
Haematuria	3 (0.2%)
Bleeding time increased	1 (0.1%)
Cerebral haemorrhage	1 (0.1%)
Haemorrhage retroperitoneal	1 (0.1%)
Melaena	1 (0.1%)
Thrombosis arterial leg	1 (0.1%)

May include blinded and unblinded data

Table (3.5.1) 2 - Number (%) of Patients Who Permanently Discontinued Study Drug Due to an Adverse Event in Ongoing Study EFC2441 (continued)

WHO Organ Class Adverse Events (WHO Preferred Term)	Fondaparinux sodium or enoxaparin sodium Double blind (N = 1746)
Cardiovascular disorders, general	
Total	1 (0.1%)
Cardiac failure	1 (0.1%)
Central and peripheral nervous system disorders	
Total	1 (0.1%)
Coma	1 (0.1%)
Hypertension intracranial	1 (0.1%)
Gastro-intestinal system disorders	
Total	1 (0.1%)
duodenal ulcer haemorrhagic	1 (0.1%)
Reproductive disorders, female	
Total	1 (0.1%)
Endometrial neoplasm malignant	1 (0.1%)
Respiratory system disorders	
Total	1 (0.1%)
Dyspnoea	1 (0.1%)
Pneumonia	1 (0.1%)
Secondary terms	
Total	1 (0.1%)
Post-operative wound infection	1 (0.1%)
Skin and appendages disorders	
Total	1 (0.1%)
Rash	1 (0.1%)
Urinary system disorders	
Total	1 (0.1%)
Bladder carcinoma	1 (0.1%)
Vascular (extracardiac) disorders	
Total	1 (0.1%)
Atherosclerosis	1 (0.1%)

May include blinded and unadjusted data

Sponsor's table in NDA safety update report pp. 23-24 submitted on 8/31/2001.

Treatment (63123)

The number (%) of patients who permanently discontinued study drug is summarized in the sponsor's Table below. Among the 1197 patients included before the safety update cut-off date, 27 (2.3%) permanently discontinued due to an adverse event.

Reviewer's comments: The majority of withdrawals were due to platelet, bleeding and clotting disorders (13 patients, 1.1%) and most of them were bleeding events (10 events).

Table (3.5.1) 3 - Number (%) of Patients Who Permanently Discontinued Study Drug Due to an AE in Ongoing Study 63123

WHO Organ Class Adverse Events (WHO Preferred Term)	Fondaparinux sodium or unfractionated heparin (N = 1197)
Any event	27 (2.3%)
Platelet, bleeding and clotting disorders	
Total	13 (1.1%)
Haemorrhage nos	4 (0.3%)
Embolism pulmonary	3 (0.3%)
Cerebral haemorrhage	1 (0.1%)
Coagulation disorder	1 (0.1%)
GI haemorrhage	1 (0.1%)
Haematuria	1 (0.1%)
Haemoptysis	1 (0.1%)
Melaena	1 (0.1%)
Thrombocytopenia	1 (0.1%)
Vaginal haemorrhage	1 (0.1%)
Cardiovascular disorders, general	
Total	3 (0.3%)
Aneurysm	1 (0.1%)
Cardiac failure	1 (0.1%)
Circulatory failure	1 (0.1%)
Red blood cell disorders	
Total	3 (0.3%)
Anaemia	3 (0.3%)
Body as a whole - general disorders	
Total	2 (0.2%)
Death	1 (0.1%)
Oedema	1 (0.1%)
Gastro-intestinal system disorders	
Total	2 (0.2%)
Gastric ulcer	1 (0.1%)
Tooth ache	1 (0.1%)

Study is open label, but all AE data reported as blind to minimize bias

Table (3.5.1) 3 - Number (%) of Patients Who Permanently Discontinued Study Drug Due to an AE in Ongoing Study 63123 (continued)

WHO Organ Class Adverse Events (WHO Preferred Term)	Fondaparinux sodium or unfractionated heparin (N = 1197)
Liver and biliary system disorders	
Total	2 (0.2%)
Cholecystitis	1 (0.1%)
Hepatic cirrhosis	1 (0.1%)
Respiratory system disorders	
Total	2 (0.2%)
Dyspnoea	1 (0.1%)
Pneumonia	1 (0.1%)
Central and peripheral nervous system disorders	
Total	1 (0.1%)
Convulsions	1 (0.1%)
Heart rate and rhythm disorders	
Total	1 (0.1%)
Fibrillation atrial	1 (0.1%)
Musculo-skeletal system disorders	
Total	1 (0.1%)
Skeletal pain	1 (0.1%)
Myo-, endo-, pericardial and valve disorders	
Total	1 (0.1%)
Myocardial infarction	1 (0.1%)
Neoplasm	
Total	1 (0.1%)
Neoplasm nos	1 (0.1%)
Vascular (extracardiac) disorders	
Total	1 (0.1%)
Cerebrovascular disorder	1 (0.1%)

Study is open label, but all AE data reported as blind to minimize bias

Sponsor's table in NDA safety update report pp. 25-26 submitted on 8/31/2001.

Summary of Safety Update

This safety update provides cumulative data up to 15 August 2001 for studies that were ongoing on, or begun since 01 March 2001.

The results from this safety update are consistent with results in safety database in the original NDA submission and previous 120-day safety update. Bleeding complications are the most frequent serious adverse events in ongoing clinical trials and also the main reasons for treatment discontinuation. Cases of cerebral hemorrhage, intracranial hemorrhage and retroperitoneal hemorrhage have been reported in ongoing clinical trials.

Similar to results shown in the original NDA safety database, major bleeding rate increased with decreasing creatinine clearance and body weight, and with increasing in age in ongoing studies.

Major bleeding was much higher in patients with severe renal impairment [5.7% in EFC2441 [redacted] treatment) trial], moderate renal impairment [2.5% in EFC2441 and 3.4% in 63119 [redacted] trial] as compared to those with mild renal impairment (1.2%

in EFC2441 and 0.4% in 63119) and normal renal function (0.1% in EFC2441 and 0.2% in 63119).

In EFC2441 (— treatment) trial, major bleeding rate was also higher in patients with body weight <50 kg (2.5%) as compared to those with body weight ≥50 kg (1% in 50-100 kg and 0% in ≥100 kg groups, in spite of dose adjustment treatment schedule was used in the study (Arixtra was given 5 mg for patients <50 kg, 7.5 mg for patients between 50 and 100 kg, and 10 mg for patients ≥100 kg).

Only few patients with severe renal impairment or low body weight were included in 63119 trial.

Major bleeding rate was higher in patients ≥75 years as compared to younger patients (2.4% in ≥75 years, 0.9% in 65-74 years, and 0.2% in <65 years) in EFC2441 trial.

One case of Torsade Des Points was reported in Study 63123 — treatment) ongoing study. This case has been reviewed in previous 120-day Safety Update Review (Dr. Farrell, 7/20/2001 final signoff). No conclusive evidence was identified for the association between Arixtra treatment and the event. Continued adverse event surveillance was recommended.

Evaluation of the data in this safety update report was limited by blinded data presented by the sponsor in ongoing studies. However, as seen in original NDA safety database, bleeding complications are the most frequently reported adverse events in ongoing trials. Two cases of cerebral hemorrhages have been reported in patients received Arixtra in ongoing studies in IND safety reports based on unblinded data (one in IND —— N-163, N-164, 120-day safety update review, dated 7/13/2001; one in IND —— N-149, SAE#3525 submitted on 10/15/2001). Therefore, the serious adverse events reported in ongoing studies, such as cerebral hemorrhage, intracranial hemorrhage, and retroperitoneal hemorrhage should be included in the labeling.

Post-marketing (Phase IV) Commitments

In the Approvable Letter issued on August 15, 2001, the Agency requested the sponsor to commit to conduct the following postmarketing (Phase IV) studies:

[
]

[

]

2. **A safety evaluation of ARIXTRA in patients with varying degrees of impaired hemostasis secondary to hepatic insufficiency. Provide pharmacokinetic and pharmacodynamic data of ARIXTRA on a subset of these patients.**

The Sponsor agrees to conduct the above study. The sponsor plans to develop a study protocol over one year from the time of NDA approval and will complete the study approximately 4 years after approval of NDA 21-345.

[

]

[redacted]

Conclusions and Recommendations

From a clinical perspective, ARIXTRA should be approved for the indication of prophylaxis of deep vein thrombosis following hip fracture, hip replacement and knee replacement surgeries with the following labeling recommendations (See also Appendix 1).

1. [redacted] severe renal impairment, low body weight (<50 kg) should be added in Contraindications section.
2. "Fondaparinux sodium" should be added in Black Box Warning on Spinal/Epidural Hematomas section.
3. [redacted] should be deleted in Clinical Studies section.
4. Knee replacement surgery instead of [redacted] should be used in Indication and Usage section and in the entire labeling.
5. Results on Symptomatic PE should be included in Tables in Clinical Studies section.
6. Figure on [redacted] should be deleted in Clinical Studies section.
7. The paragraph stating that [redacted]
8. Monitoring serum creatinine level and platelet count should be included in the Laboratory Test subsection under Precautions section.
9. Major bleeding rate by indication should be presented in Adverse Reactions section.
10. Adverse events with occurrence ≥2% during the treatment should be included in adverse event table in Adverse Reactions section.
11. Serious adverse events reported in ongoing studies (i.e., cerebral hemorrhage, intracranial hemorrhage, and retroperitoneal hemorrhage) should be included in the Adverse Reactions section.
12. The time of first dose administration should be limited to 6 hours in Dosage and Administration section.

For Post-marketing (Phase IV) Commitments, the sponsor agrees to conduct the study to evaluate the safety of ARIXTRA in patients with varying degrees of impaired hemostasis secondary to hepatic insufficiency. The sponsor will provide pharmacokinetic and pharmacodynamic data of ARIXTRA on a subset of these patients. The sponsor plans to

develop a study protocol over one year from the time of NDA approval and will complete the study approximately 4 years after approval of NDA 21-345.

Appendix 1: Labeling Comments

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Draft

Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Min Lu
11/16/01 04:33:07 PM
MEDICAL OFFICER

Kathy Robie-Suh
11/16/01 04:39:37 PM
MEDICAL OFFICER
Concur.

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: July 19, 2001

From: Kathy M. Robie-Suh, M.D., Ph.D.
Medical Team Leader, HFD-180

Subject: NDA 21-345 (submitted 2/15/01)
Arixtra (fondaparinux sodium, Org31540/SR90107A)

To: Director, Division of Gastrointestinal and Coagulation Drug Products
(HFD-180)

Fondaparinux sodium is the sodium salt of a synthetically produced sulfated pentasaccharide. It is a potent anticoagulant. Except for the methoxygroup at its non-reducing end, it is analogous to the pentasaccharide sequence in heparin which is responsible for heparin binding to Antithrombin III (AT-III). Fondaparinux selectively inhibits activated factor X (Factor Xa). It acts by binding to AT-III thereby potentiating the physiological neutralization of Factor Xa and inhibiting thrombin formation and clot extension and formation of new clots. Potential advantages of fondaparinux over heparins include: more selective anti-Xa activity versus binding to platelet factor 4 (PF4) and likely less bleeding, less antigenicity and less likelihood of heparin-induced thrombocytopenia, more predictable pharmacokinetics, and greater subcutaneous bioavailability,

This application seeks approval of fondaparinux (Org31540/SR90107A) for "the prevention of venous thromboembolic events in patients undergoing major orthopedic surgery of the lower limbs such as hip fracture, major knee or hip replacement surgeries." To support this use the sponsor has submitted four pivotal studies as follows:

- Study EFC2698 [redacted] (hip fracture surgery; non-U.S.A.)
- Study 63118 (EPHESUS)(hip replacement surgery; Europe)
- Study EFC2442 [redacted])(hip replacement surgery; U.S.A., Canada, Australia)
- Study 095-002 (knee replacement surgery; U.S.A., Canada)

Each of the studies was multicenter, randomized, double-blind, double-dummy, used enoxaparin (a low molecular weight heparin) as active control and was designed to demonstrate superiority of Org31540/SR90107A over the comparator. These studies were conducted from November 1998 through January 2000.

The four pivotal studies are supplemented by data from a pilot, dose-ranging study of Org31540/SR90107A in total hip replacement (Study DRI2643) and a dose-ranging study of Org31540/SR90107A in total knee replacement (Study 095001 ———

Chemistry Issues:
Fondaparinux is a white powder produced completely by chemical synthesis from non-animal sources. Two companies (Organon and Sanofi-Synthelabo) have been involved in the drug development. The final drug product is an injectable dosage form (2.5mg/0.5mL) formulated with water and sodium chloride which is then sterilized. The drug product is packaged in a pre-filled syringe.

FDA Chemistry, Manufacturing and Controls (CMC) Review (A.Al-Hakim, 6/22/01) found the application approvable from a CMC perspective but identified a number of deficiencies that need to be addressed. An information request letter with these deficiencies has been sent (6/26/01) mainly requesting additional information on stability, methods for identifying impurities, and drug product specifications.

Microbiology: Microbiology review (S.E. Langille, 7/12/01) found the application approvable pending submission of information regarding holding times between ——— and ——— sterilization and results for ——— sterilization ——— Response from the sponsor to an information request letter (7/16/01) is pending at the time of this review.

Center for Devices and Radiological Health (CDRH): FDA CDRH review of the pre-filled syringe is pending at the time of this review.

Non-Clinical Pharmacology and Toxicology Issues:
The application has been reviewed by FDA Pharmacology/Toxicology (See FDA Pharmacology/Toxicology Review, T.K. Chakraborti, 7/10/01). Findings of that review include the following:

In vitro studies demonstrated high affinity binding of Org31540/SR90107A to antithrombin III of various species and enhances inactivation of Factor Xa with only weak effects on other coagulation factors. It did not potentiate ADP or collagen-induced platelet aggregation.

It is fully bioavailable after subcutaneous administration (T_{max}, 1-2 hrs). Terminal elimination half-life varies across species from about 1-2 hrs in rats and rabbits to 5-6 hrs in macaques to 15-20 hrs in humans. It is 92-93% bound to plasma proteins. It distributes rapidly and widely among tissues and a small amount appears in breast milk and crosses the placenta. Excretion is almost totally via the kidney and does not appear to undergo metabolism.

In single-dose studies Org31540/SR90107A was lethal to animals at doses 65-260 times the proposed theraputic dose. In 2- and 13-week intravenous toxicity studies and a 4-week subcutaneous toxicity study the no-observed-effect-level (NOEL) was 2 mg/kg/day.

No target organ of toxicity was identified in these studies. In a 13-week intravenous toxicity study in monkeys target organs of toxicity appeared to be spleen (reactive extramedullary hematopoiesis), bone marrow (increased erythropoiesis), and mesenteric lymph node (macrophage infiltration).

Fertility, early embryonic development and teratogenicity studies of Org31540/SR90107A did not reveal any adverse effects. In vitro mutagenicity and clastogenicity tests did not reveal any mutagenic or clastogenic effects.

Antigenicity of Org31540/SR90107A was tested in using active systemic anaphylaxis and passive cutaneous anaphylaxis assays in guinea pigs and rats. No evidence for anaphylactic was seen suggesting that Org31540/SR90107A is not antigenic.

Clinical Pharmacology and Biopharmaceutics Issues:
Biopharmaceutics review is pending at time of this review. However, the clinical data suggest that there may be need for some ——— in patients with significant renal impairment. The sponsor should address this issue ———

Clinical Studies: Efficacy:
Hip fracture surgery:
Study EFC2698 ——— Study EFC2698 was conducted in 99 centers in Europe, Australia, South Africa and Argentina. Patients were consenting adults undergoing standard surgery within 48 hours after admission for fracture of the upper third of the femur, including femoral head and neck. Important exclusion criteria were active bleeding or bleeding risk, concurrent use of medications that might affect coagulation, significant renal impairment (serum creatinine >2.0), multiple trauma affecting more than 1 organ system and more than 24 hours elapsing between event causing hip fracture and hospital admission. The protocol provided for eligible patients to be randomized within 24 hours of admission and prior to surgery to one of two treatments: (1) Org31540/SR90107A 2.5 mg subcutaneously once daily or (2) enoxaparin 40 mg subcutaneously once daily. Enoxaparin dosing was always to begin 12 hours before surgery and continued daily thereafter. For Org31540/SR90107A, when surgery took place within 24 hours of admission, dosing was to start 6 hours postoperatively and be continued daily thereafter. When surgery took place 24 to 48 hours after admission, Org31540/SR90107A dosing was to start 12 hours preoperatively and to be given 6 hours postoperatively, then daily thereafter. Dosing of both treatments was to continue for 7±2 days (from day of surgery). The primary efficacy endpoint was a composite of venous thromboembolic events (VTE) up to Day 11 consisting of deep vein thrombosis (DVT) and fatal or non-fatal pulmonary embolus (PE). Evaluation for thromboembolic events could occur for cause (symptoms) at any time during the study. For all asymptomatic patients the study protocol called for mandatory bilateral venography to look for DVT not more than 2 days after the last treatment dose. All VTE assessments were adjudicated blindly by a central board. The main safety endpoint was major bleeding (fatal bleeding; clinically overt bleeding including retroperitoneal bleeding, intracranial bleeding or bleeding into a critical organ; reoperation due to

bleeding; clinically overt bleeding with hematocrit drop of ≥2g/dL and/or transfusion of ≥2 units of packed red blood cells or whole blood and for which the combined calculated index was ≥2).

A total of 1711 patients were randomized (849 Org31540/SR90107A; 862 enoxaparin) and 1673 were treated. Of these all except 2 enoxaparin patients underwent the appropriate surgery. Seventy-three percent of randomized patients (626 Org31540/SR90107A and 624 enoxaparin) had efficacy data available for primary efficacy evaluation. Proportions of patients not treated and missing efficacy data were similar in the two treatment groups. Patients ranged in age from 17-101 years (median, 79 yrs; mean, 77 yrs) and 75% of patients were female. Almost all patients (99.2%) were Caucasian. Nine percent of patients had history of cancer, 7.5% history of stroke, 5.8% history of myocardial infarction, and 3.6% history of VTE. Demographic and medical history characteristics were comparable in the two treatment groups. Characteristics of type of fracture, type of surgery and features of surgery were comparable in the two treatment groups. Most surgeries were cervical only (47%) or trochanteric (44%). About 66% of patients underwent surgery using regional anesthesia. Demographics, medical history and surgical characteristics of the population with efficacy data available (sponsor's primary efficacy population) were similar to those of the all treated population. Proportions of patients discontinuing treatment prematurely and reasons for discontinuation were similar in the two treatment groups.

Dosing of the study drug differed somewhat from that prescribed in the protocol. Most patients in both treatment groups started treatment post-operatively. In both treatment groups about one-third of patients underwent surgery <12 hours after admission, one-third underwent surgery 12-24 hours after admission and one-third underwent surgery ≥24 hours after admission. However, only 26% of patients in the enoxaparin group and 12% of patients in the Org31540/SR90107A group received active treatment pre-operatively. Among patients undergoing surgery ≥24 hours after admission 33% in the Org31540/SR90107A group and 46% in the enoxaparin group received active drug pre-operatively. Among patients undergoing surgery ≥24 hours after admission and having general anesthesia only (i.e., no regional anesthesia) 45% in the Org31540/SR90107A group and 58% in the enoxaparin group received active drug pre-operatively. Among the one-third of patients who underwent surgery <12 hours after admission, few had active pre-operative injections (10 patients in enoxaparin group; 2 patients in Org31540/SR90107A group). It appears that generally investigators were inclined to begin dosing post-operatively, regardless of protocol directions. Overall, mean time between the last active pre-operative injection and start of surgery was similar for both treatment groups (16-17 hours). However, mean time between the end of surgery and the first active post-operative injection was 6 hours in the Org31540/SR90107A group and 18 hours in the enoxaparin group. Mean duration of treatment was 7 days in both treatment groups.

Efficacy results for this study are shown in the table below:

Study EFC2698 [redacted] : Efficacy Results – Patients Having Qualifying Examination up to Day 11

Endpoint	Number of Patients with Events (%)		
	Org31540/SR90107A	Enoxaparin	p-value
Total VTE	52/626 (8.3%)	119/624 (19.1%)	2.6×10^{-8}
Total DVT	49/626 (7.8%)	117/624 (18.8%)	1.0×10^{-8}
Proximal DVT	6/650 (0.9%)	28/646 (4.3%)	0.0001
Distal DVT only	42/627 (6.7%)	94/626 (15.0%)	2×10^{-6}
Total PE	3/626 (0.5%)	3/624 (0.5%)	
Fatal PE	3/626 (0.5%)	2/624 (0.3%)	
Non-fatal PE	0 (0.0%)	1/624 (0.2%)	

Table based on tables in Medical Officer's Review (M. Lu), pp. 59 and 61

Org31540/SR90107A was clearly superior to the comparator for the protocol primary efficacy analysis (VTE) and for all other analyses where there was a sufficient number of events to allow a comparison. The efficacy result reflected almost exclusively effect on DVT. There were too few PE events to allow a meaningful comparison of the treatment groups. There were few deaths in this study. By Day 11 there were 0 deaths in the Org31540/SR90107A group and 2 deaths in the enoxaparin group. By end of followup (up to Day 60) there were 2 deaths (1 fatal PE) in the Org31540/SR90107A group and 5 deaths (no fatal PE) in the enoxaparin group. All PE were symptomatic; but nearly all DVT were asymptomatic. Up to Day 11 only 1 DVT in each treatment group was symptomatic. Patients were followed up to Day 49 for symptomatic VTE and experienced the following additional VTE:

Study EFC2698 [redacted] Additional VTE Occurring from Day 11 – Day 49

	Number of Patients with Events (%)	
	Org31540/SR90107A	Enoxaparin
VTE	13/831 (1.6%)	9/840 (1.1%)
DVT	7/831 (0.8%)	2/840 (0.2%)
Non-fatal PE	3/831 (0.4%)	3/840 (0.4%)
Fatal PE	5/831 (0.6%)	5/840 (0.6%)

Based on table in Medical Officer's Review (M. Lu), p. 64

The treatment effect in favor of Org31540/SR90107A was reasonably consistent across a variety of covariates, including country, center, age, gender, different surgery characteristics, and previous history of VTE. There were too few non-Caucasian patients to evaluate effect of race; however, there is no reason to expect that the result should differ with regard to this demographic parameter.

Hip Replacement Surgery:

Study 63118 (EPHESUS): Study 63118 was conducted in 74 centers in Europe. Patients were consenting adults undergoing elective, primary, total hip replacement (THR) surgery or revision of a THR. Important exclusion criteria were active bleeding or bleeding risk, concurrent use of medications that might affect coagulation, and significant

renal impairment (serum creatinine >2.0). Patients were randomized pre-operatively to one of two treatments: (1) Org31540/SR90107A 2.5 mg subcutaneously once daily beginning 6 hours post-operatively or (2) enoxaparin 40 mg subcutaneously once daily beginning 12 hours pre-operatively. Pre-operative dosing was omitted for patients undergoing surgery using spinal/epidural anesthesia or catheterization according to the precautions in the local enoxaparin label. Dosing of both treatments was to continue for 7±2 days (from day of surgery). The primary efficacy endpoint was a composite of venous thromboembolic events (VTE) up to Day 11 consisting of deep vein thrombosis (DVT) and fatal or non-fatal pulmonary embolus (PE). Evaluation for thromboembolic events could occur for cause (symptoms) at any time during the study. For all asymptomatic patients the study protocol called for mandatory bilateral venography to look for DVT not more than 2 days after the last treatment dose. All VTE assessments were adjudicated blindly by a central board. The main safety endpoint was major bleeding (fatal bleeding; clinically overt bleeding including retroperitoneal bleeding, intracranial bleeding or bleeding into a critical organ; reoperation due to bleeding; clinically overt bleeding with hematocrit drop of ≥2g/dL and/or transfusion of ≥2 units of packed red blood cells or whole blood and for which the combined calculated index was ≥2).

A total of 2324 patients were randomized. Of these, 15 were excluded from all efficacy analyses, 12 due to lost CRFs and limited credibility of the data at one site and 3 because of error in randomization. (None of these 15 patients were reported to have VTE or major bleeding event). Of the remaining 2309 patients (1155 Org31540/SR90107A; 1154 enoxaparin), 2273 received study medication. Twenty-two patients (11 Org31540/SR90107A and 10 enoxaparin) did not undergo scheduled surgery (mainly due to withdrawn informed consent). Seventy-nine percent of all randomized patients (908 Org31540/SR90107A and 919 enoxaparin) had efficacy data available for primary efficacy evaluation. Proportions of patients not treated and missing efficacy data were similar in the two treatment groups. Patients ranged in age from 24-97 years (median, 67 yrs; mean, 65 yrs) and 57.5% of patients were female. Almost all patients (99.2%) were Caucasian. A somewhat greater proportion of patients in the enoxaparin group had history of cancer than in the Org31540/SR90107A group (7.1% versus 4.9%, p=0.025) and numerically more patients in the enoxaparin group had possibly predisposing medical history as summarized below:

Study 63118 (EPHESUS): Specific Medical History – All Treated Patients

Specific Medical or Surgical History	Number of Patients (%)	
	Org31540/SR90107A (N=1140)	Enoxaparin (N=1133)
VTE	45 (3.9%)	56 (4.9%)
Stroke	16 (1.4%)	26 (2.3%)
Myocardial infarction	40 (3.5%)	44 (3.9%)
Cancer	56 (4.9%)	81 (7.1%)

From sponsor's table

The two treatment groups had similar proportion of patients with orthopedic surgery with the previous 12 months (9.9% in the Org31540/SR90107A group, 9.3% in the enoxaparin group). Demographic characteristics, type of surgery and features of surgery were comparable in the two treatment groups.

Demographics, medical history and surgical characteristics of the population with efficacy data available (sponsor's primary efficacy population) were similar to those of the all treated population. Proportions of patients discontinuing treatment prematurely were similar in the two treatment groups (6.1% in the Org31540/SR90107A group; 5.1% in the enoxaparin group). However, the number of patients withdrawn due to serious bleeding adverse events in the Org31540/SR90107A group was double that in the enoxaparin group (7 versus 3); but the number of these events was very small. Most premature withdrawals in both treatment groups were due to withdrawn consent or protocol violations.

Virtually all patients in the Org31540/SR90107A groups (99.2%) started treatment post-operatively as directed in the protocol. In the enoxaparin group though all patients were to receive enoxaparin prior to surgery unless spinal/epidural anesthesia was to be used, 22% of patients had enoxaparin started only after surgery (19% of patients using general anesthesia only; 24% of patients using regional anesthesia only or in combination). Mean doses of active treatment was 7.6 in both treatment groups.

Efficacy results for this study are shown in the table below:

Study 63118 (EPHESUS): Efficacy Results – Patients Having Qualifying Examination up to Day 11

	Number of Patients with Events (%)		
Endpoint	Org31540/SR90107A	Enoxaparin	p-value
Total VTE	37/908 (4.1%)	85/919 (9.2%)	9×10^{-6}
Total DVT	36/908 (4.0%)	83/919 (9.0%)	1.1×10^{-5}
Proximal DVT	6/922 (0.7%)	23/927(2.5%)	0.0021
Distal DVT only	30/909 (3.3%)	67/917 (7.3%)	0.0001
Total PE	2/908 (0.2%)	2/919 (0.2%)	
Fatal PE	0/908 (0.0%)	0/919 (0.0%)	
Non-fatal PE	2/908 (0.2%)	2/919 (0.2%)	

Table based on tables in Medical Officer's Review (M. Lu), pp. 93 and 94

Org31540/SR90107A was clearly superior to the comparator for the protocol primary efficacy analysis (VTE) and for all other analyses where there was a sufficient number of events to allow a comparison. The efficacy result reflected almost exclusively effect on DVT. There were too few PE events to allow a meaningful comparison of the treatment groups. There were few deaths in this study, 1 in the Org31540/SR90107A group and 2 in the enoxaparin group up to 11 days; up to Day 60 there were 2 deaths in the Org31540/SR90107A group and 5 in the enoxparin group. All PE were symptomatic. Up to Day 11 three DVT in the Org31540/SR90107A group and 1 DVT in the enoxaparin group were symptomatic. These symptomatic DVT accounted for 8.3% (3/36) of Org31540/SR90107A DVT and 1.2% (1/83) of enoxaparin DVT, suggesting that the

benefit of Org31540/SR90107A over enoxaparin may not necessarily relate to clinically significant DVT events. Patients were followed up to Day 49 for symptomatic VTE and experienced few additional events and these were similar in the two treatment groups (6 DVT and 2 PE in the Org31540/SR90107A group and 5 DVT and 1 PE in the enoxaparin group).

The treatment effect in favor of Org31540/SR90107A was reasonably consistent across a variety of covariates, including country, center, age, gender, different surgery characteristics, and previous history of VTE. There were too few non-Caucasian patients to evaluate effect of race; however, there is no reason to expect that the result should differ with regard to this demographic parameter.

Study EFC2442 [redacted]: Study EFC2442 was conducted at 139 centers in the U.S., Canada and Australia. The study population was essentially the same as that for Study 63118, except that patients had to have established hemostasis on the calendar day of surgery no later than 8 hours after incision closure to enter the study. Patients were randomized post-operatively to one of two treatments: (1) Org31540/SR90107A 2.5 mg subcutaneously once daily beginning 6 hours after incision closure or (2) enoxaparin 30 mg subcutaneously twice daily beginning on the day after surgery (Day 2) but at least 12 hours after the test drug would have been given (i.e., at least 18 hours after surgery). Dosing was to continue up to Day 7±2. Efficacy endpoints and evaluations of the data were the same as for Study 63118.

A total of 2275 patients were randomized (1138 to Org31540/SR90107A, 1137 to enoxaparin). Of these 2257 (1128 in the Org31540/SR90107A group, 1137 in the enoxaparin group) were treated and all except 3 of these underwent scheduled surgery. About 58% of randomized patients were from the U.S. sites. About 70% of randomized patients had efficacy data available for primary efficacy evaluation. Proportions of patients not treated and missing efficacy data were similar in the two treatment groups. Patients ranged in age from 18-92 years (median, 67 yrs; mean, 65 yrs) and 52.2% of patients were female. About 94% of patients were Caucasian and 4% were Black. The treatment groups had similar proportions of patients with history of possibly predisposing medical history as summarized below. Relative to Study 63118, patients in this study had a higher percentage of patients with history of cancer and possibly of patients with history of myocardial infarction.

Study EFC2442 [redacted] Specific Medical History – All Treated Patients

Specific Medical or Surgical History	Number of Patients (%)	
	Org31540/SR90107A (N=1128)	Enoxaparin (N=1129)
VTE	52 (4.6%)	63 (5.6%)
Stroke	25 (2.2%)	34 (3.0%)
Myocardial infarction	65 (5.8%)	60 (5.3%)
Cancer	151 (13.4%)	145 (12.8%)

From sponsor's table

The two treatment groups had similar proportion of patients with orthopedic surgery with the previous 12 months (11.9% in the Org31540/SR90107A group, 11.0% in the enoxaparin group). Demographic characteristics, type of surgery and features of surgery were comparable in the two treatment groups.

Demographics, medical history and surgical characteristics of the population with efficacy data available (sponsor's primary efficacy population) were similar to those of the all treated population. Proportions of patients discontinuing treatment prematurely were similar in the two treatment groups (5.4% in the Org31540/SR90107A group; 5.8% in the enoxaparin group). Reasons for premature withdrawal were similar in the two treatment groups. The major reason for premature withdrawal was serious adverse events (about 2.6% of patients in the Org31540/SR90107A group and 3.1% of patients in the enoxaparin group); half of these serious events were bleeding events. About 1.6% of patients withdrew consent.
Mean time between the end of surgery and the first active post-operative injection was 7 hours in the Org31540/SR90107A group and 20 hours in the enoxaparin group. Patients in the Org31540/SR90107A group received an average of 7 active doses and patients in the enoxaparin received an average of 11 active doses. Thus, patients in the enoxaparin group received active drug starting later than in the Org31540/SR90107A group and received fewer total daily doses of active drug. This may bias the result in favor of Org31540/SR90107A.

Efficacy results for this study are shown in the table below:

Study EFC2442 [redacted]: Efficacy Results – Patients Having Qualifying Examination up to Day 11

Endpoint	Number of Patients with Events (%)		
	Org31540/SR90107A	Enoxaparin	p-value
Total VTE	48/787 (6.1%)	66/797 (8.3%)	0.099
Total DVT	44/787 (5.6%)	65/797 (8.2%)	0.047
Proximal DVT	14/816 (1.7%)	10/830 (1.2%)	0.42
Distal DVT only	34/796 (4.3%)	54/800 (6.8%)	0.037
Total PE	5/787 (0.6%)	1/797 (0.1%)	0.122
Fatal PE	0/787 (0.0%)	1/797 (0.1%)	
Non-fatal PE	5/787 (0.2%)	0/797 (0.0%)	

Table based on tables in Medical Officer's Review (M. Lu), pp. 123 and 124

In this study enoxaparin appears to have performed a little better and Org31540/SR90107A a little worse than in Study 63118. The net result was no statistically difference between groups for the primary efficacy endpoint (VTE) and a marginally significant result for DVT, due mainly to effect on distal DVT. The incidence of events differed among countries as summarized below. In the U.S.A. and Australia Org31540/SR90107A tended to perform better while in Canada enoxaparin tended to perform better. Generally, results were similar across covariates other than country.

Even after adjustment for treatment-by-country interaction the difference for the primary endpoint was still not statistically significant (p=0.069 [M. Fan, FDA Biometrics].

Study EFC2442 ——— Incidence of VTE by Country

	Number of Patients (%)	
	Org31540/SR90107A	Enoxaparin
U.S.A.	21/422 (5.0%)	35/436 (8.0%)
Canada	21/238 (8.8%)	18/241 (7.5%)
Australia	6/127 (4.7%)	13/120 (10.8%)

From sponsor's table

There were few deaths in this study, 3 in the Org31540/SR90107A group and 1 in the enoxaparin group up to 11 days; up to Day 60 there were 6 deaths (1 due to PE) in the Org31540/SR90107A group and 5 (2 due to PE) in the enoxparin group. All PE were symptomatic. Up to Day 11 five DVT in the Org31540/SR90107A group and 0 DVT in the enoxaparin group were symptomatic. These symptomatic DVT accounted for 11.4% (5/44) of Org31540/SR90107A DVT and 0% (0/65) of enoxaparin DVT, suggesting again that any benefit of Org31540/SR90107A over enoxaparin may not necessarily relate to clinically significant DVT events. Patients were followed up to Day 49 for symptomatic VTE and experienced additional events as summarized in the following table:

Study EFC2442 ——— Additional VTE Occurring from Day 11 – Day 49

	Number of Patients with Events (%)	
	Org31540/SR90107A	Enoxaparin
VTE	19/1126 (1.7%)	12/1128 (1.1%)
DVT	13/1126 (1.2%)	10/1128 (0.9%)
Non-fatal PE	6/1126 (0.5%)	2/1128 (0.2%)
Fatal PE	1/1126 (0.1%)	1/1128 (0.1%)

Based on table in Medical Officer's Review (M. Lu), p. 127

Study DRI2643: Study DRI2643 was a multicenter, randomized, dose ranging study of Org31540/SR90107A (0.75 mg, 1.5 mg, 6.0 mg and 8.0 mg) once daily subcutaneously started post-operatively and enoxaparin 30 mg twice daily started post-operatively in patients undergoing elective total hip replacement. Treatments were given for 5 to 10 days and mandatory bilateral venography was performed at Day 11. The study was blinded with regard to Org31540/SR90107A dose but not to enoxaparin treatment. Primary efficacy endpoint was incidence of DVT and/or symptomatic PE.

A total of 950 patients were randomized and 933 received study drug. The 6.0 mg and 8.0 mg doses were terminated prematurely because of unacceptable rate of major bleeding (>3%). Patients ranged in age from 18 to 92 years (mean, 64.6 yrs; median, 67 years) and 53.6% of patients were males. Sixty-two percent of patients had data available for efficacy evaluation. Mean days of exposure ranged from 6.0 (enoxaparin) to 7.1 days.

Efficacy results for the efficacy evaluable population are summarized in the following table.

Study DRI2643: Efficacy Results – Patients Having Qualifying Examination up to Day 11

Endpoint	Number of Patients (%)					
	Org31540/SR90107A					
	0.75 mg	1.5 mg	3.0 mg	6.0 mg	8.0 mg	Enoxaparin
Total VTE	14/119 (11.8%)	8/120 (6.7%)	2/115 (1.7%)	2/45 (4.4%)	0/23 (0.0%)	16/171 (9.4%)
Total DVT	12/119 (10.1%)	8/120 (6.7%)	2/115 (1.7%)	2/45 (4.4%)	0/23 (0.0%)	16/171 (9.4%)
Proximal DVT	3/119 (2.5%)	6/120 (5.0%)	1/115 (0.9%)	1/45 (2.2%)	0/23 (0.0%)	5/171 (2.9%)
Distal DVT only	9/119 (7.6%)	3/120 (2.5%)	1/115 (0.9%)	1/45 (2.2%)	0/23 (0.0%)	13/171 (7.6%)

Table based on tables in Medical Officer's Review (M. Lu) pp.145 and 146

Additional events occurring outside the protocol specified timeframe included 2 non-fatal PE in the Org31540/SR90107A 0.75 mg group, 3 non-fatal PE in the Org31540/SR90107A 3.0 mg group, 1 non-fatal PE in the Org31540/SR90107A 8.0 mg group and 2 non-fatal and 1 fatal PE in the enoxaparin group.
There was a statistically significant dose-response relationship within the Org31540/SR90107A dose range for the efficacy efficacy evaluable (pITT) and per protocol populations for VTE (all DVT).

Knee Replacement Surgery:
Study 095-002 ——— Study 095-002 was conducted in 64 centers in the U.S.A. and Canada. Patients were consenting adults undergoing elective major knee surgery or major revision. Pastients were required to have established hemostasis on the calendar day of surgery and not later than 8 hours after incision closure. Exclusion criteria were the same as in the hip fracture studies. Patients were randomized post-operatively to either: (1) Org31540/SR90107A 2.5 mg once daily subcutaneously started 6 hours after surgery closure or (2) enoxaparin 30 mg subcutaneously twice daily beginning on morning of the day after surgery (Day 2) but at least 12 hours after the test drug would have been given (i.e., at least 18 hours after surgery). Dosing was to continue up to Day 7±2. Efficacy endpoints and evaluations of the data were the same as for Study 63118.

A total of 1049 patients were randomized (526 to Org31540/SR90107A, 523 to enoxaparin). Of these 1034 (517 in the Org31540/SR90107A group, 517 in the enoxaparin group) were treated and had appropriate surgery. About 82% of randomized patients were from the U.S. sites. Sixty-nine percent of randomized patients had efficacy data available for primary efficacy evaluation. Proportions of patients not treated and missing efficacy data were similar in the two treatment groups. Patients ranged in age from 19-94 years (median, 69 yrs; mean, 67.5 yrs) and 58.7% of patients were female. About 88.4% of patients were Caucasian and 7.8% were Black. The enoxaparin group tended to have more patients with history of VTE, stroke and myocardial infarction.

Proportions of patients with history of possibly predisposing medical history are summarized below.

Study 095-002 [redacted] Specific Medical History – All Treated Patients

Specific Medical or Surgical History	Number of Patients (%)	
	Org31540/SR90107A (N=517)	Enoxaparin (N=517)
VTE	23 (4.4%)	28 (5.4%)
Stroke	11 (2.1%)	18 (3.5%)
Myocardial infarction	38 (7.4%)	49 (9.5%)
Cancer	86 (16.6%)	78 (15.1%)

From sponsor's table

The two treatment groups had similar proportion of patients with orthopedic surgery with the previous 12 months (16.8% in the Org31540/SR90107A group, 14.9% in the enoxaparin group). Demographic characteristics, type of surgery and features of surgery were comparable in the two treatment groups.

Demographics, medical history and surgical characteristics of the population with efficacy data available (sponsor's primary efficacy population) were similar to those of the all treated population. Seven percent of patients in each of the treatment groups discontinued treatment prematurely. Seven (1.4%) Org31540/SR90107A patients discontinued due to serious bleeding events as compared to 2 (0.4%) enoxaparin patients. Six (1.2%) enoxaparin patients discontinued treatment due to lack of efficacy as compared to 2 (0.4%) Org31540/SR90107A patients. The major reason for premature withdrawal was serious adverse events (about 3.9% of patients in the Org31540/SR90107A group and 2.5% of patients in the enoxaparin group); most of these were non-bleeding events. About 1.7% of patients withdrew consent.

Mean time between the end of surgery and the first active post-operative injection was 6 hours in the Org31540/SR90107A group and 21 hours in the enoxaparin group. Patients in the Org31540/SR90107A group received an average of 5.5 active doses and patients in the enoxaparin received an average of 9.2 active doses. Thus, patients in the enoxaparin group received active drug starting later than in the Org31540/SR90107A group and received fewer total daily doses of active drug. This may bias the result in favor of Org31540/SR90107A.

Efficacy results for this study are shown in the table below: