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APPLICATION NUMBER:

20-873

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Duke

NOV - 1 2000

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-873

Serial no: N-000/AZ

Trade Name: ANGIOMAX®

Stamp Date: 7/17/2000

Active Ingredient: Bivalirudin

Sponsor: The Medicines Company

Reviewer: Suliman I. Al-Fayoumi, Ph.D.

Type of Submission: Response to Agency Comments

Background

Bivalirudin is a 20 amino acid synthetic peptide that acts as a direct thrombin inhibitor. It is believed that bivalirudin can block both circulating and clot-bound thrombin, in effect preventing abrupt vessel closure which can occur during and after percutaneous transluminal coronary angioplasty (PTCA).

The proposed dosing regimen is a 4-hour IV infusion at a rate of 2.5 mg/kg/h with an IV bolus dose of 1.0 mg/kg administered immediately after initiation of the infusion. After completion of the 4-hour infusion, an additional IV infusion may be initiated at a rate of 0.2 mg/kg/h for up to 20 hr as clinically warranted.

The Medicines Company submitted NDA 20-873 for the approval of bivalirudin on 12/23/97. The Agency sent out a non-approval letter to the sponsor on 11/18/98. After submission of additional information and data to the Agency, the application was deemed approvable provided the sponsor adequately responded to several issues of concern outlined in the FDA letter dated 10/28/99. A primary concern raised by the Agency was the lack of information in the labeling on dose adjustment of bivalirudin in patients with severe renal impairment. In response, the sponsor submitted the results of a study in the corresponding patient population in the current submission. The current submission also includes the sponsor's response to other Agency comments outlined in the FDA letter dated 5/11/00. See attachment 1 for the Clinical Pharmacology and Biopharmaceutics-related labeling in the package insert.

Primary Review Issues

- **Is there a need for dosage adjustment of bivalirudin in severe renal impairment patients?**

Study TMC-BIV-00-02

Study Design

Eight male and female patients with severe renal impairment (GFR=10-29 ml/min, M/F=7/1, age 37-72 years, Wt 66-88 kg) received a 1 mg/kg I.V. bolus dose followed by a 0.5 mg/kg I.V. infusion. Plasma and Activated clotting time (ACT) samples were collected at the following time points:

- **During the infusion**: At 0, 10, 20, 40, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, 390, 420, 450, 480, 510, 540 and 600 min post-dose.
- **Post-infusion**: At 10, 20, 40, 60, 80, 100, 120, 150, 180, 210, 240, 270, 300, 330, 360, 390, 420, 480, 540 and 600 min.

Bivalirudin plasma concentrations were determined using a validated LC/MS assay.

Results and Conclusions

Table 1. Mean estimates of the primary pharmacokinetic and pharmacodynamic parameters of bivalirudin in patients with varying renal function states

	Normal Renal Function		Mild RF*		Moderate RF*		Severe RF*
Infusion rate (mg/kg/hr)	2.5	0.5	2.5	0.5	2.5	0.5	0.5
CL (ml/min/kg)	3.4 ± 0.5	3.7 ± 1.0	3.4 ± 0.7	3.2 ± 0.9	2.7 ± 0.4	2.5 ± 0.2	2.8 ± 0.7
$t_{1/2}$ (min)	24.9 ± 12.1		22.2 ± 8.0		33.5 ± 6.8		56.8 ± 24.0
ACT last 60 min (sec)	362 ± 9	225 ± 17	365 ± 13	234 ± 35	391 ± 23	268 ± 33	246 ± 32

* RF = Renal Failure

Reviewer's comments

While bivalirudin half-life was significantly prolonged in severe renal impairment patients, total clearance did not seem to appreciably change relative to moderate renal impairment state. The sponsor attributed this observation to an increased volume of distribution in patients with severe renal impairment. It should be noted that the current study consisted of one treatment arm only, thus, there was no control arm to compare to, such as subjects with normal renal function, which may partially explain the large observed variability in the current study.

The sponsor's recommendation for a 60% dose reduction in patients with severe renal impairment along with careful ACT monitoring is acceptable by OCPB.

Effect of covariates on bivalirudin PK/PD

1. Gender: It does not seem there is any significant gender effect on bivalirudin PK/PD. Nevertheless, it should be noted that the sample size is too small to make definitive conclusions.

Table 2
Effect of Gender on Bivalirudin Pharmacokinetics and Pharmacodynamics (Extracted from Table 19 from TMC 98-09)

PARAMETER	MALES (n=17)		FEMALES (n=8)	
Infusion dose	2.5 mg/kg/hr	0.5 mg/kg/hr	2.5 mg/kg/hr	0.5 mg/kg/hr
Total clearance (ml/min/kg)	3.2±0.7	3.2±1.1	3.4±1.2	3.1±1.2
ACT last 90 mins (secs)	375±21	245±38	361±7	227±17

All values are mean ± standard deviations

2. Age: As age increases, bivalirudin clearance decreases while ACT increases. A reduced clearance of bivalirudin may be related to a decrease in renal function with age.

Figure 1 – Regression of Age Against Total Plasma Clearance

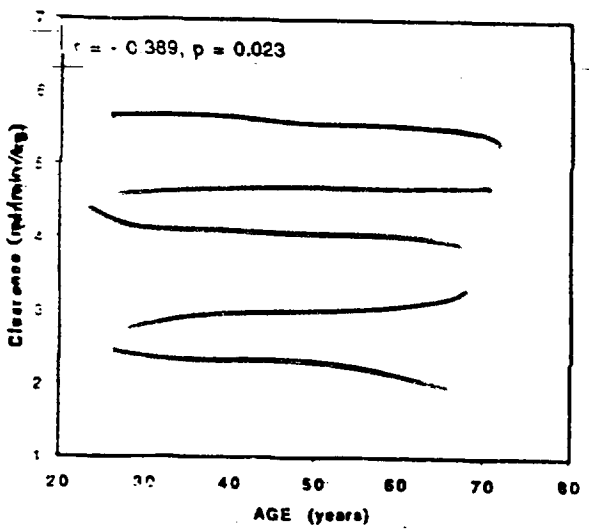
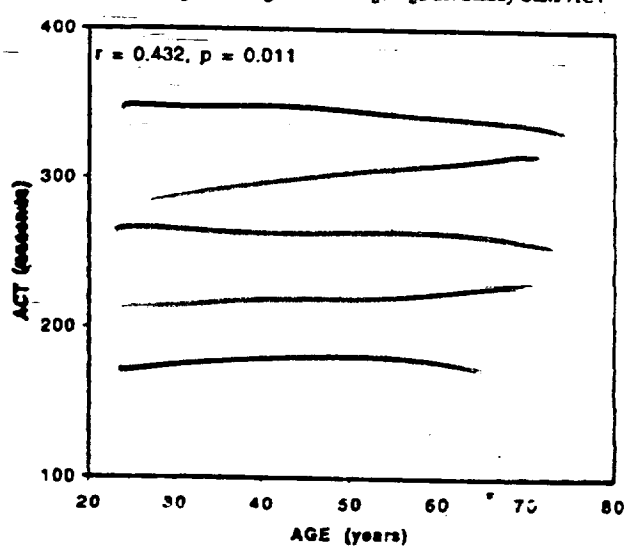


Figure2 - Regression of Age Against Steady State ACT



3. GFR: Since a significant proportion of systemic bivalirudin is cleared renally, it is not surprising that GFR exhibits strong correlations with both total bivalirudin clearance and ACT.

Figure 3 – Regression of GFR Against Steady State ACT

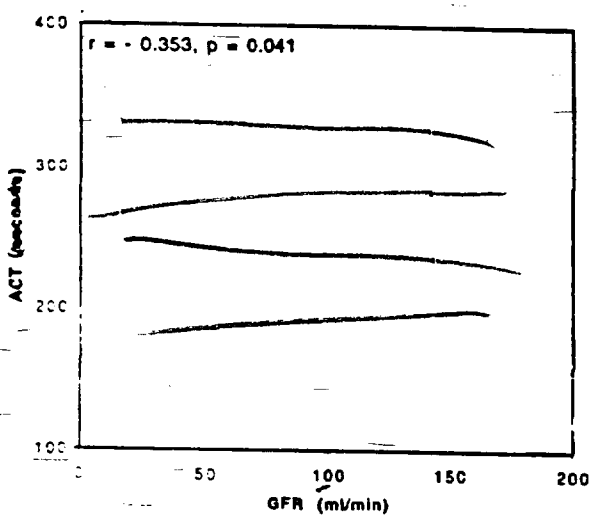
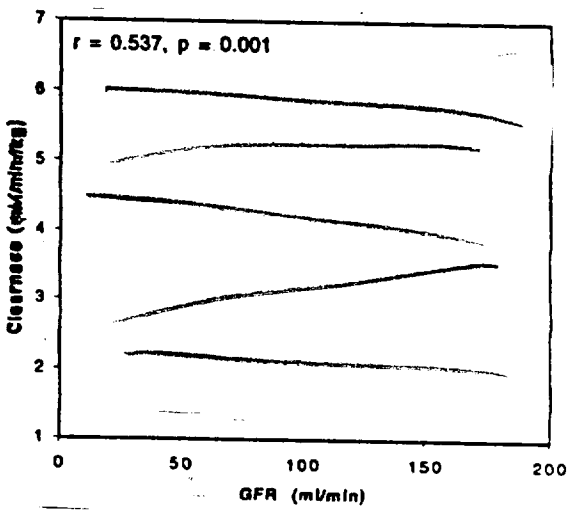


Figure 4 –Regression of GFR Against Total Plasma Clearance.



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Responses to FDA letter of 5/11/00 regarding Biopharmaceutics issues

Explain why the dose of bivalirudin is to be reduced by half for patients with moderate renal impairment as specified in Table 1 of your proposed package insert submitted November 11, 1999. Results from your ongoing study entitled "The influence of dose and kidney function on bivalirudin pharmacokinetics (PK) and pharmacodynamics (PD) in patients undergoing percutaneous coronary artery angioplasty (PTCA)' (Study No. TMC98-09) demonstrate that there is only a 21% reduction in total clearance of bivalirudin in this group.

We agree with the reviewer. Based on the bivalirudin plasma clearance data from study TMC 98-09, which showed a 21% reduction in clearance in the moderately renally impaired patients (GFR 30-59 ml/min), we would recommend the infusion dose in this group should be reduced 20% (to 1 mg/kg bolus, 2 mg/kg/hr 4 hour infusion, 0.16 mg/kg/hr for up to 20 hours). This reduction is reflected in the revised package insert.

Reviewer's comments
The sponsor's response is found acceptable by OCPB.

1. Explain why the proposed 0.2 mg/kg/h dosing regimen is not adjusted for renal function.

We agree that the 0.2 mg/kg/hr infusion should be proportionately adjusted in moderately renally impaired patients (See 1 above and the revised package insert).

Reviewer's comments
The sponsor's response is found acceptable by OCPB.

2. Determine the half-lives of bivalirudin in patients with normal renal function and in patients with mildly and moderately impaired renal function by modeling the observed data obtained from Study No. TMC-98-09.

The data from TMC 98-09 was modeled using [redacted] a copy of the report entitled "Report on Bivalirudin (Hirulog®) Pharmacokinetics- Volume of distribution, Clearance and half-life" is enclosed with this submission (Vol. 5.003). The estimated elimination half-lives (mean +/- sd) are:

- Normal patients (GFR ≥ 90 ml/min): 24.9 ± 12.1 min
- Mildly renally impaired patients (GFR 60-89 ml/min): 22.2 ± 8.0 min
- Moderately renally impaired patients (GFR 30-59 ml/min): 33.5 ± 6.8 min

Reviewer's comments
The sponsor's response is found acceptable by OCPB.

3. Upon completion of Study No. TMC-98-09, provide PK/PD analyses of the activated clotting time (i.e. PK/PD modeling, etc. if appropriate) along with analyses for age and gender effects on PK and PD When gender analyses have been completed, please assess PK/PD as a function of glomerular filtration rate (GFR). If recruitment of patients with severe renal disease is problematic, please contact the Division to discuss possible study modifications that might make patient enrollment easier (e.g., a reduced blood collection scheme).

In response to this question, and as agreed at the May 22, 2000 telephone conference call between the company and the division, we have conducted a new study, TMC-BIV-00-02, in 10 renally impaired patient volunteers (9 of whom received study medication, 8 of whom had a GFR of 10-29ml/min). The study report for this study is attached. Also, the main results have been consolidated with those from TMC 98-09 (normal and mild or moderately renally impaired patients) in Table 1.

Using linear regression analysis and [redacted] we have analysed the combined data from studies TMC 98-09 and TMC-BIV-00-02 to provide the following analyses:

1. Calculation of the pharmacokinetic parameters plasma clearance and elimination half life using modeling (Table 1a)
2. Regression of age against total plasma clearance (Fig 1)
3. Regression of age against steady state ACT (Fig 2)
4. Regression of GFR against steady state ACT (Fig 4)
5. Regression of GFR against total plasma clearance (Fig 5)
6. Regression of mean steady state (last 60 min) ACT against mean steady state plasma concentration (Fig 6).

We have not conducted an additional combined analysis of gender effects. Our previous analysis presented in the TMC 98-09 suggested no effect of gender on bivalirudin pharmacokinetic and pharmacodynamic parameters (table 19 from TMC 98-09 is reproduced in Table 2). In study TMC-BIV-00-02 we studied only 1 female. An analysis including this group would obviously confound renal status with gender. Since table 2 indicates no significant effect of gender on either clearance or ACT it can be considered that adjustment of dose based on severity of renal impairment (GFR levels) should be gender independent. A further discussion of gender is also contained on page seven of "Report on Bivalirudin (Hirulog®) Pharmacokinetics- Volume of distribution, Clearance and half-life" enclosed with this submission (vol. 5.003).

Reviewer's comments

The sponsor's response is found acceptable by OCPB.

Recommendations

The sponsor's responses to Agency comments outlined in the FDA letter dated 5/11/00 is acceptable from the viewpoint of the Office of Clinical Pharmacology and Biopharmaceutics.

/S/ 11/1/00

Suliman I. Al-Fayoumi, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Suresh Doddapaneni, Ph.D., Team leader /S/ 11/1/00

cc: HFD-180: NDA 20-873 (1x); DIV FILE (1x); JDUBEAU: (1x); SDODDAPANENI (1x); SALFAYOUMI (1x); HMALINOWSKI (1x); CDR: ATTN ZOM ZADENG

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Attachment 1

3 page(s) of revised draft labeling has been redacted from this portion of the review.

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20-1

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

NDA 20-873
(Amendment No. 50)

Submission Date: 4/10/00

Bivalirudin Injection
Angiomax™

APR 24 2000

The Medicines Company
Cambridge, Massachusetts 02142

Reviewer: John Hunt

Type of Submission: Response to FDA Request for Information

Synopsis

Bivalirudin (Angiomax™) is a 20-amino acid synthetic peptide inhibitor of thrombin. It is believed that bivalirudin can block both circulating and clot-bound thrombin and be useful in preventing abrupt vessel closure which can occur during and after percutaneous transluminal coronary angioplasty (PTCA). The recommended dosing regimen is a 4-hour IV infusion at a rate of 2.5 mg/kg/hr with an IV bolus dose of 1.0 mg/kg administered immediately after initiation of the infusion. After completion of the 4-hour infusion period, an additional IV infusion may be initiated at a rate of 0.2 mg/kg/hr for up to 20 hr as clinically warranted.

As the result of different reviews that have been done for this product, obtaining accurate pharmacokinetic (PK) information/data, plus determining what the appropriate dose adjustment recommendations for renally impaired patients should be have been the outstanding Office of Clinical Pharmacology and Biopharmaceutics (OCPB) issues. To address these issues,The Medicines Company (TMC) initiated a renal impairment study (Protocol No. TMC-98-09). Different concerns and recommendations related to this study were also addressed in different OCPB reviews. [Note: In an OCPB review dated 4/3/00, a history of OCPB's regulatory review involvement is given.] Now, in the 4/10/00 NDA amendment more updated information/data are provided for this product from the renal impairment study.

Can the proposed package insert/labeling be updated based upon the information/data that has now been provided in the new NDA amendment?

In the new NDA amendment (No. 50) dated 4/10/00, TMC is responding to some of the comments that were recommended to be sent to them in the 4/3/00 OCPB review. Based upon the responses that have been submitted, plus the updated results that have also been provided for the renal study, it is now felt that the product's package insert/labeling can be updated with more accurate information. (See Labeling Comments below.)

[Note: In the cover letter for the new amendment (No. 50), it indicates that the "final study report" is enclosed. In a discussion with the NDA's project manager on 4/18/00, it was learned that TMC has now indicated that the "final study report" is not really submitted in the amendment. In previous OCPB reviews dated 3/12/99 (i.e., for IND [redacted] and 10/4/99 (i.e., for NDA 20-873) it was requested that patients with severe renal impairment (i.e., GFR <30 mL/min) be studied. Although TMC has expressed their concerns regarding studying these patients, they indicated in the new amendment's cover letter that do intend to try

and enroll some now that they have "recently obtained ethical committee approval at Green Lane Hospital to proceed with this study." Once this is completed the final study report will be submitted for which further modifications may need to be made to the package insert.]

Summary of Study Protocol

Title

The influence of dose, gender and kidney function on bivalirudin pharmacokinetics and pharmacodynamics in patients undergoing percutaneous coronary artery angioplasty (PTCA).

Investigators

There were 2 investigators who participated in this study.

Investigator	Title	Affiliation
Professor Harvey White, MB ChB, DSc, FRACP, FACC, FESC, MRSNZ	Director of Cardiovascular Research and Coronary Care	Green Lane Hospital, Auckland, New Zealand
Dr Philip Aylward, MA (Oxon), BM, BCh, PhD, FRCP, FRACP	Director of Cardiovascular Medicine	Flinders Medical Centre, Adelaide, Australia

Studied Period

13 April 1999 (first patient enrolled) until 16 September 1999 (last patient enrolled).

Study Objectives

- To determine bivalirudin clearance and pharmacodynamics (Activated Clotting Time - ACT) in angioplasty patients at the recommended bivalirudin dose
- To determine if bivalirudin clearance and pharmacodynamics are dose dependent
- To determine if bivalirudin clearance and pharmacodynamics are dependent on kidney function and gender
- To assess the proportion of unchanged bivalirudin that is cleared renally

Methodology

This study was an open, serially recruiting trial in patients scheduled for PTCA. Thirty patients were planned to be recruited into this study. Twenty-six patients are now reported for study analysis. Twenty-five patients received the complete study drug regimen of a bivalirudin bolus followed by two infusions. One patient (Patient 511) unexpectedly needed administration of ReoPro™ requiring discontinuation of the bivalirudin infusion after 20 minutes.

Patients were assigned to groups based on their renal function as determined by their estimated Glomerular Filtration Rate (GFR). [Note: For determining GFR, plasma creatinine levels were determined and the Cockroft and Gault formula was employed.] The three groups were patients with normal renal function (GFR 90 ml/min or greater), with mild renal impairment (GFR 60-89 ml/min), and with moderate renal impairment (GFR 30-59 ml/min): these groups were planned to be balanced for gender. For the GFR subcategories, there were 7 patients (1 female and 6 male) with moderate renal impairment, 11 patients (5 female and 6 male) with mild renal impairment and 8 patients (3 female and 5 male) with normal renal function. [Note: See Attachment 1 for patient

demographics. See the Synopsis section above regarding the enrollment of patients with severe renal disease.]

For patients with normal renal function or mild renal impairment, bivalirudin was administered as an intravenous bolus of 1mg/kg of bivalirudin 10 to 60 minutes before crossing the lesion, followed by a 2.5-mg/kg/hour infusion of bivalirudin for 4 hours. At this point the infusion dose was reduced to 0.5mg/kg/hr for a further 4 hours, and then stopped.

For the moderate renal impairment group, each infusion was scheduled for six (6) hours. If the ACT was greater than 450 seconds after 4 hours of the higher dose infusion, that infusion was stopped and the patients transferred to the low dose infusion.

All patients received aspirin 300-mg orally a minimum of 2 hours before the procedure, followed by daily administration of aspirin (unless contraindicated). Patients allergic or intolerant to aspirin could not be randomized in this trial. For patients unable to tolerate a 300-mg daily dose, the dose could be reduced at the discretion of the clinician.

Criteria for Evaluation

Pharmacokinetics

Blood samples were taken at: 0, 10, 20, 40, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, 390, 420, 450, and 480 minutes for all patients. Patients with moderately impaired renal function had further samples taken at 510, 540, 570, 600, 630, 660, 690 and 720 minutes, depending on the length of their first infusion. Total urine was collected over the first infusion (4 or 6 hours) and over the second infusion (4 or 6 hours).

These samples were assayed by _____ using a LC/MS method. Plasma AUC and clearance and urinary clearance of bivalirudin were calculated following non-compartmental pharmacokinetic methods.

[Note: Included in the new amendment is a response to address the accuracy and method of how plasma clearance values were determined for the renal study as submitted in NDA Amendment No. 37. In OCPB's 4/3/00 review of this amendment these issues were raised. TMC has now indicated that, "For each patient the AUC for dose 1 (2.5 mg/kg/hr) and dose 2 (0.5 mg/kg/hr) were calculated from the last 90 min plasma values for each infusion (which we assume to be steady state) using 270-360 minute and 630-720 minute values for the moderately renally impaired group and 150-240 minute and 390-480 minute values for the normal and mild renal impairment groups. These AUC values where then divided into the doses given over these 90-minute intervals to yield clearance in ml/min/kg." This is acceptable.]

Pharmacodynamics

Coagulation was measured by ACT at 0, 60, 120, 180, 240, 300, 360, 420 and 480 minutes for all patients. Patients with moderate renal impairment had further samples taken at 540, 600, 660 and 720 minutes. aPTT tests were done pre-bolus, at the end of each of the two infusions, 2 hours after the infusions had been completed and at discharge from hospital.

Safety

Safety was assessed by:

- All deaths, regardless of relationship to study drug.
- All serious adverse events considered to be reasonably related to study drug.
- Incidence of major bleeding and cardiac ischemia events including abrupt vessel closure, reinfarction and requirement for revascularization prior to hospital discharge.

For this study:

- There were no deaths, myocardial infarctions or need for urgent revascularisation for any patients in this study.
- There was one serious adverse events reported. Patient 412 (Green Lane Hospital) experienced a mild groin hematoma, which required her to stay an extra day in hospital. However she did not meet the criteria for either a major or minor bleeding event.
- Two patients (410 and 506) experienced a minor bleeding episode. There were no major bleeding episodes. [Note: Patient No. 410 had moderate impairment (GFR = 56.2 mL/min and Patient No. 506 had mild impairment (GFR = 75.0 mL/min).]

Statistical Methods

The effect of renal impairment on pharmacokinetic/dynamic parameters was tested using a general linear model. If this model indicated a significant effect this was further tested between pairs of renal impairment groups using Fisher's Least significant difference test. Hypothesis testing was conducted using two-sided alternatives with a Type 1 error of 0.05.

Summary of Study Results Provided Thusfar

Pharmacokinetic and Pharmacodynamic Results

Table 1: **Effect of Renal Function on Bivalirudin Pharmacokinetics and Pharmacodynamics (ACT last 60 mins)**

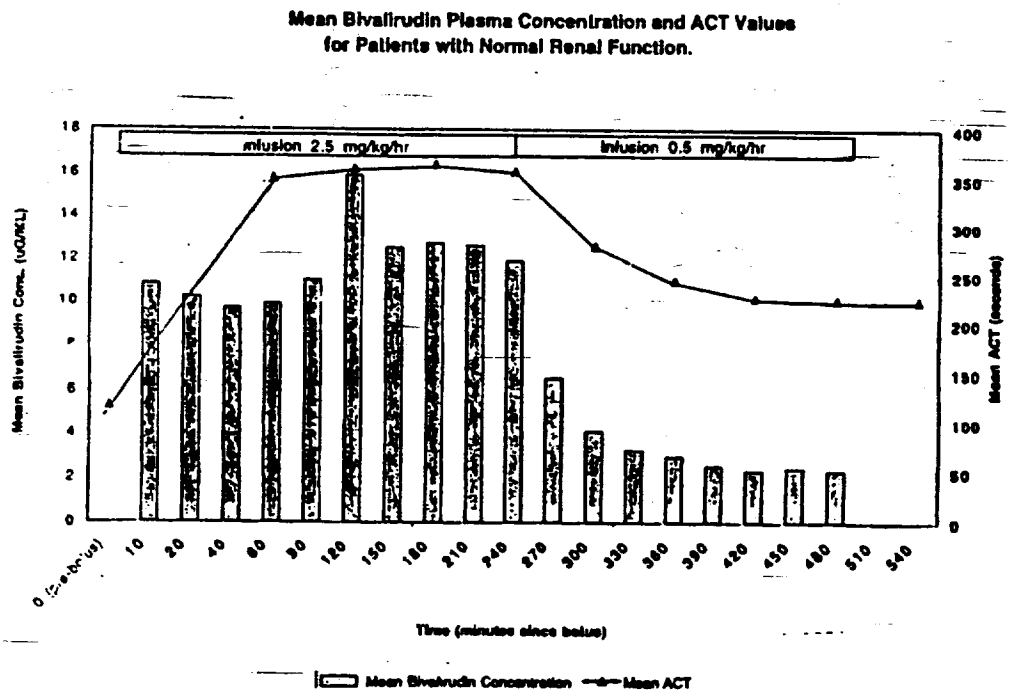
PHARMACO-KINETIC PARAMETERS	NORMAL RENAL FUNCTION MEAN ± SD		MILD RENAL IMPAIRMENT MEAN ± SD		MODERATE RENAL IMPAIRMENT MEAN ± SD	
Infusion dose	2.5 mg/kg/hr n = 8	0.5 mg/kg/hr n = 8	2.5 mg/kg/hr n = 11	0.5 mg/kg/hr n = 11	2.5 mg/kg/hr n = 6	0.5 mg/kg/hr n = 6
AUC total (h.mcg/ml)	47.0 ± 8.9	15.5 ± 2.5	48.1 ± 7.9 NS	17.6 ± 5.2 NS	94.1 ± 16.0 p< 0.001	32.4 ± 6.0 p<0.001
AUC last 90 mins (h.mcg/ml)	18.7 ± 2.6	3.5 ± 0.7	18.9 ± 3.7 NS	4.3 ± 1.5 NS	24.0 ± 3.4 p< 0.05	5.1 ± 0.4 p< 0.05
Cmax (mcg/ml)	16.8 ± 9.9		13.9 ± 2.6 NS		23.5 ± 12.9 NS	
C last 90 mins (mcg/ml)	12.3 ± 1.7	2.3 ± 0.5	12.4 ± 4.5 NS	2.8 ± 1.1 NS	15.4 ± 1.8 p< 0.05	3.4 ± 0.3 p <0.05
Tmax (hours)	2.6 ± 1.2		2.4 ± 0.8 NS		4.9 ± 1.2 p<0.001	
Total clearance (ml/min/kg)	3.4 ± 0.5	3.7 ± 1.0	3.4 ± 0.7 NS	3.2 ± 0.9 NS	2.7 ± 0.4 p< 0.05	2.5 ± 0.2 p< 0.05
ACT last 60 mins (secs)	362 ± 9	225 ± 17	365 ± 13 NS	234 ± 35 NS	391 ± 23 p<0.001	268 ± 33 p<0.05
Bivalirudin excreted in urine (mg) *	183.7 ± 108.6 (n = 6)	120.2 ± 65.2 (n = 3)	141.3 ± 111.2 NS (n = 9)	99.3 ± 89.7 NS (n = 6)	363.8 ± 264.3 NS (n = 5)	93.5 ± 59.1 NS (n = 5)
Renal clearance (ml/min/kg) *	0.75 ± 0.59 (n = 6)	1.26 ± 0.81 (n = 3)	0.74 ± 0.72 (n = 9) NS	1.49 ± 1.34 (n = 6) NS	0.73 ± 0.47 (n = 5) NS	0.58 ± 0.29 (n = 5) NS

*The numbers of patients is lower for these calculations either due to no urine sample obtained or the concentration was below the limits of quantification.
The p-values given are for comparisons of patients with mild or moderate renal impairment with patients with normal renal function.

Table 2: Effect of Renal Function on ACT Values

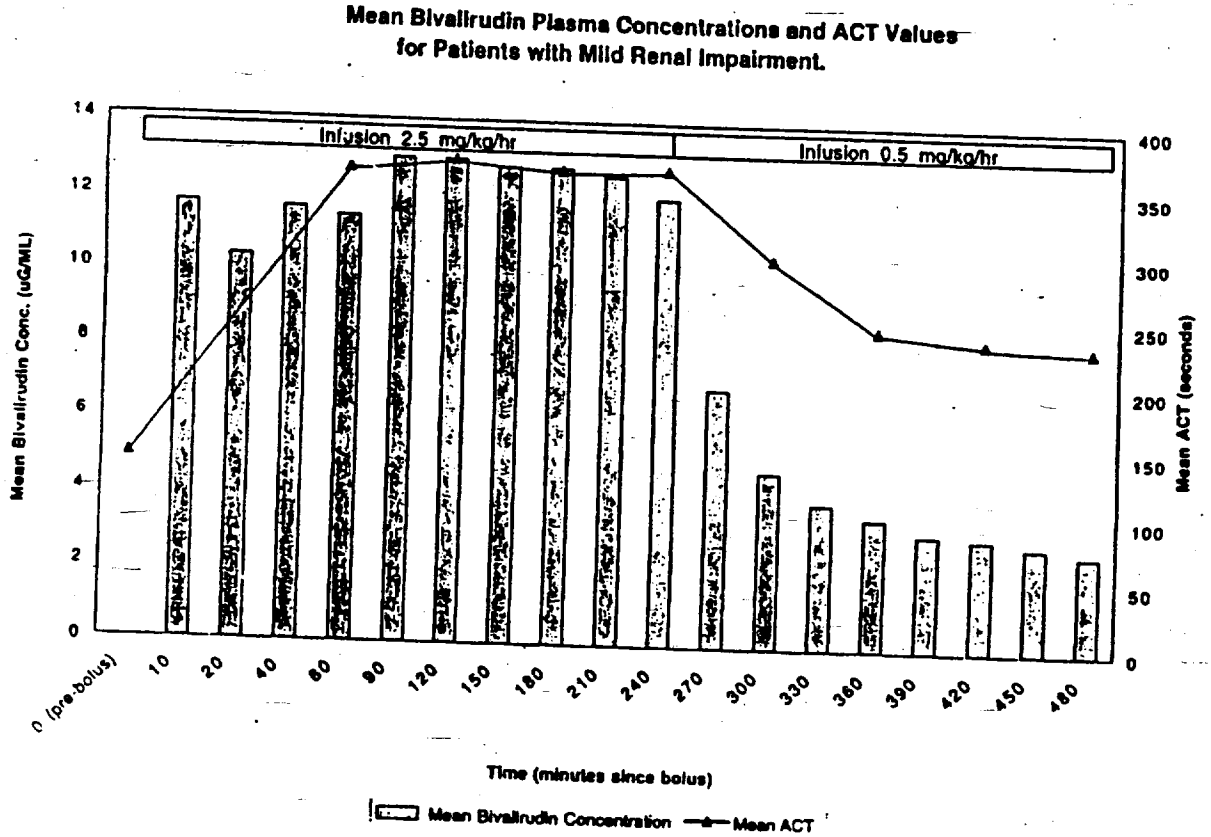
	ACT MEAN ± SD (N) (seconds)		
TIME (minutes since bolus)	NORMAL RENAL FUNCTION	MILD RENAL IMPAIRMENT	MODERATE RENAL IMPAIRMENT
0 (pre-bolus)	117 ± 12 (8)	140 ± 87 (11) NS	112 ± 12 (6) NS
60	350 ±20 (8)	363 ± 20 (11) NS	394 ± 38 (6) NS
120	360 ± 15 (7)	371 ± 15 (10) NS	400 ± 31 (6) NS
180	364 ± 10 (8)	364 ± 13 (11) NS	395 ± 19 (6) p<0.001
240	357 ± 8 (8)	365 ± 16 (11) NS	400 ± 23 (6) p<0.001
300	280 ± 33 (8)	298 ± 41 (11) NS	391 ± 26 (6) p<0.001
360	244 ± 12 (8)	244 ± 46 (11) NS	398 ± 18 (6) p<0.001
420	226 ± 18 (8)	236 ± 41 (11) NS	345 ± 34 (6) p<0.001
480	224 ± 20 (8)	233 ± 36 (11) NS	309 ± 53 (6) p<0.001
540	223* (1)		285 ± 39 (6)
600			280 ± 35 (6)
660			266 ± 46 (6)
720			271 ± 29 (6)
2 hrs post infusions	136 ± 28 (8)	155 ± 54 (9) NS	168 ± 13 (5) NS
At discharge	119 ± 9 (8)	143 ± 74 (8) NS	120 ± 15 (6) NS

Figure 1: Normal Renal Function



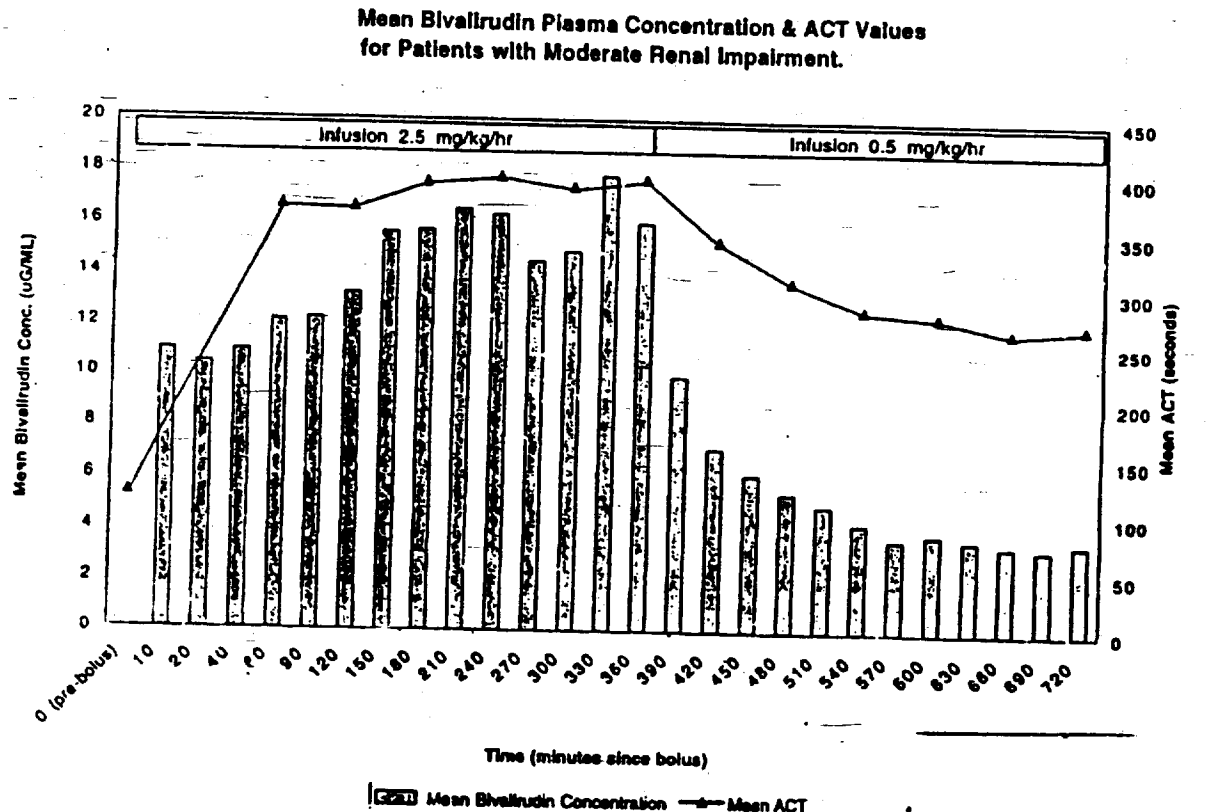
[See Attachment 2 for data used to plot Figure 1.]

Figure 2: Mild Renal Impairment



[See Attachment 3 for data used to plot Figure 2.]

Figure 3: Moderate Renal Impairment



[See Attachment 4 for data used to plot Figure 3.]

Figure 4: Renal Function and ACT Values

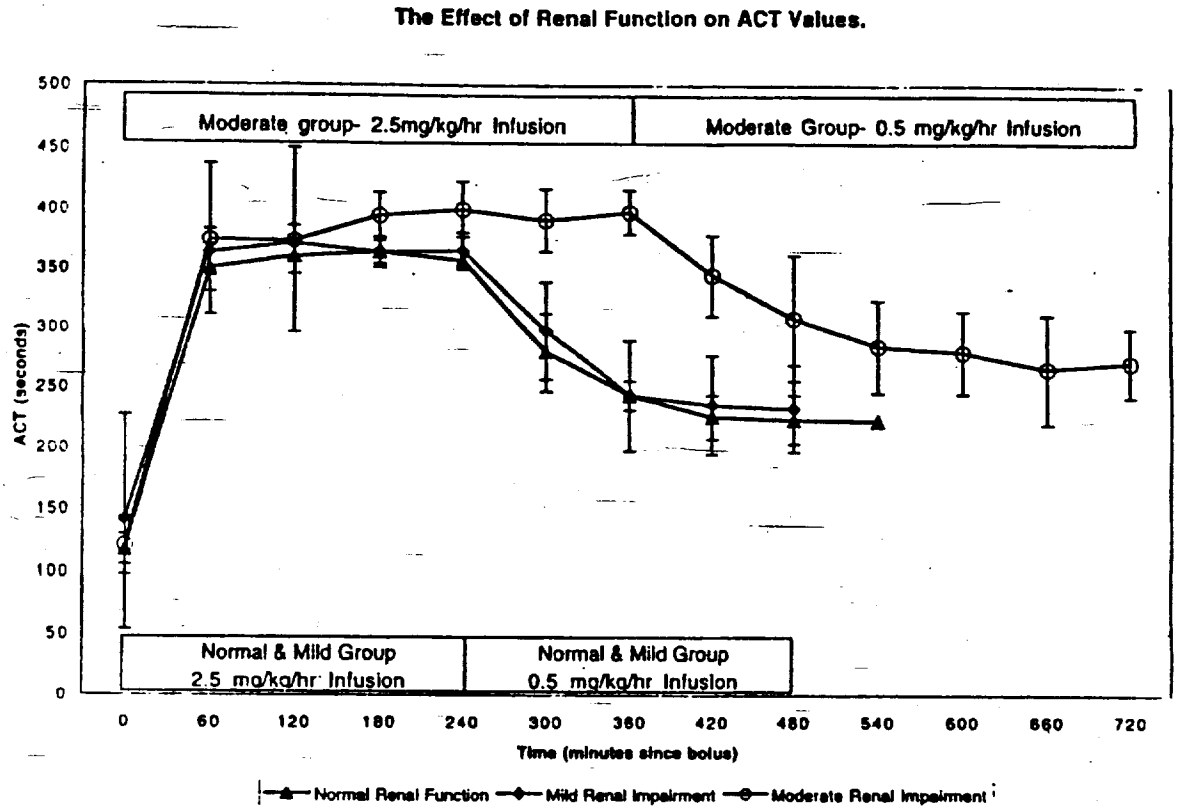


Figure 5: Renal Function and aPTT Values

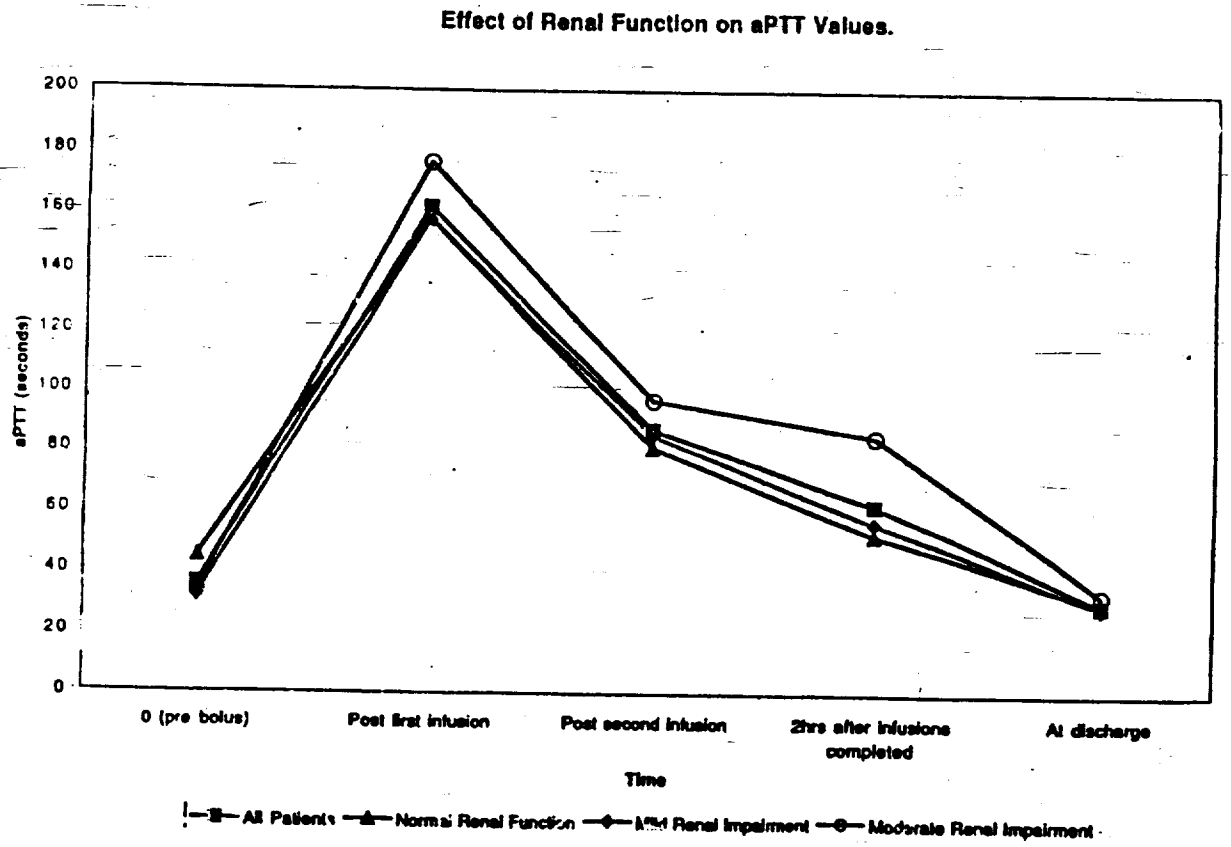


Table 3: PK and PD in Male and Female Patients

PARAMETER	MALE PATIENTS (N=17) MEAN ± SD		FEMALE PATIENTS (N=8) MEAN ± SD	
Infusion dose	2.5 mg/kg/hr	0.5 mg/kg/hr	2.5 mg/kg/hr	0.5 mg/kg/hr
AUC total (h.mcg/ml)	62.5 ± 26.1	22.4 ± 9.4	50.9 ± 20.5	16.4 ± 6.4
AUC last 90 mins (h.mcg/ml)	20.7 ± 4.5	4.4 ±1.4	18.6 ± 6.7	4.0 ± 1.5
Cmax (mcg/ml)	18.7 ± 10.6		13.6 ± 4.9	
Tmax (hours)	3.2 ± 1.6		2.8 ± 1.4	
Total clearance (ml/min/kg)	3.2 ± 0.7	3.2 ± 1.1	3.4 ± 1.2	3.1 ± 1.2
ACT last 60 mins (secs)	375 ± 21	245 ± 38	361 ± 7	227 ± 17

There were more males (n = 17) than females (n = 8) enrolled in this study. Of the eight female patients, there were two with normal renal function, five with mild renal impairment and one with moderate renal impairment. Of the 17 male patients there were six with normal renal function, six with mild renal impairment, and five with moderate renal impairment.

Table 4: Proportion of Unchanged Bivalirudin Cleared Renally

PHARMACO-KINETIC PARAMETER	NORMAL RENAL FUNCTION MEAN ± SD		MILD RENAL IMPAIRMENT MEAN ± SD		MODERATE RENAL IMPAIRMENT MEAN ± SD	
Infusion dose	2.5 mg/kg/hr n = 8	0.5 mg/kg/hr n = 8	2.5 mg/kg/hr n = 11	0.5 mg/kg/hr n = 11	2.5 mg/kg/hr n = 6	0.5 mg/kg/hr n = 6
Proportion of bivalirudin cleared renally for each infusion	0.18 ± 0.13	0.58 ± 0.33	0.18 ± 0.17	0.67 ± 0.56	0.34 ± 0.25	0.39 ± 0.23
Proportion cleared renally for both infusions	0.21 ± 0.08		0.28 ± 0.19		0.35 ± 0.22	

Assay Validation

For the analysis of plasma and urine samples for bivalirudin, a LC/MS method was used. Previously, the method for evaluating bivalirudin in plasma was evaluated in an OCPB review dated 4/3/00 for NDA Amendment No. 37. It was concluded that the plasma assay was acceptable. See that review for the provided validation data. For the urine assay however, the OCPB April 4th review requested TMC to provide validation data for it, for which it has now been provided in the new amendment (No. 50). Likewise based on the data that has been provided, it can be concluded the urine assay is acceptable. For this assay i) the limit of quantification is 10

mcg/mL, ii) it is linear over a range of [redacted] for concentrations of 30, 240, and 400 mcg/mL (n = 6 per concentration) the % Inaccuracy ranged from [redacted] and the % Imprecision ranged from [redacted]

Comments Regarding the Study's Results

1. Although in previous OCPB reviews it was recommended that patients be stratified for renal function by GFR groupings as covered in the Agency's renal impairment guidance (i.e., Normal: >80 mL/min, Mild: 50-80 mL/min, Moderate: 30-50 mL/min), TMC has stratified patients using the following GFR values:

Normal:	≥90 mL/min
Mild:	60-89 mL/min
Moderate:	30-59 mL/min

   As seen from the study results summarized below, it can probably be concluded that TMC's groupings are reasonable.

2. For the study there are different numbers of patients for the different renal function groups (i.e., normal: n = 8, mild: n = 11, moderate: n = 6). For total clearance intersubject variability (as measured by %CV) is relatively small across groupings and between the two dose levels (i.e., CVs ranged from 8 to 27%).

3. For the two doses that were studied (i.e., 2.5 mg/kg/hr and 0.5 mg/kg/hr) the results demonstrate that bivalirudin was dose proportional and exhibited linear pharmacokinetics. That is, for a 5 fold increase in dose, steady state AUC (i.e., last 90 mins.) values increased 5.3, 4.4 and 4.7 times for patients in the renal groupings of normal, mild and moderate, respectively. Although the labeling's proposed lower maintenance infusion dose of 0.2 mg/kg/hr was not studied, it is not expected that non-linearity or lack of dose proportionality would occur between the studied 0.5 mg/kg/hr dose and the 0.2 mg/kg/hr dose.

4. Patients with normal renal function and those with mild renal impairment demonstrated no significant differences for the PK and PD parameters of AUC(total), AUC(last 90 mins), Cmax, total clearance, ACT(last 60 mins), amount excreted in urine and renal clearance.

5. Patients with moderate renal impairment exhibited some different PK and PD parameters as compared with patients with normal renal function and mild renal impairment respectively:

- AUC (total) was greater for both the first infusion (94.1 h.mcg/ml compared with 47.0 h.mcg/ml and 48.1 h.mcgg/ml) and the second infusion (32.4 h.mcg/ml compared with 15.5 h.mcg/ml and 17.6 h.mcg/ml). However, it is noted that patients with moderate renal function received each dose level 2 hrs longer.
- AUC (last 90 minutes) was about 27% greater for the first infusion (24.0 h.mcg/ml compared with 18.7 h.mcg/ml and 18.9 h.mcg/ml) and about 46% and 19% greater for the second infusion (5.1 h.mcg/ml compared with 3.5 h.mcg/ml and 4.3 h.mcg/ml).
- Cmax was higher (23.5 mcg/ml compared with 16.8 mcg/ml and 13.9 mcg/ml but not statistically different.
- Tmax was later (4.9 hours compared with 2.6 hours and 2.4 hours).
- Css (last 90 mins) was higher for both the first infusion (15.4 mcg/ml compared with 12.3 mcg/ml and 12.4 mcg/ml) and the second infusion (3.4 mcg/ml compared with 2.3 mcg/ml and 2.8 mcg/ml.
- Total clearance was 21% lower for both the first infusion (2.7 ml/min/kg compared with 3.4 ml/min/kg for both other groups) and 32% and 22% lower for the second infusion (2.5 ml/min/kg compared with 3.7 ml/min/kg and 3.2 ml/min/kg).
- Steady state ACT (last 60 mins) values were about 7 % and longer for the first infusion (391 seconds compared with 362 seconds and 365 seconds) and 19% and 15% longer for the second infusion (268 seconds compared with 225 seconds and 234 seconds).

6. There were also some PK parameters which exhibited no significant differences between the three groups (results given are for patients with normal renal function, mild renal impairment and moderate renal impairment):

- The amount of bivalirudin excreted in urine during the first infusion was similar for both the patients with normal renal function and those with mild renal impairment, while the patients with moderate renal impairment had a higher value (184 ± 109 mg, 141 ± 111 mg and 364 ± 264 mg). This difference was not significant due to the large variances observed.
- The amount of bivalirudin excreted in urine during the second infusion were similar for all three groups of patients (120 ± 65 mg, 99 ± 90 mg and 94 ± 59 mg), although again, there was quite a lot of variation.
- Renal clearance was very similar for the first infusion (0.75 ml/min/kg, 0.74 ml/min/kg and 0.73 ml/min/kg). The second infusion did not show significant differences (1.26 ml/min/kg, 1.49 ml/min/kg and 0.58 ml/min/kg), however variances were large.
- Renal clearance is about 20% of total clearance at the 2.5 mg/kg/hr dose (22.1%, 21.8% and 27%)
- Mild renal dysfunction appears to have little effect on either renal or total clearance. The different bivalirudin doses of 2.5 mg/kg/hr and 0.5 mg/kg/hr also do not appear to affect total clearance (i.e., total clearance is dose independent).

7. The pharmacodynamics of bivalirudin (as measured by ACT) are dose-dependant. For the higher infusion rate mean steady-state ACT (last 60 mins) values for the groupings of normal, mild and moderate were 362, 365 and 391 seconds, respectively. For the lower infusion rate the respective mean values were 225, 234 and 268 seconds.

8. TMC has indicated that: "Patients with moderate renal impairment showed a 0.7 mg/kg/hr reduction in clearance for the first lower dose bivalirudin infusion, compared with the patients from the other two renal function groups. This reduction in clearance was associated with the higher ACTs seen in this study, however it was not associated with any clinically meaningful results. For example, the patients with moderate renal impairment did not show an increased rate of bleeding complications, but this may be due to the small numbers of patients in this study. Other data from phase 3 studies have found that higher ACTs are correlated with higher rates of bleeding complications."

9. The comparison of PK and PD data in male and female patients shows no significant differences. Mean total clearance values for male and female patients were respectively 3.2 and 3.4 ml/min/kg for the high infused dose and 3.2 and 3.1 for the low infused dose. Respective mean steady-state ACT (last 60 mins) values were 375 and 361 seconds for the high dose and 245 and 227seconds for the low dose.

10. TMC has indicated that, "combined animal and human data from this class of peptides suggests that renal clearance is the primary means of elimination and that the lack of complete recovery of bivalirudin in the urine is due to tubular reabsorption and subsequent metabolism in lysosomes."

11. In previous submissions, as well as in the new amendment, TMC is recommending the following dose adjustments for Angiomax. It is noted that the package insert/labeling also indicates in conjunction with the dosing table that, "The ACT should be monitored with any dose alterations.

RENAL FUNCTION	INITIAL BOLUS	MAINTENANCE INFUSIONS
Normal renal function >90 ml/min	1mg/kg	2.5mg/kg/h
Mild renal impairment 60-90 ml/min	1mg/kg	2.5mg/kg/h
Moderate renal impairment 30-59 ml/min	1mg/kg	1.25 mg/kg/h
Severe renal impairment 10-29 ml/min	1mg/kg	0.5 mg/kg/h
Dialysis dependent patients (monitor ACT)	1mg/kg	0.25 mg/kg/h

Comments (to be sent to sponsor)

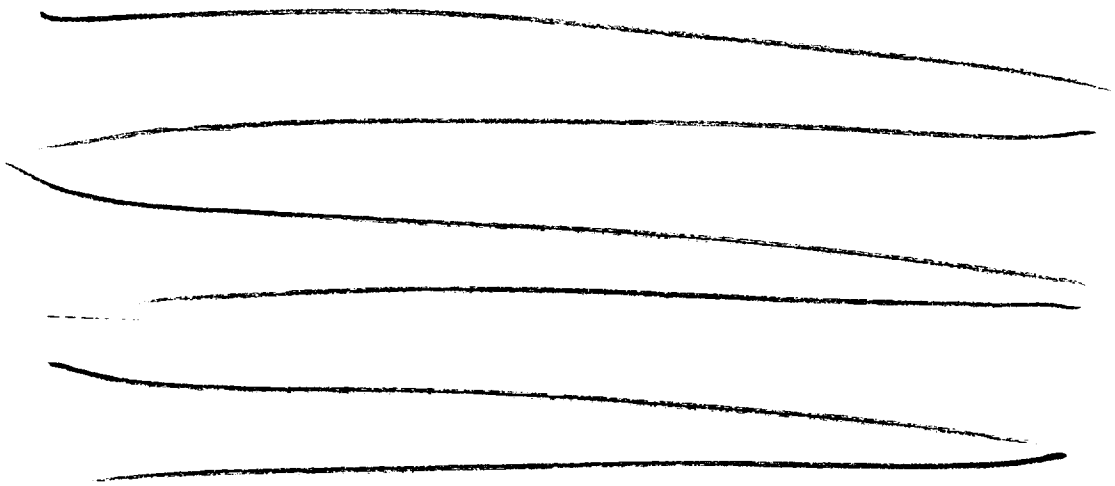
1. In Table 1 of the package insert, dosing recommendations for renal impairment are given. Please explain why the dose is to be reduced by half for patients with moderate renal impairment when results from your ongoing study (No. TMC-98-09) show that there is only a 21% reduction in total clearance. Additionally, the dose is further reduced by half for patients with severe renal impairment for which data is still pending from this study. Lastly, for the 0.2 mg/kg/h dosing regimen should this also be adjusted for renal function?

2. From the data obtained from Study No. TMC-98-09 please determine what the half-lives for bivalirudin are for the different groups of patients via modeling the observed data.

3. Once Study No. TMC-98-09 is completed with additional data for patients with severe renal impairment, please provide further pharmacokinetic (PK)/pharmacodynamic (PD) analyses using ACT (i.e., PK/PD modeling, etc. if appropriate) along with further updated analyses for age and gender effects on PK and PD. When gender analyses are done please assess as a function of GFR. In the event that recruitment of patients with severe renal disease is problematic due to study design issues, please contact FDA to discuss possible study modifications that might make patient enrollment easier (e.g., a reduced blood collection scheme, etc.).

Labeling Comments (to be sent to sponsor)

1. [redacted]



Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed the information and data that have been provided in NDA Amendment No. 50 that was submitted on 4/10/00. Based on the evaluation of the provided information and data, it is recommended that Comment Nos. 1 to 3 and Labeling Comment Nos. 1 and 2 be sent to the sponsor if HFD-180 concurs. Lastly, the reviewing medical officer should determine if the conclusion that TMC is making about the clinical relevance of increased ACTs in patients with moderate renal impairment is appropriate as covered in Comment No. 8 under the above review section titled, "Comments Regarding the Study's Results".

/S/
John Hunt
Div. of Pharmaceutical Evaluation II

RD initialed by Shiew-Mei Huang, Ph.D. /S/ 4/24/00

FT initialed by Shiew-Mei Huang, Ph.D. /S/ 4/24/00

cc: NDA 20-873
HFD-180 (Robie-Suh, Farrell, DuBeau)
HFD-340 (Viswanathan)
HFD-870 (Doddapaneni, M. Chen, Huang, Hunt)
Central Document Rm (Barbara Murphy)

ATTACHMENT 1

Patient Renal Function and Demographic Data

Green Lane Hospital patients: 401 – 414; Flinders Medical Centre patients: 501 –5 12

RENAL FUNCTION CATEGORY	ESTIMATED GFR (ml/min)	AGE AT STUDY ENTRY (years)	SEX	WEIGHT (kg)	INITIALS	PATIENT NUMBER
Normal	189.5	50	M	100	JMS	507
Normal	151.3	55.2	M	116	BLH	405
Normal	128.7	51	F	97	LEK	413
Normal	121.4	51.8	M	100	T-A	407
Normal	114.5	52.0	M	106	JJM	403
Normal	112.1	64	F	74	LBM	509
Normal	104.3	56.3	M	91	D-B	404
Normal	98.0	68	M	78	LSL	408
Mild impairment	87.2	55.5	M	74	LCN	503
Mild impairment	86.2	50.4	M	78	DWM	402
Mild impairment	85.4	44	F	85	SDT	505
Mild impairment	85.4	67.5	M	83	LAD	501
Mild impairment	77.5	58	F	77	AAC	412
Mild impairment	76.4	65.9	M	78	W-H	502
Mild impairment	75.0	62	F	77	CSD	506
Mild impairment	72.5	75	F	71	N-K	510
Mild impairment	71.6	70.0	M	75	JCC	401
Mild impairment	68.3	72	M	90	WJB	409
Mild impairment	64.9	65.4	F	58	PMN	406
Moderate impairment	56.2	70	M	85	RLG	410
Moderate impairment	52.4	68	M	77	OJP	411
Moderate impairment	50.7	70.7	M	74	EGL	511
Moderate impairment	48.2	77	M	81	L-T	414
Moderate impairment	44.1	75.3	M	82	JMM	512
Moderate impairment	41.3	61	M	82	HGJ	508
Moderate impairment	34.3	77.7	F	47	FEM	504

ATTACHMENT 2

Mean Bivalirudin Plasma Concentration and ACT Values for Patients with Normal Renal Function

TIME (minutes since bolus)	N	ACT MEAN (RANGE) (seconds)	N	BIVALIRUDIN CONCENTRATION MEAN (RANGE) (µg/ml)
0 (pre-bolus)	8	117	8	BLQ
10			8	
20			8	
40			8	
60	8	350	8	
90			8	
120	7	360	8	
150			8	
180	8	364	8	
210			8	
240	7	357	7	
270			8	
300	8	280	8	
330			8	
360	8	244	8	
390			8	
420	8	226	8	
450			8	
480	8	224	8	
510			1	
540	1	223		No sample required

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT 3

Mean Bivalirudin Plasma Concentration and ACT Values for Patients with Mild Renal Impairment

TIME (minutes since bolus)	N	ACT MEAN (RANGE) (seconds)	N	BIVALIRUDIN CONCENTRATION MEAN (RANGE) (µg/ml)
0 (pre-bolus)	11	140 (86 – 399)	11	BLQ
10			11	
20			11	
40			11	
60	11	363	11	
90			10	
120	10	371	11	
150			11	
180	11	364	11	
210			11	
240	11	365	11	
270			11	
300	11	298	11	
330			11	
360	11	244	11	
390			11	
420	11	236	11	
450			11	
480	11	232	11	

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT 4

Mean Bivalirudin Plasma Concentrations and ACT Values for Patients with Moderate Renal Impairment

TIME (minutes since bolus)	N	ACT MEAN (RANGE), (seconds)	N	BIVALIRUDIN CONCENTRATION MEAN (RANGE) (µg/ml)
0 (pre-bolus)	6	112	6	BLQ
10			6	
20			6	
40			6	
60	6	394	6	
90			6	
120	6	400	6	
150			4	
180	6	395	6	
210			6	
240	6	400	6	
270			6	
300	6	391	6	
330			6	
360	5	398	6	
390			6	
420	5	345	6	
450			6	
480	6	309	6	
510			6	
540	6	285	6	
570			6	
600	6	280	6	
630			6	
660	6	266	6	
690			6	
720	6	271	6	

APPEARS THIS WAY
ON ORIGINAL

DuBeau

APR - 3 200

Clinical Pharmacology and Biopharmaceutics Review

NDA 20-873
(Amendment No. 37)

Submission Date: 11/11/99

Bivalirudin Injection
Angiomax™

The Medicines Company
Cambridge, Massachusetts 02142

Reviewers: John Hunt

Type of Submission: General Correspondence - Response to NDA Approvability Letter

Synopsis

Bivalirudin (Angiomax™) is a 20-amino acid synthetic peptide inhibitor of thrombin. It is believed that bivalirudin can block both circulating and clot-bound thrombin and be useful in preventing abrupt vessel closure which can occur during and after percutaneous transluminal coronary angioplasty (PTCA). The recommended dosing regimen is a 4-hour IV infusion at a rate of 2.5 mg/kg/h with an IV bolus dose of 1.0 mg/kg administered immediately after initiation of the infusion. After completion of the 4-hour infusion period, an additional IV infusion may be initiated at a rate of 0.2 mg/kg/h for up to 20 hr as clinically warranted.

This NDA has had a somewhat complex regulatory history for which Office of Clinical Pharmacology and Biopharmaceutics (OCPB) involvement as related to pharmacokinetic (PK)/pharmacodynamic (PD)/renal impairment issues is chronologically summarized as follows.

- 12/23/97 - The Medicines Company (TMC) submitted NDA 20-873 for the approval of bivalirudin. Initially, the product's brand name was Hirulog™ but now it has been changed to Angiomax™.

- 10/23/98 – A FDA Cardiovascular and Renal Drugs Advisory Committee meeting was held. The committee voted that they could not recommend approval of bivalirudin.

- 11/18/98 - FDA sends TMC a not approval letter that stated the following.

> *"Consider conducting an additional clinical trial, prospectively designed, to demonstrate superior efficacy and safety of Hirulog™, compared to heparin, in post-MI patients undergoing PTCA for the treatment of unstable angina. In addition, for the continued clinical development of Hirulog™ for any indication, you should assess the pharmacokinetics, pharmacodynamics, and safety of Hirulog™ in patients with renal impairment."*

The latter request was based upon OCPB's review of the NDA. In the OCPB review concerns were raised about the accuracy of reported PK data and the proposed dosing recommendations for renal impairment due to i) the use of a nonspecific assay for determining bivalirudin concentrations and ii) the dose studied in normals and renally impaired patients (i.e., 0.5 mg/kg/h).

- 12/2/98 - TMC submits a protocol (No. TMC-98-09) under IND [redacted] for a new renal impairment study which is to also obtain PD data (see Attachment 1).

- 3/12/99 - OCPB completes a review of the renal impairment study protocol and five comments were forwarded to TMC on the same date (i.e., to use a specific assay, etc.).

- 4/22/99 – TMC submits information prior to their formal NDA resubmission on 4/26/99 (i.e., 2nd review cycle). Related to the pending renal impairment issues, TMC in their 4/22/99 submission re-summarized/analyzed data from the original NDA. Based upon these analyses TMC provided new dosing recommendations for renal impairment (i.e., the same recommendations that are now proposed in the updated package insert that has been submitted in Amendment No. 37; see Attachment 2).

- 8/5/99 - TMC submits an interim study report dated 6/28/99 for protocol No. TMC-98-09. Bivalirudin plasma and urine levels, plus activated clotting times (ACTs) for 11 of 30 subjects that are to be enrolled in the study were submitted. However, bivalirudin plasma and urine concentrations were again assayed using a nonspecific enzyme immunoassay.

- 10/4/99 - OCPB completes a review that evaluated the information and data that were provided in TMC's submissions dated 4/22/99 and 8/5/99.

- 10/28/99 – FDA sends TMC a letter indicating that the NDA is "approvable for the following indication: *Angiomax™ is indicated for use as an anticoagulant in patients with unstable angina who are undergoing percutaneous transluminal coronary angioplasty (PTCA).*" [Note: Although the letter indicated that the application was approvable, a number of deficiencies were covered that needed to be addressed. Example, the letter stated, "*A clinical trial that fulfills the following criteria is needed to address the deficiencies in your application before Angiomax™ is approved as an anticoagulant in patients with unstable angina undergoing PTCA or percutaneous coronary intervention: A prospective, adequate- and well-controlled clinical trial of the effects of Angiomax™ compared to heparin, as conventionally used and monitored, should be performed.*"] In this letter two comments from the 10/4/99 OCPB review that addressed the interim renal impairment study report were also included (see below).

- 11/11/99 – TMC submits NDA Amendment No. 37 (i.e., 3rd review cycle) to respond to the issues raised in FDA's letter dated 10/28/99. It is noted that TMC states as related to the outstanding clinical issues that, "*This submission does not contain new data or analyses not previously submitted to the Agency.*" Additionally in Amendment No. 37, TMC responds to the two OCPB comments that were sent in the 10/28/99 FDA letter plus they provided updated study results as an addendum to the interim report for protocol No. TMC-98-09 that originally submitted on 8/5/99.

TMC Responses to OCPB Comments

1st OCPB Comment:

"Review of the interim study report for Protocol TMC-98-09 entitled, "The influence of dose and kidney function on bivalirudin pharmacokinetics and pharmacodynamics in patients undergoing percutaneous coronary artery angioplasty (PTCA)" indicates a nonspecific assay method is being used to determine bivalirudin plasma and urine concentrations. There is a question as to what is actually being measured based upon cross reactivity information for some of the tested bivalirudin fragments and possibly others which have not been tested for interference. If sufficient collected samples are available, please re-assay samples with a specific assay method (e.g., the LC/MS method noted in your October 19, 1998 submission). In addition, for sample collections from the ongoing study, please assay bivalirudin levels by a specific method, unless it can be demonstrated that "drug" concentrations determined by the current method are the same as those determined by another method that is shown to be specific for bivalirudin."

TMC's Response:

"The LC/MS assay requested by the FDA has been developed and validated for human plasma and urine at [redacted] and is now being used. A draft assay validation report is available and is provided.

Analysis of the plasma and urine samples from patients in the renal insufficiency study using the LC/MS assay is ongoing. To date, samples from 18 patients in Protocol TMC-98-09 have been assayed using the LC/MS method. This includes the 11 patients in the Interim Study Report submitted to FDA and 7 new patients entered into the Protocol. An Addendum to the Interim Study Report has been prepared and is included with this section. This addendum includes bivalirudin plasma and urine concentrations measured with the new LC/MS assay methodology and pharmacokinetic parameters derived from this data. Demographic information on all 18 patients is also included."

2nd OCBP Comment:

"According to Protocol TMC-98-09, patients with a GFR below 30 ml/min will not be studied. Enroll patients with more compromised renal function in this ongoing study. In addition, enroll patients with renal impairment in this ongoing study in accordance with the other classifications as provided in the Agency's guidance entitled "Guidance for Industry – Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling (May 14, 1998) located in the following Internet address: http://www.fda.gov/cder/guidance/index.htm. Alternatively, study patients with more compromised renal function in the clinical trials of bivalirudin's use in HIT/HITTS patients, if appropriate." **[Note: From the previous 3/12/99 OCPB review of the protocol, similar requests were sent to TMC.]**

TMC's Response:

"In response to the Agency's request, Protocol TMC-98-09 will be amended to include patients with a GFR below 30 ml/min. New patients enrolled in this protocol will be enrolled in accordance with the Agency's guidance. Therefore, we do not intend to study renal function in HIT/HITTS patients."

Does the new assay procedure seem to be reliable for determining bivalirudin plasma and urine concentrations?

Answer:

Based upon the data provided in TMC's *Draft Method Validation Report*, the LC/MS method seems to be reliable for determining bivalirudin plasma concentrations (see validation data below). However, although TMC indicates that the method has been validated for determining bivalirudin concentrations in urine, no validation data were provided.

Limit of quantification: [redacted]

Linear calibration range/standard curve: [redacted]

Intra-batch run:

Theoretical Conc (mcg/mL)	N	Mean (mcg/mL)	% Inaccuracy	%Imprecision
[redacted]	6	0.43	-15.0	5.89
	6	1.36	-9.22	8.66
	6	13.1	8.89	5.68
	6	21.7	8.70	2.45

Inter-batch run:

Theoretical Conc (mcg/mL)	N	Mean (mcg/mL)	% Inaccuracy	%Imprecision
[redacted]	6	0.44	-11.9	9.33
	6	1.44	-4.09	6.03
	6	13.0	8.73	2.80
	6	20.8	4.14	3.24

Dilution:

Theoretical Conc (mcg/mL)	Dilution Factor	N	Mean (mcg/mL)	%Inaccuracy	%Imprecision
[redacted]	2	3	43.5	8.71	5.67
	5	3	42.6	6.62	0.68
	10	3	43.3	8.14	2.27

Stability after 3 freeze-thaw cycles:

Theoretical Conc (mcg/ml)	N	Mean (mcg/mL)	%Inaccuracy	%Impression
[redacted]	3	1.43	-4.96	2.72
	3	20.4	1.76	5.77

Comment:

Of concern has been the accuracy of the enzyme immunoassay that was used for determining bivalirudin concentrations and the resultant calculated PK parameters in previously conducted studies plus the ongoing renal impairment study. For the ongoing renal impairment study, inspection of patients plasma concentrations that have been determined by both the nonspecific enzyme immunoassay and the LC/MS method indicate that essentially all bivalirudin levels are higher with the former assay method. As an example of a worst case scenario for a given plasma

sample comparision, patient No. 504 (i.e., with moderate renal impairment) had a 12 hr bivalirudin concentration of 16.0 mcg/mL using the enzyme immunoassay method versus 3.21 mcg/mL using the LC/MS assay method. (See Attachment 3 for mean bivalirudin plasma concentration versus time curves for the patients studied thus far using the LC/MS assay method).

In the event that Angiomax™ is approved during this 3rd review cycle, are the provided interim PK data sufficient for labeling purposes?

Answer:

It is preferred that the ongoing renal impairment study (No. TMC-98-09) be completed and that the study's final results be incorporated into the product's labeling. Currently, the accuracy and appropriateness of the proposed dosing adjustments (see Attachment 2) in renal disease can not be completely assessed due to the lack of PK data for patients with more compromised kidney function (e.g., GFR $\leq$ 30 mL/min) using an accurate assay procedure. Also of concern, as related to being able to accurately assess the proposed dose adjustments based upon the newly submitted data, is the accuracy of the calculated clearance values that have been submitted. Random checking of several calculated plasma clearance values suggests that there is a problem with the provided results (Attachment 4 has the reported PK parameters). No information was provided as to how TMC calculated the clearance values. Unless TMC can explain/justify their reported results, a reanalysis of their data is needed (see Comments section below). Similarly there are concerns of the accuracy of the reported steady state concentrations. However, if it is determined that the NDA is to be approved before the ongoing renal study is completed, useful information can be provided in the package insert from the data that is currently available, provided the applicant addresses the Comments given in the Recommendation section below. (Attachment 5 has the most recent version of the package insert)

Comment:

For the proposed renal impairment dose adjustments, the updated package insert requires that ACT be monitored for anticoagulant effect.

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluations II (OCPB/DPEII) has reviewed the information and data that have been provided in NDA Amendment No. 37 that was submitted on 11/11/99. From an OCPB/DPEII perspective it is felt that the final results for the ongoing renal impairment study (No. TMC-98-09) should be obtained and evaluated in order to assess the accuracy and appropriateness of the proposed dose adjustment recommendations for renal impairment, as well as providing accurate pharmacokinetic and updated pharmacodynamic labeling information.

However, if it is determined that the NDA resubmission is to be approved prior to the applicant submitting the final results for the ongoing renal impairment study, it is requested that Comment Nos. 1, 2, 3 and 4 be addressed by the applicant for the purpose of updating the proposed package insert with the available information and data from the ongoing study; that is, unless it is strongly felt from a safety and efficacy perspective that it is not necessary to update the product's package insert with the interim study results at this time.

Comment Nos. 1 through 6 should be communicated to the applicant, as appropriate.

1. For ongoing study Protocol No. TMC-98-09 please provide i) the body weights for the completed patients, ii) assay validation data for the LC/MS assay method used for determining bivalirudin concentrations in urine, iii) results for the urine samples that were indicated to be reanalyzed, iv) the percent of bivalirudin excreted per infused dosing regimen per patient, and v) descriptions of the methods used for determining plasma clearance values and steady state bivalirudin concentrations since there is a concern regarding the accuracy of the reported values. If it is determined that the reported values are incorrect, please reanalyze and provide corrected values.

2. In the event that additional patients have been enrolled in study Protocol No. TMC-98-09 and results are now available for them, please submit those results.

3. For the currently proposed package insert, please delete any information that is based upon the nonspecific enzyme immunoassay (e.g., t1/2 if appropriate) and replace it with results based on the LC/MS assay. From the currently available data from study Protocol No. TMC-98-09 include in the package insert's Pharmacokinetics section information on plasma clearance, Cmax and Tmax as a function of GFR plus percent urinary excretion data.

4. Although information is currently pending on patients with severe renal impairment, please address whether dosage adjustment would be needed for patients with moderate or severe renal impairment or patients on dialysis who would be continued on bivalirudin after the initial infusion phase. Currently the proposed package insert indicates that patients can go on an infusion of 0.2 mg/kg/h for up to 20 hours as clinically warranted.

5. Once study Protocol No. TMC-98-09 is completed, please provide pharmacokinetic(PK)/pharmacodymic(PD) analyses (i.e., modeling, etc. if appropriate) along analyses to assess age and gender effects on PK and PD.

6. It is noted that once study Protocol No. TMC-98-09 is completed, the package insert will need further updating based on the additional study findings.

/S/

John Hunt
Div. of Pharmaceutical Evaluation II

RD initialed by Shiew-Mei Huang, Ph.D. /S/ 4/3/00

FT initialed by Shiew-Mei Huang, Ph.D. /S/ 4/3/00

cc: [redacted]
HFD-180 (Robie-Suh, Farrell, DuBeau)
HFD-340 (Viswanthan)
HFD-870 (Doddapaneni, M. Chen, Huang, Hunt)
HFD-880 (Selen)
HFD-903 (Strong)
Central Document Rm (Barbara Murphy)

Attachment I

Protocol No. TMC-98-09

Study objectives:

- To determine bivalirudin clearance in angioplasty patients at the recommended dose
- To determine if the clearance is dose dependant
- To determine if bivalirudin clearance is dependant on kidney function
- To assess the proportion of unchanged drug that is cleared renally

Study details:

- Study sites: Two non-US (Australia and New Zealand) centers
- Design: Open serial recruitment trial
- Patients:
  N = 30 patients (referred for elective percutaneous coronary angioplasty or intracoronary stent) with different degrees of kidney function
  Age: 18 to 85 years
  Gender: Treatment groups to be balanced for gender

- Study treatment groups as related to kidney function (n = 10 per group) and their proposed dosing regimens:

  Normal (Clcr > 90 ml/min): 1 mg/kg iv bolus followed by a 4 hr infusion of 2.5 mg/kg/h followed by a 4 hr infusion of 0.5 mg/kg/h.

  Mild (Clcr 60-89 ml/min): 1mg/kg iv bolus followed by a 4 hr infusion of 2.5 mg/kg/h followed by a 4 hr infusion of 0.5 mg/kg/h.

  Moderate (Clcr 30-59 ml/min): 1 mg/kg iv bolus followed by a 6 hr infusion of 2.5 mg/kg/h followed by a 6 hr infusion of 0.5 mg/kg/h. For this group if a patient has an activated clotting time (ACT) > 450 seconds after 4 hr of the 2.5 mg/kg/h infusion, the patient will be put on the low dose infusion (0.5 mg/kg/h).

  Plasma creatinine levels will be measured within 24 hr prior to enrollment and the GFR calculated according to the Cockroft and Gault equation.

- Plasma and urine sample were to be collected for determining bivalirudin concentrations.

- Pharmacodynamic markers of coagulation:

  ACT will be assessed i) pre-bivalirudin bolus injection, ii) hourly during the 8 or 12 hr infusions, iii) 2 hr following cessation of infusion and iv) at discharge. Activated partial thromboplastin time (aPTT) will be assessed i) pre-bivalirudin bolus injection, ii) at 4 or 6 hr (end of 2.5 mg/kg/hr infusion), iii) at 8 or 12 hr (end of 0.5 mg/kg/hr infusion), iv) 2 hr following cessation of infusion and v) at discharge.

- Concomitant medications:

  Patients are to be treated with aspirin 300 mg p.o. at least 2 hr before the planned procedure when possible, followed by daily administration unless otherwise indicated. Lower aspirin doses may be required for patients with GI intolerance. Beta-blockers, calcium channel blockers and nitrates may be used at the discretion of the investigator. Other anticoagulation or antiplatelet therapy should be avoided. Ticlopidine may be given at a dose of 250 mg po bid. Warfarin or low molecular weight heparin is not started until after the index intervention.

"Table 1. Dose Recommendations for Renal Impairment"

Renal Function (GFR mL/min)	Initial Bolus	Infusion for 4-hours
Normal renal function (≥90 ml/min)	1mg/kg	2.5mg/kg/h
Mild renal impairment (60-90 ml/min)	1mg/kg	2.5mg/kg/h
Moderate renal impairment (30-59 ml/min)	1mg/kg	1.25mg/kg/h
Severe impairment (10-29 ml/min)	1mg/kg	0.5mg/kg/h
Dialysis dependant patients patients	1mg/kg	0.25mg/kg/h

The ACT should be monitored with any dose alterations."

Attachment 3

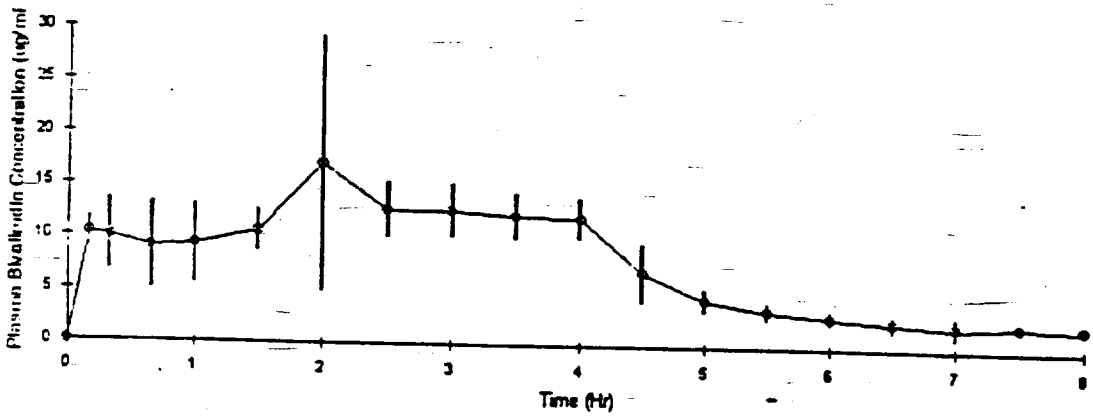


Figure 1. Mean Plasma Bivalirudin Conc. in Patients With Normal Renal Function. LC/MS Assay

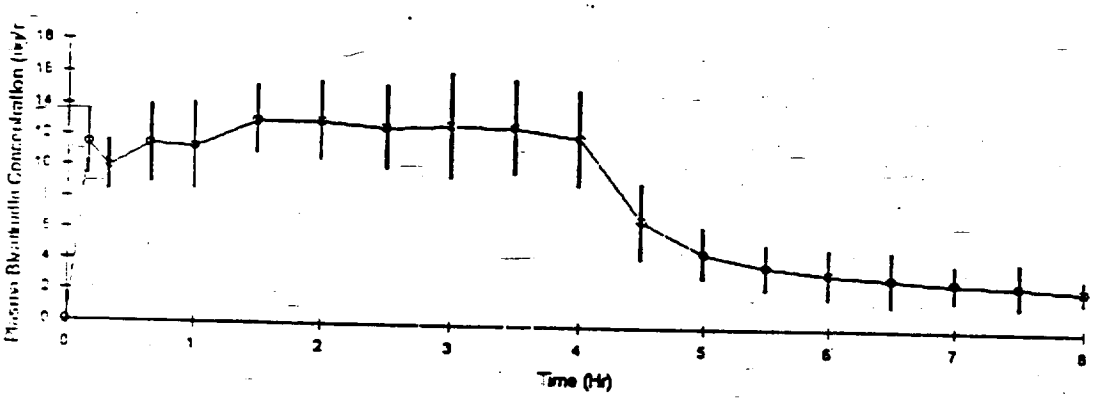


Figure 2. Mean Plasma Bivalirudin Conc. in Patients with Mild Renal Impairment. LC/MS Assay

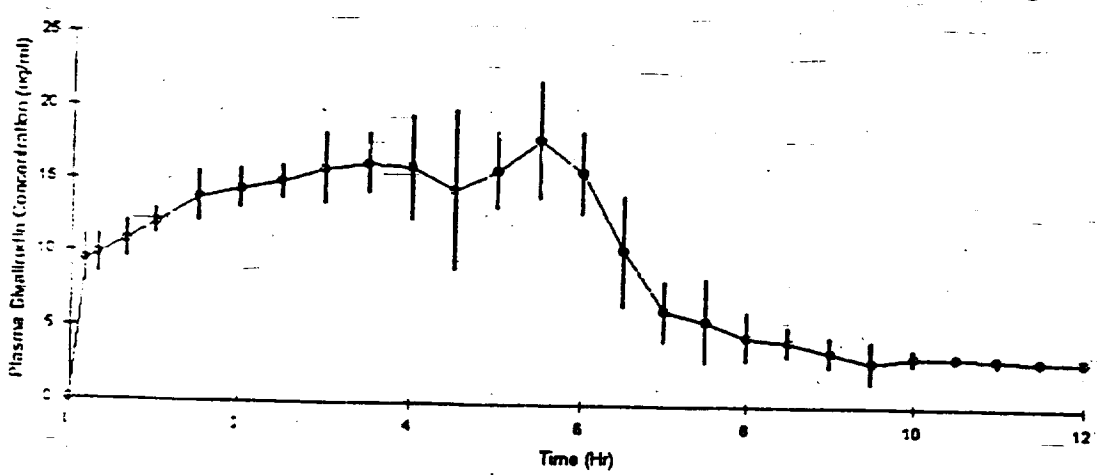


Figure 3. Mean Plasma Bivalirudin Conc. in Patients With Moderate Renal Impairment. LC/MS Assay

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Table 4. Pharmacokinetic Parameters for Patients Using the LC/M... say

Renal Function	Subject Number	AUC Total (hr*µg/mL)	AUC 2.5 mg/kg/hr (hr*µg/mL)	AUC 0.5 mg/kg/hr (hr*µg/ml)	AUC last 90 min 2.5 mg/kg/hr (hr*µg/ml)	AUC last 90 min 0.5 mg/kg/hr (hr*µg/ml)	Cmax (µg/mL)	T max (hr)
Normal	403	64.8	48.9	15.9	18.6	3.4	13.2	2.5
Normal	404	67.2	49.3	17.9	23.5	3.9	17.1	2.0
Normal	405	68.1	51.3	16.8	21	3.8	14.7	2.5
Normal	407	53.2	34.4	18.8	15.9	3.3	11.8	4.5
Normal	408	55.4	40.3	15.2	16.2	3.7	11.3	3.5
Normal	507	54.6	43.8	10.7	16.2	2.1	12.3	0.2
	Mean	60.6	44.6	15.9	18.6	3.4	13.4	2.5
	S.D.	6.9	6.5	2.8	3.1	0.7	2.2	1.5
Mild	401	48.4	36.5	11.8	13.8	2.7	11	2.0
Mild	402	57.4	43.1	14.3	16.4	3	11.8	1.5
Mild	406	58.8	42	16.9	16.3	3.6	12.2	1.5
Mild	409	83.8	54.4	29.5	23	7.2	16.5	4.0
Mild	501	85.3	60.4	24.9	23.5	6.8	17.1	2.0
Mild	502	77.1	58.5	18.6	25.3	4.9	18.8	3.0
Mild	503	50.9	37.2	13.8	14.5	3.4	10.4	3.5
Mild	505	60.9	47.7	13.2	17.4	3.4	13.2	2.5
Mild	506	66.6	50.4	16.2	19.3	3.8	13.8	2.0
	Mean	65.5	47.8	17.7	18.8	4.3	13.9	2.4
	S.D.	13.7	8.8	5.9	4.2	1.6	3	0.9
Moderate	410	135.6	99.4	36.3	29.1	5.1	20.4	5.5
Moderate	504	95.8	73.9	21.9	19.4	4.6	14.5	5.0
Moderate	508	116.8	84.6	32.2	24.4	4.7	19.8	5.5
	Mean	116	86	30.1	24.3	4.8	18.2	5.3
	S.D.	19.9	12.8	7.4	4.9	0.3	3.2	0.3

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Table 4. Pharmacokinetic Parameters for Patients Using the LC/MS Assay (Continued)

Renal Function	Subject Number	Conc at ss 2.5 mg/kg/hr (µg/ml)	Conc at ss 0.5 mg/kg/hr (µg/ml)	Clearance 2.5 mg/kg/hr (ml/min/kg)	Clearance 0.5 mg/kg/hr (ml/min/kg)	Renal Exc 2.5 mg/kg/hr (mg)	Renal Exc 0.5 mg/kg/hr (mg)
Normal	403	12.2	2.2	3.4	3.8	36.8	tbr
Normal	404	15.4	2.5	2.7	3.3	17.0	0
Normal	405	13.7	2.5	3.0	3.3	3.62	7.37
Normal	407	10.6	2.2	3.9	3.8	15.1	0
Normal	408	10.8	2.4	3.9	3.5	29.9	0
Normal	507	10.8	1.4	3.9	5.9	tbr	tbr
	Mean	12.3	2.2	3.5	3.9	20.5	1.84
	S.D.	2.0	0.4	0.5	1	13.0	3.7
Mild	401	9.4	1.8	4.4	4.6	12.6	2.5
Mild	402	10.8	1.9	3.9	4.4	7.4	26.5
Mild	406	10.8	2.3	3.9	3.6	34.8	6.1
Mild	409	15.4	4.5	2.7	1.8	20.8	0
Mild	501	15.7	4.2	2.7	2.0	0	0
Mild	502	16.9	3.1	2.5	2.7	8.2	0
Mild	503	9.4	2.4	4.4	3.1	9.8	8.1
Mild	505	11.8	2.5	3.5	3.3	0	0
Mild	506	12.6	2.4	3.3	3.5	3.0	0
	Mean	12.5	2.8	3.5	3.2	10.7	4.8
	S.D.	2.8	1	0.7	1	11	8.7
Moderate	410	19.0	3.3	2.2	2.5	79.3	15.3
Moderate	504	13.5	3.1	3.1	2.7	3.0	2.2
Moderate	508	16.7	3.1	2.5	2.7	0	tbr
	Mean	16.4	3.2	2.6	2.6	27.4	8.75
	S.D.	2.8	0.1	0.5	0.1	44	9

tbr - to be reassayed

10 page(s) of revised draft labeling has been redacted from this portion of the review.

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OCT - 4 1999

Clinical Pharmacology and Biopharmaceutics Review

10/19/98 D

NDA 20-873 **Submission Date:** 4/22/99
8/05/99
9/15/99

Bivalirudin Injection
ANGIOMAX

The Medicines Company
Cambridge, Massachusetts 02142

Reviewers: John Hunt
Arzu Selen, Ph.D.

Type of Submission: NDA Resubmission

Background:

Bivalirudin (ANGIOMAX) is a 20-amino acid synthetic peptide inhibitor of thrombin. It is believed that bivalirudin can block both circulating and clot-bound thrombin and be useful in preventing abrupt vessel closure which can occur during and after percutaneous transluminal coronary angioplasty (PTCA). [Note: For this resubmission the product's brand name has been changed. Since all previous submissions and reviews used the brand name Hirulog, this review will continue to use this brand name to minimize confusion.]

* On 12/23/97 The Medicines Company (TMC) submitted NDA 20-873 for the approval of Hirulog. The proposed package insert stated in the INDICATION section that, "Hirulog is indicated for use as an anticoagulant in patients undergoing percutaneous transluminal coronary angioplasty." [Note: Now in the resubmission the INDICATION section states, "ANGIOMAX is indicated for use as an anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty in order to prevent ischemic and hemorrhagic complications."] The recommended dosing regimen is a 4-hour IV infusion at a rate of 2.5 mg/kg/h with an IV bolus dose of 1.0 mg/kg administered immediately after initiation of the infusion. After completion of the 4-hour infusion period, an additional IV infusion may be initiated at a rate of 0.2 mg/kg/h for up to 20 hr as clinically warranted. [Note: In a Cardiovascular and Renal Drugs Advisory Committee Meeting that was held on 10/23/98, the committee voted that they could not recommend approval of Hirulog.] On 11/18/98 FDA sent TMC a not approval letter that included the following.

> "Consider conducting an additional clinical trial, prospectively designed, to demonstrate superior efficacy and safety of Hirulog™, compared to heparin, in post-MI patients undergoing PTCA for the treatment of unstable angina. In addition, for the continued clinical development of Hirulog™ for any indication, you should assess the pharmacokinetic, pharmacodynamic, and safety of Hirulog™ in patients with renal impairment."

* On 1/15/99, as a result of FDA's not approval letter, TMC met with the Agency. TMC was given different strategies that may be pursued in order to address the clinical safety and efficacy issues observed during review of the NDA (i.e., reanalyze the findings from the original pivotal clinical studies or conduct a new prospectively targeted clinical study). Suggested additionally were clinical trials in 3 separate populations (i.e., heparin-induced thrombocytopenia (HIT), heparin-induced thrombocytopenia and thrombosis (HITTS) and patients taking GP IIb/IIIa inhibitors. TMC indicated they were currently investigating clinical safety/efficacy in two patient populations (i.e., HIT/HITTS).

Historical and ongoing issues:

Related to the review and evaluation of what has now been submitted and proposed by TMC for renal impaired patients in this 4/22/99 NDA resubmission, the following historical and ongoing issues need to be considered.

---

* For the original NDA submission, the 11/19/98 Office of Clinical Pharmacology and Biopharmaceutics (OCPB) review indicated the following in the Recommendation section.

> "If the Sponsor decides to continue development of the Hirulog injectable product, then it is important that the Sponsor discusses the issues raised below with the Office of Clinical Pharmacology and Biopharmaceutics. The primary issues that were noted during the review of this NDA are the following:
>
> - The Sponsor has reported that clearance of bivalirudin in patients with renal impairment is significantly lower than that of the patients with normal renal function and had proposed dose-adjustment in these patients in summary documents but not in the proposed package insert. In response to the Agency's request, in the October 19, 1998 Amendment, the Sponsor has proposed a "questionable" dosing scheme for patients with renal impairment and for patients undergoing dialysis. The dosing scheme proposed by the Sponsor is considered questionable because it refers to doses not even tested in the renal impairment study and furthermore, issues related to non-specificity of the ELISA assay have not been resolved. As a result, accuracy of bivalirudin clearance estimates is unknown. The Sponsor has indicated that they will be continuing to work on assay related issues.
>
> If the Sponsor decides to continue development of bivalirudin, it is recommended that the Sponsor conducts a pharmacokinetic/pharmacodynamic study in patients with renal impairment, and use a specific assay (such as the LC/MS method used in the October 1998 Amendment) for quantitation of bivalirudin. This study may be conducted according to the OCPB guidance (Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function-Study Design, Data Analysis, and Impact on Dosing and Labeling) and per guidance, it will include control group subjects as well as patients with renal impairment. Use of a specific bivalirudin assay in this study will allow accurate assessment of bivalirudin pharmacokinetic parameters and appropriate dosing recommendation for this patient population.....
>
> - In addition, the draft report on LC/MS analysis of bivalirudin metabolites in plasma included in the October 1998 Amendment, suggests that additional metabolite isolation and identification efforts may be warranted."

Additionally covered in the 11/19/98 OCPB review were issues/problems regarding linking the clinically tested formulation to the to-be-marketed formulation (i.e., assay specificity concerns for the bioequivalence studies, manufacturing process change issues, etc.; See Attachment 1).

* After the January 99 meeting, TMC resubmitted the bivalirudin NDA in April 99 and made two additional submissions to the NDA in August and September 99.

TMC's proposal for dose adjustment in patients with renal impairment as addressed in the resubmitted NDA (4/22/99):

* In this 4/22/99 NDA resubmission, TMC only provided re-analyses for the previously conducted clinical studies. Also, regarding the renal impairment issue that was raised in FDA's not approval letter, TMC re-summarized/analyzed data from the original NDA submission (See further discussion below.) Based upon these analyses, TMC now proposes in the package insert the following dosing recommendations for renal impaired patients.

"The dose of ANGIOMAX may need to be reduced, and anticoagulation status monitored, in patients with renal impairment. Recommendations for dosage adjustment are provided in Table 5.

Table 5. Dose Recommendations for Renal Impairment

Renal Function (GFR mL/min)	Initial Bolus	Infusion for 4-hours
Normal renal function (≥90 ml/min)	1mg/kg	2.5mg/kg/h
Mild renal impairment (60-90 ml/min)	1mg/kg	2.5mg/kg/h
Moderate renal impairment (30-59 ml/min)	1mg/kg	1.25mg/kg/h
Severe impairment (10-29 ml/min)	1mg/kg	0.5mg/kg/h
Dialysis dependant patients (monitor ACT)"	1mg/kg	0.25mg/kg/h

TMC's new protocol for studying bivalirudin in patients with renal impairment and FDA's comments on the protocol:

* As a result of OCPB's request for a renal impairment study in the NDA's not approval letter, TMC submitted a protocol (No. TMC-98-09) on 12/2/98 via IND No. ——— In this IND submission TMC stated the following.

"Although the preclinical and clinical pharmacology of bivalirudin is well documented, review of the existing clinical pharmacology data, in combination with the clinical

experience in PTCA, raises a number of questions, which will be addressed in this study:

- What is the clearance of bivalirudin in PTCA patients at the recommended dose (1.0 mg/kg intravenous bolus followed by 2.5 mg/kg/hr for 4 hours), and is clearance independent of dose of bivalirudin administered? The majority of clinical pharmacology data available on bivalirudin is in volunteers who, for safety reasons, were maximally given doses of 0.6 mg/kg. In volunteers clearance was dose independent but when these data are compared with those in patients, the clearance of bivalirudin appears to be dose dependent. There is a need to determine whether clearance is dose independent.

- What is the influence of age and kidney function on bivalirudin clearance at the recommended dose in patients undergoing PTCA? The bivalirudin clinical data show that patients over 65 years are at more than twice the risk of major hemorrhage than those under 65 years (5% vs. 2% for patients given bivalirudin). Furthermore, a study in renally impaired patients showed a reduction in bivalirudin clearance with increasing kidney impairment, although this study was conducted at a dose of 0.50 mg/kg/hr (over four hours), well below that recommended for use in angioplasty. A reasonable hypothesis is that the increased bleeding in the elderly is a consequence of their reduced kidney function and hence reduced clearance.

- What proportion of unchanged bivalirudin is cleared renally? The current data from volunteers suggests only 20% of bivalirudin is renally excreted, whereas a study in renally impaired patients suggests a value closer to 80%. It is necessary to more accurately determine the proportion of drug cleared by the kidney in patients at the dose recommended for angioplasty."

The sponsor further indicated that in addition to determining bivalirudin plasma and urinary clearance, hemostatis as assessed by ACT would be evaluated along with secondary endpoints to include, the incidence of major bleeding and cardiac ischemic events including abrupt vessel closure, reinfarction, requirement for revascularisation and death prior to hospital discharge.

* A summary of the submitted protocol is as follows:

Objectives:

- To determine bivalirudin clearance in angioplasty patients at the recommended dose
- To determine if the clearance is dose dependant
- To determine if bivalirudin clearance is dependant on kidney function
- To assess the proportion of unchanged drug that is cleared renally

Study details:

- Study sites: Two non-US (Australia and New Zealand) centers
- Design: Open serial recruitment trial
- Patients:
  N = 30 patients (referred for elective percutaneous coronary angioplasty or intracoronary stent) with different degrees of kidney function
  Age 18 to 85 years
  Gender: Treatment groups to be balanced for gender

- Study treatment groups as related to kidney function (n = 10 per group) and their proposed dosing regimens:

  Normal (Clcr > 90 ml/min): 1 mg/kg iv bolus followed by a 4 hr infusion of 2.5 mg/kg/h followed by a 4 hr infusion of 0.5 mg/kg/h.

  Mild (Clcr 60-89 ml/min): 1mg/kg iv bolus followed by a 4 hr infusion of 2.5 mg/kg/h followed by a 4 hr infusion of 0.5 mg/kg/h.

  Moderate (Clcr 30-59 ml/min): 1 mg/kg iv bolus followed by a 6 hr infusion of 2.5 mg/kg/h followed by a 6 hr infusion of 0.5 mg/kg/h. For this group if a patient has an activated clotting time (ACT) > 450 seconds after 4 hr of the 2.5 mg/kg/h infusion, the patient will be put on the low dose infusion (0.5 mg/kg/h).

  Plasma creatinine levels will be measured within 24 hr prior to enrollment and the GFR calculated according to the Cockroft and Gault equation.

- Plasma and urine sample were to be collected for determining bivalirudin concentrations.

- Pharmacodynamic markers of coagulation:

  ACT will be assessed i) pre-bivalirudin bolus injection, ii) hourly during the 8 or 12 hr infusions, iii) 2 hr following cessation of infusion and iv) at discharge. Activated partial thromboplastin time (aPTT) will be assessed i) pre-bivalirudin bolus injection, ii) at 4 or 6 hr (end of 2.5 mg/kg/hr infusion), iii) at 8 or 12 hr (end of 0.5 mg/kg/hr infusion), iv) 2 hr following cessation of infusion and v) at discharge.

- Concomitant medications:

  Patients are to be treated with aspirin 300 mg p.o. at least 2 hr before the planned procedure when possible, followed by daily administration unless otherwise indicated. Lower aspirin doses may be required for patients with GI intolerance. Beta-blockers, calcium channel blockers and nitrates may be used at the discretion of the investigator. Other anticoagulation or antiplatelet therapy should be avoided. Ticlopidine may be given at a dose of 250 mg po bid. Warfarin or low molecular weight heparin is not started until after the index intervention.

* In a 3/12/99 OCPB review of protocol No. TMC-98-09, 5 comments (See Attachment 2) were recommended to be sent to the sponsor. A FDA letter was sent to the sponsor on 3/12/99. Three of the 5 comments that were sent addressed the need for i) using an assay that was "specific and accurate for measuring bivalirudin and ideally its metabolite(s)", ii) using "bivalirudin from a representative production size batch using the manufacturing procedures and the site of manufacture where the drug product would be made if ultimately approved for marketing", and iii) the use of a group of normal volunteers plus 4 patient groupings with different degrees of renal impairment that comply with FDA's renal guidance (e.g., including patients with Clcr <30 mL/min). Also, alternative dosing regimens were recommended. Regarding the OCPB protocol review comments, it is noted that due to i) concerns of not having accurate bivalirudin pharmacokinetic (PK) information/data as a result of the use of a non-specific assay in the originally submitted studies, ii) issues regarding linking the clinically tested and to-be-marketed formulations, and iii) a new manufacturing process change, it was felt that this new study would allow FDA to get "accurate" bivaluridin PK data plus pharmacodynamic (PD) data for the "final" product that is to actually be marketed (i.e., if eventually

approved), plus get better information on how to best dose this drug in renal impaired patients.

[Note: Recently it was learned that the sponsor submitted a response on 3/26/99 to FDA's letter of 3/12/99 which indicated that TMC would use "validated assays" and that the bivalirudin used in this study would meet FDA's requested requirements. They also addressed maintaining their protocol's proposed dosing groups and doses. On 8/5/99, TMC submitted an interim study report for Protocol No. TMC-98-09. This interim report provided results for 11 of the 30 patients that are to be enrolled. In a 9/15/99 faxed submission, the sponsor has indicated that the final study report would probably be submitted in December, 1999. See below for more discussion on this interim study report.]

Issues related to linkage of the bivalirudin product used in pivotal clinical trials to the to-be-marketed product:

* On 5/6/99 there was a telecon between TMC and HFD-180 chemists. This telecon focused on the linkage between the drug product used in the pivotal clinical trials and the to-be-marketed drug product. In the telecon, TMC was asked to provide a side-by-side comparison of the two formulations for assay and impurities, absorbance scans, thrombin inhibition activity (anti-IIa), sequencing and mannitol content. It is also noted that the firm was told that biopharmaceutics would not request use of retained samples for a Phase I PK/PD study due to sterility assurance issues (i.e., six year old retained samples). Upon inquiry as to the formulation comparisons that were requested, it was learned from the reviewing chemist that:

- The batch/lot size of the to-be-marketed product, although not technically from a commercial full scale batch/lot, it was sufficiently representative of a commercial full scale batch/lot to be considered acceptable.
- The to-be-marketed product was made at the site where it will be manufactured if approved (
- It was concluded that the compared products are i) chemically equivalent in terms of bivalirudin, ii) equivalent in terms of impurity profiles and iii) equivalent in terms of formulation (i.e., inactive ingredients). In a 9/30/99 review memo it is stated that, "This data demonstrates the equivalence of the formulations used in the pivotal clinical trials and the formulation to be marketed. ACCEPTABLE"

Review of section on bivalirudin PK/PD, etc. information in patients with renal impairment (section included in the resubmitted NDA):

Attachment 3 provides the information/data that were provided in the NDA resubmission that relates to renal impairment issues. Some points related to the provided information/data are noted as follows.

1. Summarized is PK information for hirudin and desirudin. Although this is informative, it does not necessarily impact on the dosing assessment/recommendations for bivalirudin.

2. Two studies from the original NDA submission are briefly summarized again (Nos. C90-041 and C93-313). The former was a study in patients undergoing PTCA. TMC states, "The calculated clearance in these PTCA patients was lower than in volunteers. This difference may be due to reduced glomerular filtration rate in the patient population or may be due to sparse sampling, which would have overestimated AUC and underestimated clearance." The latter study was a renal impairment study that studied a

4-hr IV infusion dose of 0.5 mg/kg/h. One of the concerns for these studies, plus others noted during the review of the original NDA, was the use of a non-specific assay which would result in incorrect "drug" clearance determinations.

3. PD relationships (i.e., for aPTT response) were addressed for "SC" administration (Attachment 3, Figure 2) and for Study No. C93-313 that only used the 0.5 mg/kg/h IV infusion dose (Attachment 3, Figure 3). TMC claims that there is a direct relationship between plasma concentrations and effect as measured by aPTT. However, for higher bivalirudin IV doses, from Study No. C90-041 that was submitted originally (See Appendix 4), such a relationship is questioned (i.e., similar aPTT Emax values over a wide range of "drug" Cmax concentrations following IV infusion doses covering 0.6 to 2.2 mg/kg/h). This is probably due to the aPTT PD response maximizing out.

4. Revisited were the two Phase III clinical trials (Nos. C92-304-1 and C92-304-2) where it appears that TMC has retrospectively calculated baseline GFR values for the patients studied in these trials using the Cockcroft and Gault formula. They have stratified patients into 4 groups according to renal function and assessed major hemorrhage incidence rates (Attachment 3, Table 2). From the GFR analyses it demonstrates that a significant number of PTCA patients have some degree of impaired renal function which necessitates having meaningful dosing recommendations as related to renal impairment (e.g., for the 1914 patients who received bivalirudin, 884 had GFR between 60 - < 90 mL/min, 529 were between 30 - < 60 mL/min but only 18 had GFR < 30 mL/min). TMC states, "The incidence of major bleeding increased for heparin and bivalirudin as the degree of renal function deteriorated, except for the severe group for bivalirudin. The number of patients with severe renal impairment on bivalirudin was small and therefore, this analysis may have underestimated the incidence of severe bleeding in this group." Also analyzed were ACT measurements taken at 45 minutes for the 4 groupings (Attachment 3, Figure 4). TMC notes that all groups were similar in ACT measurements except the severely impaired patients where there was an increased ACT.

Comments Regarding the NDA Resubmission:

In this resubmission TMC states the following based upon their re-analyses of the previously provided data for bivalirudin as related to dosing in renal impaired patients.

> "For bivalirudin the pharmacodynamic data in renal impairment and the analysis of incidence of major hemorrhage *versus* calculated GFR in the phase III data provides evidence that dose reduction is only required in patients with moderate and severe degrees of renal impairment (GFR<60 ml/mm, <1ml/sec). In these patients the same loading dose should be used, followed by reduction in the maintenance infusion dose according to the degree of renal impairment."

It is certainly agreed that dose adjustment is needed in renal impaired patients who are to receive bivalrudin, but the outstanding question is what are the appropriate dosing adjustments that are needed. When dosing in renal impaired patients was raised during the review of the original NDA, TMC proposed the following dosing adjustments in a 10/19/98 submission.

GFR:	≥ 60 ml/min	1 mg/kg IV bolus	plus 2.5 mg/kg/h for 4 h
	30-59 "	"	" 1.25 "
	<30 "	"	" 0.75 "

Now TMC is proposing to modify this to include i) a GFR range of 10-29 ml/min for which the IV infusion is 0.5 mg/kg/h and ii) add a regimen for dialysis dependent patients where the IV infusion is 0.25 mg/kg/h. [Note: In the resubmission, from the table that addressed the GFR breakout for patients studied in the two pivotal clinical studies, the least represented group were patients (N = 18) with a GFR <30 ml/min.] Due to the concerns that have been noted above regarding the usefulness of the originally submitted PK/PD data to support renal impairment dosing recommendations, which triggered the request for a study in renal disease in the NDA not approval letter, it is interesting to note what TMC stated in the 12/2/98 IND protocol submission (See pages 3 to 4 above). From what TMC states it can be interpreted that they certainly agree that more PK and PD data are needed to be better able to define renal impairment dosing regimens.

Review of the interim report of the ongoing renal impairment study:

On 8/5/99 TMC submitted an interim study report (Attachment 5) for the ongoing renal impairment study (No. TMC-98-09). Data for 11 of the 30 subjects that are to be enrolled were provided. The GFR range breakout for completed subjects is as follows.

Renal Function Category	N	GFR Range (mL/min)
Normal	5	95.6 to 151.3
Mild	5	64.8 to 86.1
Moderate	1	36.3

Based upon a review of the provided information/data, the following key items are noted. For Item Nos. 1 and 2, two comments are recommended to be sent to TMC (See Recommendation section below).

1. Review of the assay methodology/validation data indicates that a non-specific method is again being used to determine bivalirudin plasma and urine concentrations. An enzyme immunoassay method is being used. From the validation report it indicates, "As part of this validation the possible cross reactivity of 6 synthesized peptide fragments (not 12 as estimated in the protocol) of bivalirudin was examined,..." Under the Cross Reactivity section, for three fragments it states, "Fragments CTMC-01, CTMC-02, and CTMC-03 gave 1037%, 405% and 399% cross reactivity respectively." Lastly it is also stated that, "It was not possible to assess the interference of fragments 1 to 3 in the assay due to the cross reactivity." [Note: In a consult with FDA analytical expert Dr. John Strong (HFD-903), he noted/confirmed numerous problems with the assay method.]

2. For this study, the worst degree of renal impairment will only be patients with a GFR between 30-60 ml/min. In OCPB's review of the protocol patients with GFR <30 ml/min were recommended along with a different stratification scheme. [Note: Based on individual data in Attachment 5 they have enrolled 3 patients with mild renal impairment and 7 controls as defined in FDA's renal guidance.]

3. For the lot (No. 42376) of bivalirudin used in this study, it has been determined that it was made at the site of manufacture where the product would be made if approved and it can be considered to be a representative production scale lot as determined by the reviewing chemist However, it was made using the "old" manufacturing procedure that was modified. Based upon the reviewing chemist's recent review of all relevant CMC

information/data, he concludes that overall this lot can be considered to be equivalent to the final to-be-marketed product.

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics/Divisions of Pharmaceutical Evaluations II and III (OCPB/DPEII/III) have reviewed the renal impairment information/data provided in the NDA resubmission dated 4/22/99 plus the interim report dated 8/5/99 (NDA Amendment No. 25) for the ongoing renal impairment study (Protocol No. TMC-98-09) that was requested in the original NDA not approval letter. For the NDA resubmission, it is felt that the provided data analyses (that are based on the information/data that were provided in the original NDA) still leave a question as to what the best dosing recommendations should be for renal impaired patients who are to receive bivalirudin. The provided information/data do reaffirm the need for special dosing requirements for renal impaired patients. For the ongoing renal impairment study, see review pages 3 and 4 above for the sponsor's comments on the study's importance as presented in their 12/2/98 IND protocol submission. However, for this ongoing study there are concerns/problems for which it is hoped that they can be corrected as covered under Comment Nos. 1 and 2 below.

The reviewing medical officer should be made aware of the above review sections that address i) the NDA resubmission as related to PK/PD, etc. information/data (page 6), ii) comments regarding the NDA resubmission (page 7) and iii) the renal study interim report (page 8).

If it is determined that the NDA resubmission is to be approved, from an efficacy perspective for treating renal impaired patients using the applicant's now proposed dosing recommendations (i.e., until at least more data is available from the ongoing renal impairment study), it might be prudent/warranted to request that more monitoring of ACT be carried out for other renal impairment groupings other than just dialysis patients as is currently proposed in Table 5 of the package insert, assuming that it is felt that ACT is the best clinical endpoint/surrogate marker for efficacy.

Lastly, if the NDA is to be approved, the Pharmacokinetics section of the package insert's Clinical Pharmacology section should include a sentence that indicates that, "Bivalirudin plasma concentrations were estimated with a non-specific assay which also detected bivalirudin metabolites." Additionally the statements that provide volume of distribution and plasma clearance values should be deleted.

Comment Nos. 1 and 2 below should be communicated to the applicant.

1. Upon review of the interim study report for Protocol No. TMC-98-09 that was submitted 8/15/99, it indicates that a non-specific assay method is being used to determine bivalirudin plasma and urine concentrations. It can be questioned as to what is actually being measured based upon cross reactivity information for some of the tested bivalirudin fragments plus possibly others which have not been tested for interference. It is suggested that if sufficient collected samples are available they be re-assayed with a specific assay method (e.g., the LC/MS method noted in a

10/19/98 NDA Amendment submission). For ongoing study sample collections they too should be assayed by a specific method, unless it can be demonstrated that "drug" concentrations determined by the current method are the same as those determined by another method that is shown to be specific for bivalirudin.

2. In Protocol No. TMC-98-09, patients with a GFR below 30 mL/min will not be studied. As was previously recommended in FDA's letter of 3/12/99 for IND [redacted] it is suggested that patients with more compromised renal function be enrolled in the ongoing study or possibly be studied in the trials where you are investigating bivalirudin's use in HIT or HITTS patients, if appropriate. Similarly, if possible, the use of patients with renal impairment in accordance with the other classifications as provided in the FDA guidance should be considered and implemented in the ongoing study

/S/

John Hunt
Div. of Pharmaceutical Evaluation II

/S/

Arzu Selen, Ph.D.
Div. of Pharmaceutical Evaluation III

RD initialed by Mei-Ling Chen, Ph.D. /S/ 10/4/99

FT initialed by Mei-Ling Chen, Ph.D. /S/ 10/4/99

cc: [redacted]
HFD-180 (Robie-Suh, Farrell, DuBeau)
HFD-340 (Viswanthan)
HFD-870 (M. Chen, Hunt, Lee)
HFD-880 (Selen)
HFD-903 (Strong)
Central Document Rm (Barbara Murphy)

studies, C93-317 and C90-010. Lack of an appreciable effect of aspirin on bivalirudin pharmacokinetics and pharmacodynamics is reported. Again uncertainty regarding analytical methods preclude further assessment of these results. When switching from continuous iv infusion of heparin to bivalirudin, a transient increase in activated partial thromboplastin times (aPTT), and from bivalirudin to heparin a transient decrease in aPTT was observed (and is reflected in the proposed package insert).

Patients with renal impairment and patients undergoing dialysis:

Slower clearance of Hirulog in patients with moderate to severe impairment (GFR < 60 ml/min) was noted and this is also stated in the proposed package insert. In addition, a dose-adjustment recommendation is made for patients undergoing dialysis (Study C93-313).

As communicated to the Sponsor earlier, dose-adjustment recommended for patients with severe and moderate renal impairment in the summary documents needs to be also reflected in the package insert.

In study C93-313, 0.5 mg/kg/h doses of bivalirudin were administered for 4 h to normal subjects and patients with varying degrees of renal impairment. The recalculated "clearance" values of bivalirudin is approximately 4-5 ml/min/kg in subjects with GFR values equal to or greater than 60 ml/min. Whereas in subjects with GFR values between 30 to 59 ml/min and GFR values less than 30 ml/min, the mean (SD) bivalirudin "clearance" values were 2.41 (1.47) and 1.11 (0.46) ml/min/kg, respectively. In dialysis patients, the mean (SD) bivalirudin "clearance" values were 0.83 (0.44) ml/min/kg for patients off-dialysis and 1.81 (0.63) ml/min/kg for patients on-dialysis.

In response to the Agency's request, the Sponsor has proposed a dosing scheme for bivalirudin in Attachment 6 of the October 19, 1998 Amendment. The proposed bivalirudin dose for the patients with GFR values equal to or greater than 60 ml/min is 2.5 mg/kg/h for 4 h (plus 1 mg/kg iv bolus dose) and for patients with GFR values 30 ml/min to 59 ml/min, the proposed bivalirudin dose is 1.25 mg/kg/h for 4 h (plus 1 mg/kg iv bolus dose). And for patients with GFR values less than 30 ml/min, the proposed bivalirudin dose is 0.75 mg/kg/h for 4 h (plus 1 mg/kg iv bolus dose). It is important to note that even the proposed adjusted dosing scheme is based on doses higher than the dose evaluated in the renal impairment study, C93-313, and is based on approximations. Furthermore, unresolved analytical issues such as use of a nonspecific assay, precludes an accurate determination of clearance values. The proposed dosing scheme is considered unacceptable and needs to be further studied in a relevant clinical setting following quantitation of bivalirudin by a specific assay.

<u>Bioequivalence of Hirulog Formulations</u>

Specificity of the bivalirudin assay as well as other analytical method related issues need to be resolved prior to further evaluation of bioequivalence of Hirulog formulations. In this NDA, the Sponsor refers to two studies (C93-310 and C93-316) to link the clinical trial formulations to the proposed injectable product. Because of the peptide nature of the product, it is possible that differences in manufacturing processes may result in Hirulog batches with different antithrombin activity. As a result, to ensure that the clinical trial formulations and formulations tested in Phase I and preclinical studies were comparable and linked, during early development of Hirulog, Hirulog formulations were compared in clinical bioavailability/bioequivalence studies. The major assumption in these studies was that comparable plasma bivalirudin concentrations, as determined by an ELISA assay, reflected the antithrombin activity of these Hirulog products.

In Study C93-310, the pilot scale frozen Hirulog formulation (Lot 67Z01S), used in efficacy trials was compared against the pilot scale synthesis, lyophilized Hirulog formulation (Lot 67Z04S).

In Study C93-316, intended to be the pivotal bioequivalence study, the two formulations of Hirulog, pilot scale frozen formulation (Lot 67A04Z) and commercial scale synthesis lyophilized formulation (Lot 67A02Q) were compared. However, because of lack of temperature control, the Sponsor has indicated that bivalirudin concentrations could not be measured in Study C93-316. Subsequently, the Sponsor has amended the report for Study C93-310 to reflect the reanalysis of data (calculation of 90% confidence intervals for bioequivalence assessment) in order to support the bioequivalence of the lyophilized formulation (commercial scale synthesis) to the frozen formulation (pilot scale).

The Sponsor has proposed linking of the two studies C93-310 and C93-316 based on aPTT measurements. However, as discussed in the main review section, bivalirudin concentrations are needed for accurate comparison of Hirulog formulations and that aPTT measurements are not suitable to link the data from C93-310 and C93-316 to support comparability of Hirulog products.

Furthermore, during review of this NDA, the Sponsor has also indicated that they can no longer manufacture Hirulog injectable product according to the method submitted in this NDA and they need to modify the manufacturing method. As a result, if the Sponsor decides to continue with development of bivalirudin, and will not use the data in this NDA for future submission(s), then the bioequivalence assessments or comparisons made in this NDA are not pertinent for future considerations.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics/Divisions of Pharmaceutical Evaluation II and III have reviewed the clinical pharmacology and biopharmaceutics information of the Hirulog NDA 20-873 and the responses from [redacted] dated February 25, March 25, and May 11, 1998. The information needed for complete review of Hirulog NDA 20-873, requested in several FDA letters dated February, March and June 1998 were not available during review of this NDA. Although some of the responses to the questions raised by the Agency have been provided in the Sponsor's October 19, 1998 submission, in the same amendment, the Sponsor has also indicated that they will continue to work on assay related issues.

If the Sponsor decides to continue development of the Hirulog injectable product, then it is important that the Sponsor discusses the issues raised below with the Office of Clinical Pharmacology and Biopharmaceutics. The primary issues that were noted during review of this NDA are the following:

- The Sponsor has reported that clearance of bivalirudin in patients with renal impairment is significantly lower than that of the patients with normal renal function and had proposed dose-adjustment in these patients in summary documents but not in the proposed package insert. In response to the Agency's request, in the October 19, 1998 Amendment, the Sponsor has proposed a "questionable" dosing scheme for patients with renal impairment and for patients undergoing dialysis. The dosing scheme proposed by the Sponsor is considered questionable because it refers to doses not even tested in the renal impairment study and furthermore, issues related to non-specificity of the ELISA assay have not been resolved. As a result, accuracy of bivalirudin clearance estimates is unknown. The Sponsor has indicated that they will be continuing to work on assay related issues.

  If the Sponsor decides to continue development of bivalirudin, it is recommended that the Sponsor

Attachment 2

Comments (to be sent to sponsor):

1. It is not clear how much blood is to be drawn per sample for determining bivalirudin concentrations or for ACT and aPTT analyses. This should be clarified.

2. From the review of NDA 20-873, there were concerns regarding the reliability (i.e., specificity) of an ELISA assay method that was used for determining bivalirudin plasma concentrations. In an October 19, 1998 Amendment to the NDA, you acknowledge a LC/MS method. For this new study you should employ an assay that is specific and accurate for measuring bivalirudin and its metabolite(s).

3. For this proposed study, the bivalirudin that is to be administered should be from a representative production size batch made by the manufacturing procedures and at the site of manufacture where the product would be made if ultimately approved for marketing.

4. For the proposed treatment groups, it is recommended that they be modified to include the following and use the respective dosing regimens.

1) Control group (healthy volunteers; Clcr > 80 mL/min):	0.5 mg/kg/hr infusion for 4 hr
2) Patients (Clcr >80mL/min):	1.0 mg/kg iv bolus then 2.5 mg/kg/hr infusion for 4 hr then 0.2 mg/kg/hr " " 4 hr
3) Patients (Clcr 50-80 mL/min):	1.0 mg/kg iv bolus then 2.0 mg/kg/hr infusion for 4 hr then 0.2 mg/kg/hr " " 4 hr
4) Patients (Clcr 30-49 mL/min):	1.0 mg/kg iv bolus then 1.0 mg/kg/hr infusion for 4 hr then 0.2 mg/kg/hr " " 4 hr
5) Patients (Clcr <30 mL/min)	1.0 mg/kg iv bolus then 0.5 mg/kg/hr infusion for 4 hr then 0.2 mg/kg/hr " " 4 hr

Each treatment group should enroll 10 volunteers/patients balanced for gender. Ideally, males and females within a treatment group should be matched for age and body weight. Administration of bivalirudin to the treatment groups should be done in a sequential manner if possible (i.e., 1 through 5).

5. You are referred to the Agency's guidance entitled *Guidance for Industry – Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling* (http://www.fda.gov/cder/guidance/index.htm) to assist you in your data analyses, labeling recommendations, etc.

Background to Studies of Bivalirudin in Renal Impairment

The anticoagulant properties of hirudin derived from the salivary glands of medicinal leeches (Hirudo medicinalis) has been known about for centuries. The active component, native hirudin was not isolated until the late 1950's[1].

Bivalirudin Structure Derived from Native Hirudin

Hirudin is a single-chain polypeptide of 65 amino acids with three intra-molecular disulfide bridges and a sulfated tyrosine residue.[2] Variations in the amino acid sequence and the N-terminal amino acids have been reported due to the existence of different forms of native hirudin.[2]

The advent of DNA recombinant technology allowed the development of methods to produce r-hirudins in sufficient quantities for therapeutic use. A number of r-hirudin analogues have been produced. The initial recombinant products were identical to natural hirudin except for the absence of a sulfate residue on Tyr-63. Subsequent modifications produced new derivatives including hirugen and bivalirudin. Hirugen is a synthetic dodecapeptide comprising residues 53-64 of the carboxy-terminal region of hirudin. The addition of D-phe-pro-arg-pro-(glyc) to amino terminal region produced bivalirudin, a 20-amino acid bivalent inhibitor of alpha thrombin.[3]

Bivalirudin Mode of Action

Native hirudin is a potent natural inhibitor of alpha thrombin. It binds specifically and irreversibly to thrombin and inactivates the enzyme. Kinetic analysis of the inhibition of thrombin by hirudin identified two steps. Initial electrostatic interactions at the anion-binding exosite for fibrinogen recognition and subsequent binding at the enzyme catalytic centre.[4] The combination of these two interactions explains the high affinity binding of the thrombin-hirudin complex. It is the interaction of the ten-carboxy terminal amino acids of hirudin with the anion-binding exosite that is responsible for the inhibition of thrombin activity. Hirudin and r-hirudins block both clotting activity and factor V activation.

Hirugen, which comprises the carboxy-terminal 20 amino acids, blocks clotting activity but not factor V activation. Hirugen does not interact with the catalytic site of thrombin, but instead binds to the anion-binding exosite.

Bivalirudin blocks both the anion-binding exosite and the catalytic site. However, the catalytic site inhibition is transient because once complexed, thrombin slowly cleaves the pro-arg bond on the amino-terminal extension, converting hirulog to a hirugen-like molecule. This property makes bivalirudin a reversible inhibitor of thrombin, and enables temporary inhibition of thrombin without completely preventing factor V activation.[5] This reversible mode of action may account for the safety profile of bivalirudin.

Bivalirudin Pharmacokinetics

The pharmacokinetics of native hirudin has been determined in healthy volunteers after subcutaneous and intravenous administration.[6] The pharmacokinetics was independent of dose and route of administration. Intact hirudin is rapidly cleared by renal excretion with the calculated renal clearance similar to creatinine clearance indicating that glomerular filtration was

the main mechanism of elimination. However only 39%to 44%, after intravenous administration, of the dose was recovered in the urine. Similarly desirudin, a recombinant hirudin, is rapidly cleared from plasma by renal clearance. The recovery of drug in the urine accounts for 50% of the dose.[7] The total plasma clearance of desirudin exceeds glomerular filtration rate. This suggests that there is either no renal clearance or that active tubular secretion also occurs. Animal data and studies in renal impairment in animals and man suggest that nonrenal clearance is not important and that the lack of complete recovery in the urine is due to tubular reabsorption and subsequent metabolism in lysosomes.

In healthy volunteers the intravenous pharmacokinetics of bivalirudin are linear and are characterized by rapid plasma clearance (6.74ml/min/kg), a small volume of distribution (0.24L/kg) and an elimination half life between 20 and 40 minutes. In volunteers, to avoid undue risks of anticoagulation, doses were lower than those proposed for therapeutic effect. Limited pharmacokinetic data was obtained from patients undergoing PTCA. In the study (C90-041) pharmacokinetic data was obtained after a regimen where 1mg/kg IV bolus was given initially followed by an infusion of 2.5mg/kg/hr for 4 hours, followed by an infusion of 0.2mg/kg/hr for a further 17 hours. The calculated clearance in these PTCA patients was lower than in volunteers. This difference may be due to reduced glomerular filtration rate in the patient population or may be due to sparse sampling, which would have overestimated AUC and underestimated clearance. The maximum plasma concentrations over a range of doses measured increased proportionally. In vitro studies indicated that there is no evidence of significant protein binding.

As for hirudin and the recombinant hirudins renal clearance of bivalirudin is the major route of elimination. Consideration of renal function is therefore an important fact in the clinical use of bivalirudin.

Bivalirudin Studies in Patients with Renal Impairment

The patient population in whom bivalirudin is likely to be used may have renal impairment from either the aging process or from underlying disease, such as nephrosclerosis or diabetes. It was therefore important to examine the pharmacokinetic and pharmacodynamics in patients with varying degrees of renal impairment.

An open-labeled study of bivalirudin (C93-313) was performed in 5 groups with varying degrees of renal impairment as determined by inulin clearance.

Total clearance of bivalirudin ranged between 3.15 and 6.62 ml/min/kg in healthy subjects and between 0.44 and 1.47 ml/mm/kg in the group of subjects with the greatest degree of renal impairment. Clearance of bivalirudin was greater than glomerular filtration rate, as measured by inulin clearance. There was a significant correlation (r^2=0.54, p=0.0001) between the clearance of bivalirudin and inulin (Figure 1), where observed data, the regression line, and the 95% confidence intervals in the regression are presented. When corrected for nominal values of body surface area and total body weight (1.73m^2 and 70 kg) the y intercept is 0.84 ml/mm/kg and the slope is 1.79.

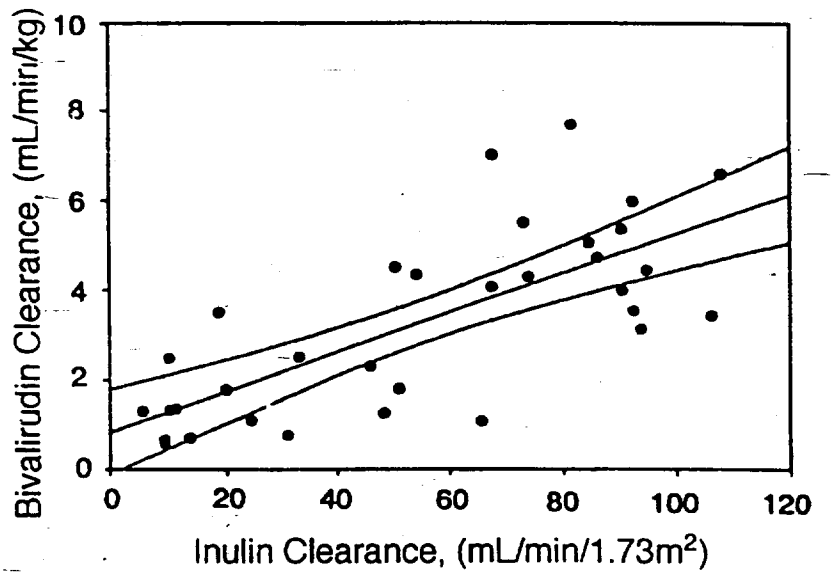


Figure 1. Total Clearance of Bivalirudin Versus Inulin Clearance in Subjects with Varying Degrees of Renal Function (Data from Study C93-313)

Total bivalirudin clearance is predicted to be 1.8 fold greater than the glomerular filtration rate, a relationship that is consistent regardless of the degree of renal impairment.

As indicated by the 95% confidence interval the y intercept is not substantially different from zero. This observation is typically consistent with drugs for which renal clearance is the primary clearance route. The presence of extra renal clearance mechanisms would result in a larger y axis intercept. Total clearance of bivalirudin exceeds glomerular filtration by 1.8 suggesting that renal secretion, in addition to filtration, must be occurring. In such circumstance the urinary excretion of a drug exceeds that predicted from the product of the fraction of unbound drug and glomerular filtration rate. In healthy volunteers urinary excretion of bivalirudin is typically between 10 and 20%, which is inconsistent for a drug which is cleared by renal excretion alone, unless reabsorption and/or breakdown of the drug occurs in urine.

Bivalirudin is a low molecular weight protein, and urinary excretion data typically underestimates the renal clearance of low molecular weight proteins and polypeptides. These compounds are usually filtered at the glomerulus, secreted in the proximal convoluted tubule and reabsorbed in the distal convoluted tubule. Following reabsorption these low molecular weight peptides are degraded within intercellular lysosomes to their amino acids.

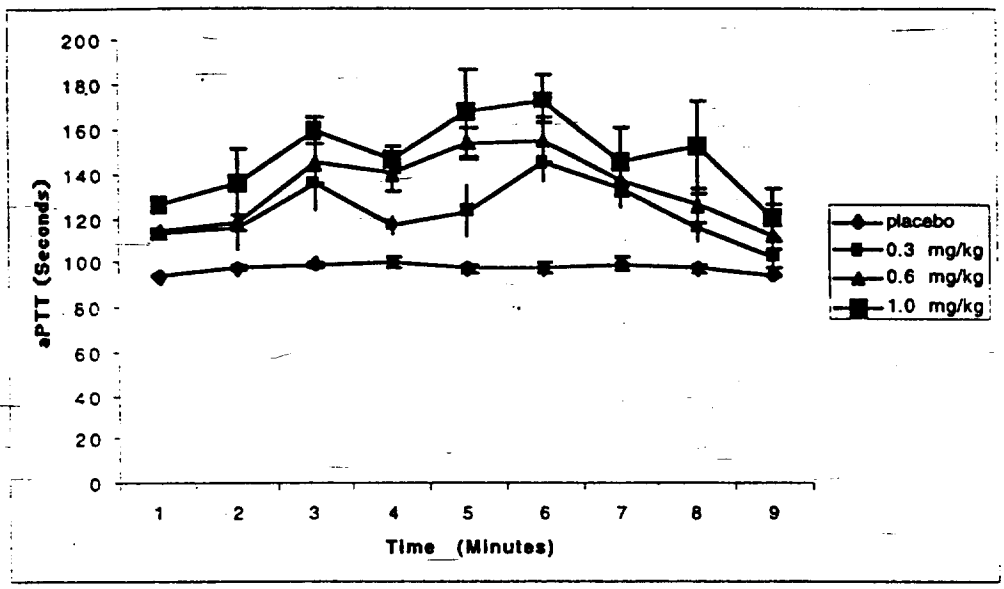
Filtration and renal secretion account for Bivalirudin's total clearance. There is no evidence for extra-renal clearance mechanisms, which is consistent with data for natural and recombinant forms of hirudin and other low molecular weight polypeptides.

Bivalirudin Pharmacodynamics

Healthy Volunteers and Patients

In healthy volunteers there is a direct relationship between dose and aPTT response (Figure 2). Clear dose-response relationships are also reported for aPTT and/or ACT in PTCA and in unstable angina patients.

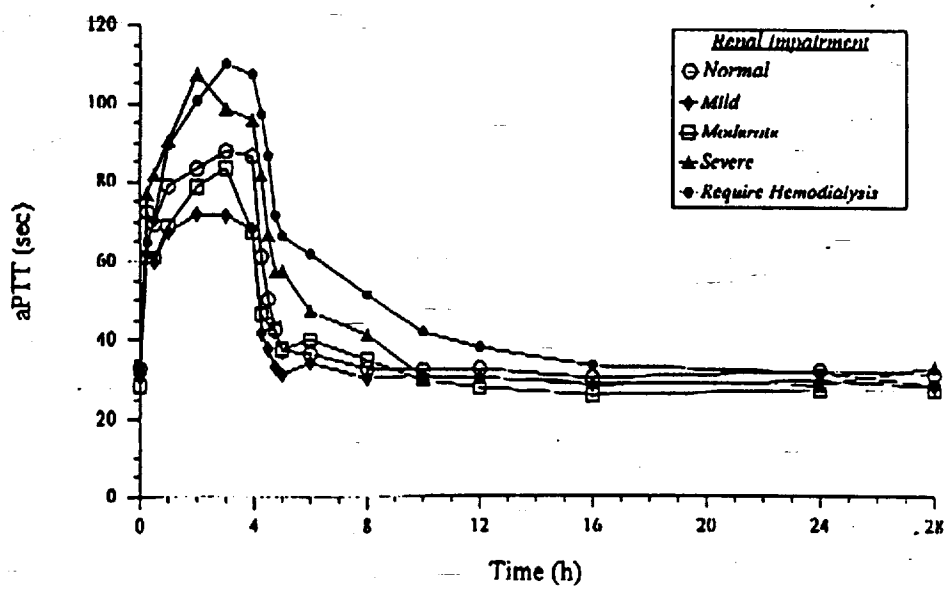
Figure 2. Average (±SE) aPTT Response Following SC Administration of Bivalirudin in Study C90-010



Renal Impairment

In the renal impairment study (C93-313) aPTT profiles were obtained at the same time as the pharmacokinetic samples were obtained. The aPTT-time profiles for the normal and moderately impaired groups were similar, with the mild group having a lower mean aPTT than either (Figure 3). The mean aPTT was higher in the groups with severe renal impairment and those patients requiring hemodialysis (non-dialysis day) than in the other 3 groups.

Figure 3. Mean aPTT in 0.5 mg/kg/h IV Infusion of Bivalirudin



The pharmacodynamic data in renal impairment is therefore consistent with the data from volunteer studies indicating a direct relationship between plasma concentrations and effect as measured by aPTT.

Analysis of Phase III Data in Patients with Unstable Angina Undergoing PTCA

Analysis of the data base of 4,312 patients with unstable angina undergoing PTCA in two phase III trials (C92-304-1 and 2) also supports the pharmacokinetic clearance data. The glomerular filtration rate for each patient in Phase III trials was calculated using the Cookcroft and Gault formula applied to baseline values. Patients were then stratified into the same 4 groupings as in the renal impairment study described above. Normal renal function GFR≥90ml/min, mild renal impairment GFR 60-89ml/min, moderated renal impairment GFR 30-59 ml/min, and severe renal impairment GFR<30ml/min. The incidence of major bleeding rates versus renal function was plotted (Table 2).

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Table 2. Major Hemorrhage Incidence Rates Across Levels of Renal Function and Treatment. Studies C92-304-1 and C92-304-2 Combined.

	BIVALIRUDIN	HEPARIN
Degree of Impairment (GFR; mL/min)	n/N (%)	n/N (%)
None (≥ 90 mL/min)	6/483 (1.2%)	15/481 (3.1%)
Mild (60 - < 90 mL/min)	17/884 (1.9%)	74/870 (8.5%)
Moderate (30 - < 60 mL/min)	32/529 (6.0%)	65/513 (12.7%)
Severe (< 30 mL/min)	0/18 (0%)	4/15 (26.7%)

The incidence of major bleeding increased for heparin and bivalirudin as the degree of renal function deteriorated, except in the severe group for bivalirudin. The number of patients with severe renal impairment on bivalirudin was small and therefore this analysis may have underestimated the incidence of severe bleeding in this group. Although bleeding times are increased with increasing degrees of renal impairment due to platelet dysfunction, this data is also consistent with decreased clearance of bivalirudin in renal impairment.

The ACT measurements taken at forty-five minutes were similar in all groups (and within "therapeutic" range) except for the severely impaired patients, where there was an increased ACT (Figure 4). In a covariate analysis of potential parameters contributing to bleeding, GFR accounts for twice the variability in bleeding events as either age or gender.

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