CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-345

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NDA 21-345 (AMENDMENT 015) SUBMISSION DATE: 08/31/01

FONDAPARINUX SODIUM INJECTION (ARIXTRA®) 2.5 MG

FONDA BV

TRIPOLIS 300
BURGENWEESHUISPAD 311
1076 HS AMSTERDAM
THE NETHERLANDS

AUTHORIZED U.S. AGENT: RICHARD P. GURAL, Ph.D.
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MALVEM, PA 19355 REVIEWER: David G. Udo, Ph.D.

TYPE OF SUBMISSION: RESPONSE TO APPROVABLE LETTER

SUBMISSION CODE: 1P

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1. SYNOPSIS/BACKGROUND

Amendment 015 was submitted to NDA 21-345 for fondaparinux sodium (Arixtra®), by the sponsor, on August 31, 2001. Fondaparinux sodium is proposed as an anticoagulant for the prophylaxis of venous thromboembolic event (VTE) in adult patients undergoing major orthopedic surgery of the lower limbs such as hip fracture and major knee or hip replacement surgeries.

In this amendment, the sponsor provides responses on the issues raised in the Agency's Approvable Letter dated August 15, 2001.

II: REVIEW OF SPONSOR'S RESPONSES ON CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS ISSUES

Section II: Clinical Pharmacology Issues

Anti-Factor Xa Activity per Milligram Dose of Fondaparinux: The sponsor was requested to include anti- Factor Xa (anti-Xa) per mg of fondaparinux sodium in the drug product labeling and to use it to describe the pharmacodynamic properties of the drug. The sponsor states (i) that expressing the pharmacodynamic properties of fondaparinux sodium in terms of anti-Xa activity would require a common system for expressing the anti-Xa activities of fondaparinux sodium and LMWH or UFH, (ii) that since such a system currently does not exist, the use of the International UFH or LMWH standard for expressing the pharmacodynamics of fondaparinux sodium is not appropriate, (iii) that the pharmacodynamic activity of fondaparinux sodium is best expressed in gravimetric units since the drug can be accurately quantified in biological fluids by physiochemical methods and (iv) that the only scientifically valid standard for assessing the anti-Xa activity of fondaparinux sodium is fondaparinux sodium itself.

The sponsor then submits the following information to support these statements:

(a) Following the development of LMWH, the International UFH standard was used initially to calibrate the anti-Xa and anti-IIa activities of both UFH and LMWH. In the early 1980s, data emerged demonstrating a differential influence of experimental conditions on these UFH and LMWH activities (primarily due to their divergent chemical structures and molecular weights) which resulted in non-parallel dose response curves for these drugs. Accordingly, a separate International standard of anti-Xa and anti-IIa was developed for LMWH.

(b) During the development of fondaparinux sodium, it was noted that its anti-Xa activity was also influenced by experimental conditions. The presence of calcium ions lowered the IC_{50} of heparin (UFH) but did not affect the IC_{50} of LMWH or fondaparinux sodium. A change in pH from 7.35 to 8.4 decreased the antithrombin affinity of UFH, LMWH and fondaparinux sodium to different extents.

Based on this information, the sponsor feels that the use of International UFH or LMWH standard to assess the anti-Xa activity of fondaparinux sodium could also result in non-parallel dose response curves and that neither standard would be appropriate for assessing the anti-Xa activity of fondaparinux sodium.

Regarding the potential for problems with the use of the International UFH or LMWH standard for the assessment of the anti-Xa activity of fondaparinux sodium, the sponsor's response seems reasonable. However, the need for such assessment in clinical practice, may necessitate a discussion with the sponsor on developing a reliable standard for accurate assessment of the anti-Xa activity of the drug in patients (see Recommendation [page 10]).

In the interim, the following anti-Xa activity statement should be included in the proposed labeling:

[

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The estimated anti-Xa activity $t_{max(ss)}$ of 3 h postdose is based on the fondaparinux $t_{max(ss)}$ of approximately 3 h.

2. Descriptive Statistics of Anti-Xa Activity for the 2.5 mg Subcutaneous Dose of Fondaparinux in Clinical Trials: The sponsor was requested to provide the descriptive statistics of the anti-Xa activity achieved with fondaparinux sodium in the clinical trials evaluating the labeling recommended dose of 2.5 mg administered by subcutaneous injection. The sponsor states that in the clinical trials, fondaparinux sodium was quantified in gravimetric units and not in terms of anti-Xa activity. The reason is as explained under item 1 above.

Section III: Post Marketing (Phase IV) Commitment (Agency's Comment #11)

The sponsor was requested to commit to post-marketing (Phase IV) studies evaluating [

] (b) the safety, pharmacokinetics and pharmacodynamics of fondaparinux sodium in patients with varying degrees of impaired hemostasis secondary to hepatic insuficiency ——— This review focuses on the pharmacokinetic and pharmacodynamic aspects of the sponsor's response.

[

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(b) Phase IV Study Evaluating the Safety, Pharmacokinetics and Pharmacodynamics of Fondaparinux Sodium in Patients with Varying Degrees of Impaired Hemostasis Secondary to Hepatic Insuficiency

The sponsor acknowledges that hepatic impairment is accompanied by impaired hemostatis which, in turn, increases the risk of bleeding. Accordingly, the sponsor agrees to the requested Phase IV study to evaluate the safety, pharmacokinetics and pharmacodynamics of fondaparinux sodium in patients with varying degrees of impaired hemostasis secondary to hepatic impairment. The sponsor states that the following steps would be involved in the study:

1. Development of a clinical protocol "under the advice of three independent experts —— in hemostasis and liver disease"

2. Conducting the study with —— monitoring all aspects of it and determining the fondaparinux dose for each Child-Pugh class of hepatic impairment

3. Obtaining pharmacokinetic and pharmacodynamic data in at least six patients and safety data in at least 12 patients in each Child-Pugh class following subcutaneous administration of fondaparinux sodium injection 2.5 mg "in the absence of premature discontinuation of the study per —— independent decision"

4. Presenting study results approximately 4 years after the approval of NDA 21-345.

The number of subjects for pharmacokinetic and pharmacodynamic evaluation in the proposed study (see item 3 above) seems reasonable. HFD-180 will assess the suitability of the proposed study plan and of the due date for submission of study results to the Agency.

V. RECOMMENDATION

Amendment 015 submitted to NDA 21-345 for fondaparinux sodium (Arixtra®) injection by the sponsor on August 31, 2001 has been reviewed by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Bipharmaceutics. From a pharmacodynamic perspective, the sponsor's response related to the Agency's request for descriptive statistics of anti-Factor Xa (anti-Xa) activity for the 2.5 mg subcutaneous dose of fondaparinux in clinical trials, inclusion of anti-Xa per mg of fondaparinux sodium in the drug product labeling and the use of anti-Xa activity to describe the pharmacodynamic properties of the drug seems reasonable. However, if assessment of the anti-Xa activity of fondaparinux in patients is an inalienable component of clinical practice, then it would be necessary to initiate a discussion with the sponsor on developing a reliable and accurate standard for it.

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Please convey this Recommendation and Overall Comments 1 and 2 (page 9), as appropriate, to the sponsor.

David G. Udo, Ph.D.
Division of Pharmaceutical Evaluation II

Concurrence: Suresh Doddapaneni, Ph.D. _____

cc: NDA 21-345, HFD-180, HFD-180 (Oliver), HFD-870 (Malinowski, Hunt, Doddapaneni and Udo), CDR (Attn: Zom Zadeng).

APPEARS THIS WAY
ON ORIGINAL

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

/s/

David Udo
11/15/01 11:00:20 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
11/16/01 08:48:03 AM
BIOPHARMACEUTICS

APPEARS THIS WAY
ON ORIGINAL

NDA 21-345 SUBMISSION DATE: 02/15/01

FONDAPARINUX SODIUM INJECTION (XANTIDAR®) 2.5 MG

FONDA BV

TRIPOLIS 300
BURGENWEESHUISPAD 311
1076 HS AMSTERDAM
THE NETHERLANDS

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REVIEWER: David G. Udo, Ph.D.

PHARMACOMETRICS CONSULTANT: Sam Haidar, R.Ph, Ph.D.

TYPE OF SUBMISSION: ORIGINAL NDA: NEW MOLECULAR ENTITY (NME)

SUBMISSION CODE: 1P

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1. SYNOPSIS/BACKGROUND

What Is the Drug? The drug is fondaparinux sodium injection (Xantidar®) 2.5 mg.

What is the Pharmacologic Class of the Drug? Xantidar® is an anticoagulant.

What Is the Indication? Xantidar® is proposed for the prophylaxis of venous thromboembolic event (VTE) in adult patients undergoing major orthopedic surgery of the lower limbs such as hip fracture and major knee or hip replacement surgeries.

What is the Mechanism of Drug Action? The sponsor states that fondaparinux exerts antithrombotic activity via antithrombin III (ATIII)-mediated inhibition of Factor Xa as follows: (i) fondaparinux selectively binds to and enhances the activity of ATIII, (ii) the activity-enhanced ATIII inhibits the activity of Factor Xa, (iii) inhibition of Factor Xa diminishes the conversion of prothrombin to thrombin and (iv) thrombin deficiency inhibits the conversion of fibrinogen to fibrin for blood clot formation.

What Is the Scientific Rationale for Proposing Xantidar® for the Stated Indication when other Therapies (i.e., Unfractionated Heparins (UFHs) and Low Molecular Weight Heparins (LMWHs) with the Same Indication and Similar Mechanism of Action Are already on the Market? Based on the information contained in the NDA, the currently marketed drugs with the same mechanism of action (the UFHs and LMWHs) exhibit significant anti-IIa activity and also bind to the endothelium, platelets and non specific proteins (in the order of UFHs > LMWHs). Subsequently, these drugs exhibit low bioavailability, dose dependent and variable pharmacokinetics and require therapeutic drug monitoring. Fondaparinux, on the other hand, is shown to exhibit high bioavailability (≈ 100%) and dose independent kinetics (at therapeutic doses), and subsequently, requires no therapeutic drug monitoring. Thus, the use of fondaparinux for the proposed indication is expected to be more advantageous as compared to the use of the UFHs and LMWHs.

What Are the Labeling Recommended Dosage and Route of Administration? The labeling recommended dosage is 2.5 mg administered by subcutaneous injection once daily. It is recommended that the initial dose be administered 6 h following the closure of surgery, provided that hemostasis has been established. The sponsor further states that, in controlled clinical trials, the average duration of treatment was 7 days and that treatment up to 11 days was well tolerated.

What Is the Nature of this NDA Submission? This NDA is submitted in accordance with the provisions of section 505(b)(1) of the Federal Food, Drug and Cosmetics Act (the Act). The sponsor submits 55 pharmacokinetic/pharmacodynamic studies in 309 volumes to support NDA approval. The submitted studies are consistent with the Agency's bioiavailability study requirements set forth in the **CFR** under **"Guidelines for the conduct of an in vivo bioavailability study"** [CFR 320.25 (a) (2) and (3)].

What Are the Clinical Safety and Efficacy End-points? The clinical safety and efficacy end-points are assessment of major bleeding and venous thromboembolic events, respectively.

What Is the Drug Product Composition? The drug product contains fondaparinux sodium ~mg/mL in a sodium chloride solution containing ——— The recommended dose (2.5 mg) is supplied in a 0.5 mL/ pre-filled syringe.

Is Adequate Information Provided on the Methods of Sample Analysis? The submitted pharmacokinetic studies utilized adequately described and validated anti-Factor Xa (anti-Xa) methods for analysis of biological samples.

Is Adequate Information Provided on the Methods of Pharmacokinetic Analysis? The non-compartmental and population pharmacokinetic methods used in the submitted studies are adequately described. The population pharmacokinetic analyses were evaluated by a Division of Pharmaceutical Evaluation II (DPE II) pharmacometrics expert and were considered acceptable (see Attachment I).

Summary of Pharmacodynamic Findings: Fondaparinux binding of $\geq$ 94% to ATIII in the expected range of steady state, therapeutic, plasma levels of fondaparinux ($\leq$1.5 mg/mL) was demonstrated *in vitro*. Fondaparinux does not significantly affect the activities in the blood coagulation cascade other than inhibition of Factor Xa.

Summary of Pharmacokinetic Findings: The absolute bioavailability of subcutaneously administered fondaparinux is 100%. The proposed market formulation and the clinical tested formulation of fondaparinux 2.5 mg are bioequivalent. Single dose C_{max} and t_{max} are 0.34 mg/mL and 2 h, respectively. In the target patient population treated with the 2.5 mg dose, $C_{ss(min)}$ is ——— mg/mL, $C_{ss(max)}$ is ——— mg/mL and $t_{max(ss)}$ is 3 h. Fondaparinux distributes mainly in blood (both V_d and a V_{ss} are in the range of 7 L and 11 L). It dose not bind significantly to plasma proteins other than ATIII. In individuals with normal renal function, fondaparinux is eliminated in urine mainly as unchanged drug. In patients with moderate or severe renal impairment or over 75 years old, the incidents of major bleeding related to reduced drug clearance warrant dosage adjustment as recommended in the Labeling Comments. In-vivo metabolism of fondaparinux has not been studied. Fondaparinux does not interact significantly with aspirin, piroxicam, warfarin and digoxin. Based on *in vitro* study findings, significant interactions of fondaparinux with drugs metabolized by CYPs 2A1, 2A6, 2C9, 2C19, 2D6, 3A4 and 3E1 are not expected. Fondaparinx clearance is low in patients weighing less than 50 kg and monitoring of these patients for bleeding is recommended (see Labeling Comments). The pharmacokinetics of fondaparinux is not significantly affected by race or gender.

Summary of Pharmacokinetic/Pharmacodynamic Relationship: In the single dose range of 0.75 mg to 8 mg, drug efficacy increases and incidents of major bleeding increased with increasing dose. Furthermore, the increase in major bleeding incidents in patients with moderate or severe renal impairment secondary to decreased drug clearance suggests that major bleeding incidents increase with increasing drug concentration (which results from reduced drug clearance).

What is the Recommendation? The submitted pharmacokinetic and pharmacodynamic information is deemed acceptable for consideration in the NDA approval decision process.

II. SUMMARY OF INFORMATION ON PHARMACOKINETICS AND PHARMACODYNAMICS

1. *Is Adequate Information Provided on Absorption and Bioavailability of Fondaparinux Following Subcutaneous Administration of Xantidar®?*

(a) Absorption Pharmacokinetic Parameters: The absorption pharmacokinetic characteristics of fondaparinux were evaluated in 24 healthy caucasian subjects (13 males [age range = 60-75 years, weight range = 57-117 kg and eleven females [age range = 60-75 years, weight range = 51-85 kg) treated with fondaparinux (Xantidar® [Org3154/SR901072A]) 2, 4 and 8 mg by subcutaneous injection and 4 mg by intravenous injection in an open label, four-period, crossover study (Protocol 63106). The washout period between treatments was $\geq$ 7 days. For each treatment regimen, fondaparinux pharmacokinetic parameters were determined by non-compartmental analysis. The mean fondaparinux profiles for all treatment regimens are presented in Fig. 1. The absorption kinetics results are presented in Table 1.

Fig. 1. Plot of Mean Concentration of Fondaparinux Versus Time Following Single Dose of Fondaparinux Sodium 4 mg Administered by Intravenous Injection and 2, 4 and 8 mg Administered by Subcutaneous Injection (Dotted line represents limit of quantification [LOQ: ——— in acid equivalence])

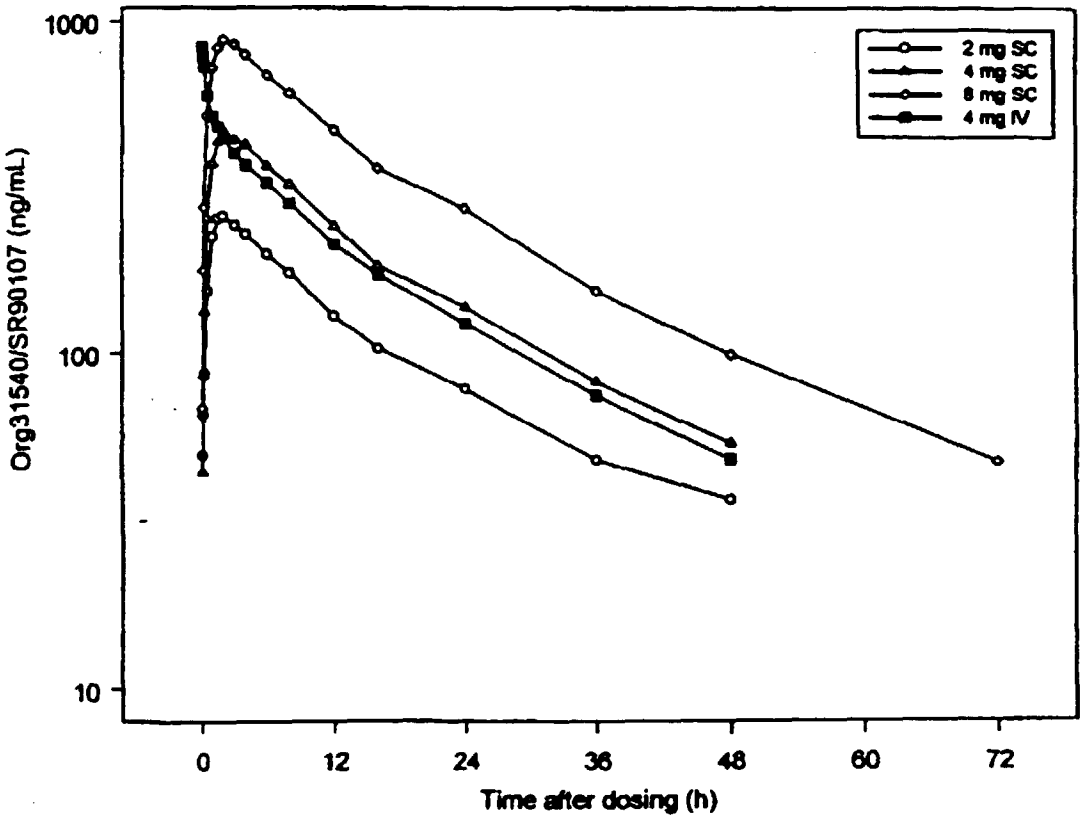


Table 1. Mean (CV%) Absorption Pharmacokinetic Parameters of Fondaparinux Following Single Doses of Fondaparinux Sodium 4 mg Administered by Intravenous Injection and 2, 4 and 8 mg Administered by Subcutaneous Injection

Mean (%CV) Absorption Kinetic Parameter	4 mg IV (n=25)	2 mg Sc (n=23)	4 mg Sc (n=24)	8 mg Sc (n=24)
C_{max} (ng/mL)	858.7 (18.3%)	278.8 (29.8%)	478.3 (21.6%)	911.0 (19.9%)
t_{max} (h)	n/a	2.2 (37.7%)	2.6 (46.2%)	2.3 (35.2%)
AUC_{0-t} ($ng.mL^{-1}.h$)	8639 (20.0%)	4633 (22.5%)	8918 (25.1%)	17910 (18.1%)
$AUC_{0-\infty}$ ($ng.mL^{-1}.h$)	9673 (18.9%)	5632 (22.3%)	10003 (23.9%)	19237 (19.2%)

Based on these data, C_{max} and AUC increased with increasing subcutaneous dose but t_{max} was dose independent.

(b) Absolute Bioavailability: In the study described above, for each subcutaneous dose (2 mg, 4 mg and 8 mg), absolute bioavailability of fonadparinux was determined as the ratio of dose normalized AUC_{sc} to AUC_{iv} values. Log-transformed AUC values were utilized. Point estimates and 90% confidence intervals were determined by analysis of variance (ANOVA), thus taking into consideration the effects of treatment, period and subject on bioavailability. Equivalence of AUC_{sc} to AUC_{iv} was concluded when the 90% confidence interval was in the range of ——— The results are summarized in Table 2.

Table 2. Bioavailability Assesment of Fondaparinux Following Single Doses of Fondaparinux 2, 4 and 8 mg Administered by Subcutaneous Injection using Fondaparinux 4 mg Administered by Intravenous Injection as Reference

Parameter (Dose Normalized)	Test/Reference of Ratio	Point Estimate	90% Confidence Interval	P-value
$AUC_{0-\infty}$	2 mg_{sc}/4 mg_{iv}	1.12	1.07 – 1.18	0.0002
	4 mg_{sc}/4 mg_{iv}	1.07	1.02 – 1.12	0.0233
	8 mg_{sc}/4 mg_{iv}	1.07	1.02 – 1.12	0.0153

The 90% confidence intervals of the dose-normalized, log transformed $AUC_{0-\infty}$ ratios (test/reference) were in the range of ——— required for bioequivalence. Based on these data, absolute bioavailability was 112% for the 2 mg subcutaneous dose and 107%

for the 4 mg and 8 mg subcutaneous doses. These results suggest 100% absolute bioavailability of fondaparinux in the range of 2 - 8 mg administered by subcutaneous injection (i.e., this dose range is completely absorbed at the subcutaneous injection site).

The sponsor relates F values > 100% to possible under-estimation of AUC for the intravenous dose.

2. ***Is Adequate Information Provided on Dose Proportionality of Fondaparinux Kinetics?***

In the study described in item 1 above (Protocol 63106), dose proportionality of AUC and C_{max} following subcutaneous Xantidar® 2, 4, and 8 mg was assessed by the bioequivalence approach (described in item 1). Furthermore, the potential for deviation from dose proportionality was assessed for these parameters in a mixed effect model using the following log-transformed power model.

Log(parameter) = Log(α) + β*Log('dose') + 'gender' + 'period'

The effect of increasing the dose r-fold on AUC and C_{max} was estimated at the 95% confidence level by exponentiation of r to the power of the estimated value (βcap) of β (**i.e.,** $r^{\beta cap \pm t_{0.975,df}} * SE * \beta cap$, where df is the degree of freedom calculated using Satterthwaite's procedure and SE is the standard error). The results for the bioequivalence method of dose proportionality assessment are summarized in Table 3.

Table 3. Dose Proportionality Assessment of Fondaparinux Following Single Doses of Xantidar® 2, 4 and 8 mg Administered by Subcutaneous Injection

Parameter (Dose Normalized)	Ratio of Means (Test/Reference)	Point Estimate	90% Confidence Interval	P-value
$AUC_{0-\infty}$	4 mg_{sc}/2 mg_{sc}	0.95	0.91 – 1.00	0.0917
	8 mg_{sc}/2 mg_{sc}	0.96	0.91 – 1.00	0.1274
	8 mg_{sc}/4 mg_{sc}	1.00	0.96 – 1.05	0.8641
C_{max}	4 mg_{sc}/2 mg_{sc}	0.96	0.88 – 0.97	0.0690
	8 mg_{sc}/2 mg_{sc}	0.93	0.91 – 1.00	0.0114
	8 mg_{sc}/4 mg_{sc}	0.98	0.93 – 1.03	0.4503

In each case, the 90% confidence intervals of the ratio, test/reference for log-transformed AUC and C_{max} were in the range of ——— required for bioequivalence..

Based on these findings it is considered that in the Xantidar® dose range of 2-8 mg, fonadaparinux AUC is dose proportional.

It needs to be noted, however, that dose proportionality is not an issue of concern at this time since, in the drug product labeling, only one dose level of Xantidar® (2.5 mg) is recommended for subcutaneous administration.

3. ***Is Bioequivalence of the Xantidar® Formulation Proposed for Marketing and the Clinically Tested Xantidar® Formulation Adequately Assessed?***

(a) Pharmacokinetic Parameters: The bioequivalence of proposed market formulation (Formulation 2B2) of Xantidar® and the clinically tested formulation of Xantidar® was assessed in 16 healthy male subjects (age range: 20-31 years, weight range: 65.0-91.2 kg) (Protocol BDR3780). This was an open-label, randomized, two-period, single dose, crossover study conducted at a single center. Each subject was treated with subcutaneous injection of Xantidar® 2.5 mg as the proposed market formulation (5 mg/mL [supplied in a 0.5 mL pre-filled syringe]) (Test) and as the clinically tested formulation (10 mg/mL [supplied in a 0.25 mL pre-filled syringe]) (Reference), in a crossover fashion, under fasted conditions. In each treatment regimen, the drug was injected into the skin of the abdomen of each subject by a physician and the skin fold was held throughout the injection. The washout period between treatments was $\geq$ 7 days. Fondaparinux pharmacokinetic parameters were determined by non-compartmental analysis. The mean fondaparinux plasma concentration profiles for both treatment regimens are presented in Fig. 2. The pharmacokinetic results are summarized in Table 4.

Fig. 2. Plot of Mean $\pm$ SD Concentration of Fondaparinux Versus Time Following for the Proposed Market Formulation and the Clinically Tested Formulation of Xantidar® 2.5 mg following a Single Subcutaneous Injection (Dashed line represents limit of quantification [LOQ: — . mg/mL in acid equivalence])

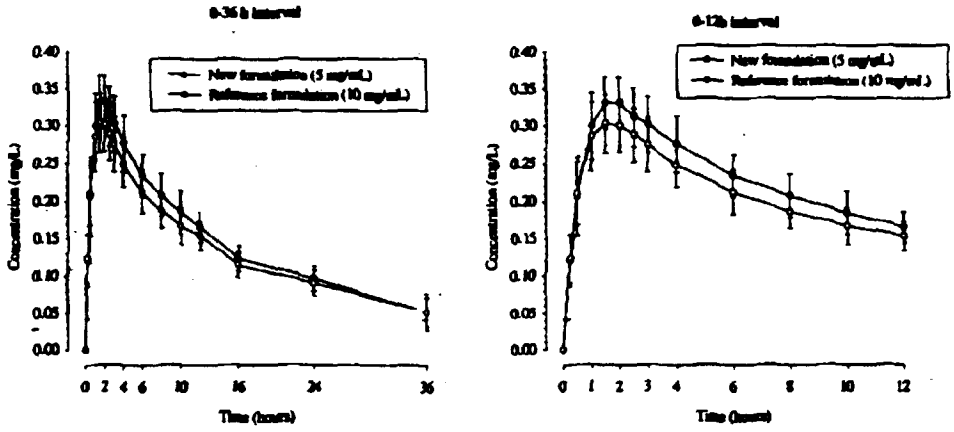


Table 4. Summary of Fondaparinux Pharmacokinetic Parameters for the Proposed Market Formulation and the Clinically Tested Formulation of Fondaparinux sodium 2.5 mg following a Single Subcutaneous Injection.

Parameter	n	Clinically Tested Formulation		Proposed Market Formulation	
		Mean	SD	Mean	SD
C_{max} (mg/mL)	16	0.318	0.039	0.340	0.037
T_{max} (h)	16	1.69	0.52	1.67	0.36
AUC_{0-t} ($mg.mL^{-1}h$)	16	4.90	0.93	5.30	1.07
$AUC_{0-\infty}$ ($mg.mL^{-1}h$)	16	6.29	1.18	6.65	1.20
$t_{1/2}$ (h)	16	18.3	3.7	17.2	3.2
MRT (h)	16	24.5	4.3	23.2	3.9

Based on these data, the pharmacokinetic parameters of fondaparinux for the clinically tested formulation (10 mg/mL) and the proposed market formulation (5 mg/mL) of fondaparinux sodium are similar.

(b) Assessment of Bioequivalence: Bioequivalence of the clinically tested formulation (10 mg/mL) and the proposed market formulation (5 mg/mL) of Xantidar® was assessed in the study described in item 3(a) above (Protocol BDR3780) with the proposed market formulation as test and the clinically tested formulation (10 mg/mL) as reference. The mixed model method was utilized. The effects of formulation on C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, was assessed using the following equation:

Parameter = Sequence + Period + Formulation + Subject(Subject)

Log transformed values of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were used. The subject term was considered a random effect within sequence. Formulation, period and sequence were considered fixed effects. Formulation and period effects were tested against the within-subject variability. Sequence effect was tested against the between-subject variability. The significance level was set at 0.05.

To assess bioequivalence of the test and the reference formulations, estimates of the formulation ratios (test/reference) were determined for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, at the 90% confidence level, by computing differences of the estimates of the means within the mixed model framework. These (test/reference) ratios were then converted to ratios of adjusted geometric means using an anti-log transformation. Bioequivalence was concluded where the 90% confidence intervals of the ratio (test/reference) of adjusted geometric means were within the equivalence reference intervals of ——— The results are summarized in Table 5.

Table 5. Summary of Bioequivalence Assessment of the Proposed Market Formulation and the Clinically Tested Formulation of Fondaparinux Sodium 2.5 mg following a Single Subcutaneous Injection

Parameter	n	Reference Formulation		Test Formulation		Ratio (Test/Reference) of Geometric Means	
		Mean	SD	Mean	SD	Point Estimate	90% C.I.
C_{max} (mg/mL)	16	0.32	0.04	0.34	0.04	1.07	1.03 – 1.11
AUC_{0-t} ($mg.mL^{-1}h$)	16	4.90	0.93	5.30	1.07	1.08	1.04 – 1.12
$AUC_{0-\infty}$ ($mg.mL^{-1}h$)	16	6.29	1.18	6.65	1.20	1.06	1.03 – 1.09

The confidence intervals of the ratios (test/reference) of the geometric means of log transformed $AUC_{0-\infty}$ and C_{max} were within the interval of ———— required for bioequivalence. Based on these findings, it is considered that for this method of bioequivalence assessment, the proposed market formulation of Xantidar® (5 mg/mL) and the Xantidar® formulation that was used in the Phase III clinical studies and most of the other clinical studies (10/mg/mL) are bioequivalent.

It needs to be noted that the sponsor did not use the two one-sided t-test method for bioequivalence assessment as recommended by the Agency. However, the only formulation differences were in the strengths of fondaparinux (10 mg/mL in Formulation 1A1 and 5 mg/mL in Formulation 2B2) and saline solution — mg/mL in Formulation 1A1 and — mg/mL in Formulation 2B2) (see item 14 [pages 36-38]). These differences are considered relatively minor. Subsequently, a comment to the sponsor related to the use the two one-sided t-test method for bioequivalence assessment is not necessary.

5. Is Adequate Information Provided on the Basic Pharmacokinetic Characteristics of Fondaparinux in Subjects Treated with Xantidar®?

The basic pharmacokinetic characteristics of fondaparinux were characterized in healthy, subjects 60-75 years old in the study described in item 1 above (Protocol 63106) and in Protocol 63105 as well as in healthy, young subjects 31 years old or younger (BDR3780 [item 3 above]). In each study, the subjects were treated with single doses of Xantidar®. The mean (SD) pharmacokinetic parameters obtained in these studies are presented in Table 6. The Xantidar® doses and route(s) of administration, intravenous (iv) or subcutaneous (sc), are included in the table.

Table 6. Pharmacokinetic Characteristics of Fondaparinux Following Single Subcutaneous or Intravenous Doses of Fondaparinux Sodium Injection

Prot[a].. #	Dose (mg)	n	AUC_{0-72} (mg.h/L)	$AUC_{0-\infty}$ (mg.h/L)	V_d/F (L)	V_{ss} (L)	$Cl_{T(0-72)}/F$ (mL/min)	$Cl_{R(0-72)}$ (mL/min)	D_u[b] (0-72 h) (%)	$t_{1/2}$ (h)
63106	2_{sc}	23	4.6	5.6	10.2	----	6.0	4.0	64	20.7
			(1.0)	(1.3)	(2.4)		(1.4)	(0.9)	(6)	(7.3)
	4_{sc}	24	8.9	10.0	10.0	----	6.2	4.4	66	19.2
			(2.2)	(2.4)	(2.7)		(1.6)	(1.2)	(6)	(4.2)
	8_{sc}	24	17.9	19.2	10.1	----	6.3	4.4	65	18.8
			(3.2)	(3.7)	(1.7)		(1.3)	(1.1)	(6)	(2.1)
	4_{iv}	25	8.6	9.7	10.8	9.3	6.2	4.3	64	20.3
			(1.7)	(1.8)	(2.4)	(1.9)	(1.3)	(0.8)	(7)	(4.2)
63105	2_{iv}	8	----	6.0	7.4	----	5.3	-----	-----	16.9
				(1.8)	(1.9)		(1.8)			(4.1)
	4_{iv}	8	----	12.2	7.9		5.1	4.8	77	18.4
				(2.9)	(1.8)	----	(1.4)	(1.0)	(12)	(2.4)
	5.5_{iv}	8	----	12.6	10.2	----	6.6	4.5	70	18.3
				(2.7)	(1.2)		(1.2)	(1.2)	(4)	(3.2)
	12_{iv}	8	----	28.1	9.1	----	6.5	4.6	69	16.6
				(6.3)	(1.4)		(1.4)	(0.9)	(10)	(2.2)
	16_{iv}	8	----	30.9	10.9	----	7.9	6.5	71	16.4
				(7.3)	(1.2)		(1.8)	(1.8)	(11)	(2.5)
	18_{iv}	8	----	37.9	10.3	----	7.1	6.8	75	17.0
				(6.9)	(1.5)		(1.2)	(1.6)	(4)	2.2)
	20_{iv}	8	----	38.8	10.9	----	7.8	7.9	77	16.5
				(8.3)	(0.9)		(1.6)	(2.2)	(7)	(2.6)
BDR3780	2.5_{sc}	16	5.3	6.7	8.2	----	5.56	-----	----	17.2
			(1.1)	(1.2)	(1.1)		(0.9)			(3.2)

(a) Overall Extent of Distribution: Across studies, in healthy, young subjects and healthy subjects 60-75 years of age treated with intravenous doses of Xantidar® (2-20 mg) (Protocol 63105), the mean non-steady state apparent volume of distribution of fondaparinux ranged ——————— and was essentially dose independent. In the healthy subjects 60-75 years of age treated with intravenous Xantidar® 4 mg (Protocol 63106), the mean steady state volume of distribution was 9.3 mL. These data suggest that in healthy, adult individuals 75 years old or younger treated with subcutaneous injection of Xantidar®, fondaparinux distributes mainly in blood and only to a minor extent in other tissue fluids.

(b) Elimination

(i) Urinary Excretion: The urinary excretion of fondaparinux was evaluated in subjects 60-75 years of age Protocols 63105 and 63106 described above. The results are presented in Table 6 above. The mean percentage of fondaparinux in the administered doses of Xantidar® eliminated unchanged in urine in 72 h was 64-66% in Protocol 63106 (dose range = 2-8 mg) and 69-77% in Protocol 63105 (dose range = 2-20 mg). In each study, urinary excretion of fondaparinux was independent of dose and route of administration.

In this subject population 60-75 years of age, following intravenous Xantidar® injection, the mean renal clearance was 4.3 mL/min in Protocol 63106 (dose = 4 mg) and ranged from — mL/min to — mL/min in Protocol 63105 (dose range = 2-12 mg). The mean total clearance in Protocol 63106 for the 4 mg dose (6.2 mL/min) was in the range of the values (—— mL/min) for Protocol 63105. In the dose range of 2-12 mg (Protocol 63105), renal clearance and total clearance of fondaparinux were dose independent. For the higher doses in Protocol 63105 (16-20 mg), the mean renal clearance (6.5-7.9 mL/min) and the mean total clearance (7.1-7.8 mL/min) of fondaparinux were higher as compared to the corresponding values (4.5-4.8 mL/min and 5.1-6.5 mL/min, respectively) for the 2-12 mg dose range. The sponsor attributes the higher clearance at the higher doses to a higher fraction of unbound fondaparinux secondary to saturation of ATIII binding sites at the higher doses.

Based on these findings, renal excretion of unchanged drug is the major route of fondaparinux elimination following the administration of Xantidar®. However, at the lower doses (2-12 mg [which do not cause the saturation ATIII binding sites]), renal clearance values are, generally, 68-71% of total clearance values suggesting that another/other route(s) of fondaparinux elimination, albeit minor, may exist.

In healthy adult subjects (≤75 years of age) treated with single, subcutaneous or intravenous doses of Xantidar®, the mean elimination half-life of fonaparinux was similar across studies (16.4-18.4 h in Protocol 63105 [dose range = 2-20 mg], 18.8-20.7 h in Protocol 63106 [dose range = 2-8 mg] and 17.2 h in Protocol BDR3780) and was essentially independent of patient's age or route of administration.

(ii) ***In Vitro*** **Metabolism**: *In vitro* metabolism of ^{35}S-labeled fondaparinux was evaluated in isolated rat hepatocytes (3.1 x 10^6 cells per mL) and in human hepatocytes (6.4 x 10^6 cells per mL) following incubation for 3 h at 37°C (Protocol SDGR4255). Fondaparinux metabolism was assessed at 0, 0.5, 2, 2 and 3 h from the initiation of incubation. In this study, there was no evidence of fondaparinux metabolism in the rat or human hepatocytes. In a similar *in vitro* study (Protocol SDGR4238), ^{35}S-labeled fondaparinux was also not metabolized in postmitochondrial liver fractions of male and female rats, rabbits, monkeys and humans.

(iii) ***In Vivo*** **Metabolism**: No studies were conducted to investigate in vivo metabolism of fondaparinux. In the proposed labeling, it is stated that "there is no evidence that fondaparinux is metabolized". *In vitro*, fondaparinux inhibits 17-hydroxylation of coumarin by CYP2A6 by 17-28% (page 18). This finding suggests that metabolism by CYP2A6 is a pathway of fondaparinux elimination.

6. Is Adequate Information Provided on Steady State Kinetics of Fondaparinux?

(a) Steady State Kinetics in Healthy Subjects

The steady state kinetics of fondaparinux was characterized in young, healthy, adult, male subjects ≤ 31 years of age (Protocols 63108, 63109 and INT3933) (see page 19 for study description) and in healthy, elderly, male and female, Caucasian subjects 65-79 years of age (Protocol 63103) treated with subcutaneous doses of Xantidar® injection. The results of these studies are summarized in Figure 3, Figure 4 and Table 7. The dose, dosing interval and the number of subjects per treatment are included in Table 7.

Fig. 3. Steady State Plasma Levels of Fondaparinux Following Once Daily 4 and 10 mg Subcutaneous Doses in Healthy, Young Subjects (Protocols 63108, 63109 and INT3933)

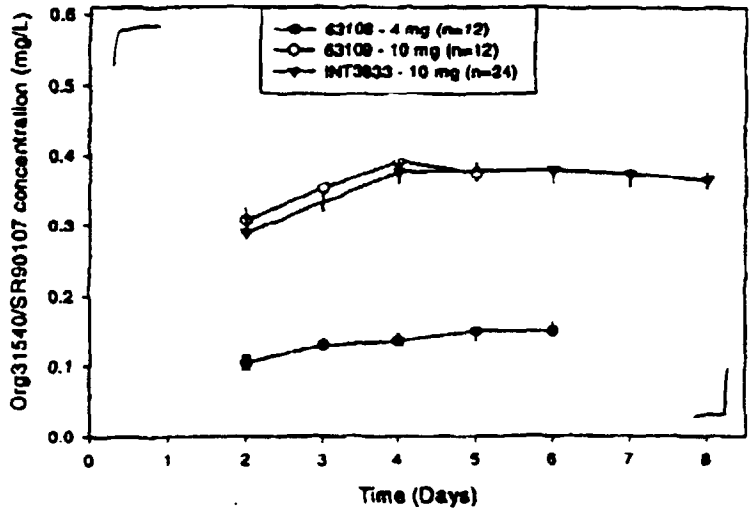
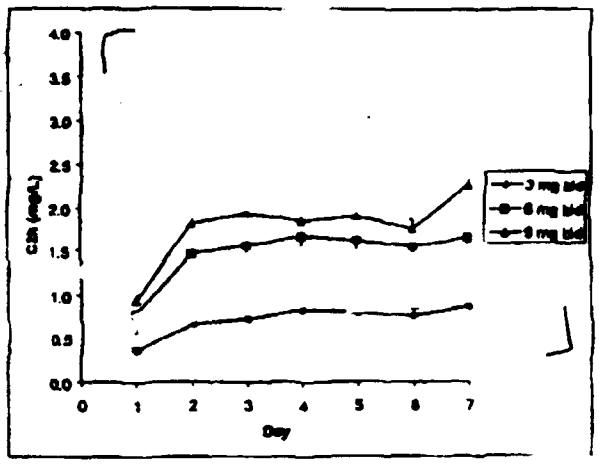


Fig 4. Steady State Plasma Levels of Fondaparinux Following Once Daily 4 and 10 mg Subcutaneous Doses in Healthy, Young Subjects (Protocols 63103)



Note: n=3 for 9 mg bid group.
Data have been taken from Annex 3, Appendix V.

Table 7. Steady State Kinetic Characteristics of Fondaparinux Following Subcutaneous Doses of Fondaparinus Sodium Injection in Healthy, Young Subjects and Healthy Elderly Subjects

Prot[a].. #	Dose (mg)	t_{max} (h)	$C_{ss(max)}$ (mg/L)	$C_{ss(min)}$ (mg/L)	$AUC_{0-\tau}$ (mg.h/L)	R[b]	V_d/F (mL)	Cl_T/F (mL/min)	Cl_R (mL/min)	$D_u^e{}_{(0-t)}$ (%)	$t_{1/2}$ (h)
63108 (n=12)	4[d]	1.5 (0.5)	0.56 (0.04)	0.15 (0.5)	7.34 (0.1)	1.3 (0.1)	9.0 (1.0)	8.0 (0.9)	---- ----	---- ----	13.1 (1.3)
63109 (n=12)	10[d]	2.5 (1.4)	1.5 (0.3)	0.37 (0.1)	18.3 (3.0)	1.3 (0.1)	9.6 (1.4)	7.9 (1.3)	---- ----	---- ----	14.2 (2.0)
INT3933 (n=24)	10[d]	1.8 (0.6)	1.4 (0.1)	0.36 (0.07)	17.4 (2.3)	---- ----	---- ----	8.5 (1.2)	5.3 (1.3)	61 (11)	---- ----
63103 (n=12[f])	3[e]	1.5 (0.01)	0.9 (0.3)	0.5 (0.1)	8.1 (1.5)	2.4 (0.2)	7.2 (2.5)	5.3 (1.2)	2.8 (0.7)	53 (14)	15.6 (2.8)
	6[e]	1.3 (0.2)	1.8 (0.2)	1.0 (0.1)	15.6 (1.8)	2.3 (0.3)	8.1 (1.1)	5.4 (0.6)	4.1 (1.1)	75 (15)	17.5 (0.7)
	9[e,g]	2.1 (0.7)	2.5 (0.5)	1.4 (0.1)	23.0 (3.8)	2.3 (0.5)	8.8 (2.6)	5.5 (0.8)	3.9 (1.0)	69 (11)	19.3 (9.1)

[a]Protocol, [b]Accumulation ratio, [c]Drug eliminated unchanged in urine as a percentage of dose, [d]once daily, [f]n=4 per dose group unless otherwise specified, [e]twice daily, [g]n=3

In general, the time to reach fondaparinux steady state was 4-5 days (Figs. 3 and 4). Steady accumulation ratio of fondaparinux in healthy young subjects (mean total clearance normalized for absorbed dose [Cl_T/F] = 8.0 mL/min) was 1.3 (Protocols 63108 and 63109) versus 2.3-2.4 in subjects 65-79 years old (Cl_T/F = 5.3-5.5 mL/min) (Protocol 63103). In healthy, young subjects, the range of mean steady state t_{max} (1.5-2.5 h) was similar to the values of 1.3-2.1 h observed for the dose range of 3-9 mg in subjects 65-79 years old. These values are comparable to the t_{max} of 1.7 h for a single dose of the proposed market and clinically tested 2.5 mg formulations evaluated in healthy, young, male subjects in the bioequivalence study (Protocol BDR3780 [see page 8]).

The mean steady state apparent volume of distribution (normalized for absorbed dose [V_d/F]), 9.0-9.6 mL for healthy, young subjects and 7.2-8.8 mL in subjects 65-79 years old (Protocol 63103) are comparable to the mean Vss value (9.3 mL) in subjects 60-79 years old receiving a single, 4 mg intravenous dose of Xantidar® injection (Protocol 63106). These findings suggest that in healthy young or elderly subjects, under steady state or non-steady state conditions, systemically available fondaparinux distributes mainly in blood and only to a minor extent in other fluids following the administration of Xantidar® injection.

Following the administration of Xantidar® injection, the range of the mean fraction of the fondaparinux dose eliminated unchanged in urine at steady state in one dosing interval, in healthy, subjects 65-79 years of age was 53-75%. This range encompasses the mean steady state values in young, healthy subjects (61% [Protocol INT3933 only]) as well as

the single dose mean values (64-66%) in healthy subjects 60-75 years old (Protocol 63106 [see page 10]). However, the mean steady state total clearance of fondaparinux was 9.9-8.5 mL/min in healthy, young subjects versus 5.3-5.5 mL/min in healthy, subjects 65-79 years old and its mean elimination half-life was 13.1-14.2 h in healthy, young subjects versus 15.6-19.3 h in healthy subjects 65-79 years old. These findings suggest that at steady state, there is a trend towards slower steady state elimination of fondaparinux in healthy individuals 65-79 years old as compared to healthy, young individuals.

(b) Steady State Kinetics in Target Patient Population

The steady state kinetics of fondaparinux was characterized in patients in a Phase II study evaluating Xantidar® doses of 0.75-8.00 mg once daily for 5-10 days (Protocol DR12643) and two Phase III studies evaluating the proposed market dose of Xantidar® (2.5 mg) once daily for 5-10 days (Protocols ECF2442 and ECF2698). In each study, the patient population consisted of patients under 65 years of age, 65 –75 years of age and older than 75 years. Each patient was on prophylaxis treatment of venous thromboembolic event following elective hip surgery (Protocol ECF2442), hip fracture surgery (Protocol ECF2698) and elective, total hip replacement surgery (Protocol DR12643). Pharmacokinetic parameters were determined by population pharmacokinetic analysis. The results of these studies are summarized in Table 8.

Table 8. Steady State Kinetic Characteristics of Fondaparinux in Patients Treated with Subcutaneous Fondaparinux Sodium Injection

Prot[a].. #	Dose (mg)	t_{max} (h)	$C_{ss(max)}$ (mg/L)	$C_{ss(min)}$ (mg.h/L)	$AUC_{0-\tau}$ (mg/L)	R[b]	V_{SS}/F (mL)	Cl_T/F (mL/min)	Cl_R (mL/min)	$D_u^c{}_{(0-t)}$ (%)	$t_{1/2}$ (h)
EFC2442 (n=64)	2.5	2.9 (0.52)	0.39 (0.12)	0.14 (0.08)	5.7 (2.5)	---- ----	16.5 (11.0)	7.3 (2.3)	---- ----	---- ----	36.7 (22.6)
EFC2698 (n=141)	2.5	2.8 (0.69)	0.50 (0.16)	0.19 (0.11)	7.58 (3.19)	---- ----	9.83 (4.13)	5.53 (2.07)	---- ----	---- ----	27.3 (13.8)
DR12643 (n=24)	0.75	2.80 (0.20)	0.11 (0.02)	0.03 (0.02)	1.57 (0.49)	---- ----	7.70 (0.90)	7.50 (1.90)	---- ----	---- ----	14.0 (4.7)
	1.5	2.7 (0.3)	0.22 (0.05)	0.07 (003)	3.20 ((0.84)	---- ----	7.7 (1.3)	7.2 (1.7)	---- ----	---- ----	14.2 (3.9)
	3	2.7 (0.4)	0.43 (0.10)	0.12 (0.07)	5.93 (1.87)	---- ----	8.3 (2.8)	8.0 (2.1)	---- ----	---- ----	14.4 (6.5)
	6	2.9 (0.6)	0.82 (0.17)	0.23 (0.11)	11.45 (3.26)	---- ----	7.80 (1.7)	8.2 (2.2)	---- ----	---- ----	13.0 (4.1)
	8	2.9 (0.5)	1.08 (0.29)	0.29 (0.14)	14.88 (4.83)	---- ----	7.9 (1.8)	8.8 (2.7)	---- ----	---- ----	12.4 (3.0)

[a]Protocol, [b]Accumulation ratio, [c]Drug eliminated unchanged in urine as a percentage of dose

Across studies and dose groups, the mean values of total clearance (normalized for absorbed dose [Cl_T/F]) ranged from 5.5 mL/min to 8.2 mL/min and were comparable to the steady state values in healthy subjects (5.3- 8.5 mL/min) in Table 7 above. In patients on prophylaxis treatment of venous thromboembolic event following elective hip surgery (Protocols EFC2442) prolonged drug exposure ($t_{1/2}$=36.7 h) was related, at least in part, to a larger extent of distribution (V_{ss}/F= 16.5 mL [versus 7.7-9.8 mL for the other studies]). In patients with hip fracture surgery (Protocol EFC2698), prolonged drug exposure ($t_{1/2}$=27.3 h) was related to reduced clearance (Cl_T/F= 5.5 mL/min [versus 7.2-8.2 mL/min for the other studies]). It is not understood why the extent of fondaparinux distribution was larger in patients with venous thrombotic event who underwent elective hip surgery (Protocol EFC2442).

7. *Is Adequate Information Provided on Fondaparinux Binding to Biomolecules in Subjects Treated with Xantidar®?*

(a) Binding to Plasma Proteins: No information is provided on *in vivo* binding of fondaparinux. Plasma protein binding of fondaparinux was evaluated *in vitro* using human plasma and purified plasma proteins (Protocol LPH0013). Following incubation at 37°C for ≥ 30 min, samples were analyzed using an adequately validated, ultrafiltration method [redacted]. Binding parameters were determined using the Scatchard model which describes drug-protein binding with one class of binding sites and non-specific binding:

$$B = \frac{B_{max} \cdot F}{K_D + F} + pNS.F$$

where B and F are respectively the bound and free drug concentrations, K_D the dissociation constant, B_{max} the total receptor concentration, and pNS the nonspecific binding constant.

Bound fraction was determined as 100%(bound concentration/total concentration).

At a concentration of 500 ng/mL, fondaparinux was 98.6% bound in plasma and 97.4% bound in ATIII. Binding decreased with increasing concentration to 80.7% in plasma and 27.2% in ATIII at a concentration of 500 µg/mL (Table 9).

Table 9. *In Vitro* Binding of Fondaparinux in Plasma and to Purified Antithrombin

concentration (ng/mL)	500	1000	2000	3000	5000	7500	10000	30000	50000
binding fraction in human plasma (%)	98.6	98.4	97.0	95.3	91.1	87.5	85.1	80.3	80.7
binding fraction with antithrombin (%)	97.4	96.4	94.0	90.7	72.2	52.1	42.4	28.7	27.2

The magnitudes of the specific binding parameters of fondaparinux (B_{max} and K_D) in human plasma and purified antithrombin (Table 10.A) suggest specific binding.

Fondaparinux binding to purified albumin, α_1-acid glycoprotein, γ-globulin and plasma without antithrimbin is non-specific (Table 10.B). Non-specific binding fractions in plasma with antithrombin (78.5% [Table 10.A]) and without antithrombin (75% [Table 10.B]) are similar suggesting that the specific binding in plasma in Table 10.A is due to its antithrombin component.

Table 10. Assessment of Binding Specificity of Fondaparinux

(A)

parameter	specific binding B_{max} (nM)	specific binding K_d (nM)	non specific binding pNS	non specific binding NSB fraction (%)
human plasma	2072	28	3.67	78.6
human purified antithrombin	1627	32	0.36	26.4

NSB fraction corresponds to the binding fraction of compound bound non specifically to plasma proteins

(B)

parameter	specific binding B_{max} and K_d	non specific binding NSB fraction (%)
α1 acid glycoprotein	NON significant	36
gamma globulin	NON significant	36
albumin	NON significant	52
antithrombin depleted plasma	NON significant	75

The fraction of fondaparinux bound to albumin, α_1-acid glycoprotein, γ-globulin and plasma without antithrombin was generally low and dose independent (Table 11). Dose independent binding further suggests non-specific binding of fondaparinux to these molecules.

Table 11. Binding of Fondaparinux to Albumin, α_1-Acid Glycoprotein, γ-Globulin and Plasma without Antithrombin

Org31540/SR90107 nominal concentration (ng/mL)	5	50	500	5000	50000
binding with α1 acid glycoprotein (%)	43.6	30.4	34.9	35.5	35.2
binding with gamma globulin (%)	40.8	33.2	32.1	39.4	34.9
binding with serum albumin (%)	49.2	53.6	59.1	49.9	56.5
binding with antithrombin depleted plasma (%)	nd	77.1	77.4	73.7	73.5

In the Phase III clinical studies evaluating Xantidar®injection 2.5 mg, the highest mean (+SD) $C_{ss(max)}$ was 5.0±1.6 mg/mL (see page 14 [Table 8]). This equals 500±160 ng/mL. Based on clinical study findings, the sponsor feels that in clinical practice, individual patient plasma concentration of fondaparinux following subcutaneous Xantidar®injection 2.5 mg would be below 1.5 mg/L (1500 ng/mL). This reviewer feels that, based on these data, the clinically relevant statement of binding, based on the *in vitro* findings (Table 9), is that fondaparinux is **> 94% bound to antithrombin and > 97% bound in plasma.**

At fondaparinux concentrations > 2 mg/L (2000 ng/mL) plasma binding sites are saturated (Protocols LPR0524). In such cases, excessive amounts of the free drug would be present in the plasma.

(b) Binding to Plasma Red Blood Cells: Red blood cell binding of ^{35}S-labeled fondaparinux (0.05. 0.5, 2, 5, 10 and 50 mg/L) was assessed following incubation at 37°C in whole blood for 30 min. Binding was determined as total radioactivity by

The fraction of fondaparinux bound to red blood cell calculated as $(C_R \times HCT)/C_B$. C_R, C_B and HCT represent concentration in red blood cell, concentration and hematocrit, respectively. The results are presented in Table 12.

Table 12: *In Vitro* Binding of ^{35}S-labeled fondaparinux to Rat, Monkey and Human Red Blood Cells

Concentration (mg/l)	0.05	0.5	2	5	10	50
Binding in rat erythrocytes (%)	5	0	-1	6	10	8
Binding in monkey erythrocytes (%)	7	6	2	5	1	6
Binding in human erythrocytes (%)	6	-4	-5	-2	1	-1

(n=2 at all concentrations)

Note: Negative values due to the high plasma concentration v blood concentrations and method of calculation. Acceptable within bounds of experimental accuracy.

Based on these findings, *in vitro* binding of fondaparinux to rat, monkey or human red blood cells is not significant.

8. ***Is Adequate Information Provided on Drug-drug Interactions with Fondaparinux in Subjects Treated with Xantidar®?***

(a) *In Vitro* Metabolic Interaction: The potential of fondaparinux to inhibit CYP450 isozymes was evaluated *in vitro* using in human liver microsomes (Protocol MIH0031). Isozyme selective substrates were incubated in the liver microsomes at 37°C with fondaparinux (346 mg/mL or without or selective inhibitor (needed to show verify the ability of the assay methods to detect inhibition. fondaparinux (The highest mean C_{max} in Phase I studies was 2.25 mg/ mL and highest mean $C_{ss(max)}$ for the 2.5 mg daily doses of Xantidar® in Phase III studies was 0.50 mg/L]). NADPH generating system was added in

a timed sequence and additional incubation period was added as required by each specific assay. Analysis was performed by [redacted] methods specific for each substrate. Fondaparinux inhibition > 30% of control value was to be considered significant. The results are summarized in Table 13.

Table 13. Assessment of *In Vitro* Inhibition of Metabolism of Selected CYP450 Isozyme Substrates by Fondaparinux and Specific Isozyme Inhibitors

Probe Assay	Human Liver	Percent of Control	
		ORG31540/SR90107A	Selective Inhibitor
CYP1A2[a]	HG6	99.3	12.2
Phenacetin	HG56	101	14.1
O-deethylation	HG89	94.0	18.2
CYP2A6[b]	HG30	82.0	46.8
Coumarin	HG56	72.1	44.2
7-hydroxylation	HG66	82.6	50.8
CYP2C9[c]	HG6	94.0	5.82
Tolbutamide	HG23	101	6.32
methylhydroxylation	HG56	84.3	16.2
CYP2C19[d]	HG30	97.8	16.5
Mephenytoin	HG43	90.6	17.2
4'-hydroxylation	HG56	100	16.9
CYP2D6[e]	HG3	96.5	<LOQ
Bufuralol	HG23	95.6	<LOQ
hydroxylation	HG56	106	21.0
CYP2E1[f]	HG42	106	68.9
Chlorzoxazone	HG70	92.9	57.8
hydroxylation	HG89	96.2	52.2
CYP3A4[g,h]	HG30	103	5.45
Nifedipine	HG42	91.7	6.77
oxidation	HG70	97.6	5.21

Selective inhibitors were: [a] furafylline (100 μM); [b] pilocarpine (50 μM); [c] sulfaphenazole (50 μM); [d] tranylcypromine (100 μM); [e] quinidine (10 μM); [f] diethyldithiocarbamate (100 μM); [g] ketoconazole (1 μM); [h] data for CYP3A4 selective inhibition from a later experiment
<LOQ: data was below the LOQ of the assay (LOQ = [redacted])
Bolded values indicate > 30% inhibition (< 70% of control values)

Across the CYP450 isozyme classes tested, *in vitro* inhibition of substrate metabolism was 53.2-94.8% for specific isozyme inhibitors and 0-28% for fondaparinux. Based on these findings, it is considered that fondaparinux is not significantly metabolized by CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP3E1 and CYP3A4. Subsequently, interactions of fondaparinux with drugs metabolized by these enzymes are not expected.

It is noted, however, that fondaparinux inhibited 17-hydroxylation of coumarin by CYP2A6 by 17-28%. This finding suggests that metabolism by CYP2A6 is likely to be a minor elimination pathway of fondaparinux. This would further support the finding that renal elimination of unchanged fondaparinux in urine, though predominant, may not be its only elimination pathway due to the differences observed in its total clearance and renal clearance (see items 5 and 6 [pages 10 and 13]).

(b) *In Vivo* Pharmacokinetic Interaction

The effect of co-administration of fondaparinux and warfarin on the steady state kinetics of fondaparinux (Protocol 63108) and of fondaparinux and digoxin on the steady state kinetics of each other (Protocol INT3933) was evaluated in healthy male subjects. Protocol 63108 was a three-way crossover study in which each subject received each of the following treatments: 4 mg subcutaneous active Xantidar® injection every 24 h for 96 h and placebo warfarin tablets at 72 and 96 h (Treatment A), subcutaneous placebo Xantidar® injection every 24 h for 96 h and active warfarin tablets 15 mg at 72 h and 10 mg at 96 h (Treatment B) and 4 mg subcutaneous active Xantidar® injection every 24 h for 96 h and active warfarin tablets 15 mg at 72 and 10 mg at 96 h (Treatment C). In each treatment regimen involving warfarin, each subject received oral, 10 mg, active vitamin K as fytomenadion (Konakion®) solution at 132 h to terminate the effect of warfarin. The washout out period between treatments was 14 days.

In Protocol INT3933, each subject received one of two treatment sequences (Sequence 1 and Sequence 2). In Sequence 1, each subject received subcutaneous fondaparinux 10 mg once daily on Days 1-7 (Period 1), oral digoxin 0.25 mg twice daily on Day 1, once daily on Days 2-7 and once daily co-administered with subcutaneous fondaparinux 10 mg once daily on Days 8-14 (Period 2). In Sequence 2, each subject received oral 0.25 mg digoxin twice daily on Day 1, once daily on Days 2-7 and and once daily co-administered with fondaparinux 10 mg once daily on Days 8-14 (Period 1) and subcutaneous fondaparinux 10 mg once daily on Days 1-7 (Period 2). For each period, treatment was initiated at 8.00 a.m. For twice daily dosing, the second dose was administered 12 h following the initial dose. For each treatment sequence, the washout period between treatment periods was 12 days.

In two other crossover studies in healthy male subjects (n=12 per study), possible interactions of fondaparinux with N-acetyl salicylic acid (aspirin), a platelet inhibitor under steady state conditions (Protocol INT2767) and another NSAID, piroxicam (Protocol 63109) under steady state and non-steady state conditions, were evaluated. The results of these studies are presented in Tables 14, 15, 16, 17 and 18.

Table 14. Summary of Fondaparinux Steady State Kinetics Following Concomitant Administration with Warfarin or Placebo (Protocol 63108)

Treatment											
Org31540/SR90107A + placebo	43.0	37.5	41.8	36.6	7.6	19.7	17.2	13.8	646	552	2.0
	4.6	3.6	3.6	3.2	0.7	2.1	1.6	1.6	46	42	0.4
	8.3 %	8.3 %	8.7 %	8.7 %	8.9 %	10.6 %	10.6 %	10.9 %	7.8 %	7.9 %	21 %
Org31540/SR90107A + warfarin	44.6	38.4	42.9	37.4	7.6	20.2	17.8	14.1	676	591	1.8
	3.2	2.8	3.1	2.7	0.6	1.7	1.8	1.8	64	47	0.7
	7.4 %	7.4 %	7.2 %	7.2 %	7.5 %	8.4 %	8.4 %	12.8 %	9.5 %	8.0 %	39 %

n = 12 for each parameter
Data are derived from Appendix F. AUC and C_{max} values are expressed here in nmol (as in the appendices) and mcg equivalents. t_{max} has been converted to hours.
*C_{max}, t_{max} and $t_{1/2}$ were calculated after repeated, once daily dosing on day 8

Table 15. Summary of Fondaparinux Steady State (Day 7) Kinetics Administered Alone or Concomitantly with Digoxin (n=24) (Protocol INT3933)

Parameters	Mean (±SD)	
	Org31540/SR90107 alone	Org31540/SR90107+digoxin
Org31540/SR90107		
C_{max} (mg/L)	1.36 (0.13)	1.41 (0.13)
C_{min} (mg/L)	0.36 (0.07)	0.38 (0.07)
t_{max} (h)	1.79 (0.64)	1.83 (0.65)
AUC_{0-24h} (mg.h/L)	17.41 (2.33)	18.17 (2.05)
CL/F (mL/min)	8.51 (1.22)	8.10 (0.87)
Ae_{0-24h} (mg)	5.36 (0.92)**	5.48 (1.16)**
fe %	61.4 (10.5)**	62.8 (13.4)**
CL_R (mL/min)	5.25 (1.28)**	5.04 (1.15)**

** : n=22, missing values for subject Nos. 16 and 22 (Org31540/SR90107A alone) and for subject Nos. 10 and 20 (Org31540/SR90107A+digoxin)

Table 16. Summary of Digoxin Steady State (Day 7) Kinetics Administered Alone or Concomitantly with Fondaparinux (n=24) (Protocol INT3933)

Parameter (units)	Mean (±SD)	
	Digoxin alone (Day 7)	Digoxin+Org31540/SR90107A (Day 14)
Digoxin		
C_{max} (ng/mL)	1.57 (0.29)	1.54 (0.37)
C_{min} (ng/mL)	0.31 (0.17)	0.27 (0.19)
t_{max} (h)	1.13 (0.37)	1.04 (0.41)
AUC_{0-24h} (ng.h/mL)	12.00 (3.72)	11.35 (4.20)
Ae_{0-24h} (mg)	0.086 (0.022)**	0.091 (0.022)**
fe %	34.3 (9.0)**	36.3 (8.8)**
CL_R (mL/min)	122.78 (39.03)**	131.70 (36.64)**

** : n=22, missing values for subject Nos. 3 and 10 (digoxin alone) and for subject Nos. 10 and 20 (digoxin+Org31540/SR90107A)

Table 17. Summary of Fondaparinux Steady State Kinetics Following Concomitant Administration with Aspirin or Placebo (Protocol INT2767)

Parameters		Day 4		Day 8	
		Treatment regimen [1]		Treatment regimen [1]	
		SR90107A/ Org31540 + placebo	SR90107A/ Org31540 + aspirin	SR90107A/ Org31540 + placebo	SR90107A/ Org31540 + aspirin
C_{max} (mg/L)	Mean	1.46	1.47	1.52	1.54
	SD	0.13	0.10	0.11	0.12
	CV%	9	7	7	8
t_{max} (h)	Mean	2.14	1.95	2.13	2.13
	SD	0.50	0.44	0.34	0.62
	CV%	23	23	16	29
AUC_{0-24h} (mg.h/L)	Mean	19.60	19.82	20.66	20.39
	SD	1.41	1.49	1.66	1.64
	CV%	7	8	8	8
C_{min} (mg/L)	Mean	0.39	0.39	0.42	0.41
	SD	0.06	0.06	0.06	0.06
	CV%	15	15	13	14

[1] Aspirin or placebo only administered at Day 4

Table 18. Summary of Fondaparinux Steady State Kinetics Following Concomitant Administration with Piroxicam or Placebo (Protocol 63109)

	Org31540/SR90107A + piroxicam N=13			Org31540/SR90107A + placebo N=12		
Parameter	Mean	SD	CV%	Mean	SD	CV%
AUC_{0-last} (mg.h/L)	74.1	10.5	14 %	75.7	10.7	14 %
$t_{1/2}$ (h)	13.9	1.9	14 %	13.6	1.5	11%
$AUC_{0-\infty}$ (mg.h/L)	76.8	11.5	15 %	78.3	11.5	15 %
CL/F (mL/h)	464	72	16 %	455	68	15 %
V_z/F (L)	9.2	0.9	10 %	8.8	1.0	11 %
C_{max} 1st dose (ng/mL)	1068	134	13 %	1139	144	13 %
t_{max} 1st dose (h)	2.27	0.60	26 %	2.54	0.49	19 %
$AUC_{72-last}$ (mg.h/L)	24.3	4.3	18 %	24.3	4.2	17 %
$AUC_{72-\infty}$ (mg.h/L)	27.0	5.4	20 %	26.8	5.1	19 %
C_{max} last dose (ng/mL)	1453	214	15 %	1459	292	20 %
t_{max} last dose (h)	2.01	0.41	20 %	2.25	1.43	64 %

Data have been taken from Appendix F, page F71. AUC and C_{max} values are expressed in acid equivalents.

The steady state kinetics of fondaparinux is not significantly affected by concomitant administration of warfarin, digoxin, aspirin and piroxicam. The steady state kinetics of digoxin is also not significantly affected by concomitant of fondaparinux.

(c) ***In Vivo* Pharmacodynamic Interaction:**

The effects of co-administration of fondaparinux and warfarin on prothrombin time (PT) and related parameters (time to reach maximal PT value [t_{max}] and area under the effect curve [AUEC]) and the effects of co-administration of fondaparinux and aspirin on bleeding time and activated thromboplastin time (aPTT) were assessed in Protocol 63108 and INT2767, respectively. Both studies have been described in item b (*In Vivo* Pharmacokinetic Interaction) above. The results are presented in Fig. 5 and Tables 19 and 20 for Protocol 63108 and in Fig. 6 and Tables 21 and 22 for Protocol INT2767. The effects of fondaparinux administered with placebo or warfarin on prothrombin disposition (Fig.7), Factors VII and VIIa levels (Fig. 8 and Tables 23 and 24) and bleeding time (Table 25) were also assessed. The effects of fondaparinux administered with placebo or aspirin on bleeding time and activated partial thromboplastin time are presented in Fig. 9.

Fig. 5. Mean PT Values for Fondaparinux Administered Alone or Concomitantly with Warfarin or Placebo (Protocol 63108)

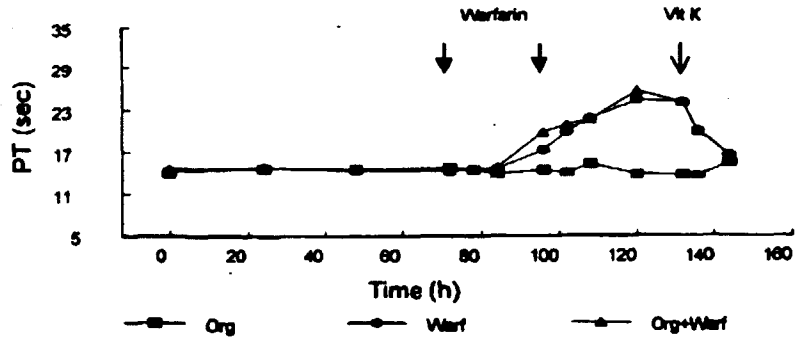


Table 19. Unadjusted Mean (SD) Values of AUEC, Maximal PT Value (E_{max}) and t_{max} for Fondaparinux Administered Alone or Concomitantly with Warfarin or Placebo (Protocol 63108)

Treatment	$AUEC_{time\ corrected}$ (s)	E_{max}* (s)	t_{max}** (h)
Org31540/SR90107A + placebo	14.47 (1.08)	17.1 (6.3)	***
Warfarin + placebo	17.09 (1.45)	25.3 (5.1)	122.4 (5.5)
Org31540/SR90107A + warfarin	17.35 (1.99)	28.2 (6.7)	117.3 (7.1)

*E_{max} = maximal PT value
** t_{max} = average time to reach maximal PT value, from start of Org31540/SR90107A administration
*** since PT did not exceed base-line levels following Org31540/SR90107A-only treatment, calculation of t_{max} was not performed.

Table 20. Weighted Mean (SD) Change of PT from Baseline for Fondaparinux Administered Alone or Concomitantly with Warfarin or Placebo (Protocol 63108)

Treatment	Change from baseline (s)
Org31540/SR90107A + placebo	0.15 (0.72)*
Warfarin + placebo	2.92 (1.42)
Org31540/SR90107A + Warfarin	2.82 (1.73)

* Mean and SD values for Org31540/SR90107A-only are not presented in Appendix F, but have been calculated from individual data (Appendix F, page F20).

Fig. 6. Mean aPTT Values for Fondaparinux Administered Alone or Concomitantly with Warfarin or Placebo (Protocol 63108)

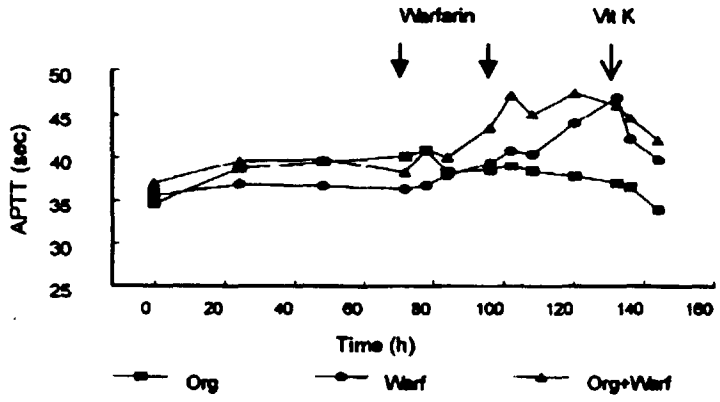


Table 21. Unadjusted Mean (SD) Values of AUEC, Maximal aPTT Value (E_{max}) and t_{max} for Fondaparinux Administered Alone or Concomitantly with Warfarin or Placebo (Protocol 63108)

Treatment	AUEC[time corrected] (s)	E_{max} (s)	t_{max} (h)
Org31540/SR90107A + placebo	38.4 (3.4)	42.5 (5.0)	77.3 (14.2)
Warfarin + placebo	38.7 (3.1)	47.8 (8.3)	125.8 (14.1)
Org31540/SR90107A + warfarin	41.6 (3.9)	51.7 (10.6)	113.9 (13.2)

*E_{max} = maximal APTT value
**t_{max} = average time to reach maximal APTT value
Data have been taken from Appendix F, pages F25-F26.

Table 22. Weighted Mean (SD) Change of aPTT from Baseline for Fondaparinux Administered Alone or Concomitantly with Warfarin or Placebo (Protocol 63108)

Treatment	Change from baseline (s)
Org31540/SR90107A + placebo	3.10 (3.84)
Warfarin + placebo	3.24 (4.59)
Org31540/SR90107A + Warfarin	4.98 (1.53)

Data have been taken from Appendix F, page F25.

Fig. 7. Mean Prothrombin Fragment 1 + 2 Values for Fondaparinux Administered Alone, Warfarin Administered Alone and Fondaparinux Administered Concomitantly with Warfarin (Protocol 63108)

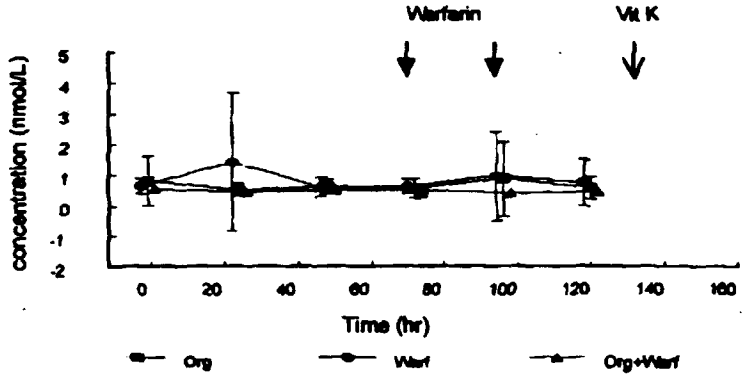


Fig. 8. Mean Factor VII Plasma Values for Fondaparinux Administered Alone, Warfarin Administered Alone and Fondaparinux Administered Concomitantly with Warfarin (Protocol 63108)

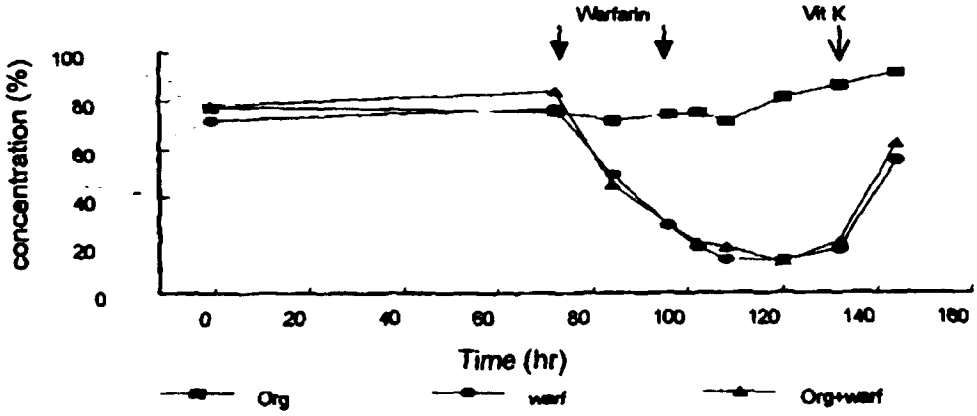


Table 23. Weighted Mean (SD) Change of Factor VII from Baseline for Fondaparinux Administered with Placebo, Warfarin Administered with Placebo and Fondaparinux Administered Concomitantly with Warfarin (Protocol 63108)

Treatment	Change from pre-value (%)
Org31540/SR90107A + placebo	-0.018 (9.5) *
Warfarin + placebo	-43.80 (17.2)
Org31540/SR90107A+ Warfarin	-49.40 (15.5)

* Mean and SD values for Org31540/SR90107A + placebo treatment are not presented in Appendix F, but have been calculated from individual data (Appendix F, page F37).
Data have been taken from appendix F, page F37.

Table 24. Unadjusted Mean (SD) Values of Factor VIIa for Fondaparinux Administered with placebo and Warfarin Administered Concomitantly with Fondaparinux or Placebo (Protocol 63108)

Treatment	$AUEC_{time\ corrected}$ (mU/mL)*
Org31540/SR90107A + placebo	52.3 (13.5)
Warfarin + placebo	37.6 (7.9)
Org31540/SR90107A + Warfarin	34.6 (7.2)

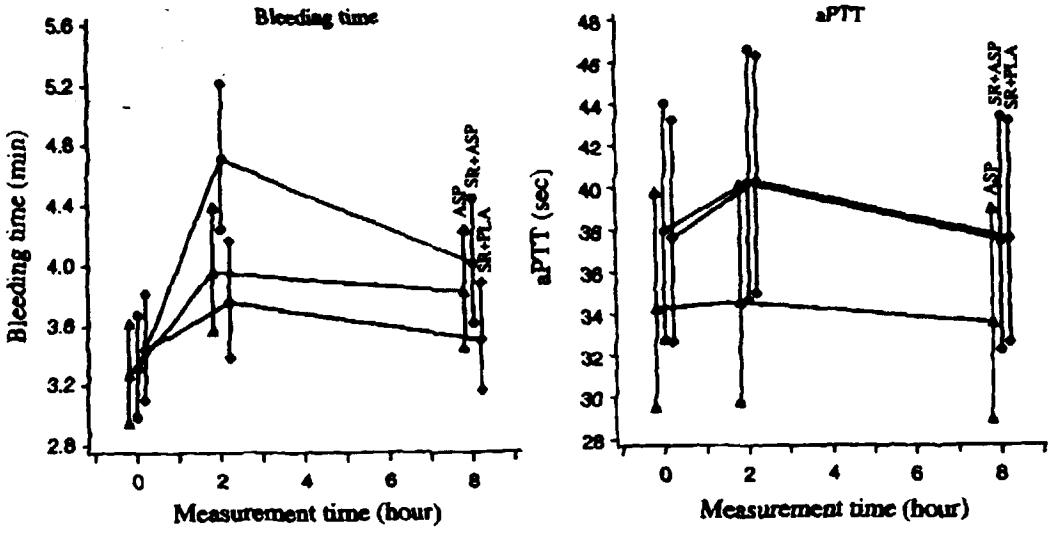
Data have been taken from Appendix F, pages F38-39

Table 25. Individual Subject Bleeding Time Following Subcutaneous Fondaparinux Administered with Placebo, Warfarin Administered with Placebo and Fondaparinux Administered Concomitantly with Warfarin (Protocol 63108)

Subject	Org31540/SR90107A + placebo			Warfarin + placebo			Org31540/SR90107A +Warfarin		
	Pre *	post *	diff *	Pre *	post *	diff *	pre *	post *	Diff *
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
mean	125	136	11	129	123	-6	122	111	-12
SD	54	52	65	50	28	54	46	29	58

* results are expressed in seconds

Fig. 9. Adjusted Mean (+SD) Bleeding Time and aPTT for Fondaparinux Administered Alone or Concomitantly with Aspirin or Placebo (Protocol INT2767)



The values of prothrombin time and activated partial thromboplastin time were not significantly different from baseline for fondaparinux administered with placebo but were higher than base line and similar for warfarin administered with placebo or fondaparinux (Figs. 5-6 and Tables 17-18). It is noted that weighting the mean difference from baseline (Table 18) masks the obvious difference in activated partial thromboplastin time between fondaparinux administered with placebo and warfarin administered with placebo in the time interval of 120-140 h postdose (Fig 6). The mean plasma concentrations of prothrombin fragments 1 and 2 were similar for the three treatments (Fig 7). The values of Factor VII were not significantly different from baseline for fondaparinux administered with placebo but were significantly lower than baseline and similar for warfarin administered with placebo or fondaparinux (Fig. 8 and Table 21). Factor VIIa values for warfarin administered with placebo or fondaparinux were similar but were lower as compared to fondaparinux administered with placebo (Table 22). For bleeding time, the individual subject values for all treatments (Table 23) showed few major pre-dose and postdose bleeding time differences. An independent literature by this reviewer revealed normal range values of 1-6 min, 12-14 s and 26-33 s (which may vary by procedure used for determination) for bleeding time, prothrombin time and activated partial thromboplastin time, respectively. For all treatment regimens, the pre-dose and postdose bleeding time range (———————) was within normal range.

In Protocol INT2767, in the time interval of 2-8 h, the bleeding times for aspirin administered alone or with placebo were lower than the values for aspirin administered with fondaparinux. Within the same time range, the activated partial thromboplastin time for fondaparinux administered with aspirin or placebo were similar and significantly higher than the values for aspirin administered alone (Fig 9). While the bleeding times are within the literature reported normal range (1-6 min) for all treatments, most of the values of the activated partial thromboplastin time for fondaparinux administered with aspirin or placebo were higher than the literature reported normal values of 26-33s. In this study, aspirin-induced platelet aggregation was not modified by steady state fondaparinux.

Based on these findings, it is considered that subcutaneous fondaparinux 2.5 mg does not significantly affect bleeding time, prothrombin time, prothrombin biotransformation, plasma levels of Factor VIIa and platelet aggregation. It does cause slight, transient increases in activated partial thromboplastin time but clinical safety findings are that these changes are not clinically significant. Fondaparinux co-administration with warfarin also does not significantly affect bleeding time and prothrombin biotransformation and does not modify warfarin-induced changes in prothrombin time, activated partial thromboplastin time and Factor VIIa levels. The slight, transient increases in activated partial thromboplastin by fondaparinux is not modified by co-administration with aspirin.

9. ***Is Adequate Information Provided on the Kinetics of Fondaparinux in Special Populations?***

(a) Patients with Renal Impairment

(i) Young Adults: The effect of impaired renal function was assessed in healthy, young adult subjects and young, adult subjects with mild, moderate and severe renal impairment (n= 5 per group) treated with a single 4 mg intravenous dose of fondaparinux (Protocol 63107). Severe, moderate and mild renal impairment were represented by creatinine clearance (Cl_{cr}) values of 10-30, 31-60, and 61-90 mL/min, respectively. Cl_{cr} > 90 mL/min represented normal renal function. The fondaparinux distribution and elimination parameters obtained in this study are summarized in Table 26.

Table 26. Mean (SD) Pharmacokinetic Parameters of Fondaparinux in Subjects with Varying Levels of Renal Function Treated with Intravenous Fondaparinux 4 mg (Protocol 63107 [n=5 per group])

Population	Creatinine clearance* (mL/min)	CL (/F) (mL/min)	V_{ss} (/F) (L)	$t_{1/2}$ (h)	Fe_{0-t} (%)	$Cl_{R,0-t}$ (mL/min)
Group I CLCr: 10-30 mL/min	20.5 (7.8)	1.4 (0.3)	8.5 (2.5)	71.5 (11.7)	17 (8)	0.5 (0.3)
Group II CLCr: 31-60 mL/min	49.2 (11.6)	3.4 (0.9)	8.0 (1.3)	28.7 (7.5)	47 (5)	2.2 (0.6)
Group III CLCr: 61-90 mL/min	81.3 (14.5)	5.2 (1.2)	8.1 (1.4)	17.9 (0.9)	61 (7)	3.8 (1.2)
Group IV 91-140 mL/min	125.1 (39.9)	7.8 (1.2)	8.8 (2.6)	13.1 (3.6)	66 (6)	5.5 (0.5)

* At screening

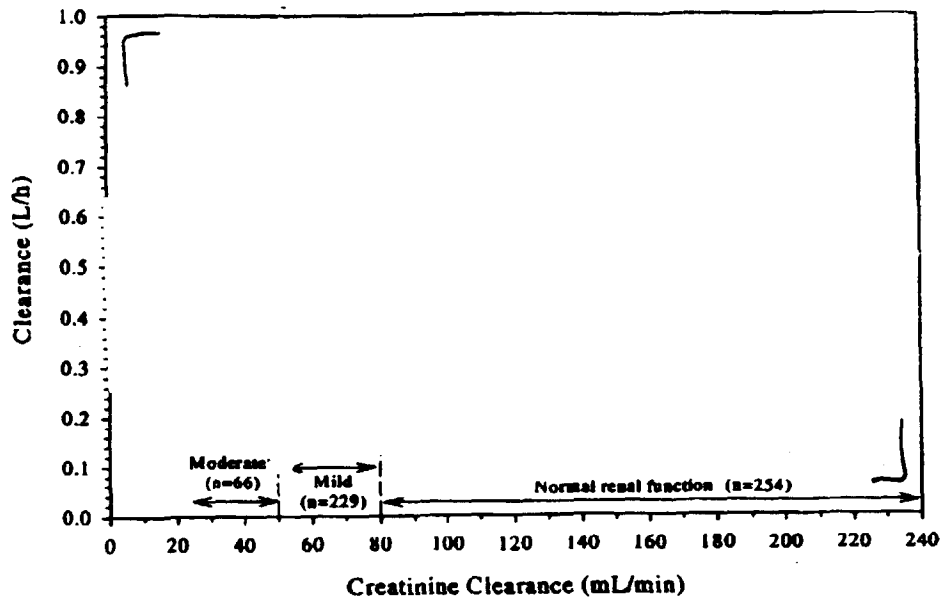
The mean apparent volume of distribution (8.0-8.8 L) was similar to the values obtained in the other studies already discussed and was independent of the degree of kidney function. These findings suggest that impairment of renal function does not affect the distribution characteristics of fondaparinux in young, adult individuals. Elimination half-life increased with decreasing renal function. Total clearance and renal clearance also decreased with decreasing renal function. Total clearance was found to be directly proportional to creatinine clearance and renal clearance.

Based on the data in Table 26, this reviewer has estimated the mean non-renal to be 27% of total clearance in the subjects with mild renal impairment and 29% of total clearance in the subjects with normal renal function. Due to the long half-life values in patients with severe or moderate renal impairment, it is likely that the sampling time was probably not long enough to allow an accurate estimation of total clearance and renal clearance. Thus, non-renal clearance has not been estimated for these two groups.

(ii) Target Patient Population: In the studies in patients treated with subcutaneous fondaparinux injection 2.5 mg (Protocols EFC2698 and EFC2442) and 3 mg (Protocol

DR12643) described in item 6(a) above, fondaparinux steady state total clearance was assessed on the basis of renal function by the population pharmacokinetic method. The results are presented in Fig. 10 and Table 27.

Fig. 10. Relation between Total Clearance (CL/F) of Fondaparinux and Renal Function (CLCr) in Protocol DR12643 Evaluating Steady Steady State Kinetics of Fundaparinux in of Patients



* : two subjects had creatinine clearance just below 30 mL/min and were included in moderate

Table 27. Fondaparinux Total Clearance (CL/F) as Function of Renal Function (CLCr) in Protocols DR12643, EFC2698 and EFC2442) Evaluating Steady State Kinetics of Fundaparinux in Patients

Study	Parameter	Creatinine Clearance category		
		Moderate* 30 to 50 mL/min	Mild 50 to 80 mL/min	Normal >80 mL/min
DRI2643	n	66	229	254
	CLCr (mL/min)	42 (6)	64 (9)	103 (21)
	Weight (kg)	63 (10)	74 (13)	91 (16)
	Age (year)	77 (6)	70 (8)	58 (11)
	CL/F (L/h)	0.337 (0.081)	0.417 (0.087)	0.536 (0.114)
EFC2698	n	55	61	25
	CLCr (mL/min)	39 (7)	63 (8)	106 (19)
	Weight (kg)	59 (11)	67 (10)	78 (14)
	Age (year)	84 (6)	76 (8)	60 (14)
	CL/F (L/h)	0.263 (0.100)	0.351 (0.114)	0.437 (0.108)
EFC2442	n	7	23	34
	CLCr (mL/min)	43 (2)	68 (8)	110 (25)
	Weight (kg)	66 (10)	73 (12)	90 (19)
	Age (year)	77 (5)	72 (8)	61 (13)
	CL/F (L/h)	0.225 (0.049)	0.374 (0.106)	0.520 (0.091)

* Very few patients had creatinine clearance just below 30 mL/min and were included in moderate

Based on the data in Table 27, the mean steady state clearance (CL/F) values in patients with mild and moderate renal impairment were, respectively, 72% and 43 % of the mean value in patients with normal renal function. Statistical significance in clearance differences between the renal function sub-groups was not concluded due to the small number of patients in some of the subgroups in the individual studies. In the three studies (combined), the sponsor states that the incidence of bleeding in patients with normal renal function, mild renal impairment, moderate renal impairment and severe renal impairment was 1.6% (25/1565), 2.4% (31/1288), 3.8% (19/504) and 4.8% (4/83), respectively.

In the drug product labeling, under the sub-section, "Pharmacokinetics", the sponsor states that

[ ]. No dosage adjustment provision is made for patients with with moderate or severe renal impairment. Based on the comparative bleeding profile in the preceding paragraph, it is considered that dosage adjustment for these patient sub-populations is necessary (see Labeling Comment 2 (e).1 [page 40]).

(ii) Patients on Chronic Intermittent Hemodialysis: In the study evaluating single, intravenous doses of fondaparinux 4, 6 and 10 mg in patients on chronic, intermittent dialysis (Protocols 63113), the mean elimination half-life of fondaparinux was 10-15 h during the dialysis and 59-70 h post dialysis. In each case the half-life was dose independent. These data suggest that fondaparinux is dialyzable.

(b) Patients with Hepatic Impairment: No studies were conducted to investigate in vivo metabolism of fondaparinux. No comment is necessary since the major pathway of fondaparinux in patients with normal renal function is urinary excretion.

(c) Geriatric Patients: In the studies in patients treated with subcutaneous fondaparinux injection 2.5 mg (Protocols EFC2698 and EFC2442) and 3 mg (Protocol DR12643) described in item 6(a) above, fondaparinux steady total clearance was assessed on the basis age (< 65 years versus 65-75 years versus >75 years) by the population pharmacokinetic method. The results are presented in Fig 11 and Table 28.

Fig. 11. Relation between Total Clearance (CL/F) of Fondaparinux and Age in Protocol EFC2698 Evaluating Steady Steady State Kinetics of Fundaparinux in of Patients

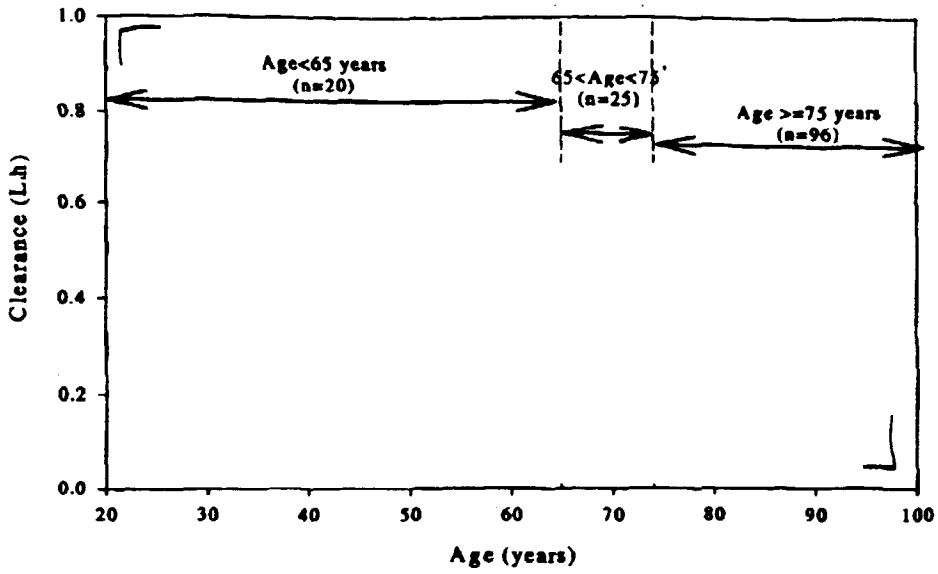


Table 28. Fondaparinux Total Clearance (CL/F) as a Function of Age in Protocols DR12643, EFC2698 and EFC2442) Evaluating Steady State Kinetics of Fundaparinux in Patients

Study	Parameter	Age Category		
		<65 years	65-75 years	>75 years
DRI2643	n	275	201	134
	Age (years)	54 (9)	70 (3)	79 (3)
	Weight (kg)	85 (19)	80 (16)	72 (14)
	CLCr (mL/min)	97 (27)[a]	72 (19)[b]	56 (16)[c]
	CL/F (L/h)	0.500 (0.114)	0.452 (0.121)	0.401 (0.111)
EFC2698	n	20	25	96
	Age (years)	53 (10)	71 (2)	82 (5)
	Weight (kg)	71 (14)	68 (15)	64 (12)
	CLCr (mL/min)	100 (26)	68 (24)	51 (16)
	CL/F (L/h)	0.410 (0.101)	0.363 (0.116)	0.308 (0.123)
EFC2442	n	23	23	18
	Age (years)	53 (9)	71 (2)	79 (3)
	Weight (kg)	87 (20)	78 (13)	78 (20)
	CLCr (mL/min)	114 (28)	77 (20)	67 (22)
	CL/F (L/h)	0.506 (0.107)	0.418 (0.131)	0.367 (0.140)

[a] =246

[b] =185

[c] =118

In each study, patients < 65 years of age, on the average, had normal kidney function whereas patients 65-75 years of age and patients > 75 years of age had, on the average, mild to moderate renal impairment (Table 28). Based on the data provided in Table 28, this reviewer has determined that as compared to patients with normal renal function (< 65 years of age), the mean total clearance of fondaparinux in patients 65-75 years of age and > 75 years of age were, respectively, 90% and 80% in Protocol DR12643, 89% and 75% in Protocol EFC2698 and 83% and 73% in Protocol EFC2442. Pharmacokinetic variability was low to moderate in all age groups. The sponsor states that the difference in fondaparinux total clearance is not statistically significant. However, In the three studies (combined), the incidence of major bleeding in patients < 65 years of age, 65-75 years of age and > 75 years of age were 1.8% (23/1253), 2.2% (24/1111), and 2.7% (33/1227), respectively.

In the drug product labeling, under the sub-section, "Geriatric Use", the sponsor states that

[ ]

Based on the comparative bleeding profile in the preceding paragraph, it is considered that dosage adjustment for patients over 75 years of age is necessary (see Labeling Comment 2.(e).iii [page 40]).

(d) Pediatric Patients: No studies were conducted to investigate the kinetics of fondaparinux in pediatric subjects. In the drug product labeling, the sponsor states that "safety and effectiveness of [redacted] in pediatric patients have not been established".

10. ***Is Adequate Information Provided on the Effect of Gender on the Kinetics of Fondaparinux?***

In the studies in patients treated with subcutaneous fondaparinux injection 2.5 mg (Protocols EFC2698 and EFC2442) and 3 mg (Protocol DR12643) described in item 6(a) above, fondaparinux steady total clearance was assessed on the basis of gender by the population pharmacokinetic method. The results are summarized in Table 29.

Table 29. Fondaparinux Total Clearance (CL/F) as a Function of Age in Protocols DR12643, EFC2698 and EFC2442) Evaluating Steady State Kinetics of Fundaparinux in Patients

Study	Gender	n	CL/F (L/h)	Weight (kg)	Age (y)	CLCr (mL/min)
DRI2643	Males	327	0.509 (0.118)	88 (16)	62 (13)	89 (29)*
	Females	283	0.408 (0.102)	72 (15)	68 (10)	69 (22)*
EFC2698	Males	35	0.392 (0.129)	78 (12)	70 (16)	82 (32)
	Females	106	0.312 (0.117)	62 (11)	78 (10)	54 (19)
EFC2442	Males	33	0.485 (0.122)	89 (18)	64 (14)	95 (30)
	Females	31	0.382 (0.132)	73 (15)	70 (9)	80 (31)

CLCr: Creatinine clearance

* n=302

* =247

Based on these data, unnormalized total clearance and renal clearance of fondaparinux tend to be higher in males as compared to females. However, incidents of major bleeding in males (2.4% [34/1429]) and females (2.1% [46/2166]) were similar. There is no need for dosage adjustment on the basis of gender.

11. *Is Adequate Information Provided on the Effect of Body Weight on the Kinetics of Fondaparinux?*

In the studies in patients treated with subcutaneous fondaparinux injection 2.5 mg (Protocols EFC2698 and EFC2442) and 3 mg (Protocol DR12643) described in item 6(a) above, fondaparinux steady total clearance was assessed on the basis body weight by the population pharmacokinetic method. The results are summarized in Fig. 12 and Table 30.

Fig. 12. Relation between Total Clearance (CL/F) of Fondaparinux and Body Weight in Protocols Dr12643, EFC2698 and EFC2442 Evaluating Steady Steady State Kinetics of Fundaparinux in of Patients

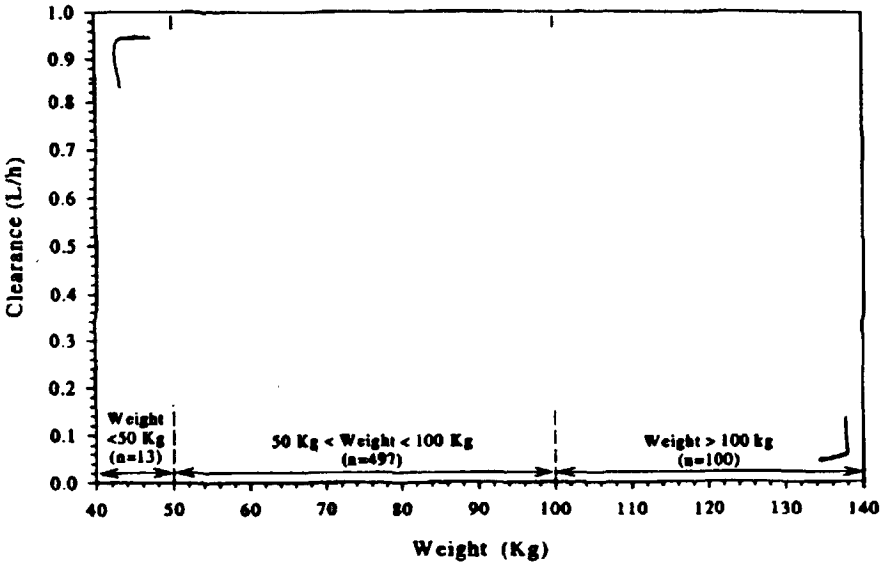


Table 30. Fondaparinux Total Clearance (CL/F) as a Function of Body Weight in Protocols DR12643, EFC2698 and EFC2442) Evaluating Steady State Kinetics of Fundaparinux in Patients

Study	Parameter	Weight Category		
		<50 kg	50-100 kg	>100 kg
DRI2643	n	13	497	100
	Weight (kg)	47 (2)	76 (12)	109 (9)
	CL/F (L/h)	0.351 (0.074)	0.440 (0.108)	0.589 (0.107)
EFC2698	n	18	122	1
	Weight (kg)	45 (5)	68 (11)	106
	CL/F (L/h)	0.238 (0.076)	0.344 (0.123)	0.560
EFC2442	n	1	54	9
	Weight (kg)	48	76 (12)	113 (14)
	CL/F (L/h)	0.186	0.426 (0.135)	0.517 (0.093)

In each study, as compared to the 50-100 kg subgroup, the numbers of subjects in the <50 kg and >100 kg subgroups are to small to allow for a detection of fondaparinux total clearance differences between subgroups. Furthermore, no information is provided on incidence of major bleeding in the weight sub-populations evaluated. In the drug product labeling, under the sub-section,

[ ]

Since the dose of Xantidar® is not individualized (i.e. administered as mg/kg), this cautionary statement appears to be adequate except that the word —— needs to be replaced with a less ambiguous expression (see Labeling Comment 3(e).iv [page 40]).

12. *Is Adequate Information Provided on the Effect of Race on the Kinetics of Fondaparinux?*

The kinetics of fondaparinux has been evaluated in healthy, young, male Japanese subjects treated with intravenous does of Xantidar® ranging from 2 mg to 16 mg (Protocols TDU3085 [dose range= 2-16 mg, n=6 per dose group], TDU3166 [dose=8 mg, n=6] and TDR3088 [dose=8 mg, n=6]). The pharmacokinetic data were compared to those obtained in young, healthy, male Caucasian subjects treated with subcutaneous doses of Xantidar® (Protocols BDR3780 [dose=2.5 mg, n=16 and INT3012 [dose=10 mg, n=12). The summary of the results is presented in Table 31. Fondaparinux total clearance normalized for absorbed dose (CL/F) for Caucasian and Black sub-populations in Protocol DR12643 were also compared (Table 32).

Table 31. Mean (SD) Fondaparinux Pharmacokinetic Parameters in Young, Healthy Male Japanese Subjects Treated with Intravenous Doses of Xantidar® and Young, Healthy, Male Caucasians Subjects Treated with Subcutaneous Doses of Xantidar®

Protocol No.	Race	Route of Administration Duration	Dose (mg)	CL/F (mL/min)	V_z/F (L)	$t_{1/2}$ (h)	Fe_{0-t} (%)	$CL_{R,0-t}$ (mL/min)
TDU3085	Japanese	IV - Single dose (n=6)	2	NC	NC	14.9 (1.9)	76 (9)	5.3 (0.7)
		IV - Single dose (n=6)	4	6.9 (0.5)	8.2 (0.5)	13.7 (1.1)	75 (4)	5.3 (0.3)
		IV - Single dose (n=6)	8	7.6 (0.5)	8.7 (0.7)	13.2 (1.0)	73 (3)	5.7 (0.3)
		IV - Single dose (n=6)	12	8.2 (0.6)	9.9 (1.4)	14.1 (2.7)	71 (7)	6.1 (0.8)
		IV - Single dose (n=6)	16	8.7 (0.9)	9.8 (1.5)	12.9 (1.2)	80 (4)	7.2 (0.8)
TDU3166	Japanese	IV - Single dose (n=6)	8	7.3 (0.6)	8.2 (0.6)	13.0 (1.0)	67 (11)	4.9 (0.6)
TDR3088	Japanese	IV - Repeated dose (n=6)	8	8.3 (0.8)*	8.9 (0.6)*	12.5 (1.2)*	71 (6)*	5.8 (0.5)*
BDR3780	Caucasian	SC - Single dose (n=16)	2.5	5.6 (0.9)	8.2 (1.1)	17.2 (3.2)	-	-
INT3012	Caucasian	SC - Single dose (n=12)	10	6.3 (1.0)	8.5 (0.7)	15.7 (2.2)	75 (8)	5.0 (1.0)

-: not determined, NC: not calculated due to high% of AUC extrapolated

* values after repeated dose

Table 32. Mean (SD) Fondaparinux Clearance (CL/F) in Black and Caucasian Patients Undergoing Elective, Total Hip Replacement Surgery Treated with Xantidar® 3 mg by Subcutaneous Injection (Protocol DR12643)

Race	Number of subject	CL/F (mL/min)	Body weight (kg)	Age (years)	CLCr (mL/min)
Black	*43*	*7.9 (2.3)*	*86 (21)*	*59 (16)*	*86.3 (33.0)*
Caucasian	559	7.7 (2.0)	80 (17)	65 (11)	79.1 (27.1)

Pharmacokinetic data in healthy, young Caucasian subjects are rather limited as compared to those in healthy, young Japanese subjects. However, the percentage of fondaparinux eliminated unchanged in urine in the Caucasian subjects in Protocol INT3012 (75±8%) is in the range of 67±11% and 80±4% in the Japanese subjects treated with single doses of Xantidar®. These results suggest similarity in urinary excretion unchanged fondaparinux (the major route of elimination) between Caucasians and Japanese. It is considered that Xantidar® dosage adjustment for Japanese is not necessary.

The sponsor states that in Protocol DR12643, although the number of Blacks is rather small as compared to Caucasians, the total clearance (CL/F) values in Blacks (7.9±2.3 mL/min) are similar to those observed in Caucasians (7.7±2.0 mL/min) (Table 32).

This reviewer further examines the Black and Caucasian sub-populations relative to the whole study population. In Protocol DR12643, the Blacks (age=59±16 years, CL/F=7.9±2.3 mL/min)) are mostly in the age subset of < 65 years old (CL/F = 0.500±0.114 L/h [i.e. 8.3±1.9 mL/min]). The Caucasians (age=65±11years, CL/F=7.7±2.0 mL/min)) are divided approximately equally into the subsets of < 65 years old (CL/F=0.500±0.114 L/h [i.e. 8.3±1.9 mL/min]) and 65-75 years old (CL/F = 0.452 L/h [i.e. 7.5+2.0 ml/min]). Thus, the Blacks and Caucasians are similar to the other subjects in their age groups in fondaparinux total clearance following subcutaneous injection of Xantidar® 2.5 mg. Accordingly, it is considered that Xantidar® dosage adjustment for Blacks is not necessary.

12. ***Is Adequate Information Provided on Relationsip between Pharmacokinetics and Pharmacodynamics of Fondaparinux?***

In Phase II studies evaluating fondaparinux sodium doses of 0.75-8 mg, efficacy and incidents of major bleeding increased with increasing dose (Protocols DR12643 and 095-001). Efficacy was too low at the 0.75 mg dose and excessive at doses higher than 3 mg. This was the basis for selecting the 2.5 mg dose for marketing. In the studies evaluating this dose in the target patient population (Protocols EFC2698 and EFC2442), the increase in major bleeding incidents in patients with moderate or severe renal impairment secondary to decreased drug clearance suggests that major bleeding incidents increase with increasing drug concentration (which results from reduced drug clearance).

13. ***Is Adequate Information Provided on Methods of Fondaparinux Analysis in Biological Samples?***

(a) Analytical Method: In the submitted studies, analysis of fondaparinux (Org31540/SR90107) in plasma, urine and ultrafiltrate samples utilized [redacted] methods mostly with [redacted] In these analytical procedures, [redacted] The test principle is based on [redacted] complex (Protocols DOH0061, DOH0049, DOH0087,

DOH0123, DOH0160, DOH0129, DOH0158, SDGRR4819, SDGRR5189 and SDGRR4848). Here is a brief summary of the methods.

(b) Validation of Analytical Method: Across studies, (i) the [redacted] concentration ranges (quality control) used for assay method validation ranged from 2.1-78 ng/mL to 62-998 ng/mL in plasma and from 5.1-105 ng/mL to 0-840 ng/mL in urine and 4.2-84 ng/mL in ultrafiltrate, (ii) the limits of quantification ranged from [redacted] in plasma and [redacted] in urine and was [redacted] in ultrafiltrate, (iii) in all matrices and for all concentrations at or above the limits of quantification, (a) the within-day precision ranged from 0.8% to 15.2% (b) the between-day precision ranged from 1.2% to 16.9%, (c) the within-day accuracy ranged from 88% to 114% and (d) the between-day accuracy ranged from 93% to 113%. For each assay, the linearity range was well defined and the assay specificity for fondaparinux was adequately demonstrated. Fondaparinux was shown to be stable in quality control samples stored at -20°C up to one month (ultrafiltrate) and up to two years (plasma and urine) and in clinical samples stored at the same temperature up to 5 months (plasma) and up to 7 months (urine). Short term (bench top) and freeze thaw (up to three freeze-thaw cycles) stability of fondaparinux was also adequately demonstrated.

14. *Is Adequate Information Provided on Methods of Pharmacokinetic Analysis of Fondaparinux?*

For each pharmacokinetic studies submitted in the NDA, the pharmacokinetic parameters were satisfactorily determined using standard pharmacokinetic equations based on the pharmacokinetic model (non-compartmental, compartmental or population) employed. The fondaparinux concentrations used for pharmacokinetic analysis were at and above the limits of assay quantification and within the range of assay linearity.

14. *Is Adequate Information Provided on the Formulation Xantidar®?*

The Xantidar® formulation used for the pivotal clinical studies and most of the other clinical studies (Formulation 1A1) and the proposed market formulation of Xantidar® (Formulation (2B2) are presented below. For each formulation, the reason for changing from the preceding formulation is provided.

FORMULATION 1A1: 10 mg/ml Org31540/SR90107A

Description of change: Decrease in drug substance concentration from ——— to 10 mg/ml

Reason for change: Based on efficacy demonstrated in previous clinical studies lower concentrations were needed for lower doses

Clinical Study Code	Lot Number (bulk)	Pharmaceutical Form / Strength	Batch Size	Formulation	Manufacturing Change
ACT2445 ACT2545 63105	L188S[1]	[redacted]	—	10 mg/ml Org/SR in —g/ml NaCl solution	
ACT2445 63106 63107 63108 63109-B 63113 TDU3085 TDR3088 TDU3166	M279T[2][3][4][5]	[redacted]	—		Pre-filled syringes —

amp. = ampoules syr. = pre-filled syringe

[1] Batch L188S renumbered CP095018 and CP095113 in Organon study 63105

[2] Batch M279T renumbered CP095192 in Organon studies 63106, 63107 and 63113

[3] Batch M279T renumbered CP096082 in Organon study 63108

[4] Batch M279T renumbered CP097038 in Organon study 63109-B

[5] Batch M279T renumbered 96-00522 in Sanofi studies TDU3085, TDU3088 and TDU3166

FORMULATION 1A1: 10 mg/ml Org31540/SR90107A (cont.)

Clinical Study Code	Lot Number (bulk)	Pharmaceutical Form / Strength	Batch Size	Formulation	Manufacturing Change
EFC2442 EFC2698 095-002 63118	98-01637	[redacted]	—	10 mg/ml Org/SR in —g/ml NaCl solution	
EFC2698 63118 BDR3780 INT3933 TDU4089	98-01698		—		

syr. = pre-filled syringe

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FORMULATION 2B2: 5 mg/ml Org31540/SR90107A

Description of changes: Decrease in drug substance concentration from — mg/ml to 5 mg/ml and decrease in NaCl concentration from — mg/ml to — mg/ml.

Reason for changes: Based on the results of the dose-ranging studies a dose of 2.5 mg was selected for Phase III and as the proposed to-be-marketed dose. The drug product concentration was decreased from — mg/ml to 5 mg/ml to allow an injection volume of — ml. Consequently, in order to obtain an isotonic Org31540/SR90107A 5 mg/ml solution the NaCl level was adjusted to obtain the same osmolarity as that of an isotonic — NaCl solution.

Clinical Study Code	Lot Number (bulk)	Pharmaceutical Form / Strength	Batch Size	Formulation	Manufacturing Change
BDR3780 TDU4089 TDU4289	98-01875	—	—	5 mg/ml Org/SR in — mg per ml NaCl solution	[ ]

syr. = pre-filled syringe

The compositions of Formulations 1A1 and 2B2 differ only in the changes in the strengths drug concentration and saline from — mg/mL and — mg/mL, respectively, to 5 mg/mL and — mg/mL, respectively.

III. LABELING COMMENTS

The following comments relate to the Clinical Pharmacology section of the drug product labeling:

1. The information on page 11/161 should be sub-headed as **Mechanism of Action**.

2. The information in the sub-section entitled, **Pharmacokinetics** should be replaced by the following:

(a) Absorption: Fondaparinux administered by subcutaneous injection is rapidly and completely absorbed (absolute bioavailability is 100%). Following a single subcutaneous dose of fondaparinux 2.5 mg in young, —— male ——— C_{max} of 0.34 mg/mL is reached in approximately 2 hours.

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(b) Distribution: In healthy, adult ——— intravenously or subcutaneously administered fondaparinux distributes mainly in blood and only to a minor extent in extravascular fluid as evidenced by steady state and non-steady state apparent volume of distribution of 7-11 L. Similar fondaparinux ——— occurs in patients undergoing elective hip surgery or hip fracture surgery. Fondaparinux is highly (at least 94%) and specifically bound to antithrombin III (ATIII) and does not bind significantly to other plasma proteins (including platelet Factor 4 [PF4]) or red blood cells.

(c) Metabolism:

[

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(d) Elimination: In individuals with normal kidney function fondaparinux is eliminated in urine mainly as unchanged drug. In healthy individuals 75 years ——— up to 77% of a single subcutaneous or intravenous dose fondaparinux is eliminated in urine as unchanged drug in 72 h. The elimination half-life is 17-21 h.

(e) Pharmacokinetics in Special Populations

i. ——— **Renal Impairment**: Fondaparinux elimination is prolonged in patients with renal impairment since the major route of elimination is urinary excretion of unchanged drug.

[

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[redacted]

ii. Patients with Hepatic Impairment: The pharmacokinetics of fondaparinux [redacted] not been studied in patients with hepatic impairmant.

iii. Elderly Patients: Fondaparinux elimination is prolonged in patients over 75 years of age.

[redacted]

iv: Patients Weighing Less than 50 kg:

[redacted]

(e) Effect of Gender: The [redacted] of fondaparinux [redacted] not significantly affected by gender.

(f) Effect of Race:

[redacted]

3. Drug Interactions:

[redacted]

[redacted]

[

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In the Dosage and Administration section, the duration of treatment should be explicitly specified. If "7±2" days is the recommended duration of treatment, the following should be stated: **The ———— duration of treatment is 5-9 days** (which is easier and more understandable to the consumer).

IV. OVERALL COMMENTS

1. Fondaparinux is eliminated principally as unchanged drug in urine and its elimination is substantially delayed in patients with severe renal impairment. In these patients,

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3. In Protocol BDR3780 that assessed the bioequivalence of the to-be-marketed and the clinically tested formulations of fondaparinux sodium injection, the statistical analysis did not use the Agency recommended two one-sided t-tests procedure. In the future, the sponsor is advised to use this procedure.

VI. RECOMMENDATION

NDA 21-345 submitted for fondaparinux sodium (Xantidar®) injection by the sponsor on February 15, 2001 has been reviewed by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Bipharmaceutics. The information provided by the sponsor is acceptable for consideration in the NDA approval decision process. However, the sponsor needs to satisfactorily address the issues raised in Labeling Comments 1-5 (pages 39- 41) and Overall Comments 1-3 (page 41) prior to NDA approval.

Please convey this Recommendation and Overall Comments 1-3 (page 41), as appropriate, to the sponsor. Overall Comment 2 (page 41) needs to be brought to the attention of the reviewing chemist as well.

David G. Udo, Ph.D.
Division of Pharmaceutical Evaluation II

Concurrence: Suresh Doddapaneni, Ph.D. _____

Clinpharm/Biopharm Briefing: 07/26/01 (Attendees: HFD-180 [Lu], HFD-880 [Selen], HFD-780 [Hunt, Sun, Haidar, Ling and Louis]).

cc: NDA 21-345, HFD-180, HFD-180 (Oliver), HFD-870 (Malinowski, Hunt, Doddapaneni and Udo), CDR (Attn: Zom Zadeng).

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ATTACHMENT I

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS Division of Pharmaceutical Evaluation II	
NDA:	**[redacted]**
Generic (Brand®)	**Fondaparinux Sodium Injection - Xantidar™**
Submission Date:	**February 15, 2001**
Sponsor:	**Fonda BV**
Consult:	**Population Pharmacokinetics Analysis**
Pharmacometrics Scientist:	**Sam H. Haidar**

Background

NDA 21-345 for fondaparinux (s.c.) injection (Xantidar™) was submitted by Fonda BV on February 15, 2001. The proposed indication for fondaparinux is 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 (recommended) dose of fondaparinux is 2.5 mg once daily administered post-operatively by subcutaneous injection.

According to the sponsor, fondaparinux selectively binds anti-thrombin III, increasing its ability to inhibit Factor Xa by about 300 times. Neutralization of Factor Xa interferes with the blood coagulation cascade, inhibiting thrombin formation and thrombus development.

This pharmacometrics consult evaluated the population pharmacokinetic analysis performed on a subset of patients in Study EFC2442, who were undergoing elective hip replacement or revision.

Title: Population pharmacokinetic analysis of Org31540/SR90107A in the prevention of deep vein thrombosis after elective hip replacement or revision (EFC2442).

Objectives:

1. To define and validate the best PK model (with or without inclusion of demographic characteristics – gender, age, weight, height and creatinine clearance – tested as covariates) of Org31540/SR90107A administered in prevention of deep vein thrombosis (DVT) to patients from EFC2442 study undergoing an elective hip replacement or revision.
2. To provide the best post-individual estimates of PK parameters for evaluation of the relationships between exposure and clinical outcomes.

Methods:

A total of 66 patients (out of 1128 treated with Org31540/SR90107A) had fully documented PK information. Of this subset of patients, one was dropped from the analysis due to possibly erroneous values. Data for the remaining 65 subjects were

divided (at random) into a model-development data set and a model validation data set. The former consisted of data from 45 patients, while the latter, had data from 20 patients. The program ——— was used to model Org31540/SR90107A plasma concentration. Structural models evaluated included one- and two-compartment models with different error structures (homoscedastic, heteroscedastic 1/Y and $1/Y^2$). The effect of covariates on PK parameters was evaluated using graphical methods (covariate vs. parameter plots) and using a multiple linear stepwise procedure. Covariates showing a correlation (partial $r^2 > 10\%$) with CL/F, V/F, or k_a, were tested for inclusion in the model. Individual predicted plasma concentrations and PK parameters for subjects in the validation set were computed using Bayesian estimation.

Results:

A two-compartment model with heteroscedastic error (1/Y) provided the best fit. Figure 1 suggests that the model provides a good fit. According to the sponsor, there was a correlation between CLcr and CL, and weight and V/F; however, these patient covariates were not included in the model because they did not show a statistically significant effect based on the Log-Likelihood test. Table I lists the PK parameters for the total and model-building data sets.

Table I. Final model population PK parameters obtained for all patients (N = 65) and patients in the model-building data set (N = 45).

	Total Data Set (*n=65*)		Model Building Data Set (*n=45*)	
Parameter	***Mean***	***CV %***	***Mean***	***CV %***
CL/F (L/h)	0.435	33	0.452	32
V/F (L)	4.08	19	4.34	20
k_{12} (h^{-1})	0.181	30	0.165	35
k_{21} (h^{-1})	0.076	87	0.099	70
k_a (h^{-1})	0.457	44	0.514	46
AIC	- 2.842		- 2.880	
LL	1030.4		733.0	
σ	$1.264 . 10^{-3}$		$1.266 . 10^{-3}$	
Within subject variability	8.16 %		8.14 %	

F = Bioavailability.
AIC = Akaike's criterion.
LL = Logarithm of the Maximum Likelihood.
σ = Variance of the residual error model (intra + residual variability).

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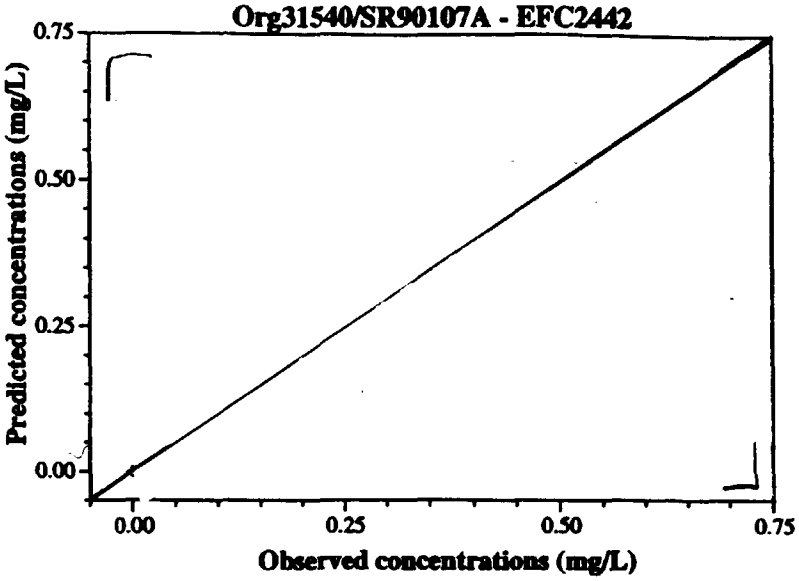

Figure 1. Observed versus predicted plasma concentrations in the model building data set (N = 45).

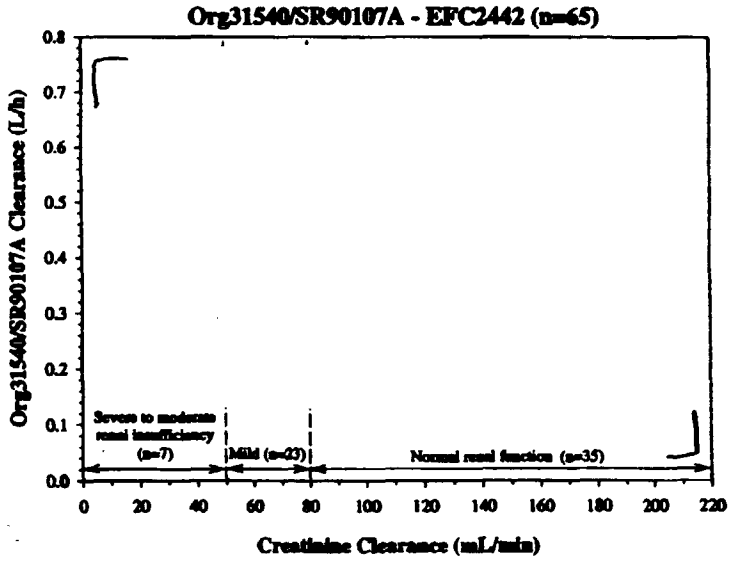

Figure 2. The relationship between creatinine clearance and Org31540/SR90107A clearance in the total data set.

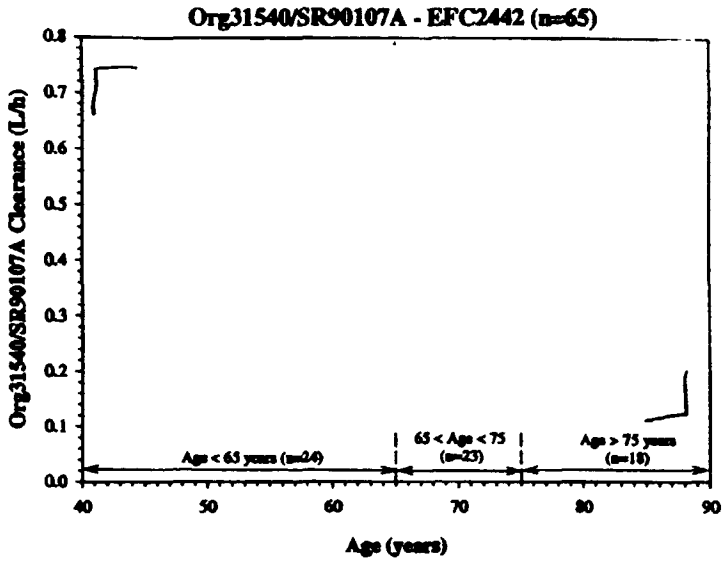

Figure 3. Org31540/SR90107A clearance as a function of age in the total data set.

Reviewer's Comments:

1. The population PK analysis is acceptable.
2. According to the sponsor, the addition of different covariates (e.g., weight, age, creatinine clearance, ...etc.) did not result in a statistically significant improvement in the model fit. In other words, no covariate had a significant effect on the PK parameters. This misleading conclusion may be the result of insufficient sample size to adequately evaluate the effect of covariates.
3. As can be seen in figures 2 and 3, creatinine clearance and age do appear to influence Org31540/SR90107A clearance. If we only consider mean effect on clearance, the effect may appear insignificant; however, if we look at outliers in the age group > 65 years old and in the moderate to severe creatinine clearance, we find clearances less than 50% of the mean of the young/normal renal function group.

[ ]

Sam H. Haidar, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

cc:
NDA 21-345
HFD-870 (Malinowski, Udo, Doddapaneni, Haidar)
HFD-180 (Lu, Oliver)
HFD-850 (Lee P.)
CDR

APPENDIX II

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-345	Brand Name	Xantidar
OCPB Division (I, II, III)	II	Generic Name	Fondaparinux sodium
Medical Division	HFD-180	Drug Class	Anticoagulant
OCPB Reviewer	David G. Udo, Ph.D.	Indication(s)	Prophylaxis of venous thromboembolic event in adult patients undergoing major orthopedic surgery of the lower limbs
OCPB Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	Solution
		Dosing Regimen	2.5 mg once daily
Date of Submission	02/15/01	Route of Administration	Subcutaneous injection
Estimated Due Date of OCPB Review	07/26/01	Sponsor	Fonda BV
PDUFA Due Date	08/15/01	Priority Classification	1P
Division Due Date	07/19/01		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	X	2	2	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	18	11	
multiple dose:	X	4	4	
Patients-				
single dose:				
multiple dose:	X	4	3	
Dose proportionality -				
fasting / non-fasting single dose:	X	2	1	
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	4	4	
In-vivo effects of primary drug:	X	4	4	
In-vitro:	X	1	1	
Subpopulation studies -				
Ethnicity:	X	2	2	
Gender:	X	1	1	
Pediatrics:				
Geriatrics:	X	1	1	
renal impairment:	X	2	2	
hepatic impairment:				
PD:				
Phase 2:	x	1	1	
Phase 3:	x	1	1	

PK/PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 1 and/or 2, proof of concept:		1	1	
Phase 3 clinical trial:		2	2	
Population Analyses -	[redacted]	[redacted]	[redacted]	[redacted]
Data rich:				
Data sparse:	x	1	1	
II. Biopharmaceutics	[redacted]	[redacted]	[redacted]	[redacted]
Absolute bioavailability:	x	1	1	
Relative bioavailability -	[redacted]	[redacted]	[redacted]	[redacted]
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	[redacted]	[redacted]	[redacted]	[redacted]
traditional design; single / multi dose:	x	1	1	
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	[redacted]	[redacted]	[redacted]	[redacted]
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	[redacted]	53	44	

Filability and QBR comments

	"X" if yes	Comments
Application filable ?		Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

Note: Metabolism Studies:	**Submitted**	**Reviewed**
In vitro	**2**	**2**
In vivo	**0**	**0**
Sub-Total	**2**	**2**

Previous Page Sub-total	**53**	**44**
Total	**55**	**46**

CC: NDA 21-345, HFD-850 (Electronic Entry or P. Lee), HFD-180 (Oliver), HFD-870 (Malinowski, Hunt, Doddapaneni and Udo), CDR (Attn: Zom Zadeng)

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

/s/

David Udo
7/30/01 12:51:01 PM
BIOPHARMACEUTICS

Sam H. Haidar
8/1/01 08:26:14 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
8/1/01 08:30:40 AM
BIOPHARMACEUTICS

APPEARS THIS WAY
ON ORIGINAL