

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
20-883

CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)

Du Ball

JUN 5 2000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-883

SUBMISSION DATE: 04/20/00

**ARGATROBAN INJECTION CONCENTRATE
NOVASTAN[®]**

**TEXAS BIOTECHNOLOGY CORPORATION
7000 FANNIN STREET, SUITE 1920
HOUSTON, TEXAS 77030**

REVIEWER: David G. Udo, Ph.D.

TYPE OF SUBMISSION: RESPONSE TO APPROVABLE LETTER (#N-000 BZ)

SYNOPSIS/BACKGROUND

This amendment (serial #N-000 BZ) was submitted to NDA 20-883 for argatroban injection concentrate Novastan[®], by the sponsor, on April 20, 2000. Novastan[®] is proposed as an anticoagulant therapy in patients with heparin-induced thrombocytopenia and is administered by intravenous infusion. The recommended initial dose is 2 $\mu\text{g}/\text{kg}/\text{min}$. The sponsor states that the dose may be adjusted as clinically indicated until a steady state activated partial thromboplastin time (aPTT) of 1.5-3.0 times the initial baseline value is attained. The sponsor further states that the administered dose should not exceed 10 $\mu\text{g}/\text{kg}/\text{min}$. The dosing interval is not stated in the labeling. Accordingly, it appears that Novastan[®] is administered as needed to maintain aPTT within normal limits.

In this amendment, the sponsor provides responses on the labeling issues raised by the Agency in the Approvable Letter dated February 18, 2000.

**REVIEW OF SPONSOR'S RESPONSES ON THE CLINICAL
PHARMACOLOGY LABELING COMMENTS**

Overall, the sponsor has revised the proposed Novastan[®] labeling as requested by the Agency. However, the sponsor has modified the sub-section, "Distribution and Protein Binding" to include the apparent volumes of distribution in the central compartment and at steady state (see the attached labeling).

OVERALL COMMENTS

1. Under the sub-section, "**Distribution and Protein Binding**" the following is stated:

"Volume of the central compartment and steady state volume of distribution are 84 and 174 mL/kg, respectively"

It is recommended (i) that the sub-section title be **Distribution** and (ii) that the above statement be replaced with the following:

Argatroban distributes mainly in the extracellular fluid as evidenced by an apparent steady state volume of distribution of 174 mL/kg (12.18 L in a 70 kg adult).

Rationale for this Recommendation: Protein binding is an aspect of distribution and need not be included separately in the sub-section title. The sub-section, **Distribution** should contain information as to where, in the body, argatroban distributes following Novastan® administration. The apparent volume of distribution at steady state is used to substantiate the claim that argatroban is distributed mainly in the extracellular fluid.

2. It is noted that in the current version of the proposed drug product labeling, the sub-section, **Drug Interactions** is located under the **Precautions** section. In this format, even the findings of drug-drug interaction studies that reveal no significant drug-drug interactions with argatroban are included in the **Precautions** section.

It is recommended that the sub-section, **Drug Interactions** be relocated to the **Clinical Pharmacology** section of the drug product labeling following the sub-section entitled, **Age, Gender**. Only the information on clinically relevant interactions of argatroban with the evaluated drugs (oral anticoagulant agents, thrombolytic agents and antiplatelet agents) should also be included in the **Precautions** section of the labeling. This information should also be included in **Dosage and Administration** sections of the labeling.

Rationale for this Recommendation: **Drug-drug Interactions** is a legitimate component of the **Clinical Pharmacology** section of the drug product labeling. Only the clinically relevant drug-drug interactions need be included in the **Precautions** and **Dosage and Administration** sections of the labeling.

RECOMMENDATION

This amendment (serial #N-000 BZ) submitted to NDA 20-883 for argatroban injection concentrate (Novastan[®]), by the sponsor, on April 20, 2000 has been reviewed by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics. The Clinical Pharmacology section of the revised drug product labeling is considered acceptable provided that it is further revised as recommended under Overall Comments 1 and 2 (page 2).

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

/S/ 06/05/00

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

/S/ 6/5/00

Concurrence: Suresh Doddapaneni, Ph.D. _____

cc: NDA 20-883, HFD-180, HFD-180 (DuBeau), HFD-870 (M. Chen, Huang, Hunt, Doddapaneni and Udo), CDR (Attn: Zom Zadeng).

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-883

SUBMISSION DATE: 03/17/99

JAN - 7 2000

**ARGATROBAN INJECTION CONCENTRATE
NOVASTAN®**

**TEXAS BIOTECHNOLOGY CORPORATION
7000 FANNIN STREET, SUITE 1920
HOUSTON, TEXAS 77030**

REVIEWER: David G. Udo, Ph.D.

TYPE OF SUBMISSION: ORIGINAL AMENDMENT (SERIAL #AZ)

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I. SYNOPSIS/BACKGROUND

Amendment AZ to NDA 20-883 for sterile argatroban (Novastan[®]) Injection Concentrate was submitted by the sponsor on March 17, 1999. Novastan[®] is proposed as anticoagulation therapy in patients with heparin-induced thrombocytopenia and is administered by intravenous infusion. The recommended, initial dose for adult patients with normal liver function is 2 $\mu\text{g}/\text{kg}/\text{min}$. The sponsor states that the dose may be adjusted as clinically indicated until a steady state activated partial prothrombin time (aPTT) of 1.5-3.0 times the initial baseline value is attained. The sponsor further states that the administered dose should not exceed 10 $\mu\text{g}/\text{kg}/\text{min}$.

The clinical pharmacology review of the original NDA was completed on February 25, 1998 (see Appendix II). The NDA was considered approvable with only Labeling Comments. Because the Overall decision on the NDA was "Not Approvable" (NA), the clinical pharmacology Labeling Comments were not communicated to the sponsor in the Agency action letter to the sponsor.

In this amendment, the sponsor voluntarily submits three studies (Protocols SKF001, SKF002 and SKF003) further evaluating the pharmacokinetics, pharmacodynamics and drug-drug interactions of argatroban.

Based on the information contained in this amendment, the sponsor has demonstrated (i) that erythromycin has no effect on the steady state kinetics of argatroban, (ii) that the values of International Normalized Ratio (INR) obtained upon co-administration of warfarin with an argatroban dose of 1 or 2 $\mu\text{g}/\text{kg}/\text{min}$ can be used to predict INR values for warfarin administered alone and (iii) that in the therapeutic range of INR (0 to 3.8) and for the two thromboplastin sensitivities (thromboplastins with International Sensitivity Indices [ISI] of 0.88 and 1.78) tested, the activated Factor X (Factor Xa) values following co-administration of warfarin and argatroban were not significantly different from the INR values when warfarin was administered alone. The sponsor's attempt to demonstrate that argatroban has no effect on the steady state kinetics of digoxin is considered unsatisfactory.

The Clinical Pharmacology Approvable Recommendation in the review of the original NDA dated February 25, 1999 is upheld. However, the sponsor is requested to revise the proposed drug product labeling to address the issues raised in Labeling Comments 1 and 2 of the aforesaid review of the original NDA and incorporate the study findings summarized in the preceding paragraph (see Labeling Comments 1 and 2 [page 10]).

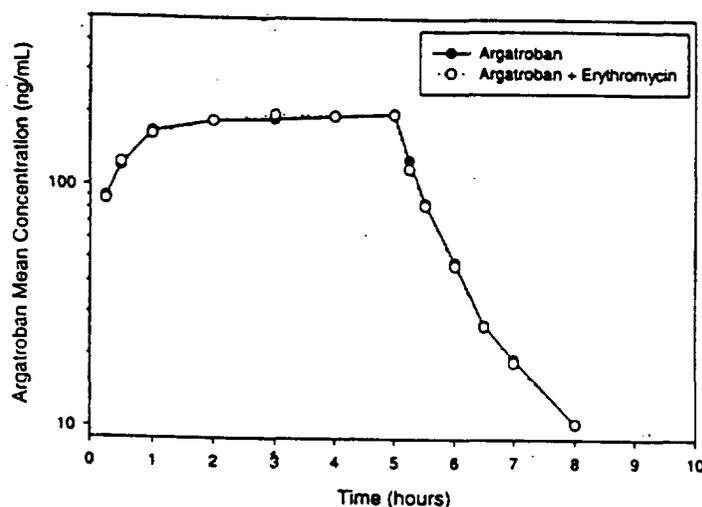
II. SUMMARY OF INFORMATION ON PHARMACOKINETICS, PHARMACODYNAMICS AND DRUG-DRUG INTERACTIONS

1. CO-ADMINISTRATION OF NOVASTAN® AND ERYTHROMYCIN

The effect of erythromycin on the pharmacokinetics and pharmacodynamics of argatroban was evaluated in 10 healthy subjects. Each subject received an intravenous infusion of argatroban 1 $\mu\text{g}/\text{kg}/\text{min}$ for 5 h (Regimen A) and oral erythromycin 500 mg q.i.d. for seven days plus an intravenous infusion of argatroban 1 $\mu\text{g}/\text{kg}/\text{min}$ for 5 h on Day 6 of the oral erythromycin treatment (Regimen B) in a crossover fashion.

(i) **Pharmacokinetics:** Plots of mean concentration of argatroban versus time for the two regimens are presented in Fig. 1.

Fig. 1. Plots of Mean Argatroban Concentration (n=10) Versus Time Following Administration of Argatroban Alone or with Erythromycin



The mean concentration profiles of argatroban with and without erythromycin were essentially identical. These results suggest similarity in argatroban pharmacokinetic characteristics between the two treatment regimens.

(ii) **Assessment of Pharmacokinetic Interactions:** Log transformed total area under the serum concentration versus time curve (AUC) and maximum steady state concentration (C_{max}) for the two treatment regimens were compared, with Regimen A as reference and Regimen B as test, using ANOVA for the 95% confidence intervals. The results are presented in Table 1.

Table 1. Argatroban Pharmacokinetic Results with and without Erythromycin

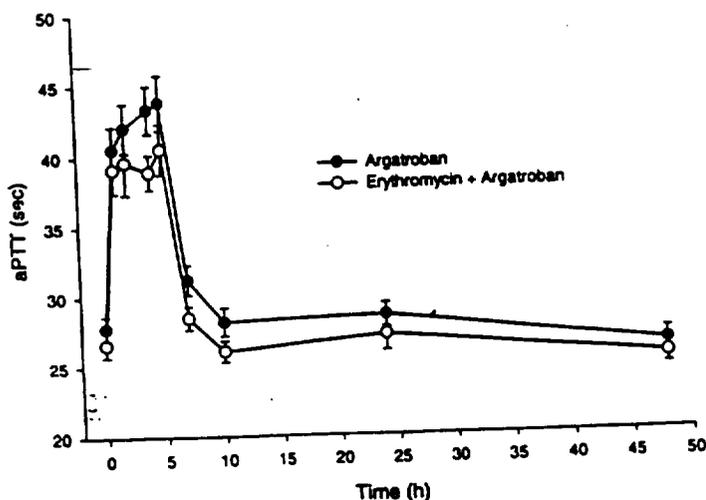
Parameter (units)	Argatroban Alone	Argatroban + Erythromycin	Ratio (95% CI)
AUC(0-inf) (ng.h/mL)	1015 (234)	1018 (193)	1.01 (0.92, 1.11)
C _{max} (ng/mL)	209 (46)	210 (38)	1.01 (0.88, 1.16)
T _{1/2} * (minutes)	54.5 (13.2)	60.2 (18.4)	5.64 min (-4.59 to 15.87 min)
V _{ss} (mL/kg)	231 (65)	232 (52)	
CL (mL/min/kg)	5.18 (1.22)	5.07 (0.97)	

* Data represents the difference of the adjusted means

The ratios (test/reference) of the mean AUC and C_{max} and their 95% confidence intervals were within the interval of 0.80 and 1.25. These results suggest that argatroban exposure is not significantly altered by co-administration of erythromycin. The similarity in argatroban elimination half-life, total clearance and apparent volume of distribution at steady state for Regimens A and B suggest that these argatroban pharmacokinetic parameters are also not significantly affected by co-administration of erythromycin.

(ii) **Pharmacodynamics:** Plots of the mean (\pm SE) aPPT during intravenous infusion of argatroban for the two regimens are presented in Fig. 2. Overall, the difference between the aPPT profiles during argatroban infusion with and without erythromycin does not appear to be significant.

Fig. 2. Plots of Mean (SE) Activated Partial Prothrombin Time (aPTT) Versus Time for Argatroban Administered with and without Erythromycin



(iii) **Assessment of Pharmacodynamic Interactions:** The desired pharmacodynamic end-point was to attain an aPTT ratio (end of infusion aPTT/pre-infusion aPTT) of 1.5-3.0. The mean \pm SE aPTT ratios attained, 1.52 \pm 0.04 following treatment with argatroban alone and 1.57 \pm 0.03 following treatment with argatroban and erythromycin (see Table 2), were within this range. These data suggest that the aPTT values attained during argatroban infusion are not significantly affected by co-administration of erythromycin.

Table 2. Mean (SE) aPTT Ratio during Administration of Argatroban with and without Erythromycin

	Argatroban (n=10)	Argatroban + Erythromycin (n=10)
Pre-infusion aPTT	27.8 (0.9) sec	26.6 (0.9) sec
End of infusion (5h) aPTT	43.8 (2.0) sec	40.5 (1.8) sec
aPTT Ratio*	1.57 (0.03)	1.52 (0.04)

Sources: Tables 11.10 and 11.11

* aPTT ratio is determined as aPTT obtained at the end of 5h infusion relative to that obtained at pre-infusion (baseline).

Based on the findings of this study, it is considered that the pharmacokinetics and pharmacodynamics of intravenously infused argatroban are not significantly affected by concomitant administration of erythromycin.

2. COADMINISTRATION OF DIGOXIN AND NOVASTAN[®] OR PLACEBO

The effect of Novastan[®] or placebo on the steady state pharmacokinetics of digoxin was evaluated in 12 healthy subjects. Each subject received oral digoxin 0.375 mg daily for 15 days plus intravenously infused argatroban 2 μ g/kg/min for 5 h (Regimen A) or placebo (Regimen B) on Days 11-15 of digoxin administration in a crossover fashion.

(i) **Pharmacokinetics:** Plots of mean plasma concentration of digoxin versus time for the two regimens are presented in Fig. 2. The mean (\pm SD) steady state pharmacokinetic parameters of digoxin with argatroban and with placebo are presented in Tables 3.

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Fig. 2. Plots of Day 15 Mean Digoxin Concentration Versus Time Following Oral Digoxin 0.375 mg Daily for 15 Days and Continuous Intravenous Infusion of Argatroban 2 μ g/kg/min or Placebo on Days 11-15

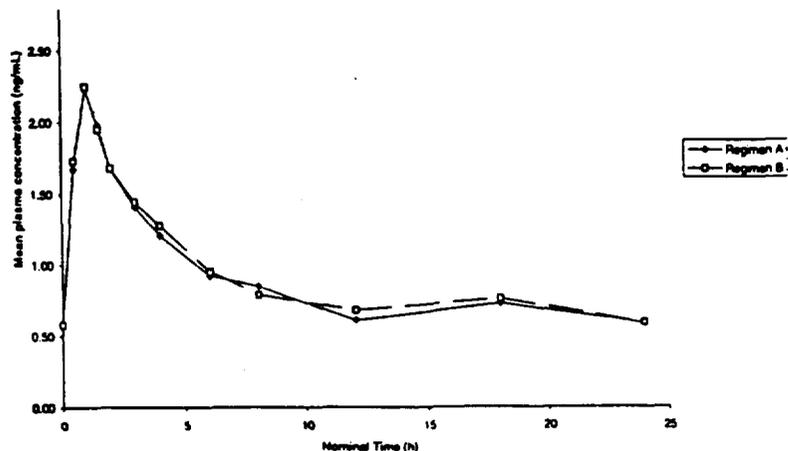


Table 3. Day 15 Mean (SD) Digoxin Pharmacokinetic Parameters with Argatroban or Placebo

Parameter (units)	Digoxin + Placebo	Digoxin + Argatroban
AUC(0-24) (ng.h/mL)	21.7 (3.4)	21.1 (4.5)
C(24h) (ng/mL)	0.596 (0.155)	0.591 (0.151)
C _{max} (ng/mL)	2.35 (0.45)	2.33 (0.39)
CL _r (mL/min)	131 (18)	134 (33)
T _{max} * (hours)	1.00 (0.50-1.50)	1.00 (0.50-1.50)

Source: Tables 10.10 to 10.14.
* Median (range)

The mean concentration profiles and steady state pharmacokinetic parameters of digoxin with argatroban or placebo were similar. These results suggest that the effects of argatroban and placebo on the kinetics of co-administered digoxin are similar.

(ii) **Assessment of Pharmacokinetic Interactions:** Log transformed AUC_{0-24h} and C_{max} of digoxin for the two treatment regimens were compared, with Regimen A as reference and Regimen B as test, using ANOVA for the 95% confidence intervals for C_{max} and 90% confidence intervals for AUC_{0-24h}. The results are presented in Table 4.

Table 4. Point Estimates and Confidence Intervals (95% for C_{max} and 90% for AUC_{0-24h}) for Digoxin Pharmacokinetic Parameters Administered with Argatroban or Placebo

Parameter	Digoxin + Argatroban: Digoxin + Placebo
AUC(0-24) ¹	0.96 (0.90, 1.03)
C(24h) ¹	0.99 (0.90, 1.07)
C _{max} ²	0.99 (0.87, 1.13)
CL _r ²	1.00 (0.84, 1.18)
T _{max} ³	0.00 h (-0.25, 0.44 h)

Source: Appendix D
¹ 90% confidence interval
² 95% confidence interval
³ Estimated median difference (95% confidence interval)

The ratios (test/reference) of the mean digoxin AUC_{0-24h} and C_{max} , and their respective confidence intervals were within the interval of 0.80 and 1.25. These results suggest that argatroban and placebo have similar effects on AUC_{0-24h} and C_{max} of co-administered digoxin at the evaluated confidence levels.

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3. CO-ADMINISTRATION OF ARGATROBAN® AND WARFARIN

The effect of argatroban on baseline International Normalized Ratio (INR) was evaluated in subjects whose INR values when treated with warfarin alone had been established (Protocol SKF001). In this study, the activated Factor X (Factor Xa) values for treatment with warfarin alone or warfarin plus argatroban were also compared. The argatroban doses tested were 1, 2, 3 and 4 $\mu\text{g}/\text{kg}/\text{min}$ infused intravenously over 5 h (see page 18). The warfarin doses (7.5 mg on Day 1 and 3-6 mg on subsequent days [see page 18]) were such that would produce INR values between 1.0 and 3.0 based on an International Sensitivity index (ISI) value of 1.0 approximately. Plots of INR for warfarin plus argatroban versus INR for warfarin alone, for the evaluated ISI values (0.88 and 1.78), are presented in Figs. 3 and 4. Factor Xa values for warfarin plus argatroban and for warfarin alone are presented in Tables 5 and 6. The n values in these Tables represent the total number of subjects at all warfarin dose levels evaluated in each INR category. The relationship between the Xa values for the two treatments is further explored in Fig. 5.

Fig. 3. Plots of INR for Argatroban Plus Warfarin Versus INR for Warfarin Alone (ISI = 1.78)

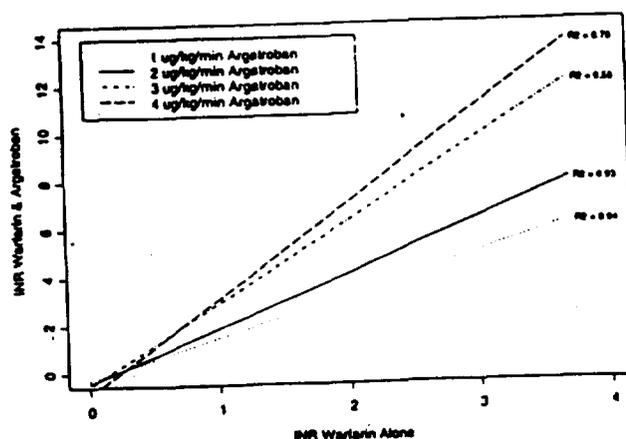


Fig. 3. Plots of INR for Argatroban Plus Warfarin Versus INR for Warfarin Alone (ISI = 0.88)

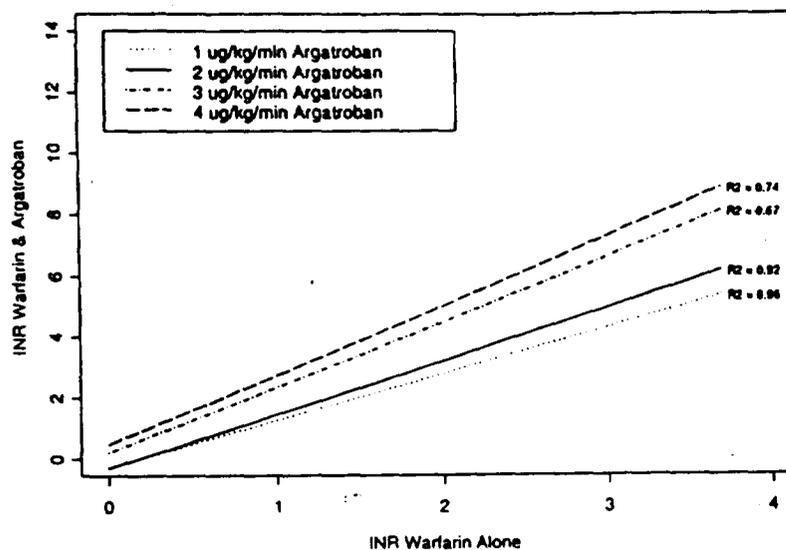


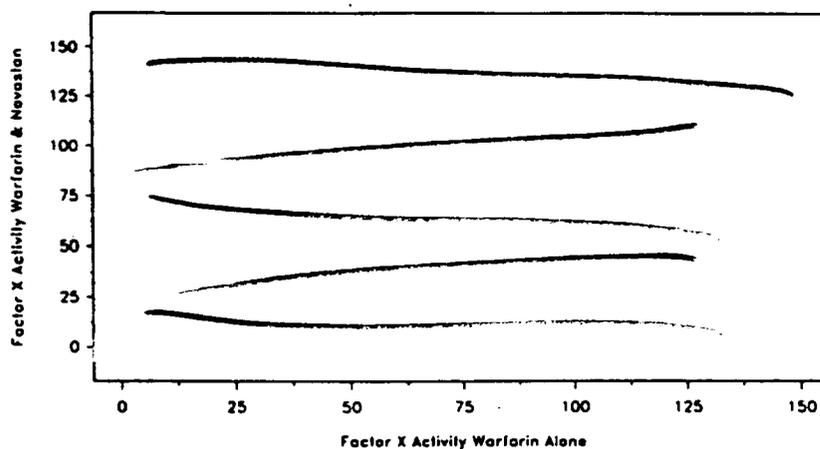
Table 5. INR and Factor Xa Activity Levels for Warfarin Alone and Warfarin Plus Argatroban for Each INR Range Evaluated when ISI is 0.88

INR	n	INR		Factor Xa Activity	
		Warfarin Alone	Warfarin & Argatroban	Warfarin Alone	Warfarin & Argatroban
0.0 to 1.0	10	0.97 (0.022)	1.37 (0.082)	95 (13.0)	100 (12.4)
1.0 to 1.5	87	1.24 (0.136)	1.88 (0.450)	76 (14.9)	75 (17.1)
1.5 to 2.0	43	1.73 (0.147)	2.88 (0.703)	58 (9.7)	56 (12.2)
2.0 to 2.5	37	2.20 (0.142)	4.22 (1.339)	42 (7.9)	41 (8.3)
2.5 to 3.0	23	2.73 (0.166)	4.88 (1.164)	39 (10.1)	38 (9.9)
3.0 >	7	3.34 (0.234)	5.55 (0.710)	37 (8.4)	36 (11.1)

Table 6. INR and Factor Xa Activity Levels for Warfarin Alone and Warfarin Plus Argatroban for Each INR Range Evaluated when ISI is 1.78

INR	n	INR		Factor Xa Activity	
		Warfarin Alone	Warfarin & Argatroban	Warfarin Alone	Warfarin & Argatroban
0.0 to 1.0	37	0.91 (0.058)	1.73 (0.297)	88 (13.1)	90 (14.9)
1.0 to 1.5	79	1.21 (0.138)	2.38 (0.624)	69 (13.3)	68 (15.4)
1.5 to 2.0	46	1.76 (0.153)	3.81 (1.273)	50 (8.8)	48 (10.6)
2.0 to 2.5	29	2.21 (0.148)	5.69 (2.261)	38 (6.3)	37 (7.5)
2.5 to 3.0	12	2.70 (0.147)	6.28 (1.676)	40 (11.8)	38 (11.9)
3.0 >	4	3.32 (0.229)	7.87 (1.105)	40 (11.2)	40 (12.8)

Fig. 5. Plot of Factor Xa Activity for Warfarin Co-administered with Argatroban Versus Factor Xa Activity for Warfarin Administered Alone



Note: Solid line is the line $y = x$ (i.e., slope of 1). Dashed lines are at 30.

i. For the therapeutic range of INR values for warfarin (≤ 3.8), there was a linear relationship between INR following co-administration of warfarin with argatroban and INR following administration of warfarin alone at all argatroban doses (1, 2, 3 and 4 $\mu\text{g}/\text{kg}/\text{min}$) and for both ISI values (0.88 and 1.78) evaluated.

ii. The INR values increased with increasing ISI value. This would be expected since $\text{INR} = (\text{PTR})^{\text{ISI}}$.

iii. For warfarin co-administered with argatroban doses of 1 and 2 $\mu\text{g}/\text{kg}/\text{min}$ and for both ISI values (0.88 and 1.78) evaluated, INR variability was relatively low as evidenced by coefficients of variation (R^2) of $\geq 93\%$ for plots of INR for warfarin plus argatroban versus INR for warfarin alone. The sponsor states that for these argatroban doses, the precision of predicting INR values for warfarin administered alone from INR values for warfarin co-administered with argatroban is 0.3-0.4 INR unit and is clinically acceptable.

iv. For warfarin co-administered with argatroban doses of 3 and 4 $\mu\text{g}/\text{kg}/\text{min}$ and for both ISI values (0.88 and 1.78) evaluated, INR variability was relatively high as evidenced by R^2 of $\leq 78\%$ for the plots of INR for warfarin plus argatroban versus INR for warfarin alone. The sponsor states that for these argatroban doses, the precision of predicting INR values for warfarin administered alone from INR values for warfarin co-administered with argatroban is 1.0 INR unit and is not clinically acceptable.

For all INR values (0-3.8) at for both ISI values (0.88 and 1.78) tested, Factor Xa values for warfarin co-administered with argatroban were not significantly different from the corresponding values for warfarin administered alone. This would be expected

since argatroban and warfarin exert anticoagulant effects by distinctly different mechanisms.

4. **SAMPLE ANALYSIS:** See the **Sample Analysis** section of each individual study in Appendix I.

5. **PHARMACOKINETIC ANALYSIS:** See the **Pharmacokinetic Analysis** section of each individual study in Appendix I.

6. **PHARMACODYNAMIC ANALYSIS:** See the **Pharmacodynamic Analysis** section of each individual study in Appendix I.

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III. LABELING COMMENT

In the **Pharmacokinetics/Pharmacodynamics** section of the proposed drug product labeling, under the sub-heading, **Effect on International Normalized Ratio (INR)**, the following should be added to the information provided just below Table 3:

Thus, for argatroban doses of 1 or 2 $\mu\text{g}/\text{kg}/\text{min}$, INR_w can be predicted from INR_{wA} . For argatroban doses greater than 2 $\mu\text{g}/\text{kg}/\text{min}$, the error associated with predicting INR_w from INR_{wA} is ± 1.0 . Thus, INR_w cannot be reliably predicted from INR_{wA} at these dose levels.

Note: Labeling Comment 1 in the review of the original NDA dated February 25, 1998 (see Appendix II) is upheld. Labeling Comment 2 of that review is also upheld, however, only the doses of heparin, aspirin/acetaminophen and warfarin should be requested as the doses of the other drugs under **Drug Interactions** have been stated in the currently proposed labeling. This results in a total of three Labeling Comments to be sent to the firm.

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IV. OVERALL COMMENTS

1. In this submission, it is stated that plasma samples were analyzed by ~~_____~~ and mass spectrometric detection (LCMS/MS) in Protocol SKF 002 and by radioimmunoassay (RIA) in Protocol SKF 003. The limits of quantification are stated as 5 ng/mL for LC/MS/MS and 1 ng/mL for RIA. No other assay validation data are provided.

For each of these studies (Protocols SKF 002 and SKF 003), the following assay validation information needs to be submitted to the Agency for review:

- (a) Linearity range
- (b) Precision (intra-day and inter-day)
- (c) Accuracy (intra-day and inter-day)
- (d) Specificity

2. The investigational batch size of Novastan[®] used in Protocols SKF001, SKF002 and SKF003 and the proposed commercial batch size of this drug product should be submitted to the Agency for review.

3. In Protocol SKF 001, under the Assay Method for INR determination, the following it is stated:

“Prothrombin time tests ~~_____~~ method on file) were performed at ~~_____~~ using two (2) different thromboplastins”

A description of the assay method that is “on file” needs to be submitted to the Agency for review.

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V. RECOMMENDATION

Amendment AZ to NDA 20-883 for argatroban (Novastan[®]) Injection Concentrate, submitted by the sponsor on March 17, 1999, has been reviewed by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics. The Clinical Pharmacology Approvable Recommendation in the review of the original NDA dated February 25, 1998 is upheld. However, the issues raised in Labeling Comments 1 and 2 in that review, the Labeling Comment in this review (page 10) and Overall Comments 1, 2 and 3 in this review (page 11) need to be satisfactorily addressed by the sponsor prior to NDA approval.

Please convey this Recommendation, Labeling Comments 1 and 2 in the Clinical Pharmacology Review of the original NDA dated February 25, 1998, the Labeling Comment in this review (page 10) and Overall Comments 1, 2 and 3 in this review (page 11), as appropriate, to the sponsor.

Appendices I and 2 are retained in the Office of Clinical Pharmacology and Biopharmaceutics and may be obtained upon request.

- 12/18/99
David G. Udo, Ph.D.
Division of Pharmaceutical Evaluation II

RD Initialed by David Lee, Ph.D. 12/08/99

FT Initialed by David Lee, Ph.D. 1/7/2000

cc: NDA 20-883, HFD-180, HFD-180 (DuBeau), HFD-870 (M. Chen, Hunt, Lee and Udo), CDR (Attn: Zom Zadeng).

VI. APPENDIX I: SUMMARIES OF INDIVIDUAL STUDIES

1. PROTOCOL NUMBER: SKF002

A: **TITLE:** A Study to Assess the Effect of Erythromycin on the Safety, Tolerability Pharmacokinetics and Pharmacodynamics of Novastan[®] (Argatroban) in Healthy Volunteers

B: **PRINCIPAL INVESTIGATOR AND CLINICAL SITE:** Sunita B. Sheth, MD, SmithKline Beecham Clinical Pharmacology Unit, Presbyterian Medical Center of Philadelphia, 51 North 39th Street, Philadelphia, PA 19104

C: **ANALYTICAL SITE:** Same as clinical site.

D: **Objectives:** The objectives of the study were as follows:

1. To estimate the effect of steady state erythromycin on the pharmacokinetics of argatroban
2. To describe the pharmacodynamic effect of argatroban on activated partial thromboplastin time (aPPT) in the presence or absence of steady state erythromycin
3. To assess the safety and tolerability of argatroban in the presence of steady state erythromycin

E: **DOSAGE FORM:** Novastan[®] (argatroban): The injection concentrate 250 mg/2.5 mL (Texas Biotechnology Corporation, Lot #M295PK) was used for the study. The investigational batch size and the proposed commercial batch size were not provided.

Erythromycin: Erythromycin 500 mg tablets (Abbot Laboratories, Lot #27853AF21) were used for the study.

F. STUDY DESIGN:

1. **Type of Design:** This was an open label, two-way crossover study conducted at a single center. Each subject received each of two treatment regimens: Regimens A and B (see item 3 below). The washout period was 5 days
2. The study population consisted of 10 healthy adult subjects.
3. **Dose Administration:** In Regimen A, each subject received a single intravenous infusion of Novastan[®] 1 μ g/kg/min for 5 h on Day 1. In Regimen B, each subject

received erythromycin 500 mg daily for 7 days plus a single intravenously infusion Novastan[®] 1 μ g/kg/min for 5 h on Day 6.

4. Blood Sampling Schedule for Pharmacokinetic Evaluation: Blood samples for pharmacokinetic evaluation were obtained pre-dose and at 0.25, 0.5, 1, 2, 3, 4, 5, 5.25, 6, 6.5, 7, 8, 10, 12, 16, 24, 32 and 48 h postdose. The 5 h sample was obtained just before the termination of infusion.

5. Blood Sampling Schedule for Pharmacodynamic Evaluation: Blood samples for pharmacodynamic evaluation were obtained pre-dose and at 1, 2, 3, 5, 7, 10, 24 and 48 h postdose. The 5 h sample was obtained just before the termination of infusion.

G. SAMPLE ANALYSIS: Argatroban was quantified in plasma by _____ and mass spectrometric detection (LC/MS/MS). The sponsor states that the limit of detection for argatroban was 5.00 ng/mL. No other assay validation information was provided.

H. PHARMACOKINETIC ANALYSIS: Pharmacokinetic analysis of argatroban was performed by non-compartmental methods. A SmithKline Beecham computer program referred to as "#PROTOCOL, version 1.2", was used for the analysis. AUC_{0-t} , $AUC_{0-\infty}$, Cl_T , V_{ss} , MRT , C_{max} , t_{max} and $t_{1/2}$ were determined. Gender effect on pharmacokinetics was not evaluated in this study.

I. PHARMACODYNAMIC ANALYSIS: The values of aPTT were determined for argatroban, with and without erythromycin, pre-dose and at the end of infusion (5 h postdose). Gender effect on pharmacodynamics was not evaluated in this study.

J. PHARMACOKINETIC RESULTS: See pages 2-3.

K. PHARMACODYNAMIC RESULTS: See pages 3-4.

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2. PROTOCOL NUMBER: SKF003

A: **TITLE:** A Study to Assess the Effect of Novastan[®] (argatroban) on the Pharmacokinetics of Digoxin in Healthy Volunteers

B: **PRINCIPAL INVESTIGATOR AND CLINICAL SITE:** Thomas L. Hunt, MD, Ph.D., PPD Pharmaco, Inc. Clinics, 706 A Ben White Boulevard West, Austin, Texas 78704.

C: **ANALYTICAL SITE:** Department of Drug Analysis, SmithKline Beecham Pharmaceuticals, King of Prussia, PA.

D: **Objectives:** The objectives of the study were as follows:

1. To demonstrate a lack of effect of argatroban on the pharmacokinetics of digoxin.
2. To assess the effect of concomitant dosing with oral digoxin and intravenous argatroban.

E: **DOSAGE FORM:** The following dosage forms were used for the study:

Novastan[®](argatroban) injection concentrate 100 mg/2.5 mL (Texas Biotechnology Corporation, Lot #M295PK), (ii) Placebo (0.9% sodium chloride injection, USP [Baxter; Lot #C382192]), and (iii) Digoxin (Lanoxin[®] 0.125 mg; Glaxo Wellcome; Lot #7F2311). The investigational batch size and the proposed commercial batch size of Novastan[®] were not provided.

F. STUDY DESIGN

1. **Type of Design:** This was a two-period, single blind, placebo-controlled, randomized, period balanced, crossover study conducted at a single center. Each subject received each of two treatment regimens: Regimens A and B (item 3 below). The washout period was ≥ 7 days.
2. The study population consisted of 12 healthy adult subjects.
3. **Dose Administration:** In Regimen A, each subject received digoxin 0.325 mg daily for 15 days plus a daily, continuous, intravenous infusion of Novastan[®] 2 $\mu\text{g}/\text{kg}/\text{min}$ for 5 h on Days 11-15. In Regimen B, each subject received digoxin 0.325 mg daily for 15 days plus a daily, continuous, intravenous infusion of placebo for 5 h on Days 11-15.
4. **Blood Sampling Schedule for Evaluation of Digoxin Kinetics:** Blood samples for pharmacokinetic evaluation of digoxin were obtained on Day 15 pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18 and 24 h postdose.

G. **SAMPLE ANALYSIS:** Digoxin was quantified in plasma by radioimmunoassay (RIA). The sponsor states that the lower limit of quantification was 0.15 ng/mL. No other assay validation data were provided

H. **PHARMACOKINETIC ANALYSIS:** Pharmacokinetic analysis of digoxin was performed by non-compartmental methods using WinNonlin (Version 1.5). AUC_{0-24} , Cl_r , $C_{ss(max)}$, C_{0-24} ($C_{ss(min)}$), t_{max} and Cl_R were determined for digoxin with placebo and with argatroban. Gender effect on pharmacokinetics was not evaluated in this study.

I. **PHARMACOKINETIC RESULTS:** See pages 4-6.

J. **PHARMACODYNAMIC RESULTS:** Pharmacodynamic analysis was not performed in this study.

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3. PROTOCOL NUMBER: SKF001

A: **TITLE:** Effect of Novastan[®] (Argatroban) on International Normalized Ratio (INR) in Healthy Adult Volunteers Receiving Daily Warfarin

B: **PRINCIPAL INVESTIGATOR AND CLINICAL SITE:** Sunita B. Sheth, MD, SmithKline Beecham Clinical Pharmacology Unit, Presbyterian Medical Center of Philadelphia, 51 North 39th Street, Philadelphia, PA 19104

C: **ANALYTICAL SITE:** Same as clinical site.

D: **Objectives:** The objectives of the study were as follows:

1. To describe the safety and tolerability of argatroban in healthy volunteers anticoagulated with warfarin
2. To describe the effect of argatroban on baseline INR
3. To describe the effect of argatroban plus warfarin when the range of INR in subjects receiving warfarin alone is 1.0-3.0, using two different thromboplastins with International Sensitivity Index (ISI) values of approximately 1.0 and 2.0
4. To describe the effect of thromboplastin sensitivity (ISI) on the relationship established in objective 3 above
5. To describe the relationship of activated plasma Factor X (Factor Xa) activity to INR when subjects are receiving argatroban plus warfarin.

E: **DOSAGE FORM:** Novastan[®] (argatroban injection): 250 mg/2.5 mL supplied by Texas Biotechnology Corporation from a single lot was used in the study. The sponsor does not state the lot number, investigational batch size or the commercial batch size.

Coumadin[®] (warfarin sodium, Dupont): 1, 2, 2.5 and 5 mg tablets from single commercial lots were used in the study.

F. STUDY DESIGN

1. **Type of Design:** This was an open label, parallel group, repeat dosing study conducted at a single center.
2. The study population consisted of 24 healthy adult volunteers. The number of subjects per dose level of each test drug is provided in Tables 7 and 8 below:

3. Dose Administration

Table 7. Number of Subjects Receiving Each Dose of Warfarin

Warfarin Dose (mg/day)	Number of Subjects
3	6
4	2
5	14
6	2
7.5	24*

* All subjects received 7.5 mg warfarin on Day 1 only

Table 8. Number of Subjects Receiving Each Dose of Novastan®

Infusion Rate (ug/kg/min)	Number of Subjects
1	19
2	24
3	18
4	15

(a) Day 1: At 9.00 a.m., argatroban 2 $\mu\text{g}/\text{kg}/\text{min}$ was infused intravenously for 5 h. At 9.00 p.m., oral warfarin 7.5 mg was administered.

(b) Days 2-8: At 9.00 a.m., argatroban 1 or 2 $\mu\text{g}/\text{kg}/\text{min}$ was infused intravenously for 5 h. At 9.00 p.m., an appropriate, oral dose of warfarin (see Tables 7 and 8) was administered.

(c) Days 9-11: At 9.00 a.m., argatroban 1, 2, 3 or 4 $\mu\text{g}/\text{kg}/\text{min}$ was infused intravenously for 5 h. At 9.00 p.m., an appropriate, oral dose of warfarin (see Tables 7 and 8 above) was administered.

4. **Blood Sampling Schedule:** On each study day, blood samples were obtained pre-dose and at 5 h postdose (just before termination of infusion).

G. **INR: SAMPLE ANALYSIS AND DETERMINATION:** To determine INR, prothrombin time (PT) tests were performed on blood samples by the _____ method using two different thromboplastins with ISI of 0.88 and 1.78.

INR was estimated as $(PTR)^{ISI}$, where PTR is the prothrombin time ratio (i.e., the ratio of subject's PT to normal PT value for the assaying laboratory).

The sponsor states that _____ method is "on file" and has not provided it in this submission.

H. FACTOR Xa: SAMPLE ANALYSIS AND DETERMINATION: Factor Xa activity was determined in plasma photometrically by a two-stage method (Chromogenic AB). In stage one, Factor X was activated to Factor Xa by _____ venom in the presence of calcium. In stage 2, Factor Xa hydrolyzed the chromogenic substrate, S-2337 releasing a chromophoric group. The color was then read at 405 nm. The percentage Factor Xa activity was determined by comparing the observed value to the standard normal value for the assaying laboratory.

Gender effect on pharmacodynamics was not evaluated in this study.

I. PHARMACOKINETIC RESULTS: Pharmacokinetic analysis was not performed in this study.

J. PHARMACODYNAMIC RESULTS: See pages 6-8.

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Dustan

Clinical Pharmacology & Biopharmaceutics Review

NDA:	20-883
Compound:	Novastan® (argatroban) Injection Concentrate
Submission Date:	August 11, 1997 October 14, 1997 November 21, 1997
Sponsor:	Texas Biotechnology Corp.
Type of Submission:	Original NDA (1P)
Reviewers:	Michael J. Fossler, Pharm. D., Ph. D. K. Gary Barnette, Ph. D.

FEB 25 1998

Synopsis

Argatroban is a highly-substituted arginine derivative which acts as a direct, reversible inhibitor of thrombin. By binding directly to the active site of thrombin, argatroban inhibits fibrin formation, and the activation of clotting factors (Factors VII, V, VIII, protein C) as well as platelet aggregation. The proposed indication is as anticoagulant therapy in patients with heparin-induced thrombocytopenia. The recommended initial dose is 2 µg/kg/min. The dose may be titrated at 1-3 hour intervals until the steady-state aPTT is 1.5-3.0 times control. The maximum recommended dose is 10 µg/kg/min.

Several different assays have been used for the quantitation of argatroban in human plasma. Two of the studies submitted in support of the NDA were performed by Genentech. These studies used an _____ assay; however, no details of the method or validation data for this method are available. In a study which examined the pharmacokinetics of the individual stereoisomers, _____ /UV method was used. Some validation data was included with this method. In the remainder of the studies, the assay work was performed either at _____ using an _____ method with fluorescence detection or at _____ using an LC/MS/MS method. Some limited cross-validation work was performed between the _____ and the chiral _____. The data indicate reasonable agreement between the two methods.

After an intravenous infusion, steady-state concentrations of argatroban are reached within 1-3 hours. Mean clearance in normal volunteers ranges from 1.9-6.5 ml/kg/minute. The mean half-life of argatroban ranges from 37-92 minutes in normal volunteers. Mean steady-state plasma concentrations of argatroban after infusions of 0.5-40 µg/kg/min showed that the pharmacokinetics of argatroban is essentially linear within this range. Argatroban is 54% bound to human serum proteins, with binding to albumin and α₁-acid glycoprotein being 20% and 34%, respectively. The maximum recommended dose in the labeling is 10 µg/kg/minute, as this was the maximum dose studied clinically.

Pharmacokinetics studies were performed in patients with unstable angina and patients undergoing percutaneous transluminal coronary angioplasty (PTCA). Patients undergoing PTCA appear to have lower clearance values as compared with normal volunteers (2.8±1.1 vs. 4.9±1.6 ml/kg/minute) and unstable angina patients (4.6±1.6 ml/kg/minute), although the number of subjects studied in most of the groups is small (n=6 for PTCA). No initial dose adjustment appears to be necessary,

since the drug is titrated to the desired effect by monitoring the aPTT.

Since the compound is a racemate (R:S ratio 1.86:1) a chiral assay was used in several studies to assess whether there are any stereo-specific differences in the clearance of argatroban. The results from this study appear to indicate that both isomers are cleared at about the same rate (R: 4.3 ± 1.0 , S: 4.0 ± 0.83).

Studies were performed in patients with renal disease and hepatic impairment. The mean clearance of argatroban in 5 subjects with hepatic impairment given $2.5 \mu\text{g/kg/min}$ (one patient given $1.25 \mu\text{g/kg/min}$) was only 32% of that in 12 normal volunteers (5.9 ± 1.4 vs. $1.9 \pm 1.2 \text{ ml/kg/min}$), resulting in higher plasma argatroban levels and greater pharmacologic effect. Both the R and S isomers were equally affected. Based on this result, the recommended initial dose of argatroban for patients with hepatic impairment is $0.5 \mu\text{g/kg/min}$. The effect of renal disease on the pharmacokinetics of argatroban was studied in patients with no (mean $\text{Clcr} = 95 \pm 16 \text{ ml/min}$), mild (mean $\text{Clcr} = 64 \pm 10 \text{ ml/min}$), moderate (mean $\text{Clcr} = 40 \pm 5.8 \text{ ml/min}$), or severe (mean $\text{Clcr} = 5 \pm 7 \text{ ml/min}$) impairment. Renal function status had no effect on either the pharmacokinetics or the pharmacodynamics of argatroban.

The pharmacokinetics and pharmacodynamics of argatroban were examined in elderly (aged 65-80) and young (18-45) men and women ($n=10$ for each group) given a $125 \mu\text{g/kg}$ bolus followed by a $2.5 \mu\text{g/kg/min}$ infusion for 4 hours. Although the numbers are small, there does not appear to be any difference between the four groups. Looking at the impact of gender, women (young and elderly combined) appeared to have a slightly higher clearance than men (5.1 vs. 4.2 ml/kg/min , $p < 0.05$). Age alone also has a small impact on clearance, with the elderly group having a slightly lower clearance than young subjects (4.3 vs. 5.0 ml/kg/min , $p < 0.05$). Although both these comparisons show statistical significance, the clinical impact is likely to be small.

A mass balance study in 6 healthy subjects (4 men, 2 women) using radio-labeled ^{14}C -argatroban showed that the majority (65.4%) was excreted in the feces, with 14% present as unchanged drug. About 22% of radioactivity was excreted in the urine, with the majority (16.4%) present as argatroban. In the plasma, the $t_{1/2}$ of argatroban was slightly shorter than that of total radioactivity (1.03 vs 1.66 hrs, respectively). Overall, it appears that argatroban undergoes extensive hepatic metabolism and fecal excretion, primarily as metabolites. Seven metabolites of argatroban have been identified; however, only four (M1-M4) have been assayed, with M1 being the major metabolite in plasma. None of the metabolites have significant pharmacologic activity.

The enzymes that catalyze the metabolism of argatroban were identified by *in vitro* testing. Argatroban was incubated with microsomes from fourteen human liver samples. The formation of each metabolite was assessed for each liver sample and compared to the rate of metabolism of well characterized marker substrates. It should be noted that $5 \mu\text{M}$ argatroban was used in the incubations. This compares favorably to the approximately $4.2 \mu\text{M}$ concentrations observed at steady state after a $10 \mu\text{g/kg/min}$ infusion. The results of this study show that the only P450 isozyme involved in the metabolism of argatroban is 3A4/5. The conclusion that CYP3A primarily catalyzes the formation of each of the four primary argatroban metabolites was confirmed with chemical inhibition studies with nifedipine, a specific substrate for CYP3A (competitive inhibitor) and troleadomycin, a suicide inhibitor of CYP3A. Both inhibitors inhibited the formation of all 4 metabolites by more than 90%.

In vivo pharmacokinetic drug interactions were conducted to assess coadministration of argatroban

with aspirin, warfarin, heparin, acetaminophen and lidocaine. These studies assessed the potential effect of argatroban on the pharmacokinetics of each coadministered compound, as well as the effect of each coadministered compound on the pharmacokinetics of argatroban. It was determined that no pharmacokinetic interaction occurred between argatroban and aspirin, warfarin, heparin and acetaminophen. However, plasma argatroban levels (average C_{ss}) decrease by ~20% when administered with lidocaine. Since lidocaine has not been shown to possess inductive properties, the mechanism for this decrease in argatroban concentrations is unknown.

A clear relationship exists between the anticoagulation effect of argatroban (as measured by aPTT) and its steady-state concentration. The pharmacodynamic effect of argatroban appears to fit a classical E_{max} model with respect to plasma concentration and/or dose. A similar relationship is seen with concentration/dose and ACT. Based on the tight correlation between plasma concentration and effect and the t_{1/2} of argatroban (40-60 minutes), at any given infusion rate, one would expect to reach pharmacodynamic steady-state in 2-4 hours. In fact, in subjects given infusion rate of 1.25-10 µg/kg/min, the time to pharmacodynamic steady-state was found to range between 0.7-3.3 hours. This time might be shortened considerably if a loading dose were given. Simulations were performed in which a 2 µg/kg/min infusion was given for 4 hours with or without a 50 µg/kg loading dose. Pharmacodynamic steady state is reached immediately with a loading dose. Although this may be important for future indications, a loading dose is probably not of much clinical use for the present indications.

Recommendation

The clinical pharmacology/biopharmaceutics portion of NDA 20-883 is approved. The text under Labeling Comments should be forwarded to the firm.

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Appendix I: Study Summaries

Protocol Number	Title	Page
ARG-101	Comparison of the anticoagulation effect of four infusion doses of heparin vs. Agatroban in normal human volunteers	24
ARG-102	Comparison of the anticoagulation effect of four infusion doses of Agatroban over four hours in normal human volunteers	29
ARG-103	Pharmacokinetics and anticoagulant effect of an infusion dose of agatroban in humans with impaired renal function	31
ARG-107	Mass balance study of agatroban injection in healthy volunteers following administration of the ¹⁴ C-labeled compound.	32
ARG-951	Study of the new formulation of agatroban alcoholic solution in healthy volunteers.	35
ARG-105	An open-label evaluation of the pharmacokinetics and pharmacodynamics of a four-hour infusion of Novastan in elderly and young male and female volunteers.	36
B0147g	A phase 1 study of agatroban in patients with unstable angina	37
B0272g	A phase 1 study in patients undergoing percutaneous transluminal coronary angioplasty	38
ARG-106	Pharmacokinetic/pharmacodynamic study of agatroban injection in healthy volunteers and patients with hepatic disease	39
ARG-108	Bioequivalence of two NOVASTAN injections in healthy volunteers	40

ARG-109	Comparative, randomized, three-way crossover drug-drug interaction study of NOVASTAN concentrate and Coumadin in healthy volunteers	43
ARG-110	A pharmacodynamic interaction of the transition from intravenous anticoagulation with argatroban to oral anticoagulation with coumadin in healthy volunteers.	47
ARG-112	Comparative, randomized, three-way crossover drug-drug interaction study of NOVASTAN concentrate and heparin in healthy volunteers	51
ARG-113	Investigation of the steady-state pharmacokinetic interaction between NOVASTAN and acetaminophen in healthy subjects	54
ARG-114	Investigation of the steady-state pharmacokinetic interaction between NOVASTAN and lidocaine in healthy subjects	57

Abbreviations used in text

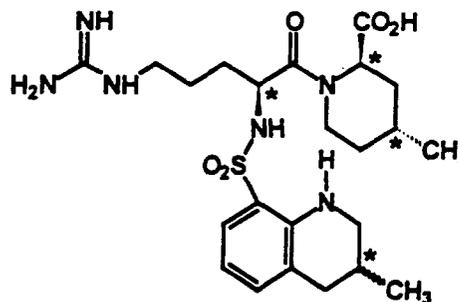
aPTT: activated partial thromoplastin time

CaTT: calcium-thrombin time

I. Background

Texas Biotechnology Corporation has submitted NDA 20-883 in support of Novastan® (argatroban) Injection Concentrate. Argatroban is a highly-substituted arginine derivative which act as a direct, reversible inhibitor of thrombin. By binding directly to the active site of thrombin, argatroban inhibits fibrin formation, and the activation of clotting factors (Factors VII, V, VIII, protein C) as well as platelet aggregation. The proposed indication is as anticoagulant therapy in patients with heparin-induced thrombocytopenia. The recommended initial dose is 2 µg/kg/min. The dose may be titrated at 1-3 hour intervals until the steady-state aPTT is 1.5-3.0 times control. The maximum recommended dose is 10 µg/kg/min. The chemical structure is shown to the right.

Argatroban (C₂₃H₃₆N₆O₅S MW=508.63) is a white crystalline powder that is freely soluble in glacial acetic acid, slightly soluble in ethanol, and insoluble in acetone, ether, and ethyl acetate. The compound has 4 asymmetric centers denoted by asterisks in the figure; all are fixed as in the structure above except at position 21 (wiggle bond in figure). The 21R and 21S diastereomers are present in a 1.86:1 ratio. Both isomers are active.



II. Assay

Several different assays have been used for the quantitation of argatroban in human plasma. Two of the studies submitted in support of the NDA were performed by Genentech. These studies used an _____ assay; however, no details of the method or validation data for this method are available. In a study which examined the pharmacokinetics of the individual stereoisomers, an _____ /UV method was used. Some validation data was included with this method. In the remainder of the studies, the assay work was performed either at _____ using a _____ method with fluorescence detection or at _____ using an LC/MS/MS method. Some limited cross-validation work was performed between the _____ method and the _____ method. The data indicate reasonable agreement between the two methods.

Of the two assays which were used the most often (/LC/MS) the assay appears to be the most reliable. The overall quality of the chromatography is poor. The retention time for argatroban is short (~ 4.2 min) and as a result, the argatroban peak frequently appears on the tail of the solvent front. More disturbing is the peak shape of the internal standard (quinine). The peak is very broad (area/height = 83) which will obviously affect the accuracy of the peak height ratios computed from these data.

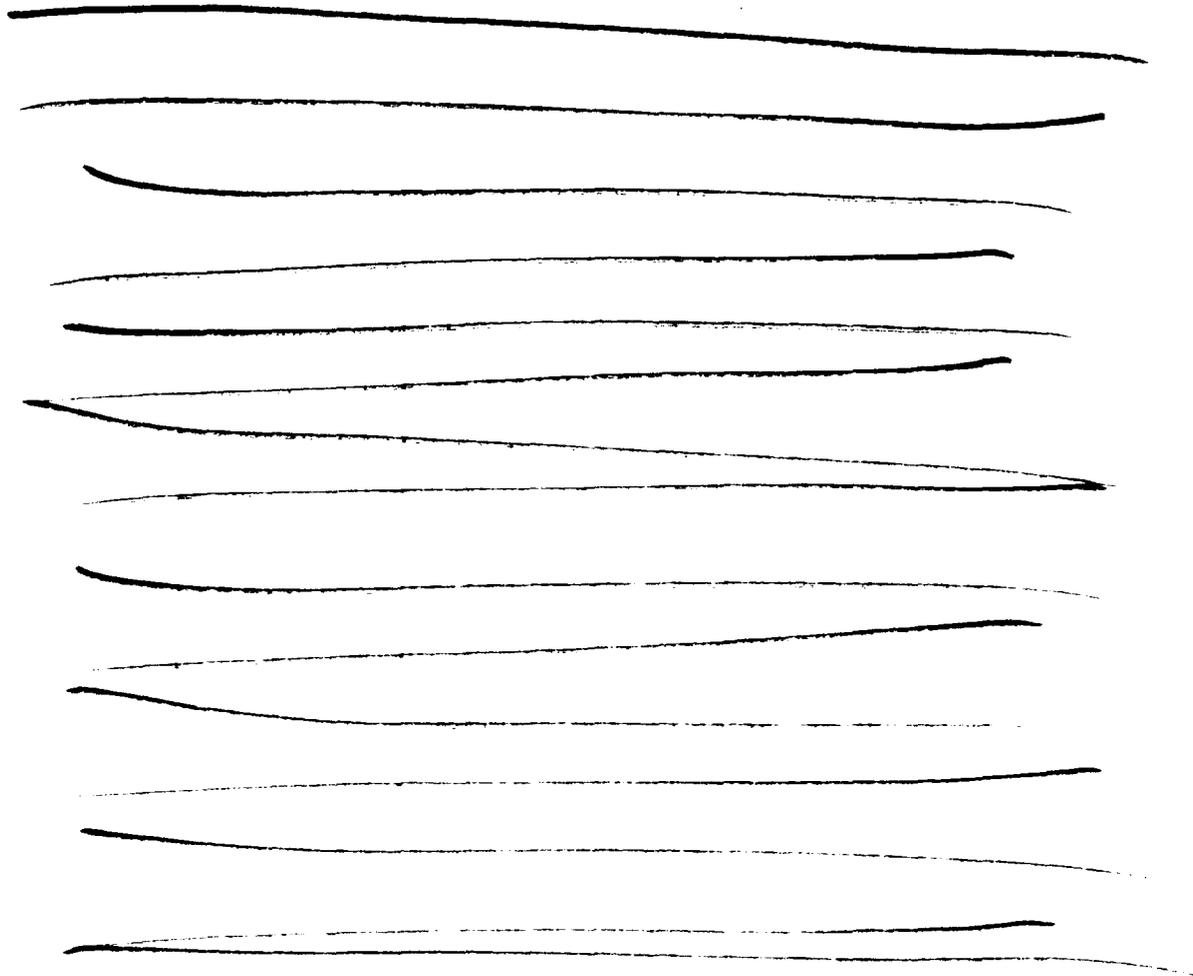
Summaries of the validation data for the three assays are shown in Table 1.

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Table 1: Assay validation summaries.



III. Bioequivalence

A bioequivalence study was performed in 18 normal volunteers (17 completed) comparing the clinical supplies formulation (manufactured by the University of Iowa) with the to-be-marketed formulation. As shown in Table 2, the two formulations are bioequivalent¹.

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¹The Division of Scientific Investigations issued a Form 483 to _____ for thier failure to have on hand a copy of the certificate of analysis for the reference standard used in the analysis of plasma samples. The firm has since provided the certificate, which shaows that the reference standard used was 99.4% pure.

(CYP1A2), coumarin 7-hydroxylation (CYP2A6), tolbutamide methyl-hydroxylation (CYP2C9), S-mephenytoin 4'-hydroxylation (CYP2C19), dextromethorphan O-demethylation (CYP2D6), chlorzoxazone 6-hydroxylation (CYP2E1), dextromethorphan N-demethylation (CYP3A4), testosterone 6 β -hydroxylation (CYP3A4/5) and lauric acid 12-hydroxylation (CYP4A9/11). The correlation analysis of the sample-to-sample variation is included in Table 4. It should be noted that 5 μ M argatroban was used in the incubations. This compares favorably to the approximately 4.2 μ M concentrations observed at steady state after a 10 μ g/kg/min infusion (data from Study ARG-101).

Table 4. Regression Coefficients (r^2)

Enzyme	Metabolite			
	M-1	M-2	M-3	M-4
CYP1A2	0.03	0.06	0.05	0.11
CYP2A6	0.06	0.05	0.06	0.09
CYP2C9	0.19	0.17	0.18	0.07
CYP2C19	0.01	0.01	0.01	0.07
CYP2D6	<0.005	<0.005	<0.005	0.13
CYP2E1	0.17	0.18	0.17	0.11
CYP3A4	0.71	0.70	0.71	0.73
CYP3A4/5	0.80	0.80	0.79	0.73
CYP4A9/11	0.02	0.01	0.01	<0.005

The conclusion that CYP3A primarily catalyzes the formation of each of the four argatroban metabolites was confirmed with chemical inhibition studies with nifedipine, a specific substrate for CYP3A (competitive inhibitor) and troleandomycin, a suicide inhibitor of CYP3A. The mean (\pm SD) percent inhibition of the formation of each of the four metabolites of argatroban by these chemical inhibitors in 5 human liver microsomal samples is outlined in Table 5.

Table 5. Percent inhibition of formation of argatroban metabolites by two 3A4 inhibitors

Inhibitor	Metabolites			
	M-1	M-2	M-3	M-4
Nifedipine (200 μ M)	94.2 \pm 1.9	94.0 \pm 0.4	92.6 \pm 0.9	85.8 \pm 2.8
Troleandomycin (100 μ M)	98.1 \pm 0.5	98.6 \pm 0.1	98.8 \pm 0.4	99.2 \pm 0.8

B. In Vivo Testing

A mass balance study in 6 normal subjects (4 males, 2 females) showed that the majority of radioactivity (65.4%) was excreted in the feces, with 14% present as unchanged drug. About 22% of radioactivity was excreted in the urine, with the majority (16.4%) present as argatroban. In the

plasma, the $t_{1/2}$ of argatroban was slightly shorter than that of total radioactivity (1.03 vs 1.66 hrs, respectively). Overall, it appears that argatroban undergoes extensive hepatic metabolism and fecal excretion, primarily as metabolites.

V. Pharmacokinetics

A. Patients vs. Normal Volunteers

Pharmacokinetics studies were performed in patients with unstable angina and patients undergoing percutaneous transluminal coronary angioplasty (PTCA). The results are shown in Table 6 below compared with two sets of normal volunteer data. Patients undergoing PTCA appear to have lower clearance values as compared with normal volunteers and unstable angina patients, although the number of subjects studied in most of the groups is small. No initial dose adjustment appears to be necessary, since the drug is titrated to the desired effect.

Table 6: Comparison of the pharmacokinetics of argatroban in normal volunteers and in patients with unstable angina or undergoing PTCA. Values in the table are mean \pm SD (range)

Parameter	PTCA (B0272g)	Unstable Angina (B0147g)	Normal Vol. (ARG-103)	Normal Vol. (B0148g)
n	6	43	6	6
Cl (ml/min/kg)	2.8 \pm 1.1	4.6 \pm 1.6	4.9 \pm 1.6	4.8 \pm 0.9
Vss (ml/kg)	215 \pm 54	183 \pm 57	206 \pm 25	174 \pm 62
Css (ng/ml)	775 \pm 288	[†] 505 \pm 216	1236 \pm 571	[†] 431 \pm 68

[†]Adjusted for dose as necessary

B. Stereoisomerism

Since the compound is a racemate (R:S ratio 1.86:1) a chiral assay was used in several studies to assess whether there are any stereo-specific differences in the clearance of argatroban. The results from Study ARG-951 are shown in Table 7. The results from this study appear to indicate that both isomers are cleared at about the same rate.

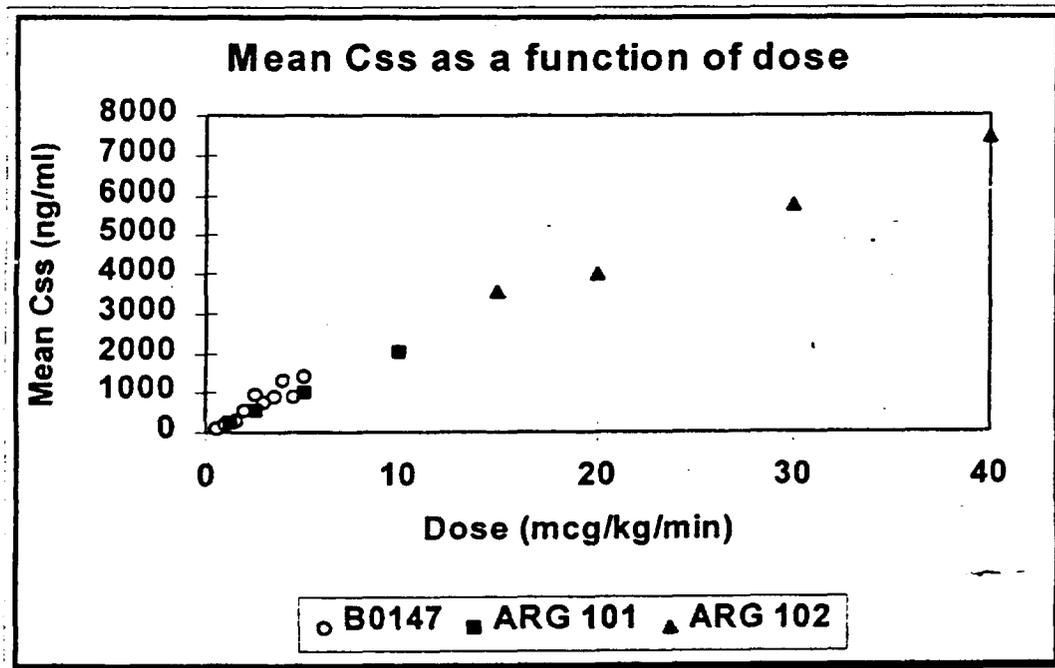
Table 7: Comparison of the pharmacokinetics of the 21R and 21S isomers of argatroban in 9 healthy volunteers given a 2 µg/kg/min infusion of argatroban for 4 hours.

	21-R argatroban	21-S argatroban	Ratio (R:S)
AUC(0-∞) (ng*hr/ml)	1246 ± 247.4	719.8 ± 130.7	1.73:1
C _{max} (ng/ml)	312.5 ± 59.6	183.0 ± 32.4	1.71:1
t _{1/2} (hr)	0.91 ± 0.28	0.64 ± 0.09	na
Cl (ml/kg/min)	4.3 ± 1.0	4.0 ± 0.83	na

VI. Dose Linearity

Mean steady-state plasma concentrations of argatroban after infusions of 0.5–40 µg/kg/min showed that the pharmacokinetics of argatroban is essentially linear within this range (Figure 1). The maximum recommended dose in the labeling is 10 µg/kg/minute.

Figure 1: Mean steady-state concentrations of argatroban as a function of dose. Data in the figure are from three separate studies (B0147, ARG101, ARG102).



VII. Dosage and Administration

The initial dose recommended in the labeling for patients with normal hepatic function is 2 $\mu\text{g}/\text{kg}/\text{min}$. The dose may be titrated at 1-3 hour intervals until the steady-state aPTT is 1.5-3.0 times control. The maximum recommended dose is 10 $\mu\text{g}/\text{kg}/\text{min}$.

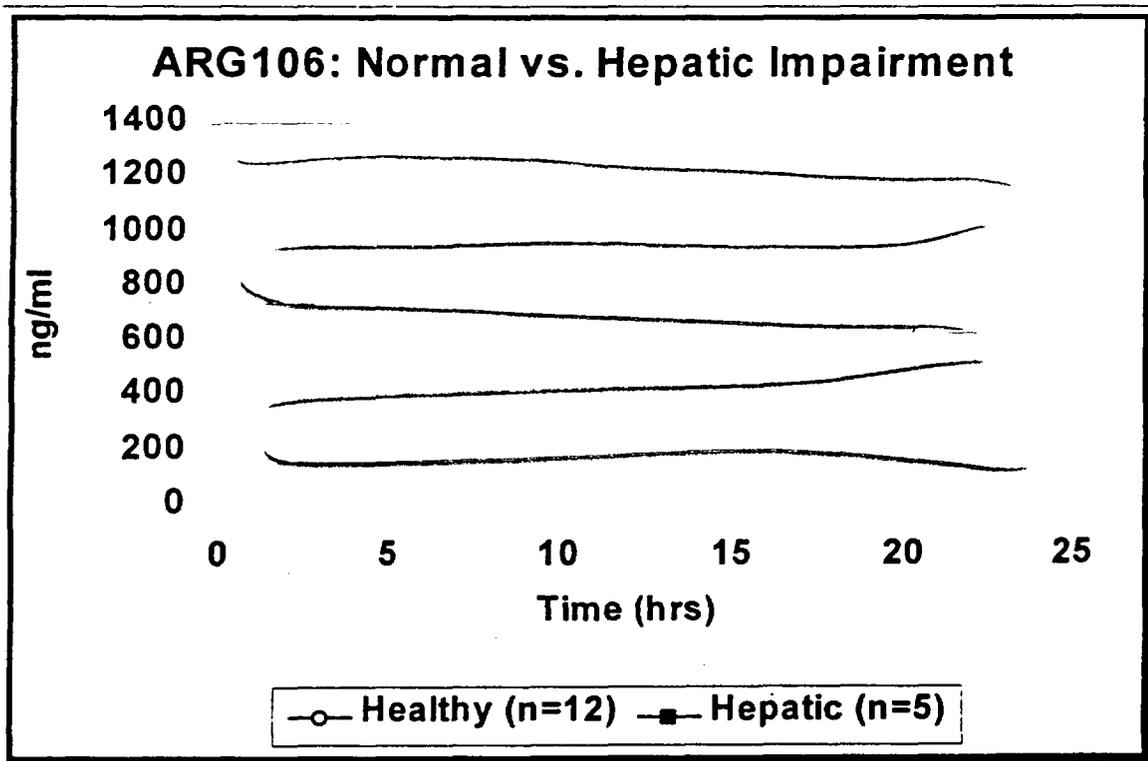
For patients with impaired hepatic function (see below) the recommended initial dose is 0.5 $\mu\text{g}/\text{kg}/\text{min}$, adjusting every 3-8 hours as needed until the aPTT is 1.5-3.0 times control.

VIII. Special Populations

Hepatic

The mean clearance of argatroban in 5 subjects with hepatic impairment was only 32% of that in 12 normal volunteers (5.9 vs. 1.9 ml/kg/min). Both the R and S isomers were equally affected. Based on this result, the recommended initial dose of argatroban for patients with hepatic impairment is 0.5 $\mu\text{g}/\text{kg}/\text{min}$, which is one-fourth the starting dose in patients with normal liver function.

Figure 2: Mean plasma argatroban levels in normal and hepatically-impaired subjects



Renal

The effect of renal disease on the pharmacokinetics of argatroban was studied in patients with no (mean Clcr=95±16 ml/min), mild (mean Clcr=64±10 ml/min), moderate (mean Clcr=40±5.8 ml/min), or severe (mean Clcr=5±7ml/min) impairment. Renal dysfunction had no effect on either the pharmacokinetics or the pharmacodynamics of argatroban in volunteers with normal to severe renal dysfunction.

Age, Gender

The pharmacokinetics and pharmacodynamics of argatroban were examined in elderly (aged 65-80) and young (18-45) men and women (n=10 for each group) given a 125 µg/kg bolus followed by a 2.5 µg/kg/min infusion for 4 hours. The results are depicted below in Table 8. Although the numbers are small, there does not appear to be any difference between the four groups. Looking at the impact of sex, women (young and elderly combined) appeared to have a slightly higher clearance than men (5.1 vs. 4.2 ml/kg/min, p < 0.05). Age alone also has a small impact on clearance, with the elderly group having a slightly lower clearance than young subjects (4.3 vs. 5.0 ml/kg/min, p < 0.05). Although both these comparisons show statistical significance, the clinical impact is likely to be small.

Table 8: Comparison of argatroban pharmacokinetic and pharmacodynamic parameter in young and elderly men and women. Values in the table are mean ±SD, except where noted.

	Young (18-45)		Elderly (65-80)	
	Men (n=10)	Women (n=10)	Men (n=10)	Women (n=10)
CL (ml/kg/min)	4.7±1.0	5.4±0.8	3.8±0.9	4.7±1.0
Vdss (ml/kg)	175±39	175±37	174±21	195±33
Css (ng/ml)	541±139	473±85	657±165	511±110
t½ (min)	46±10	39±10	51±10	49±7.6
†Peak aPTT (sec)	73 (61,80)	57 (52, 75)	63 (50, 84)	61 (52, 84)
†t½ aPTT (min)	44 (37, 56)	44 (21, 73)	53 (26, 78)	51 (26, 63)

†Median (min, max)

Pediatric

Argatroban has not been studied in the pediatric population.

IX. Drug Interactions

Pharmacokinetic Interactions

In vivo pharmacokinetic drug interactions were conducted to assess coadministration of argatroban with aspirin, warfarin, heparin, acetaminophen and lidocaine. These studies assessed the potential effect of argatroban on the pharmacokinetics of each coadministered compound, as well as the effect of each coadministered compound on the pharmacokinetics of argatroban. It was determined that no pharmacokinetic interaction occurred between argatroban and aspirin, warfarin, heparin and acetaminophen. However, plasma argatroban levels (average C_{ss}) decrease by ≈20% when administered with lidocaine. Since lidocaine has not been shown to possess inductive properties, mechanism of this decrease in argatroban concentrations is unknown (see Table 9).

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Table 9: Summary of argatroban/lidocaine interaction study

Parameter	Argatroban	Argatroban + Lidocaine	Percent Difference
Mean (SD) Argatroban Pharmacokinetic Parameters			
AUC(tau) (ng*hr/mL)	4785 (1014)	3965 (800.8)	-17.14
C _{ss} avg (ng/mL)	344.4 (82.90)	274.9 (52.76)	-20.19
Cl (mL/min/kg)	4.686 (1.590)	5.698 (1.414)	21.61
Mean (SD) Lidocaine Pharmacokinetic Parameters			
AUC(tau) (ng*hr/mL)	30077 (4823)	32080 (6103)	6.66
C _{ss} avg (ng/mL)	2545 (444)	2692 (596)	5.79
Cl (mL/min/kg)	13.45 (2.188)	12.93 (2.748)	-3.83

Pharmacodynamic Interactions

Aspirin

No pharmacodynamic interaction between argatroban (1 µg/kg/min for 4 hours) and aspirin (162.5 mg given 26 and 2 hours before start of argatroban infusion) was observed.

Warfarin

There appeared to be a synergistic effect on prothrombin time with coadministered argatroban (1-2 µg/kg/min) and warfarin (5 mg daily x 6 doses). aPTT and CaTT were only affected by argatroban, while the international normalized ratio (INR) and chromogenic factor X seem to be related to warfarin doses.

Heparin

There appears to be a synergistic effect on aPTT and CaTT when heparin (0.15 IU/kg/min x 8 hrs)

and argatroban (1.25 µg/kg/min x 10 hrs) are coadministered (see Table 10).

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Table 10: Effect on aPTT and CaTT when heparin and argatroban are coadministered

	Parameter	Heparin Alone	Argatroban + Heparin	Argatroban Alone
aPTT	E _{max} (seconds)	12.1 ± 5.41	51.3 ± 10.5	21.0 ± 5.18
	T _{max} (hours)	5.5 ± 2.5	4.5 ± 2.0	2.2 ± 2.3
CaTT	E _{max} (seconds)	0.200 ± 0.190	25.4 ± 9.89	15.61 ± 6.05**
	T _{max} (hours)	6.1 ± 2.9	6.0 ± 2.2	1.43 ± 2.14**

** The CaTT E_{max} and T_{max} parameters occurred at time = 0 in 8 out of 15 assessments.

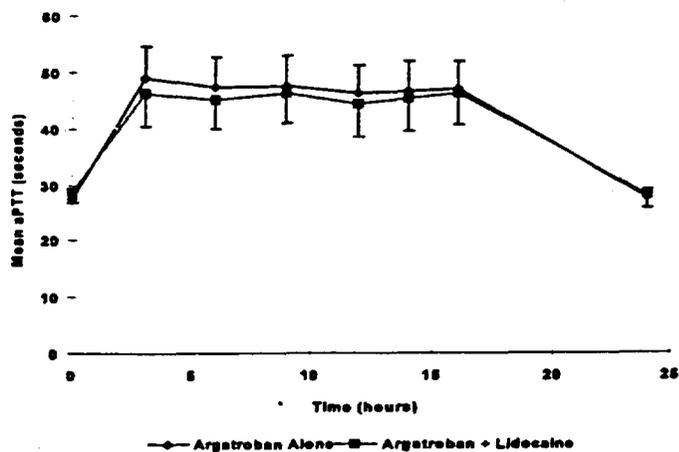
Acetaminophen

Acetaminophen (1000 mg q 6 hrs x 5 doses) and argatroban (1.5 µg/kg/min) appeared to have no additional anticoagulant effect to that of argatroban alone.

Lidocaine

Coadministration of lidocaine (1.5 mg/kg over 10 min, followed by 2 mg/kg/hr for 16 hours) with argatroban 1.5 µg/kg/min x 16 hrs results in a trend toward lower aPTT levels than argatroban administered alone. It should be noted that this difference is likely to be a result of the ~20% lower argatroban levels observed when it is coadministered with lidocaine (see *Pharmacokinetic Interactions*, above). The mean aPTT versus time profiles for argatroban administered alone and with lidocaine are depicted in Figure 3.

Figure 3: Mean aPPT values resulting from argatroban administered alone or with lidocaine.



X. Pharmacokinetic/Pharmacodynamic Relationships

A clear relationship exists between the anticoagulation effect of argatroban (as measured by aPTT) and its steady-state concentration. Figure 4 shows data compiled from a number of studies in which subjects were given doses of argatroban ranging from 1-40 µg/kg/minute. The pharmacodynamic effect of argatroban appears to fit a classical Emax model with respect to plasma concentration and/or dose. A similar relationship is seen with concentration/dose and ACT.

Using data from subjects given a single 5 µg/kg/min infusion for 4 hours, the reviewers have fit argatroban concentration-effect data to the following Emax model:

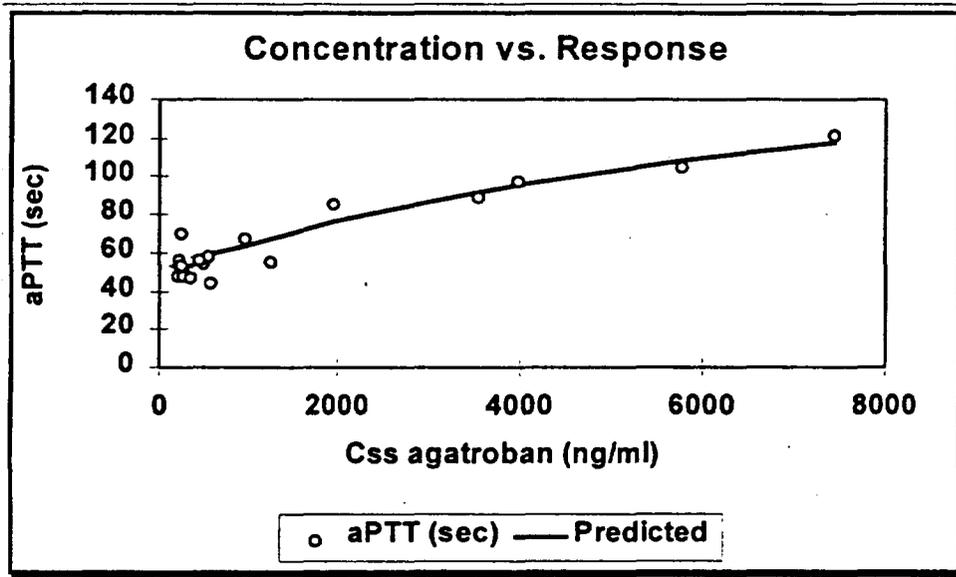
$$E(t) = E_0 + \frac{E_{\max} C(t)}{EC_{50} + C(t)}$$

Figure 5 (a-b) shows the results from a typical subject. Again, it can be seen that the pharmacodynamic effect of argatroban closely parallels the plasma concentrations, indicating that the drug may be easily titrated to the desired clinical effect. As shown previously in Table 8, the t½ of the effect on aPTT closely follows the t½ of argatroban itself, indicating that baseline aPTT should be achieved within 3 hours of discontinuing argatroban. Little or no hysteresis is seen, which would be expected, since the site of action is in the plasma.

Based on the tight correlation between plasma concentration and effect and the t½ of argatroban (40-60 minutes), at any given infusion rate, one would expect to reach pharmacodynamic steady-state in 2-4 hours. In fact, in subjects given infusion rate of 1.25-10 µg/kg/min, the time to pharmacodynamic steady-state was found to range between 0.7-3.3 hours. This time might be shortened considerably if a loading dose were given. Figure 6 shows the results of a simulation in which a 2 µg/kg/min infusion was given for 4 hours with or without a 50 µg/kg loading dose. Pharmacodynamic steady state is reached immediately with a loading dose. Although for the present indication a loading dose is probably not needed (since patients will have been on heparin and then switched to argatroban), future indications may require a loading dose.

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Figure 4: Mean concentration vs. Response plot for argatroban using data from a number of studies using doses from 1-40 $\mu\text{g}/\text{kg}/\text{minute}$.



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