Table (9.2.2)1 - *continued* - Number (%) of Patients With Serious Adverse Events From First Injection to Day 11 by WHO Organ-Class and Preferred Term - All Treated Patients

WHO OrganClass Preferred Term	Org31540/SR90107A 2.5 mg o.d. (N=1140)	Enoxaparin 40 mg o.d. (N=1133)
SKIN AND APPENDAGES DISORDERS		
TOTAL	2 (0.2 %)	1 (0.1 %)
MELANOMA MALIGNANT	1 (0.1 %)	0 (0.0 %)
RASH	0 (0.0 %)	1 (0.1 %)
SWEATING INCREASED	1 (0.1 %)	0 (0.0 %)
VASCULAR (EXTRACARDIAC) DISORDERS		
TOTAL	2 (0.2 %)	1 (0.1 %)
CEREBROVASCULAR DISORDER	2 (0.2 %)	1 (0.1 %)
URINARY SYSTEM DISORDERS		
TOTAL	2 (0.2 %)	0 (0.0 %)
RENAL FUNCTION ABNORMAL	1 (0.1 %)	0 (0.0 %)
URINARY TRACT INFECTION	1 (0.1 %)	0 (0.0 %)
APPLICATION SITE DISORDERS		
TOTAL	1 (0.1 %)	0 (0.0 %)
CELLULITIS	1 (0.1 %)	0 (0.0 %)
AUTONOMIC NERVOUS SYSTEM DISORDERS		
TOTAL	1 (0.1 %)	0 (0.0 %)
SYNCOPE	1 (0.1 %)	0 (0.0 %)
FOETAL DISORDERS		
TOTAL	1 (0.1 %)	0 (0.0 %)
HERNIA CONGENITAL	1 (0.1 %)	0 (0.0 %)
LIVER AND BILIARY SYSTEM DISORDERS		
TOTAL	1 (0.1 %)	0 (0.0 %)
CHOLELITHIASIS	1 (0.1 %)	0 (0.0 %)
URINARY SYSTEM DISORDERS		
TOTAL	1 (0.1 %)	0 (0.0 %)
URINARY TRACT INFECTION	1 (0.1 %)	0 (0.0 %)

Compound: Org31540/SR90107A (63118), SAS program: — Date:13OCT2000 23:05

[1] No haematoma, compression due to metastasis at lumbar spinal region in patient with prostate cancer

Ref: Appendix 14.2.4.2.5

Sponsor's tables volume 3.117 pp.119-121 of 215

Thrombocytopenia

Investigators coded six patients (2 fondaparinux and 4 enoxaparin) as having thrombocytopenia from first injection to Day 11. Six patients (3 fondaparinux and 3 enoxaparin) had a baseline value lower than 150,000/cc^3. All cases except one had the onset of thrombocytopenia occur within the first 3 days. ELISA tests for antiplatelet antibodies were negative. None of these patients had a VTE. No patient who developed thrombocytopenia died during the trial or follow up period.

Table (9.2.3.1) 1 - Patients Experiencing a Decrease in Platelet Count According to the Investigator's Judgment - Characteristics of the Events - All Treated Patients

Treatment Group	Patient	Description of the AE/SAE: Day of Onset[a]	Duration of the Event (day)	Day of Last Injection[a]	Serious	Action taken on Study Drug	Platelet count (10^3/L): Last Value Before Treatment	Minimum Value	Value at Date of Resolution[b]
Org31540/ SR90107A	26541184	1 (2)	5	7 (8)	No	No change			
	26541187	1 (2)	4	7 (8)	No	No change			
Enoxaparin	03510100	1 (2)	5	8 (9)	No	No change			
	08551321	2 (3)	3	9 (10)	No	No change			
	26541183	2 (3)	2	7 (8)	No	No change			
	26542153	2 (3)	4	7 (8)	No	No change			

Compound: Org31540/SR90107A (63118), SAS program: [redacted] Date:13OCT2000 23:07
Normal range: 150-400 x 10^3/L
[a] Expressed as days since surgery (days since start of study drug [active compound or placebo])
[b] Resolution date of the AE reported by the investigator
[c] Last available value for this patient (on Day 9) was [redacted]
Ref: Appendix 14.2.4.2.17

Sponsors' table volume 3.117 p. 124 of 218

Permanent Discontinuations

There were no statistically significant differences between treatment groups for patients who discontinued. The most frequent reason for discontinuation was platelet, bleeding, and clotting disorder (6 fondaparinux patients (0.5%), 1 enoxaparin patients (0.1%)).

Laboratory Parameters

There were no statistically significant differences between treatment groups for mean change from baseline for hemoglobin or hematocrit, platelet counts, biochemistry, and liver function tests. The sponsor's tables show the results for selected parameters.

Reviewer's Comment: A greater number and frequency of fondaparinux patients had hematocrit values less than 24%, experienced greater than a 6% decrease in hematocrit, or both compared with enoxaparin.

Table (9.3.1.2) 1 - Number (%) of Patients With an Hematocrit Value Below 24% and/or a Decrease Greater Than or Equal to 6.0% Compared to First Post-operative Values - All Treated Patients

Hematocrit	Org31540/SR90107A 2.5 mg o.d. (N=1140)	Enoxaparin 40 mg o.d. (N=1133)
Values <24%[a]	123 / 1098 (11.2%)	78 / 1092 (7.1%)
Decrease[b] ≥6.0%	187 / 1093 (17.1%)	107 / 1084 (9.9%)
Both	56 / 1090 (5.1%)	25 / 1084 (2.3%)

Compound: Org31540/SR90107A (63118), SAS program: [redacted] Date:13OCT2000 23:12
[a] After the first post-operative injection
[b] From the first post-operative value
Ref: Appendix 14.2.4.3.9

Sponsor's table volume 3.177 p. 130 of 218

The sponsor's table below shows the number of patients with platelet counts less than 100,000/cc^3.

Table (9.3.1.3) 1 - Number (%) of Patients With a Platelet Count Included in the [50 x 10^9/L-100 x 10^9/L[Range or <50 x 10^9/L After the First Study Drug Injection - All Treated Patients

Platelet Count	Org31540/SR90107A 2.5 mg o.d. (N=1140)	Enoxaparin 40 mg o.d. (N=1133)
[50 x 10^9/L - 100 x 10^9/L[[a,b]	30 / 1122 (2.7%)	31 / 1114 (2.8%)
<50 x 10^9/L [a,c]	3 / 1122 (0.3%)	0 / 1114 (0.0%)

Compound: Org31540/SR90107A (63118), SAS program: [redacted] Date:13OCT2000 23:12
Note: Platelet count range [50 x 10^9/L - 100 x 10^9/L[denotes platelet count from 50 x 10^9/L (included) up to <100 x 10^9/L
[a] After the first study drug injection
[b] Patients with baseline value ≥100 x 10^9/L or missing
[c] Patients with baseline value ≥50 x 10^9//L or missing
Ref: Appendix 14.2.4.3.9

Sponsor's table volume 3.117 p. 132 of 218

The sponsor's table below shows the number of patients who had a positive ELISA test for heparin specific IgG antibodies after starting study treatment.

Reviewer's Comment: A greater percentage of enoxaparin patients became ELISA positive after having a negative or missing result at baseline and developed a positive SRA compared with fondaparinux. Review of patients who became ELISA positive revealed that 2 fondaparinux patients had received heparin during the study. Thus the majority of patients who became ELISA positive did not have documented exposure to heparin prior to or during the trial. No ELISA positive patient died during the trial or follow up period.

Table (9.3.1.4) 1 - Number (%) of Patients With ELISA and SRA Tests (Among Positive ELISA Tests) Which Became Positive After Beginning of Active Study Drug - All Treated Patients with Antiplatelet Antibodies Evaluation

Test	Org31540/SR90107A 2.5 mg o.d.	Enoxaparin 40 mg o.d.
Positive ELISA test [a]	61/1061 (5.7%)	36/1067 (3.4%)
Positive Serotonin test [b]	7/61 (11.5%)	5/36 (13.9%)

Compound: Org31540/SR90107A (63118), SAS program: [redacted] Date:13OCT2000 23:20
[a] Patients with switch to positive ELISA test after beginning of active study drug from negative (or missing) ELISA test at baseline
[b] Out of patients with switch to positive ELISA test, patients with switch to positive SRA test from negative (or missing) SRA test at baseline
Ref: Appendix 14.2.4.3.15

Sponsor's table volume 3.117 p. 132 of 218

The sponsor's table below shows the number of ELISA positive patients who developed either a VTE or a platelet count below 100,000/cc^3.
Reviewer's Comment: More ELISA positive enoxaparin patients developed a DVT than fondaparinux patients. The fondaparinux patient had an asymptomatic DVT and non-fatal PE

documented. This patient was not exposed to heparin or low molecular weight heparin during the trial.

Table (9.3.1.4) 2 - Number (%) of Patients With Anti-Platelet Antibodies (Positive ELISA Test) Associated With a VTE or a Platelet Count Below 100 x 10^9/L - All Treated Patients With Anti-Platelet Antibodies Evaluation

Patients With Antiplatelet Antibodies Associated With:	Org31540/SR90107A 2.5 Mg O.D. (N=61)	Enoxaparin 40 Mg O.D. (N=36)
VTE	1 (1.6%)	5 (13.9%)
Platelet count < 100 x 10^9/L	0 (0.0%)	0 (0.0%)

Compound: Org31540/SR90107A (63118), SAS program: ——— Date:13OCT2000 23:20
NOTE: Table includes patients with switch to positive ELISA test after beginning of active study drug from negative (or missing) ELISA test at baseline
Ref: Appendix 14.2.4.3.15 and 14.2.4.3.17

Sponsor's table volume 3.117 p.133 of 218

Pharmacokinetic evaluation of main efficacy and safety endpoints
The sponsor evaluated the relationship between plasma drug levels and development of either a VTE or adjudicated major bleeding. The sponsor concluded that no relationship existed between plasma drug levels and development of an endpoint.

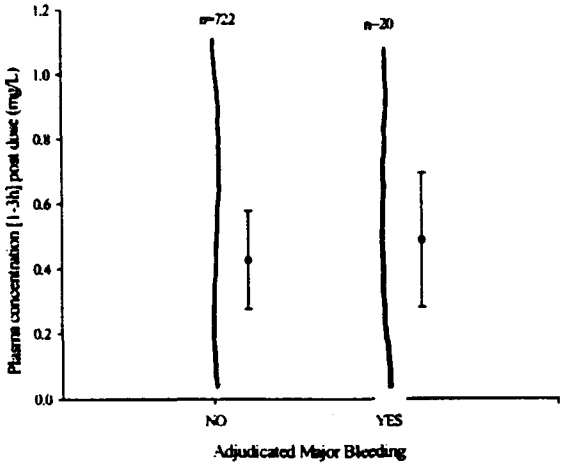

Figure (10.3) 1 - Individual and Mean (SD) Plasma Concentration [1-3 h] After Last Morning Dose of Org31540/SR90107A as a Function of the Occurrence of Adjudicated Major Bleeding - Total Data Set

Ref: Appendices 14.2.5.1.4 and 14.2.5.1.7

Sponsor's table volume 3.117 p. 138 of 218

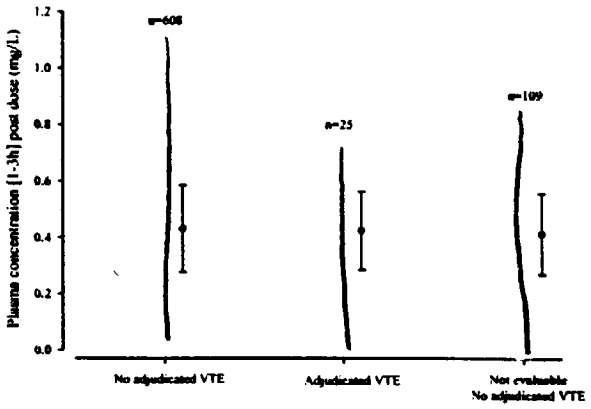

Figure (10.3) 2 - Individual and Mean (SD) Plasma Concentration [1-3 h] After Last Morning Dose of Org31540/SR90107A as a Function of the Occurrence of Adjudicated VTE - Total Data Set

Ref: Appendices 14.2.5.1.3 and 14.2.5.1.5

Sponsor's table volume 3.117 p. 139 of 218

APPEARS THIS WAY
ON ORIGINAL

C. Individual Study Safety reviews for Treatment of ——

The only clinical trial report submitted in the NDA was the ——— trial.

DR12440 ———

——— clinical trial was an international, multicenter, double-blind, dose-ranging, randomized study comparing efficacy and safety of once daily fondaparinux (5.0 mg, 7.5 mg, and 10 mg) with twice-daily dalteparin (100 IU/kg) in the treatment of ———. Oral anticoagulant therapy was initiated on post-operative Day 1 or 2.

The sponsor's safety analysis included all patients who received at least one dose of the drug. The safety analysis included three time periods. The first treatment period was from Day 1 to the end of administration of the study drug plus 2 days; the second treatment period was from day 3 after end of study treatment to Day 97; and the third time period was the entire study from Day 1 to Day 97.

The sponsor's text below gives information on the assessment criteria for major and minor bleeding.

The experts of the — had to evaluate blindly on a patient basis any event reported by the investigators. A patient was classified as having:

- Major bleeding event if the reported event satisfied one of the following criteria:
  - death because of bleeding event
  - intracranial bleeding, retroperitoneal bleeding or bleeding within a critical organ e.g., eye or adrenal gland
  - clinically overt bleeding associated with a fall in hemoglobin >2 g/dL
  - clinically overt bleeding leading to a transfusion >2 units in packed red cells
- Minor bleeding event if the reported event was clinically overt
- No bleeding event if the reported event was not clinically overt or occurred before the start of study drug

The investigators had to report any bleeding event as a SAE, when they considered that it satisfied the criteria of a major bleeding event. When they considered that a bleeding event satisfied the criteria of a minor bleeding event, they had to report it as AE.

Sponsor's text volume 3.262 p.42 of 4532

The sponsor's table below shows the bleeding event rates during the treatment period.

Reviewer's Comment: Major bleeding was seen only in the fondaparinux treatment groups during the first treatment period. Overall, the minor and all bleeding rates were lower in the fondaparinux treatment groups compared with dalteparin in the first treatment period. No statistically significant differences were observed between fondaparinux treatment groups for major or minor bleeding during the first treatment period. There were no fatal bleeds or bleeds into a critical organ.

Table (8.1.1) 1 - Number (%) of Patients [95% CI] Experiencing a Major or Minor Bleeding Event During the Treatment Period by Treatment Group - All Treated Patients

	Org31540/SR90107A				Dalteparin
Patients With	5 mg (N = 103)	7.5 mg (N = 111)	10 mg (N = 120)	Total Org/SR (N =334)	(N = 119)
Major bleeding	3 (2.91) [0.60;8.28]	2 (1.80) [0.22;6.36]	1 (0.83) [0.02;4.56]	6 (1.80) [0.66;3.87]	0 (0.00) [0.00;3.05]
Minor bleeding only	5 (4.85) [1.59;10.97]	7 (6.31) [2.57;12.56]	5 (4.17) [1.37;9.46]	17 (5.09) [2.99;8.02]	13 (10.92) [5.95;17.96]
All bleeding	8 (7.77) [3.41;14.73]	9 (8.11) [3.77;14.83]	6 (5.00) [1.86;10.57]	23 (6.89) [4.42;10.15]	13 (10.92) [5.95;17.96]

PGM= [redacted] OUT= DOC5B.txt (31JUL2000 - 10:19)
Ref: Appendices 13.2.3.1.4.1 and 13.2.3.1.1.3

Sponsor's table volume 3.262 p. 82 of 4532

Four major bleeds (66%) were related to a pre-existing cancer lesion. The other two major bleeds were either an injection site hematoma or operation site bleeding.

Blood Transfusion
During the entire study period, nine of ten patients, who experienced a major bleed, were transfused. Eight of those patients received 2-4 units of blood and the other patient received 15 units.

Adverse Events
The table below shows the frequency of adverse events during the treatment period experienced by 2% or more subjects.

Reviewer's Comment: The only statistically significant differences between treatment groups occurred in the following categories: Hepatic Enzyme Increased and Anemia.

Adverse Events for [redacted] observed with a greater than 2% frequency

Adverse Event	Fondaparinux 5 mg (N=103 patients)	Fondaparinux 7.5 mg (N=111 patients)	Fondaparinux 10 mg (N=120 patients)	Dalteparin (N=119 patients)
Gastrointestinal				
Constipation	5 (4.9%)	5 (4.5%)	5 (4.2%)	4 (3.4%)
Diarrhea	0	3 (2.7%)	2(1.7%)	2 (1.7%)
Nausea	4 (3.9%)	1 (0.9%)	1 (0.8%)	1 (0.8%)
Vomiting	1 (1%)	0	2 (1.7%)	3 (2.5%)
Platelet, Bleeding Disorders				
Epistaxis	0	2 (1.8%)	0	4 (3.4%)
Purpura	2 (1.9%)	3 (2.7%)	4 (3.3%)	5 (4.2%)
Hematoma	3 (2.9%)	4 (3.6%)	3 (2.5%)	3 (2.5%)
Body as a whole				
Chest pain	0	0	1 (0.8%)	3 (2.5%)
Fever	3 (2.9%)	4 (3.6%)	0	3 (2.5%)
Leg pain	5 (4.9%)	1 (0.9%)	1 (0.8%)	1 (0.8%)
Central and Peripheral Nervous System				
Headache	3 (2.9%)	1 (0.9%)	4 (3.3%)	6 (5%)
Skin and Appendages				
Skin Ulceration	3 (2.9%)	0	1 (0.8%)	0
Urinary System disorders				
Urinary Tract Infection	2 91.9%)	1 (0.9%)	3 (2.5%)	4 (3.4%)
Metabolic and Nutritional disorders				
Increased Non-Protein Nitrogen	0	0	0	3 (2.5%)
Liver and Biliary System Disorders				
Hepatic Enzymes Increased	0	0	0	6 (5.9%)
Red blood cell disorders				
Anemia	4 (3.9%)	1 (0.9%)	1 (0.8%)	1 (0.8%)

Reviewer's table

Deaths
No patient died during the treatment period. Twenty-two patients died during the second period and two died after the completion of the trial. The sponsor's table below lists the patients who died.

Reviewer's Comment: Only one patient (# 19320008) had an autopsy, which demonstrated widespread metastatic disease. The clinical course for the majority of these patients suggested that they died from either metastatic disease or a combination of metastatic disease and infection.

Table (9.2.1) 1 - List of Patients Who Died - Characteristics of the Serious Adverse Events

Treatment Group	Patient	Preferred Term	Onset Day	Day of Death	Day of Last Administration	Relationship to Study Drug	Adjudication	
							Related To Pe	Related To Bleeding[a]
5 mg	5110003	Death	73	73	6	No	No	NA
	5200001	Ovarian carcinoma	2	99	6	No	No	No
	12220011	Dyspnoea	8	26	7	No	No	NA
	19320008	Rectal carcinoma	4	62	7	No	No	NA
	22420014	Pulmonary carcinoma	-266	94	6	No	No	No
	22430018	Pancreas neoplasm malignant	47	47	5	No	No	NA
7.5 mg	12210015	Colon carcinoma	38	43	6	No	No	No
	19320005	GI neoplasm malignant	6	143	5	No	No	NA
	19330007	Cardiac failure	2	82	6	No	No	NA
	19340016	Ovarian carcinoma	19	19	5	No	No	NA
	22420027	Cervix carcinoma	70	79	5	No	No	No
	22430029	Skin neoplasm malignant	60	71	7	No	No	NA
10 mg	19320015	Dyspnoea	37	56	6	No	No	NA
	19340006	Coma	8	12	5	No	No	NA
		Fever	8	12	5	No	No	NA
	22420041	Cerebrovascular disorder	38	47	5	No	No	No
Dalteparin	2010052	Sepsis	67	67	6	No	No	NA
	2030003	Angina pectoris	76	92	7	No	No	NA
	5110005	Bladder carcinoma	41	74	6	No	No	NA
	5120006	Hepatic neoplasm malignant	23	48	7	No	No	NA
	5150001	Sarcoma	69	69	6	No	No	NA
	5160004	Oesophageal carcinoma	22	47	6	No	No	NA
	12210014	Cardiac failure	51	51	7	No	No	NA
	19320001	Ovarian carcinoma	17	63	5	No	No	No
	22450001	Pancreas neoplasm malignant	23	50	8	Unlikely	No	No

PGM: (21AUG00 - 13:50)
GI = gastro-intestinal
NA = not applicable
[a] in the absence of known bleeding event, the death was not adjudicated for relation to bleeding
Ref: Appendix 13.2.4.2.5.1

Sponsor's table volume 3.262 p. 98 of 4523

Serious Adverse Events
All drug-related serious adverse events involved bleeding. The sponsor's table is shown below.

Reviewer's Comment: No drug-related serious adverse event was seen in the dalteparin treatment group.

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Table (9.2.2) 2 - Number (%) of Patients Experiencing Drug-Related Serious Adverse Events During the Treatment Period by Treatment Group, WHO Organ Class and Preferred Term - All Treated Patients

WHO Organ Class Preferred Term	Org31540/SR90107A 5 mg (N = 103)	 7.5 mg (N = 111)	 10 mg (N = 120)	Dalteparin (N = 119)
Any event	2 (1.9%)	0 (0.0%)	2 (1.7%)	0 (0.0%)
Platelet,bleeding and clotting disorders				
Haematoma	1 (1.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Haematuria	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Purpura	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Total	2 (1.9%)	0 (0.0%)	2 (1.7%)	0 (0.0%)

PGM: [redacted] (08JUN00 - 17:44)
NOTE: drug-related SAEs = relationship to the study drug reported as likely or unknown by the investigators
Ref: Appendix 13.2.4.2.4.1

Sponsor's table volume 3.262 p. 100 of 4523

Permanent Treatment Discontinuations
Three patients discontinued because of adverse events. One patient (fondaparinux 7.5 mg) discontinued because of the development of influenza-like symptoms. One patient (fondaparinux 10 mg) discontinued because of purpura. One patient (dalteparin) discontinued because of bullous eruption.

Laboratory Parameters
Statistically significant differences were noted between groups on Day 3 and Day 7± 1 for the following: AST, ALT, and mean aPTT levels.
Reviewer's Comment: The statistically significant increase in mean APTT levels (Day 3 compared with Day 7) may reflect the fact that both treatment group patients were on concomitant warfarin.

No statistically significant differences were noted between groups on Day 3 and Day 7± 1 for the following: hemoglobin, hematocrit, platelet counts, total bilirubin, D-dimer, and TAT levels.

The sponsor's table below shows the number of patients with an increase in AST and ALT values above baseline.

Reviewer's Comment: Fewer fondaparinux patients had transaminase elevation compared with dalteparin.

APPEARS THIS WAY
ON ORIGINAL

Table (9.3.2.1) 1 - Number (%) of Patients With no Increase or With an Increase in AST and/or ALT Values Above One or Three Times the Upper Limit Compared to Baseline Values - All Treated Patients

Parameter	Org31540/SR90107A 5 mg (N = 103)	Org31540/SR90107A 7.5 mg (N = 111)	Org31540/SR90107A 10 mg (N = 120)	Dalteparin (N = 119)
ALT (IU/L)				
No increase[a]	89/93 (95.7%)	95/104 (91.3%)	108/115 (93.9%)	71/106 (67.0%)
Increase to a value in [ULN-3ULN[[b]	4/93 (4.3%)	9/104 (8.7%)	7/115 (6.1%)	32/106 (30.2%)
Increase to a value ≥ 3ULN[c]	0/93 (0.0%)	0/104 (0.0%)	0/115 (0.0%)	3/106 (2.8%)
AST (IU/L)				
No increase[a]	91/93 (97.8%)	99/104 (95.2%)	111/115 (96.5%)	91/106 (85.8%)
Increase to a value in [ULN-3ULN[[b]	2/93 (2.2%)	5/104 (4.8%)	4/115 (3.5%)	13/106 (12.3%)
Increase to a value ≥ 3ULN[c]	0/93 (0.0%)	0/104 (0.0%)	0/115 (0.0%)	2/106 (1.9%)

PGM: [redacted] (02AUG00 - 13:21)

NOTE: ULN = upper limit of normal

[a] no increase: values remained in the same range (i.e., <ULN, [ULN - 3ULN[or ≥3ULN) after the beginning of treatment compared to the baseline values, or values decreased

[b] increase [ULN - 3ULN[: values increased from baseline at least once to a value ≥ULN but remained <3ULN

[c] increase ≥3ULN: values increased from baseline at least once to a value ≥3ULN

Ref: Appendix 13.2.4.3.13.1

Sponsor's table volume 3.262 p. 105 of 4523

Other Trials

The following trials are ongoing and no safety information was presented:

1) EFC2441 - [redacted] - An international, multicenter, double-blind, randomized study comparing efficacy and safety of once daily fondaparinux with twice daily enoxaparin in the treatment of [redacted]
2) 63123 - [redacted] · An international, multicenter, open-label, randomized study comparing efficacy and safety of once daily fondaparinux versus adjusted dose heparin in the [redacted] treatment of [redacted]

D. Individual Study Safety Reviews for [redacted] Indications

ACT2445-Pilot Efficacy Study of a single IV injection of fondaparinux in patients undergoing [redacted] · an open-label, uncontrolled trial to assess the safety and efficacy of a single bolus dose of 12 mg fondaparinux [redacted]

The primary efficacy endpoint was the [redacted]

[redacted]

Efficacy and Safety Results
Ten patients were not evaluable for the following reasons: 8 patients had dissections noted shortly after [redacted] and two patients had insufficient results at [redacted] All ten patients received stents. Two of the 61 evaluable patients had an [redacted] The sponsor's results are shown in the table below.

Table (8.2.5) 1 - Percentage of [redacted] and 95% CI - Evaluable patients

Evaluable patients	Number of [redacted]	% of [redacted]	95% CI	
			Lower boundary	Upper boundary
61	2	3.28	0.40	11.35

PGM: [redacted]
[redacted] (09JUN97 - 17:15)

Sponsor's table volume 3.279 p.57 of 1139

Coronary dissection was observed in 26 patients (43%) on Day 1 or Day 2 [redacted] Subsequent interventions in patients included the use of thrombolytic therapy and stent placement. At the thirty day follow up, the following events were reported: two redilatations in the same patient, stent placement in one, development of sclerosis in one patient, and stroke in another patient. Twenty-three adverse events were reported in nineteen patients. No deaths were reported.

Reviewer's Comment: The Day 30 adverse events were not included in this table. The majority of adverse events were hemorrhagic.

Table (8.5.2.1) 1 - Adverse events by organ class and preferred term - All treated patients

Organ class	Preferred term	SR/ORG 12mg (N = 71)		
		n	(AE)	%
PLATELET, BLEEDING & CLOTTING DISORDERS	Haematoma	13	(14)	18.3
	Cerebral haemorrhage	1	(1)	1.4
	Total for organ class	**13**	**(15)**	**18.3**
APPLICATION SITE DISORDERS	Injection site reaction	3	(3)	4.2
	Injection site inflammation	1	(1)	1.4
	Total for organ class	**4**	**(4)**	**5.6**
MUSCULO-SKELETAL SYSTEM DISORDERS	Back pain	1	(1)	1.4
	Total for organ class	**1**	**(1)**	**1.4**
AUTONOMIC NERVOUS SYSTEM DISORDERS	Syncope	1	(1)	1.4
	Total for organ class	**1**	**(1)**	**1.4**
RED BLOOD CELL DISORDERS	Anaemia	1	(1)	1.4
	Total for organ class	**1**	**(1)**	**1.4**
BODY AS A WHOLE - GENERAL DISORDERS	Allergic reaction	1	(1)	1.4
	Total for organ class	**1**	**(1)**	**1.4**
TOTAL PATIENTS WITH AE (TOTAL AEs)% PATIENTS		19	(23)	26.8

SR/ORG: SR90107A/ORG31540, n = number of patients, (AE) = number of adverse events, % = percentage of patients
Each patient may have had more than one adverse event
PGM: [redacted]
[redacted] (27JAN97 - 14:51)

Sponsor's table volume 3.279 p.67 of 1139

Three hemorrhagic adverse events were considered moderate. One patient (#10009) had a false aneursym of the right superficial femoral artery requiring prolongation of hospitalization. Another

patient (#10033) had a hematoma at the femoral puncture site. A third patient (# 10041) suffered a cerebral hemorrhage. Patient (#10041) underwent [redacted] however experienced thrombotic occlusion during the [redacted] and received thrombolytics (rTPA 90 mg), additional intravenous heparin, ticlopidine, and two stents. On Day 4, the patient complained of headache and CT scan revealed left cerebral hematoma.

Laboratory
Laboratory results were not significantly affected for liver function tests or chemistry tests (two patients had elevated CPKs). Hematology tests were affected by the study. Decreases in hemoglobin, hematocrit, red blood cell number, and elevations of coagulation parameters were observed. ATIII and APTT were elevated two hours after administration and remained so until Day 3. The APTT results may have been affected by heparin use. Analysis of APTT results in those who did not receive heparin noted no significant change. Fibrinogen increased over Day 2 to 3. Prothrombin fragment (F_{1+2}) and TAT showed a significant decrease at two hours and remained stable at a lower level until Day 3. No changes for D-dimer were noted. Factor VII showed a decrease between baseline and two hours after administration and regained baseline value on Day 3.

Reviewer's Comment: These laboratory changes are not unexpected in this trial.

No significant changes in vital signs were noted during the trial. Electrocardiographic changes occurred during the trial.

Reviewer's Comment: The electrocardiographic changes are difficult to interpret due to the underlying disease, cardiac procedures, and complications that occurred during the trial.

DRI-3196- [redacted] A multicenter, randomized, dose-ranging study comparing fondaparinux with heparin as [redacted]

[redacted] was an international, multicenter, open-label, assessor-blind, randomized, dose-ranging, active controlled, and parallel-group study. The trial objective was to evaluate the efficacy and safety of three doses of fondaparinux with heparin. The treatment groups were:

- 4 mg fondaparinux plus [redacted]
- 8 mg fondaparinux plus [redacted]
- 12 mg fondaparinux plus [redacted]
- unfractionated heparin plus [redacted]

Three hundred thirty-three patients were enrolled with the following criteria:

- age between 21 and 75
- presentation with ischemic pain lasting at least 30 minutes
- ST-segment elevation $\geq$ 0.1 mV in two or more limb leads or $\geq$ 0.2 mV in two or more contiguous limb leads for whom planned treatment is initiated within six hours after the onset of pain
- informed consent

Anticoagulant treatment was given for 5 $\pm$ 1 days. The observation period was 28 to 32 days. The main efficacy endpoint was [redacted]

The main safety endpoints were the incidence of primary intracranial bleeding or blood transfusion.

Efficacy and Safety Results
Premature discontinuations were more frequent in the fondaparinux treatment group. The sponsor's table below shows the reasons for discontinuation.

Reviewer's Comment: The unfractionated heparin treatment group had fewer discontinuations for non-fatal lack of efficacy than fondaparinux.

Table (6.1) 3 - Number (%) of Patients by Treatment Group Who Discontinued Study Drug with Reasons for Discontinuation - All Treated Patients

	Org31540/SR90107A				UFH	Total
	4 mg (N = 81)	8 mg (N = 77)	12 mg (N = 83)	All Org/SR (N = 241)	(N = 85)	(N = 326)
Patients who discontinued study drug prematurely	15 (18.5)	19 (24.7)	23 (27.7)	57 (23.7)	15 (17.6)	72 (22.1)
Reason(s)for discontinuation						
Death	0 (0.0)	0 (0.0)	1 (1.2)	1 (0.4)	0 (0.0)	1 (0.3)
Non-fatal adverse event	2 (2.5)	10 (13.0)	11 (13.3)	23 (9.5)	5 (5.9)	28 (8.6)
Non-fatal lack of efficacy	9 (11.1)	5 (6.5)	10 (12.0)	24 (10.0)	3 (3.5)	27 (8.3)
Other reasons	4 (4.9)	4 (5.2)	1 (1.2)	9 (3.7)	7 (8.2)	16 (4.9)

PGM=, (29JUN2000 - 18:23)
Ref: Appendix13.2.1.1.2.2

Sponsor's table volume 3.284 p. 46 of 2314

The main efficacy results did not demonstrate a statistically significant difference for any fondaparinux dose or for any fondaparinux dose compared with unfractionated heparin. These results were not significant at 90 minutes after thrombolytic therapy and on Day 6 ± 1 day. The secondary endpoint was the clinical event rate. The sponsor's table below shows the clinical event rates for each treatment group.

Reviewer's Comment: There were no significant differences between treatment groups for clinical events.

Table (7.1.3) 1 - Number (%) of Patients With Clinical Endpoint Which Occurred up to Day 7 - All Treated Patients

Parameter	Up to Day 7				
	Org31540/SR90107A				UFH
	4 mg (N = 81)	8 mg (N = 77)	12 mg (N = 83)	All Org/SR (N = 241)	(N = 85)
All deaths	0 (0.0)	0 (0.0)	2 (2.4)*	2 (0.8)	0 (0.0)
Missing*	0	0	0	0	1
MI					
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non fatal	3 (3.7)	0 (0.0)	2 (2.4)	5 (2.1)	2 (2.4)
Missing*	0	0	0	0	1
Death or MI	3 (3.7)	0 (0.0)	4 (4.8)	7 (2.9)	2 (2.4)
Missing	0	0	0	0	1
Revascularisation*	21 (25.9)	25 (32.5)	26 (31.3)	72 (29.9)	34 (40.5)
Missing*	0	0	0	0	1
CABG	1 (1.2)	1 (1.3)	2(2.4)	4 (1.7)	2 (2.4)
PTCA	6 (7.4)	11 (14.3)	2(2.4)	19 (7.9)	6 (7.1)
PTCA+STENT	14 (17.3)	13 (16.9)	22 (26.5)	49 (20.3)	26 (31.0)
At least one event	22 (27.2)	25 (32.5)	29 (34.9)	76 (31.5)	34 (40.5)
Exact 95% CI	[17.9%-38.2%]	[22.2%-44.1%]	[24.8%-46.2%]	[25.7%-37.8%]	[29.9%-51.7%]
Missing*	0	0	0	0	1

PGM= [redacted]
(29JUN2000 - 18:50)
*: number of patients with no evaluation. Percentages are computed using the total of patients with an evaluation
*: excluding 90-minute revascularization
Ref: Appendix 13.2.2.1.3.2

Sponsor's table volume 3.284 p. 69 of 2314

Deaths

There were 2 deaths in the 12 mg fondaparinux dose group up to Day 7. Five additional deaths occurred up to Day 37 (2 for 4 mg, 2 for 8 mg, and 1 for unfractionated heparin). Two of the deaths occurred as a result of hemorrhage. One patient (#4040006) in the 12 mg fondaparinux treatment group died from a retroperitoneal hemorrhage and one unfractionated heparin patient died following hemorrhage at a groin puncture site. The sponsor's table below lists the causes of death for all patients.

Table (9.2.1) 1 - Deaths and Causes of Death During the Whole Study Period

Treatment group		Patient	Age	Previous MI	SAE (Verbatim)	Onset day*	Day of death*	Day of last administration*	Relationship to study drug*
Org31540/ SR90107A	4 mg	4030005	60	Yes	Acute pulmonary oedema	D1	D11	D1	No
		4070004	68	No	Haemodynamic troubles following cardiac surgery	D4	D9	D4	Unlikely
	8 mg	2020022	73	No	Cardio circulatory arrest	D11	D11	D5	Unlikely
		4030025	67	No	Ventricular fibrillation	D35	D35	D6	No
	12 mg	4020007	75	No	Cardiogenic shock	D1	D1	D1	No
		4040006	67	No	Severe retroperitoneal bleeding	D2	D6	D2	Likely
UFH		13010001	71	No	Bleed at site of groin puncture	D1	D14	D1	Likely

PGM= [redacted] (03JUL2000 - 9:29)
*: Day 1 means the Day of first administration
*: as assessed by the investigator
Ref: Appendix 13.2.4.2.1.1

Sponsor's table volume 3.284 p. 89 of 2314

Bleeding
The sponsor's table below shows the number of patients who reached the primary safety endpoint.

Reviewer's Comment: The only intracranial bleed occurred in the fondaparinux 4 mg treatment group. This patient suffered an intracranial bleed on Day 4 while on concomitant ticlopidine. There was no significant difference for intracranial bleed and number of patients requiring a transfusion between treatment groups.

Table (8.1) 1 - Number (%) of Patients Who Reached the Primary Endpoint for Safety During the 30±7 Day Study Period and 95% CIs of Percentages - All Treated Patients

	Org31540/SR90107A				UFH
	4 mg (N = 81)	8 mg (N = 77)	12 mg (N = 83)	All Org/SR (N = 241)	(N = 85)
Number of patients with a missing evaluation*	0	0	0	0	1
Number of patients with intracranial bleeding	1 (1.2)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Number of transfused patients	3 (3.7)	7 (9.1)	6 (7.2)	16 (6.6)	6 (7.1)
Exact 95% CI	[0.8-10.4]	[3.7-17.8]	[2.7-15.1]	[3.8-10.6]	[2.7-14.9]
Not due to CABG	1 (1.2)	4 (5.2)	3 (3.6)	8 (3.3)	6 (7.1)
Hemorrhage at puncture site	0 (0.0)	2 (2.6)	2 (2.4)	4 (1.7)	4 (4.8)
Hemorrhage in other organ	0 (0.0)	1 (1.3)	1 (1.2)	2 (0.8)	1 (1.2)
Other reasons	1 (1.2)	1 (1.3)	0 (0.0)	2 (0.8)	1 (1.2)
Due to CABG	2 (2.5)	3 (3.9)	3 (3.6)	8 (3.3)	0 (0.0)
Total of patients who reached the primary safety endpoint	4 (4.9)	7 (9.1)	6 (7.2)	17 (7.1)	6 (7.1)
Exact 95% CI	[1.4-12.2]	[3.7-17.8]	[2.7-15.1]	[4.2-11.1]	[2.7-14.9]

PGM= (29JUN2000 - 18:32)
*: patients who did not reach the primary endpoint for safety before Day 23 and with no evaluation from Day 23.
Percentages are computed using the total of patients with an evaluation
Ref: Appendices 13.2.3.1.1.2 and 13.2.3.2.2

Sponsor's table volume 3.284 p. 76 of 2314

Transfusions
There were no statistically significant differences for units of whole blood or packed red cell transfusions between treatment groups.

Bleeding events
Among the fondaparinux treatment groups, there appeared to be a dose-effect relationship with increased percentage of bleeding events in the 8 mg and 12 mg treatment groups. Decreases in hemoglobin were not statistically significantly different across treatment groups.

Adverse Events
There was a statistically significant difference for the category of Platelet, Bleeding, and Clotting disorders between the four groups (4 mg: 17.3%; 8 mg: 27.3%, 12 mg:34.9% and unfractionated heparin 11.8%).

The following adverse event categories reported a greater percentage of fondaparinux patients than unfractionated heparin patients:

1) Platelet, bleeding, and clotting disorders
2) Gastrointestinal Disorders
3) Heart rate and rhythm disorders
4) Musculoskeletal disorders
5) Liver and biliary system disorders
6) Myo-, endo-, pericardial and valve disorders
7) Vascular (extracardiac) disorders
8) Procedural site rejection
9) White cell and reticulo-endothelial disorders

Serious adverse events
Serious adverse events were observed in all treatment groups: 3 patients (3.7%) in the 4 mg group, 7 patients (9.1%) in the 8 mg group, 8 patients (9.6%) in the 12 mg group, and 5 patients (5.9%) in the unfractionated heparin group. These differences were not statistically significant. Most serious adverse events were observed in the category of Platelet, Bleeding, and Clotting Disorders.

Laboratory Values
No statistically significant differences were noted between groups for the following laboratory parameters: hemoglobin, hematocrit, platelet count, biochemistry, and liver function tests.

The following trial is ongoing and no safety information was presented in the NDA: 63119 ——— A double-blind, randomized, controlled, dose ranging trial of fondaparinux in patients with ———

E. Individual Safety Review for ———

CSCRO-63113-EN-E01: A randomized, assessor-blind, dose reducing, phase II study to assess the safety and efficacy of 10 mg, 8 mg, 6 mg, and 4 mg fondaparinux and standard treatment ———

The sponsor conducted a single center, open-label phase II study with an unapproved, active comparator (dalteparin). The trial design was six-period, two-block study using four sequential fondaparinux dose levels. The trial included male and female patients on chronic intermittent hemodialysis who weighed greater than 45 kg but less than 95 kg with good venous access and were willing to give informed consent. Major exclusion criteria included use of subclavian access, previous MI or stroke, history of a bleeding disorder, platelets < 120,000/cc^3, chronic use of antiplatelet, anticoagulant, or PT or APTT > 1.3 times the normal value (prior to dialysis).

Patients received a maximum of six injections. There was a one-week interval between injections.

Major Bleeding was defined as:

Major bleeding was defined as:

- Death due to bleeding complication
- Intra-cranial bleeding or bleeding within a critical organ e.g. the brain, eye or adrenal gland.
- Bleeding requiring surgery.
- Any bleeding which the investigator considered to be clearly excessive or unusual and (potentially) serious. If the investigator classified a bleeding during the entire study period as major, then the Org31540/SR90107A treatment was to be stopped.

Sponsor's text p. 26 of 1429

Subjects who experienced a major bleed were discontinued from the trial.

Safety Results
Fifteen subjects were randomized; however, three did not complete the trial. One subject discontinued after the first session (Fragmin) injection because of a shunt problem. A second subject never received an injection because of shunt problems. A third subject became confused prior to the first injection so never started the trial and eventually died.
There were 15 drug-related adverse events for 9 subjects. The events are listed in the table below.

Reviewer's Comment: The trial is too small to make any significant statements about safety.

Adverse Events in Trial 63113

Drug/Event	Mild	Moderate	Severe
Fondaparinux			
Anemia		2 (4 mg, 6 mg)	1 (8 mg)
Epistaxis	1 (4 mg)	1 (6 mg)	
Hematuria	1 (4 mg)		
Malaise		1 (8 mg)	
Rhinitis		1 (8 mg)	
Vascular Disorder		1 (6 mg)	
Dalteparin			
Abdominal Pain		3	
Dizziness			1
Gastroenteritis			1
Vascular Disorder		1	

Reviewer's table

F. Safety Review of the sponsor's labeling

The sponsor should make the following labeling revisions:

1. In the Black Warning Box include information about NSAIDs in the warning.

2. In the Black Warning Box bold the phrase (see WARNINGS, Hemorrhage and PRECAUTIONS, Drug Interactions).
3. Under the Clinical Pharmacology Section, remove the statement that starts with —
4. Under the Clinical Pharmacology Section, remove the statement that starts with
5. Under the Clinical Pharmacology Section, in the Pharmacokinetics subsection, remove the phrase
6. Under the Clinical Studies Section, remove the introduction section (i.e., the first four 4 paragraphs and the figure) that starts with
7. Under the Contraindications Section, add that fondaparinux is contraindicated "in patients with thrombocytopenia associated with a positive test *in vitro* test for anti-platelet antibody in the presence of fondaparinux".
8. Under the Warnings Section, add that the drug is not intended for use.
9. Under the Warnings section, add the sentence
10. Under the Hemorrhage section, add the following medical conditions associated with an increased risk of hemorrhage
11. Under the Hemorrhage section, add a section on thrombocytopenia similar to that in the enoxaparin and dalteparin labeling.
12. Under the Precautions section, in the General subsection, include statements about other patient populations at risk, such as bleeding diathesis, uncontrolled hypertension, recent history of recent gastrointestinal ulceration, diabetic retinopathy, and hemorrhage.
13. Under the Precautions section, in the General subsection, the sponsor needs to include information about and elderly.

14. Under the Precautions section, in the General subsection, add: "If thromboembolic events occur despite appropriate fondaparinux prophylaxis, appropriate therapy should be initiated."
15. Under the Precautions section, in the Laboratory subsection, include a recommendation to monitor complete blood count and platelet count.
16. Under the Precautions section, in the Laboratory subsection, include information about [redacted]
17. Under the Precautions section, in the Pregnancy subsection, delete the [redacted] section.
18. Under the Precautions section, in the Nursing Mothers subsection, delete the last sentence [redacted]
19. Under the Precautions section, in the Geriatric Use subsection, [redacted]
20. Under the Adverse Reactions section, remove the second paragraph, as it is not necessary.
21. Under the Adverse Reactions section, combine the adverse event information for the preoperative and post-operative dosing regimens into one table.
22. Under the Adverse Reactions section, revise the bleeding event categories in the tables. Bleeding in the clinical trials was adjudicated as either major or minor bleeding or no bleeding. Major bleeding events were either fatal bleeds, non-fatal bleeding at a critical site, reoperation due to bleeding, or Bleeding Index $\geq$2. The sponsor should add [redacted]
23. Under the Adverse Reactions section, include a footnote for the bleeding tables stating that clinically overt bleeding was required for adjudication of a bleed as major or minor.
24. Under the Adverse Reactions section, [redacted]
25. Under the Overdosage section, place the fifth paragraph before the first paragraph.

26. Under the Overdosage section, remove the third paragraph.

27. Under the Dosage and Administration section, [redacted]

[redacted]

28. Under the Dosage and Administration section, remove the last sentence in the last paragraph.

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

/s/

Ann Farrell
7/13/01 09:08:17 AM
MEDICAL OFFICER

Kathy Robie-Suh
7/20/01 10:51:16 AM
MEDICAL OFFICER

Lilia Talarico
7/20/01 03:02:00 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

Division of Gastrointestinal and Coagulation Drug Products

Medical Officer's Safety Update Review

NDA:	21345 SU, BM
IND:	[redacted]
Sponsor:	Fonda BV
Drug Product:	Arixtra™ (fondaparinux sodium, Org31540/SR90107A)
Date submitted:	June 15, 2001, July 3, 2001, June 6, 2001, June 15, 2001, June 18, 2001, June 22, 2001
Review Completed:	July 13, 2001
Reviewer:	Ann T. Farrell MD

This safety review includes the NDA Safety Update, two serious adverse events reported under the IND (not included in the safety update), IND quarterly safety update, and labeling recommendations. The NDA Safety Update includes events reported from May 11, 2000 to February 28, 2001.

NDA Safety Update

Studies
The sponsor has completed two phase I safety and pharmacokinetic studies in Japanese patients; however, the final reports are pending. The sponsor has three ongoing trials for the

[redacted]

APPEARS THIS WAY
ON ORIGINAL

Ongoing and Completed Fondaparinux Studies and Trials

Study	Objective	Dose/Duration	Planned Population	Completed Patients	Permanently Discontinued	Status
TDU4089	Phase I-Pharmacokinetic (PK) study for subcutaneous (SC) and intravenous (IV) administration	Single SC dose 0.75 mg, 2.5 mg, or 8 mg, and 2.5 mg IV administration (duration of IV drip not given)	18 healthy Japanese males 20-35 years of age	18	0	Completed, Report pending
TDU4289	Phase I-Safety and PK study for SC administration	Single SC 2.5 mg dose	6 healthy, elderly Japanese males 65-85 years of age	6	0	Completed, Report pending
EFC2441	Phase III Efficacy and Safety of daily fondaparinux compared with enoxaparin for treatment of [redacted]	Fondaparinux 5 mg or 7.5 mg or 10 mg SC once daily or enoxaparin 1 mg/kg twice daily, Duration not given	2200 patients with [redacted]	920	44	Ongoing
63123	Phase III Efficacy and Safety of daily fondaparinux compared with unfractionated heparin for treatment of [redacted]	Fondaparinux 5 mg or 7.5 mg or 10 mg SC once daily or adjusted dose IV heparin, Duration not given	523 patients with [redacted]	91	30	Ongoing
63119-[redacted]	Phase IIb- dose ranging study in patients with [redacted]	Fondaparinux 2.5 mg or 4 mg or 8mg or 12 mg SC once daily, Duration not given	1075 patients with [redacted]	696	172	Ongoing

Reviewer's Table

Completed Phase I studies

Discontinuations

No discontinuations occurred due to adverse events.

Deaths and Serious Adverse Events

No deaths or serious adverse events occurred during Phase I studies.

Adverse Events

The sponsor's table below shows the adverse events that occurred during the phase I studies.

Reviewer's Comment: Platelet, bleeding, and clotting disorders were the most frequent adverse event category.

Table (3.2.1) 1 - Number (%) of Subjects Experiencing Adverse Events in Completed Phase I Studies TDU4089 and TDU4289

WHO Organ Class Adverse Events (WHO Preferred Term)	Org31540/ SR90107A			
	< 2.5 mg SC (N = 6)	2.5 mg SC (N = 12)	2.5 mg IV (N = 6)	> 2.5 mg SC (N = 6)
Any event	2 (33.3%)	4 (33.3%)	3 (50.0%)	6 (100.0%)
Platelet, bleeding and clotting disorders				
Any event	2 (33.3%)	3 (25.0%)	3 (50.0%)	6 (100.0%)
Coagulation disorder	2 (33.3%)	3 (25.0%)	3 (50.0%)	4 (66.7%)
Prothrombin decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (83.3%)
Application site disorders				
Any event	0 (0.0%)	1 (8.3%)	0 (0.0%)	0 (0.0%)
Cellulitis	0 (0.0%)	1 (8.3%)	0 (0.0%)	0 (0.0%)

Sponsor's table p.11 of Safety Update

Ongoing Studies

Study - EFC2441- — Treatment — · An international, multicenter, double-blind, randomized study comparing efficacy and safety of once daily fondaparinux with twice daily enoxaparin in the treatment —

Thirteen hundred and fifty-three patients have enrolled. Nine hundred and twenty have completed the study.

Discontinuations
Twenty patients (1.5%) discontinued due to adverse events. Twelve patients (0.9%) discontinued due to platelet, bleeding, and clotting disorders (predominantly hemorrhage).

Deaths
The sponsor's table below shows the SAEs that led to death during the treatment period.
Reviewer's Comment: Deaths during the treatment and study periods accounted for 0.5% and 2.6% of the total population, respectively. Malignancy was the greatest contributor to deaths during the treatment and study periods. There was one death due to bleeding (retroperitoneal hemorrhage).

Table (3.3.2) 1 - Number (%) of Patients With SAEs During Treatment Period Leading to Death in Ongoing Study EFC2441

WHO Organ Class Adverse Events (WHO Preferred Term)	Double blind (N = 1353)
Any event	7 (0.5%)
Neoplasm	
Total	2 (0.1%)
Endometrial neoplasm malignant	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%)
Liver and biliary system disorders	
Total	1 (0.1%)
Bile duct carcinoma	1 (0.1%)
Platelet, bleeding and clotting disorders	
Total	1 (0.1%)
Hemorrhage retroperitoneal	1 (0.1%)
Respiratory system disorders	
Total	1 (0.1%)
Pneumonia	1 (0.1%)

Sponsor's Table p. 12 of Safety Update

Serious Adverse Events
Over 1300 patients were enrolled in the trial by the cut off date. The table below lists a summary of the 62 SAEs, which occurred during the ECF2441 treatment phase.

Reviewer's Comment: Platelet, bleeding, and clotting disorders were the most frequent adverse event during the treatment and study periods.

Serious Adverse Events during Treatment for ECF2441

Serious Adverse Events	Number of Patients (percentage) N=1353
Any SAE	62 (4.6%)
Platelet, Bleeding, and Clotting Disorders[a]	23 (1.7%)
Neoplasm	7 (0.5%)
Body as a whole	4 (0.3%)
Central and Peripheral Nervous System[b]	3 (0.2%)
Gastrointestinal Disorders[c]	3 (0.2%)
Heart Rate, Rhythm Disorders	3 (0.2%)
Metabolic and Nutritional Disorders	3 (0.2%)
Respiratory System Disorders	3 (0.2%)
Secondary Terms	3 (0.2%)
Cardiovascular disorders, general	2 (0.1%)
Liver and Biliary System disorders	2 (0.1%)
Musculo-skeletal system disorders	2 (0.1%)
Myo-, endo- pericardial and valve Disorders	2 (0.1%)
Vascular (extracardiac) Disorders	2 (0.1%)
Other[d]	

[a] Includes 5 hematoma, 5 hematuria, 5 GI hemorrhage/melena, 1 retroperitoneal hemorrhage
[b] Includes categories that are not mutually exclusive - 1 convulsion, 1 stupor, 1 coma, 1 headache, 1 hypertension intracranial
[c] Includes 1 hemorrhagic duodenal ulcer
[d] Includes 1 each of application site disorders, psychiatric disorders, red blood cell disorders, resistance mechanism disorders, skin and appendages, urinary system disorders
Reviewer's Table

Study 63123- [redacted] treatment

63123 - [redacted] An international, multicenter, open-label, randomized study comparing efficacy and safety of once daily fondaparinux versus adjusted dose heparin in the initial treatment of [redacted]

Five hundred and twenty-three patients have enrolled. Ninety-one have completed the study.

Discontinuations

Ten patients (1.9%) discontinued due to adverse events. Five patients (1.0%) discontinued due to platelet, bleeding, and clotting disorders (predominantly hemorrhage).

Deaths

The sponsor's table below shows the SAEs that led to death during the treatment period.
Reviewer's Comment: During the treatment and study periods, deaths accounted for 1.1% and 2.9% of the total population. The largest contributor to death in the treatment period is body as a whole disorders (2 patients (1 chest pain and 1 death), 0.4%). The largest contributor to death in the study period is respiratory system disorders (6 patients (1 dyspnea, 2 respiratory insufficiency, 2 pneumonia, 1 pulmonary edema), 1.1%).

Table (3.3.2) 2 - Number of Patients with SAEs During Treatment Period (plus extension of 9 days) Leading to Death in Ongoing Study 63123

WHO Organ Class Serious Adverse Events (WHO Preferred Term)	Blind* (n = 523)
Any event	6 (1.1 %)
Body as a whole - general disorders	
Total	2 (0.4 %)
Chest pain	1 (0.2 %)
Death	1 (0.2 %)
Cardiovascular disorders, general	
Total	1 (0.2 %)
Circulatory failure	1 (0.2 %)
Platelet, bleeding and clotting disorders	
Total	1 (0.2 %)
GI hemorrhage	1 (0.2 %)
Reproductive disorders, female	
Total	1 (0.2 %)
Ovarian carcinoma	1 (0.2 %)
Secondary terms	
Total	1 (0.2 %)
Metastases NOS	1 (0.2 %)

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

Sponsor's table p. 13 of Safety Update

Serious Adverse Events
Over 500 patients were enrolled in the trial by the cut off date. The table below lists a summary of the 25 SAEs occurring in 63123.

Reviewer's Comment: During the treatment period, platelet, bleeding, and clotting disorders were the most common SAE category (7 patients, 1.3%). During the study period, there were 54 SAEs. During the study period, respiratory system disorders were the most common SAE category (15 patients, 2.9%) followed by platelet, bleeding, and clotting disorders (12 patients, 2.3%).

Serious Adverse Events During Treatment for 63123

Serious Adverse Events	Number of Patients (percentage) N=523
Any SAE	25 (4.8%)
Platelet, Bleeding, and Clotting Disorders[a]	7 (1.3%)
Body as a whole	5 (1.0%)
Respiratory System Disorders	5 (1.0%)
Cardiovascular disorders, general	4 (0.8%)
Red Cell Disorders	4 (0.8%)
Central and Peripheral Nervous System[b]	2 (0.4%)
Secondary Terms	2 (0.4%)
Other[b]	4 (0.8%)

[a] Includes 3 GI hemorrhage/melena, 1 intracranial hemorrhage
[b] Includes 1 each of heart rate and rhythm disorders (torsade des pointes), myo- endo- pericaridal and valve disorders, psychiatric disorders, reproductive disorders, female
Reviewer's Table

Reviewer's Comment: Case report forms were requested on the patient (#0990) who developed Torsade Des Pointes. The [redacted] patient had a past medical history which included ischemic heart disease, hypertension, diabetes, asthma, recent graft infection from coronary artery bypass surgery performed on November 4, 2000, and a pulmonary embolism diagnosed by ventilation/perfusion scan on November 20, 2000. The patient was randomized to fondaparinux 7.5 mg daily. The patient was treated with fondaparinux and received a 6 day course from November 20 to November 25, 2000. His last dose was 8 am November 25, 2000. The patient received 27 other medications from November 20 to November 27. According to the case report forms, on November 26, 2000 at 5:30 a.m., the patient was noted to have developed Torsade Des Pointes. A transvenous pacer was inserted, medications were discontinued, and magnesium supplementation was given to treat the arrhythmia. The investigator stated on the case report form that there was no relationship between the study drug and the serious adverse event.

No conclusive evidence exists that there was a causative relationship between the Torsade Des Pointes the patient experienced and fondaparinux. Approximately 5900 subjects and patients have received fondaparinux and no additional Torsade Des Pointes cases have been reported. This reviewer recommends continued adverse event surveillance.

Study 63119- [redacted] -A double-blind, randomized, controlled, dose ranging trial of fondaparinux in patients [redacted]

Eleven hundred and seventy-five patients have enrolled. Six hundred and ninety-six have completed the study.

Discontinuations
Twenty-three patients (2.0%) discontinued due to adverse events. Eleven patients (1.0%) discontinued due to myo-, endo-, pericardial, and valve disorders and seven patients (0.6%) discontinued due to platelet, bleeding, and clotting disorders (predominantly hemorrhage).

Deaths
The sponsor's table below shows the SAEs that led to death during the treatment period.
Reviewer's Comment: Myo-, endo-, pericardial, and valve disorders were the predominant cause of death during the treatment period (8 patients, 0.7%) and study period (9 patients, 0.8 %).

Table (3.3.2) 3 - Number of Patients with SAEs During the Treatment Period Leading to Death in Ongoing Study 63119

WHO Organ Class Serious Adverse Events (WHO Preferred Term)	Double blind (N = 1147)
Any event*	13 (1.1%)
Myo-, endo-, pericardial and valve disorders	
Total	8 (0.7%)
Myocardial infarction	6 (0.5%)
Angina pectoris aggravated	1 (0.1%)
Cardiac tamponade	1 (0.1%)

* Includes multiple causes of death

Table (3.3.2) 3 - Number of Patients with SAEs During the Treatment Period Leading to Death in Ongoing Study 63119 (continued)

WHO Organ Class Serious Adverse Events (WHO Preferred Term)	Double blind (N = 1147)
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%)
Circulatory failure	1 (0.1%)
Respiratory system disorders	
Total	1 (0.1%)
Cyanosis	1 (0.1%)

Note: This table is based on non-validated data

Sponsor's table p. 14-15 of Safety Update

The sponsor's table below shows the number of patients with SAEs leading to death during the study period.

Reviewer's Comment: During the study period, body as a whole and cardiovascular disorders were increased as compared with during the treatment period.

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Table (4.2.1) 3 - Number (%) of Patients With SAEs During the Study Period Leading to Death in Ongoing Study 63119

WHO Organ Class Serious Adverse Events (WHO Preferred Term)	Double blind (N = 1147)
Any event	29 (2.5%)
Myo-, endo-, pericardial and valve disorders	
Total	9 (0.8%)
Myocardial infarction	6 (0.5%)
Angina pectoris aggravated	1 (0.1%)
Cardiac tamponade	1 (0.1%)
Myocardial rupture (post infarct)	1 (0.1%)
Body as a whole - general disorders	
Total	7 (0.6%)
Death	4 (0.3%)
Sudden death	2 (0.2%)
Condition aggravated	1 (0.1%)
Cardiovascular disorders, general	
Total	7 (0.6%)
Cardiac failure	4 (0.3%)
Cardiac failure left	1 (0.1%)
Circulatory failure	1 (0.1%)
Hypertension	1 (0.1%)
Heart rate and rhythm disorders	
Total	7 (0.6%)
Cardiac arrest	3 (0.3%)
Fibrillation ventricular	2 (0.2%)
AV block	1 (0.1%)
Bradycardia	1 (0.1%)
Respiratory system disorders	
Total	3 (0.3%)
Cyanosis	1 (0.1%)
Dyspnea	1 (0.1%)
Pulmonary edema	1 (0.1%)
Gastro-intestinal system disorders	
Total	1 (0.1%)
Gastric ulcer perforated	1 (0.1%)

Table (4.2.1) 3 - Number (%) of Patients With SAEs During the Study Period Leading to Death in Ongoing Study 63119 (continued)

WHO Organ Class Serious Adverse Events (WHO Preferred Term)	Double blind (N = 1147)
Liver and biliary system disorders	
Total	1 (0.1%)
Hepatic function abnormal	1 (0.1%)
Platelet, bleeding and clotting disorders	
Total	1 (0.1%)
Post-operative hemorrhage	1 (0.1%)
Resistance mechanism disorders	
Total	1 (0.1%)
Sepsis	1 (0.1%)
Secondary terms	
Total	1 (0.1%)
Surgical site reaction	1 (0.1%)
Urinary system disorders	
Total	1 (0.1%)
Renal failure acute	1 (0.1%)

Note: This table is based on non-validated data

Sponsor's table pp. 27-28 of Safety Update

Serious Adverse Events
Over 1100 patients were enrolled in the trial by the cut off date. The table below lists a summary of the 36 SAEs occurring in 63119.

Reviewer's Comment: Cardiac causes are the most common serious adverse events during the treatment and study periods in this study of patients with [redacted] *During the treatment period the top three categories of causes are: myo-, endo-, pericardial and valve disorders (31 patients, 2.7%), followed by cardiovascular disorders (16 patients, 1.4%), and heart rate and rhythm disorders (12 patients, 1.0%).*

Serious Adverse Events During Treatment for 63119

Serious Adverse Events	Number of Patients (percentage) N=1147
Any SAE	36 (3.1%)
Myo-, endo- pericardial and valve Disorders[a]	22 (1.9%)
Heart Rate, Rhythm Disorders[b]	8 (0.7%)
Platelet, Bleeding, and Clotting Disorders[c]	4 (0.3%)
Cardiovascular disorders, general	3 (0.3%)
Respiratory System Disorders	2 (0.1%)
Other[d]	7 (0.6%)

[a] Includes 20 myocardial infarction , 1 unstable angina, 1 cardiac tamponade
[b] Includes 3 cardiac arrest, 2 ventricular fibrillation, 1 each of AV block, bradycardia, sinoatrial block
[c] Includes 1 intracranial hemorrhage
[d] Includes 1 each of autonomic nervous system, body as a whole, gastrointestinal , liver and biliary system, metabolic and nutritional, red blood cell disorders, vascular (extracardiac) disorders
Reviewer's Table

Life-Threatening Adverse Events submitted to IND

N-163, N-164
Submitted on June 6, 2001 was an initial report of a 50-year-old DVT patient experiencing an intracranial bleed who was treated with both fondaparinux and coumadin from May 22nd to May 24th. On May 25th the patient received tissue-plasminogen activator for a suspected pulmonary embolism. Later that day the patient experienced a cerebral bleed confirmed by CT scan. Follow up reports document that the patient has received a caval filter and has not yet fully recovered.

N- 165
Submitted on June 18, 2001 was an initial report of a 57-year-old DVT patient who was treated with fondaparinux and coumadin from May 30th to June 3rd and who experienced circulatory collapse and hemorrhagic shock. No follow up information has been submitted for this patient.

Quarterly Safety Update

The sponsor submitted a quarterly update containing 189 serious adverse events documented from March 1, 2001 through May 31, 2001. The sponsor's quarterly update lists the following 5 serious adverse events investigators deemed likely to be caused by fondaparinux:

1) heparin-induced thrombocytopenia (1 patient)
2) hemorrhage NOS (3 patients)
3) hematuria (1 patient)
4) hematoma (1 patient)

Labeling Recommendations

The following serious adverse events should be listed in the Adverse Events section in a subsection entitled Serious Adverse Events Associated with Arixtra in Ongoing Studies.

Conclusions and Recommendations

1. No conclusive evidence exists that there is a causative relationship between the case of Torsade Des Pointes and fondaparinux. Approximately 5900 subjects and patients have received fondaparinux and no additional Torsade Des Pointes cases have been reported. Continued adverse event surveillance is recommended.

2. A presentation of Serious Adverse Events Associated with Arixtra in Ongoing Studies should be incorporated into the Adverse Events section of the labeling.

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/s/

Ann Farrell
7/13/01 07:53:17 AM
MEDICAL OFFICER

Kathy Robie-Suh
7/20/01 10:50:30 AM
MEDICAL OFFICER

Lilia Talarico
7/20/01 02:58:22 PM
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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA:	21-345 (BZ, BM)
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 and Knee Replacement Surgeries
Date submitted:	February 15, 2000; March 21, 2001; May 1, 2001; July 5, 2001
Review completed:	July 13, 2001
Medical reviewer:	Min Lu, M.D. (Efficacy Reviewer)

Table of Contents

Page

Table of Contents 2
List of Abbreviations 6

Executive Summary **7**
I. Recommendations 7
A. Recommendation on Approvability 7
B. Recommendation on Phase 4 Studies and/or Risk Management Steps 7
II. Summary of Clinical Findings 8
A. Brief Overview of Clinical Program 8
B. Efficacy 9
C. Safety (See Dr. Ann Farrell's Medical Review)
D. Dosing (See Dr. Ann Farrell's Medical Review)
E. Special Populations (See Dr. Ann Farrell's Medical Review)

Clinical Review **14**
I. Introduction and Background 14
A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups 14
B. State of Armamentarium for Indication(s) 14
C. Important Milestones in Product Development 15
D. Other Relevant Information 16
E. Important Issues with Pharmacologically Related Agents 16
II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews (See Dr. Ann Farrell's Medical Review)
III. Human Pharmacokinetics and Pharmacodynamics (See Dr. Ann Farrell's Medical Review)
IV. Description of Clinical Data and Sources 16
A. Overall Data 16
B. Tables Listing the Clinical Trials 17
C. Postmarketing Experience 19
D. Literature Review 19
V. Clinical Review Methods 20
A. How the Review was Conducted 20
B. Overview of Materials Consulted in Review 20
C. Overview of Methods Used to Evaluate Data Quality and Integrity 20
D. Were Trials Conducted in Accordance with Accepted Ethical Standards 20
E. Evaluation of Financial Disclosure 20
VI. Integrated Review of Efficacy 20
A. Brief Statement of Conclusions 20
B. General Approach to Review of the Efficacy of the Drug 22
C. Detailed Review of Trials by Indication 22
a. Overall Summary of Study Designs and Results 22
b. Detailed Review of Individual Trials by Indication 25

1. For Prophylaxis of DVT in Patients Undergoing Hip Fracture Surgery 25
Trial EFC2698 (Phase III Study) 25
Study Objectives 25
Overall Study Design 25
Study Population 26
Study Treatments 28
Efficacy Assessment 31
Safety Assessment 33
Statistical Methods 34
Study Committees 37
Protocol Amendment 38
Study Results 39
Disposition of patients 39
Protocol deviations 44
Demographic and baseline characteristics 46
Extent of exposure 52
Efficacy evaluation 58
Primary efficacy analysis 58
Secondary efficacy analysis 60
Reviewer's Summary 71
2. For Prophylaxis of DVT in Patients Undergoing Hip Replacement Surgery 72
Trial 63118 (Phase III Study) 72
Study Objectives 72
Overall Study Design 72
Study Population 73
Study Treatments 73
Statistical Methods 75
Protocol Amendment 76
Study Results 76
Disposition of patients 76
Protocol deviations 80
Demographic and baseline characteristics 82
Extent of exposure 86
Efficacy evaluation 92
Primary efficacy analysis 92
Secondary efficacy analysis 94
Reviewer's Summary 104
Trial EFC2442 (Phase III Study) 105
Study Objectives 105
Overall Study Design 105
Study Treatments 106
Protocol Amendment 108
Study Results 108
Disposition of patients 108
Protocol deviations 111
Demographic and baseline characteristics 113

Extent of exposure 117
Efficacy evaluation 122
Primary efficacy analysis 122
Secondary efficacy analysis 124
Reviewer's Summary 131
Trial DRI2643 (Phase II Dose-Ranging Study) 132
Study Objectives 132
Overall Study Design 132
Study Population 133
Study Treatments 134
Efficacy Endpoints 134
Safety Assessment 134
Statistical Methods 135
Protocol Amendment 136
Study Results 136
Disposition of patients 136
Protocol deviations 138
Demographic and baseline characteristics 139
Extent of exposure 142
Efficacy evaluation 143
Reviewer's Summary 147
3. For Prophylaxis of DVT in Patients Undergoing Major Knee Surgery 148
Trial 95-002 (Phase III Study) 148
Study Objectives 148
Overall Study Design 148
Study Population 148
Study Treatments 149
Statistical Methods 150
Protocol Amendment 151
Study Results 151
Disposition of patients 151
Protocol deviations 154
Demographic and baseline characteristics 156
Extent of exposure 160
Efficacy evaluation 165
Primary efficacy analysis 165
Secondary efficacy analysis 166
Reviewer's Summary 176
Trial 95-001 (Phase II Dose-Ranging Study) 177
Study Objectives 177
Overall Study Design 177
Study Population 178
Study Treatments 179
Efficacy Endpoints 179
Safety Assessment 179
Statistical Methods 179

Protocol Amendment 180
Study Results 181
Disposition of patients 181
Protocol deviations 182
Demographic and baseline characteristics 184
Extent of exposure 186
Efficacy evaluation 187
Reviewer's Summary 189
D. Efficacy Conclusions 190
VII. Integrated Review of Safety (See Dr. Ann Farrell's Medical Review)
VIII. Dosing, Regimen, and Administration Issues (See Dr. Ann Farrell's Medical Review)
IX. Use in Special Populations (See Dr. Ann Farrell's Medical Review)
X. Conclusions and Recommendations 196
A. Overall Efficacy Conclusions 196
B. Recommendations 197
XI. Appendix 199
Labeling recommendation 199

List of Abbreviations

Ab	Antibody
AE	Adverse event
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ASA	Acetyl salicylic acid
AST	Aspartate aminotransferase
ATIII	Antithrombin III
b.i.d.	Twice a day
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence interval
CIAC	Central Independent Adjudication Committee
CRF	Case report form
CT	Computed tomography
dL	Deciliter(s)
DMC	Data Monitoring Committee
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
Hct	Hematocrit
Hgb	Hemoglobin
ICU	Intensive care unit
ILFD	Intra-luminal filling defect
IPC	Intermittent pneumatic compression
IRB	Institutional Review Board
ITT	Intent-to-treat
IU	International unit
IV	Intravenous
kg	Kilogram
L	Liter
LFT	Liver function test
LMWH	Low molecular weight heparin
MI	myocardial infarction
mg	milligram
mL	milliliter
mmol	millimole(s)
MRI	magnetic resonance imaging
NSAID	Nonsteroidal anti-inflammatory drug
o.d.	Once a day
PDR	Physicians' Desk Reference
PE	Pulmonary embolism
PK/PD	Pharmacokinetic/Pharmacodynamic
PRBC	Packed red blood cell
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SGOT	Serum glutamate oxaloacetate transaminase
SGPT	Serum glutamate pyruvate transaminase
THR	Total hip replacement
TIA	Transient ischemic attack
UFH	Unfractionated heparin
US	Ultrasound
ULN	Upper limit of normal
V/Q	Ventilation/perfusion
VTE	Venous thromboembolic event
WHO	World Health Organization
WHO-ART	World Health Organization-adverse reaction terminology dictionary

Executive Summary

I. Recommendations

The sponsor has submitted an NDA for fondaparinux sodium as an antithrombotic product 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". The proposed dose regimen is 2.5 mg once daily subcutaneous injection administered post-operatively. The average treatment duration was 7±2 days in clinical trials.

A. Recommendation on Approvability

From a clinical perspective, fondaparinux sodium should be approved for prophylaxis of DVT, which may lead to PE, in patients undergoing hip fracture surgery, hip replacement surgery, or knee replacement surgery with the following labeling recommendations (See also Appendix 1).

1. The indications section of the labeling should be revised to read as follows:

   ARIXTRA™ is indicated for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism:
   - in patients undergoing hip fracture surgery
   - in patients undergoing hip replacement surgery
   - in patients undergoing knee replacement surgery.

   The proposed indication stated as "major orthopedic surgery of the lower limbs" is inappropriate. The specific populations as stated above should be used in the labeling.

   The proposed wording "prevention of venous thromboembolic events" is inappropriate. The "prophylaxis of DVT, which may lead to PE" should be used in the labeling to be consistent with labeling of other products.

2. In clinical studies section of the labeling, the following should be revised:

1) The first three paragraphs regarding [redacted] and the figure for overall efficacy should be deleted.
2) The number of patients enrolled and treated and the demographic data of patients (age, gender and race) should be presented under each clinical trial section.
3) The category of PE for each clinical trial should be added in the table of efficacy results.

3. In dosage and administration section, the last sentence [redacted] should be deleted.

See Dr. Ann Farrell's Medical Review for labeling recommendations for safety.

For prophylaxis of DVT in patients undergoing hip fracture surgery
There is no currently approved product for prophylaxis of DVT, which may lead to PE, in patients undergoing hip fracture surgery. Pulmonary embolism is one of the most common causes of death in this population. The current application has demonstrated the effectiveness of fondaparinux sodium 2.5mg SC post-operatively once daily by showing superiority to enoxaparin 40 mg SC post-operatively once daily for prophylaxis of DVT in patients undergoing hip fracture surgery in one large, multicenter study ($p<0.0001$). Fondaparinux sodium may provide significant benefit to this population.

For prophylaxis of DVT in patients undergoing hip replacement surgery
The current application has demonstrated that fondaparinux sodium 2.5 mg SC post-operatively once daily was superior to an established approved regimen, enoxaparin 40 mg SC pre-operatively once daily ($p<0.0001$). Fondaparinux sodium was not superior to enoxaparin 30 mg SC post-operatively every 12 hours, for prophylaxis of DVT in patients undergoing hip replacement surgery ($p=0.099$). Since there is a high risk of DVT, which may lead to a life-threatening complication of PE, in patients undergoing hip replacement surgery, fondaparinux sodium, a product with better effectiveness than a currently approved regimen (enoxaparin 40mg SC once daily), may provide more benefit to this population.

For prophylaxis of DVT in patients undergoing knee replacement surgery
The current application has demonstrated that fondaparinux sodium 2.5 mg post-operatively once a day is superior to an established approved product (enoxaparin 30 mg SC post-operatively every 12 hours) with high statistical significance ($p<0.0001$). Since there is a high risk of DVT, which may lead to a life-threatening complication of PE, in patients undergoing knee replacement surgery, fondaparinux sodium, a product with better effectiveness than currently approved product (enoxaparin), may provide more benefit to this population.

The effectiveness and safety have not been studied adequately in patients of races other than Caucasian.

B. Recommendation on Phase 4 Studies and Risk Management Steps

Pediatric studies waiver has been granted to this product for the proposed indication prior to NDA submission. [redacted]. See Dr. Ann Farrell's Medical Review for risk management steps.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

A total of four pivotal trials were conducted to support the proposed indications. These included one trial (Study EFC2698) in 1711 patients undergoing hip fracture surgery, two trials (Studies 63118 and EFC2442) in 4584 patients (2309 and 2275 for each study,

respectively) undergoing elective hip replacement surgery, and one trial (Study 95-002) in 1049 patients undergoing major knee surgery.

A total of 3616 patients have been exposed to fondaparinux sodium in the above four Phase III pivotal trials and an additional 1207 patients have been exposed to fondaparinux sodium in Phase II trials in orthopedic surgical patients.

B. Efficacy

For prophylaxis of VTE in patients undergoing hip fracture surgery

One pivotal trial (Study EFC2698) was submitted to support this proposed indication.

Study EFC2698 was a multicenter (99 centers in 21 countries), randomized, double-blind, double-dummy, parallel groups controlled study of Org31540/SR90107A 2.5 mg SC once daily as compared to enoxaparin 40 mg SC once daily in patients undergoing hip fracture surgery. The primary efficacy endpoint was a composite endpoint of VTE up to Day 11 that included adjudicated venographically positive DVT and adjudicated symptomatic non-fatal or fatal PE. A total of 1711 patients (849 in the Org31540/SR90107A group and 862 in the enoxaparin group) were randomized in the study, 1673 were treated, and 1250 (626 in the Org31540/SR90107A group and 624 in the enoxaparin group) were evaluable for the primary efficacy endpoint. Patients ranged in age from 17 to101 years (mean age 77.0 years) with 25% of men and 75% of women. Patients were 99.2% Caucasian, 0.8% other races. The study was an adequate and well-controlled study.

Study EFC2698 demonstrated that Org31540/SR90107A 2.5 mg once daily SC is superior to enoxaparin 40 mg once daily SC with highly statistically significance for the primary efficacy endpoint of VTE up to day 11 (8.3% vs. 19.1%, $p=2.6 \times 10^{-8}$). The difference between two groups was mainly contributed by the component of DVT (7.8% vs. 18.1%, $p=1 \times 10^{-8}$). There was a significantly lower incidence of proximal DVT (0.9% vs. 4.3%, p=0.0001) as well as distal DVT (6.7% vs. 15.0%, $p=2 \times 10^{-6}$) in the Org31540/SR901 treatment group as compared to the enoxaparin treatment group. There was no difference in the incidence of PE up to day 11 between the two treatment groups (0.5 % in each treatment group, p=1.0). For symptomatic VTE, there was no difference between two treatment groups up to day 11 (p=1.0) and up to day 49 (p=0.47).

Only a single trial, Study EFC2698, was conducted in patients undergoing hip fracture surgery. However, this was a large, multicenter study involving 99 centers in 21 countries. Efficacy results were consistent in favor of Org31540/SR90107A across the majority of countries (18/21), study centers, gender, age, body mass index, creatinine level, previous history of VTE, previous history of antithrombotic medication, type of fracture, type of anesthesia, type of prosthesis, use of cement, and duration of surgery. In addition, Study EFC2698 demonstrated a statistically very persuasive finding with very low p-value (3×10^{-8}). These characteristics of Study EFC2698 make this single adequate and well-controlled trial adequate to provide substantial support for the effectiveness claim of prophylaxis of DVT in hip fracture surgery.

Study EFC2698 did not enroll any US patient. However, the results from study 95002 which was conducted mostly in US patients undergoing knee replacement surgery supported the antithrombotic effect of Org31540/SR90107A in US patients.

Overall, the sponsor has provided substantial evidence to support the effectiveness of Org31540/SR90107A for prophylaxis of DVT, which may lead to PE, in patients undergoing hip fracture surgery.

For prophylaxis of VTE in patients undergoing total hip replacement surgery

Two pivotal trials (Studies 63118 and EFC2442) were submitted for this indication.

Study 63118 was a multicenter (74 centers in 16 European countries), randomized, double-blind, double dummy, parallel groups study of Org31540/SR90107A 2.5 mg SC once daily as compared to enoxaparin 40 mg SC once daily in patients undergoing hip replacement surgery. The primary efficacy endpoint was a composite endpoint of VTE up to Day 11 that included adjudicated venographically positive DVT and adjudicated symptomatic non-fatal or fatal PE. A total of 2324 patients (1162 in each treatment group) were randomized in the study, 2278 were treated, and 1827 (908 in the Org31540/SR90107A group and 919 in the enoxaparin group) were evaluable for the primary efficacy endpoint. Patients ranged in age from 24 to 97 years (mean age 65.3 years) with 43% of men and 57% of women. Patients were 99.2% Caucasian, 0.8% other races. This study was an adequate and well-controlled study.

Study 63118 demonstrated that Org31540/SR90107A 2.5 mg once daily SC is superior to enoxaparin 40 mg once daily SC with a highly statistically significant result for the primary efficacy endpoint of VTE up to day 11 (4.1% vs. 9.2%, $p=9 \times 10^{-6}$). The difference between two groups was mainly contributed by the component of DVT (4.0% vs. 9.0%, $p=1 \times 10^{-5}$). There was a significantly lower incidence of proximal DVT (0.7% vs. 2.5%, p=0.002) as well as distal DVT (3.3% vs. 7.3%, p=0.0001) in the Org31540/SR901 treatment group as compared to the enoxaparin treatment group. There was no difference in the incidence of PE up to day 11 between the two treatment groups (0.2% in each treatment group, p=1.0). For symptomatic VTE, there was no difference between two treatment groups up to day 11 (p=0.73) and up to day 49 (p=0.66).

Study EFC2442 was a multicenter (139 centers in 3 countries including 94 centers [58% of patients] in US), randomized, double-blind, parallel group study of Org31540/SR90107A 2.5 mg SC once daily as compared to enoxaparin 30 mg SC twice daily in 2275 patients undergoing hip replacement surgery. The primary efficacy endpoint was the same as Study 63118. The main difference between Study EFC2442 and Study 63118 was the dose regimen for enoxaparin. A total of 2275 patients (1138 in the Org31540/SR90107A group and 1137 in the enoxaparin group) were randomized in the study, 2257 were treated, and 1584 (787 in the Org31540/SR90107A group and 797 in the enoxaparin group). Patients ranged in age from 18 to 92 years (mean age 64.6

years) with 48% of men and 52% of women. Patients were 93.8% Caucasian, 4.3% Black, <1% Oriental, and 1.7% others.

Study EFC2442 failed to demonstrate the superiority of Org31540/SR90107A 2.5 mg once daily SC over enoxaparin 30 mg twice daily SC for the primary efficacy endpoint of VTE up to day 11. However, the study showed that patients treated with Org31540/SR90107A 2.5 mg once daily SC had a numerically lower incidence of VTE up to day 11 than those treated with enoxaparin 30 mg every 12 hours SC (6.1% vs. 8.3%, p=0.099). In addition, there was a significantly lower incidence of any DVT (5.6% vs. 8.3%, p=0.047) and distal DVT only (4.3% vs. 6.8%, p=0.037) in the Org31540/SR901 treatment group as compared to the enoxaparin treatment group. There was no difference in the incidence of PE (0.6% in Org31540/SR901 vs. 0.1% in enoxaparin, p=0.122) and proximal DVT (1.7% in Org31540/SR901 vs. 1.2% in enoxaparin, p=0.42) up to day 11 between the two treatment groups. For symptomatic VTE, there was a statistically significantly higher incidence in Org31540/SR901 group as compared to that in the enoxaparin group up to day 11 (p=0.006) and up to day 49 (p=0.013).

In Study EFC2442, the incidence of VTE up to day 11 was numerically lower in US (5.0% vs. 8.0%, p=0.07) and Australia (4.7% vs. 10.8%, p=0.09) but higher in Canada (8.8% vs. 7.5%, p=0.61) in Org31540/SR90107A group as compared to enoxaparin group. After adjusting for the interaction between treatment and country, the p-value for treatment defference (0.069) still failed to reach statistical significance, but was close to 0.05 significance level.

Although Study EFC2442 failed to demonstrate the superiority of Org31540/SR90107A over enoxaparin for VTE up to day 11, the overall results including the lower incidence of VTE and the significantly lower incidence of DVT (p=0.047) in patients who received Org31540/SR90107A treatment are consistent with results from Study 63118.

Overall, the sponsor has provided substantial evidence to support the effectiveness of Org31540/SR90107A for prophylaxis of DVT, which may lead to PE, in patients undergoing total hip replacement surgery.

For prophylaxis of VTE in patients undergoing major knee surgery

One pivotal trial (Study 95-002) was submitted for this indication.

Study 95-002 was a multicenter (64 centers in US and Canada), randomized, double-blind, parallel group study of Org31540/SR90107A 2.5 mg SC once daily as compared to enoxaparin 30 mg SC twice daily in 1049 patients undergoing major knee surgery. The primary efficacy endpoint was a composite endpoint of VTE up to Day 11 that included adjudicated venographically positive DVT and adjudicated symptomatic non-fatal or fatal PE. A total of 1049 patients (526 in the Org31540/SR90107A group and 523 in the enoxaparin group) were randomized in the study, 1034 were treated, and 724 (361 in the Org31540/SR90107A group and 363 in the enoxaparin group) were evaluable for the

primary efficacy endpoint. Patients ranged in age from 19 to 94 years (mean age 67.5 years) with 41% of men and 59% of women. Patients were 88% Caucasian, 8% Black, <1% Oriental, and 3% others. This study was an adequate and well-controlled study.

Study 95-002 demonstrated that Org31540/SR90107A 2.5 mg once daily SC is superior to enoxaparin 30 mg twice daily SC with a highly statistically significant result for the primary efficacy endpoint of VTE up to day 11 (12.5% vs. 27.8%, $p=2.7 \times 10^{-7}$). The difference between two groups was mainly contributed by the component of DVT (12.5% vs. 27.0%, $p=9.6 \times 10^{-7}$). There was a significantly lower incidence of distal DVT only (9.4% vs. 21.3%, $p=9 \times 10^{-6}$) in Org31540/SR901 treatment group as compared to enoxaparin treatment group. There was no difference in the incidence of PE (0.3% vs. 1.1%, p=0.37) and proximal DVT (2.4% vs. 5.4%, p=0.057) up to day 11 between the two treatment groups. For symptomatic VTE, there was no difference between the two treatment groups up to day 11 (p=0.34) and up to day 49 (p=0.30).

Only a single pivotal trial, Study 95-002, was conducted in patients undergoing major knee surgery. However, Study 95-002 was a multicenter study involving 64 centers in United States and Canada. Efficacy results were consistent in favor of Org31540/SR90107A across country, study center, gender, age, body mass index, creatinine level, previous history of VTE, type of surgery (primary or revision), type of anesthesia (regional only or other), use of cement, and duration of surgery. The trial 95-002 demonstrated a statistically very persuasive finding with a very low p-value (3×10^{-7}). These characteristics of Study 95-002 make this single adequate and well-controlled study as adequate to provide substantial support for the effectiveness claim of prophylaxis of DVT in knee replacement surgery patients.

It appears that most patients enrolled in this study underwent knee replacement surgery although a major knee surgery, a broader term, was required in the inclusion criteria. The Agency requested that the sponsor identify the specific type of major knee surgery during the review and the sponsor responded that it was unable to identify the type of major knee surgeries in this study. However, 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.

Overall, the sponsor has provided substantial evidence to support the effectiveness of Org31540/SR90107A for prophylaxis of DVT, which may lead to PE, in patients undergoing knee replacement surgery.

Critical difference between the recommended indications based on the study results and the Sponsor's proposed labeling

Indicated population

Patients undergoing hip fracture surgery, hip or knee replacement surgery were studied in separate clinical trials. However, the proposed labeling indicates the population "patients

undergoing major orthopedic surgery of the lower limbs" with the above surgeries listed as examples.

The proposed "major orthopedic surgery of the lower limbs" includes a broad range of surgeries: surgeries for fractures for any part of lower limbs and any ankle/foot surgeries besides the three specific surgeries that have been studied in the submitted clinical trials. Patients undergoing other types of surgeries have never been studied for this drug and they may well have a different benefit/risk from the treatment. Therefore, the proposed labeling for patients undergoing major orthopedic surgery is not acceptable. The indicated population should be specified as the patient population studied in the trials. Thus, three separate indications in these three different populations should be used in the labeling.

Efficacy Event

In the proposed indication, prophylaxis of VTE that includes DVT and PE was proposed. Although VTE was a primary efficacy endpoint in four pivotal trials (EFC2698, 63118, EFC2442, and 95-002), the difference in the incidence of VTE between the two treatment groups was mainly due to the difference in the incidence of DVT in the three positive trials (EFC2698, 63118 and 95-002). There were no differences in the incidence of PE between the two treatment groups in any of the four trials. Using VTE instead of DVT in the labeling may misrepresent the overall study results. For consistency with labeling for previously approved drugs for these types of indications, the phrase "deep vein thrombosis, which may lead to pulmonary embolism" should be used in the labeling in the indication statement.

Unsolved efficacy issue

Effectiveness and safety of Org31540/SR90107A have not been studied adequately in patients with races other than Caucasian.